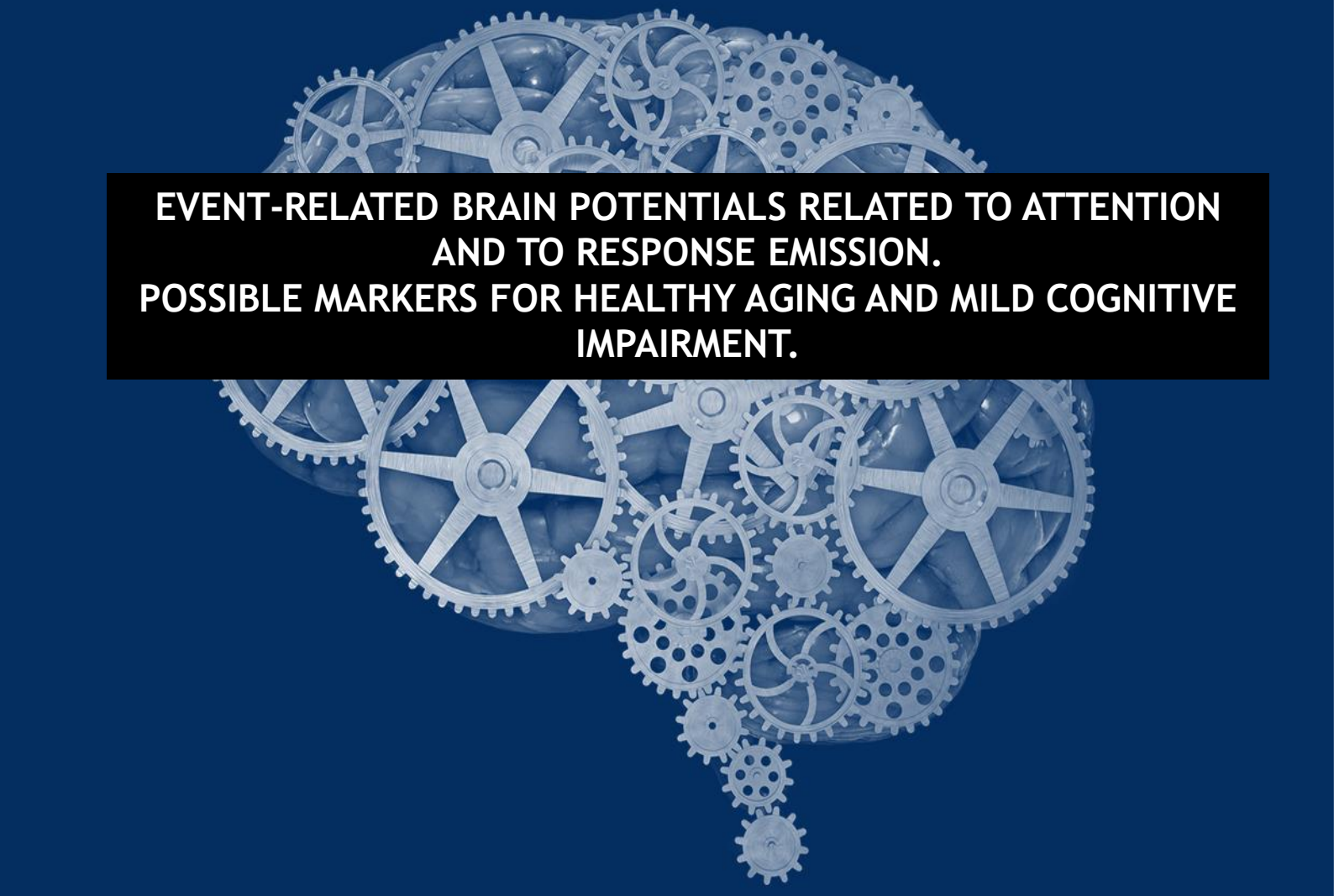
Programa de Doutoramento en Neurociencia e Psicoloxía Clínica
Departamento de Psicoloxía Clínica e Psicobioloxía
Facultade de Psicoloxía



EVENT-RELATED BRAIN POTENTIALS RELATED TO ATTENTION AND TO RESPONSE EMISSION. POSSIBLE MARKERS FOR HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT.

Doctoral thesis

Susana Cid Fernández
Santiago de Compostela, 2015

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Departamento de Psicoloxía Clínica e Psicobioloxía

Facultade de Psicoloxía

Programa de Doutoramento en Neurociencia e

Psicoloxía Clínica

EVENT-RELATED BRAIN POTENTIALS RELATED TO ATTENTION AND TO RESPONSE EMISSION. POSSIBLE MARKERS FOR HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT.

Doctoral thesis

Susana Cid Fernández

Santiago de Compostela, 2015

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

FACULTADE DE PSICOLOXÍA
Dpto. de Psicoloxía Clínica e Psicobioloxía

Campus universitario sur ● 15782 Santiago de Compostela
Tfno.: 981 563 100 ● Fax: 981 528 071

INFORME DOS DIRECTORES DA TESE

Os Doutores D. Fernando Díaz Fernández e Dna. Mónica Lindín Novo, profesores do Departamento de Psicoloxía Clínica e Psicobioloxía;

Como Directores da Tese de Doutoramento titulada:

"**EVENT-RELATED BRAIN POTENTIALS RELATED TO ATTENTION AND TO RESPONSE EMISSION. POSSIBLE MARKERS FOR HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT**"

Presentada por Dna. Susana Cid Fernández

Alumna do Programa de Doutoramento de Neurociencia e Psicoloxía Clínica, da USC.

Autorizamos a presentación da tese indicada, considerando que reúne os requisitos esixidos no artigo 33 do regulamento de Estudos de Doutoramento, así como os recollidos no artigo 40 de dito regulamento para a Mención Internacional do título de Doutor, e que como Directores da mesma non incorre nas causas de abstención establecidas na lei 30/1992.

Asdo.....

Fernando Díaz Fernández

Asdo.....

Mónica Lindín Novo

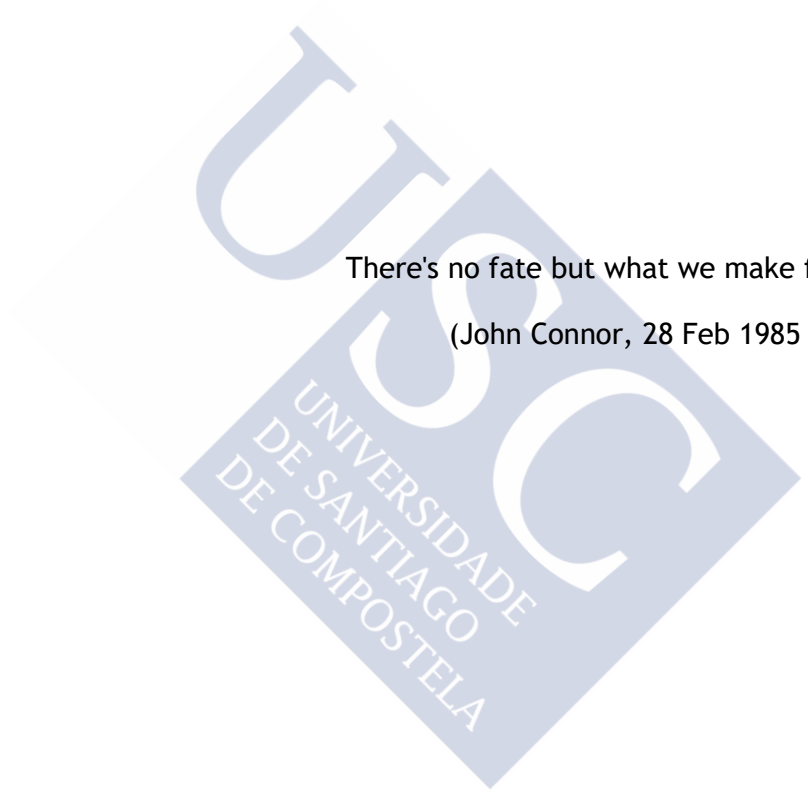
USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

E como é de ben nacidos ser agradecidos, pero o bo se breve, dúas veces bo:

A todos e todas os que me ensinaron, axudaron, apoiaron, acompañaron e aturaron (especialmente esto último, cousa que fixeron tod@s os que me ensinaron, axudaron, apoiaron e acompañaron, e algun@s máis),

¡GRAZAS!

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA



There's no fate but what we make for ourselves

(John Connor, 28 Feb 1985 – 4 Jul 2032)

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

INDEX

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

GENERAL INTRODUCTION

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Population aging is an issue that affects the world, basically due to the decrease of birth rates and the increase of life expectancy (Park & Reuter-Lorenz, 2009): in 2050 there will be more adults than children under 15 in wealthy countries (26% vs. 16%; Cohen, 2003). Because of this, the study of aging gains importance both to improve the quality of life of elder people, and to reduce the high cost that age-related diseases (especially those associated to dementias) produce, as adults aged 85 and older show a dementia rate of nearly 50% (Hebert, Scherr, Bienias, Bennett, & Evans, 2003).

The aging brain experiences structural and functional changes, some of which lead to a functional deterioration (for a review, see Park & Reuter-Lorenz, 2009). Some of these changes include cortical thinning and regional atrophy, loss of white matter integrity, and dopamine depletion (Reuter-Lorenz & Park, 2014). Functional age-related deterioration patterns have been well documented, as the decreased specificity of motor and ventral-visual areas (Bernard & Seidler, 2012; Park et al., 2004; Voss et al., 2008), dysregulation of the default mode network (Lustig et al., 2003; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007), or decreased memory-related recruitment of medial temporal lobe regions (Cabeza et al., 2004; Gutchess et al., 2005). But not every age-related functional change is thought to be maladaptative, as the posterior-anterior shift (PASA) phenomenon, which consists in an age-related enhancement in frontal activity that is positively correlated with performance and negatively correlated with the age-related occipital decreases (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). It is important to detect and study these changes, so age-related neurocognitive deficits can be slowed or even reversed.

It has been proposed that there is a continuum between healthy aging and dementias (Petersen et al., 2014), but most investigators believe that if we wait for functional impairment and perhaps even mild cognitive symptoms to emerge, it may be too late to treat the underlying disease process (Gauthier et al., 2006). There has been a growing interest in the predementia phase of these conditions because of suggestions that we may be able to identify the earliest clinical features of these illnesses before functional impairment is evident (Petersen et al., 2009). This predementia phase has been labeled Mild Cognitive Impairment (MCI; Petersen, 2004; Petersen et al., 1999, 2001, 2009; Petersen & Negash, 2008).

The concept of MCI intends to identify this intermediate state of cognitive impairment that is often a transitional phase from cognitive changes of normal aging to those typically found in dementia (Petersen et al., 2014). In a 1999 article

published in the *Archives of Neurology*, a group of investigators from the Mayo Clinic described their experience with participants with MCI in a community cohort and outlined the first clear diagnostic criteria (Petersen et al., 1999). Since then, more expansive criteria for MCI were proposed (Petersen, 2004; Petersen et al., 2001, 2009, 2014).To establish MCI diagnosis, activities of daily living must be preserved, dementia must be absent, and one or more cognitive domains must be impaired (Petersen et al., 2014).

These criteria depict the clinical phenotypes of amnestic MCI (aMCI; memory is impaired) and non-amnestic MCI (naMCI; memory is not impaired), with the subtypes of single and multiple domain classifications (when one or more cognitive domains are affected, respectively; Petersen et al., 2009). As a result, four MCI subtypes were distinguished: single-domain amnestic MCI (sdaMCI, characterized by only memory impairment), multiple-domain amnestic MCI (mdaMCI, characterized by memory impairment and impairment in other additional cognitive domains), single-domain non-amnesic MCI (sdnaMCI, characterized by preserved memory but an overt decline in another cognitive domain), and multiple-domain non-amnestic MCI (mdnaMCI, characterized by preserved memory but with evidence of decline in several cognitive domains).

It has been observed that non-amnestic MCI subtypes are in a greater risk to developing dementias different from the related to Alzheimer's Disease (AD; as vascular dementia; Howe, 2014; Vos et al., 2013). On the other hand, people with aMCI are in greater risk for developing AD (Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2011; Vos et al., 2013), with an annual conversion rate of 16-18% while healthy old population show a rate of 1-2% (Petersen et al., 1999, 2009). Several studies also suggested that patients with multiple domain cognitive impairment have a greater risk of progressing to dementia than patients with single domain impairment (Ganguli, Dodge, Shen, & DeKosky, 2004; Lenzi et al., 2011; Mitchell, Arnold, Dawson, Nestor, & Hodges, 2009; Vos et al., 2013).

The AD is the most common form of dementia (Papaliagkas, Anogianakis, Tsolaki, Koliakos, & Kimiskidis, 2009) and is not only associated to a social, but also economic and psychological high-cost state of dependence, becoming a major social and sanitary problem (Valls-Pedret, Molinuevo, & Rami, 2010).

Nowadays, the only certain AD diagnosis is *post mortem*, by inspecting the anatomopathological alterations in the brain. For the probable AD diagnosis, actual

criteria state that there must be important cognitive deficits (Albert et al., 2011; McKhann et al., 2011), so that the damage is important, affecting to several brain areas (Valls-Pedret et al., 2010). Given that there is no healing treatment for AD, early detection from prodromal stages would allow the application of pharmacological and psychological intervention programs that make possible the reversion (or at least the slowing) of the symptomatology, improving the quality of life of the patients and their caregivers. Thus, the identification of people with MCI would make possible to confront the disease even from prodromal stages.

Current AD and MCI diagnostic criteria include the presence of biomarkers (Albert et al., 2011; Jack et al., 2011; McKhann et al., 2011). Biomarkers are parameters (physiological, biochemical, anatomic) that can be measured in vivo and that reflect specific features of disease-related pathophysiological processes (Jack et al., 2011). Ideally, a marker should be able to detect the neuropathology and must be validated in neuropathologically confirmed cases, but it also should be precise, reliable, non-invasive, simple to perform and inexpensive (Thies, Truschke, Morrison-Bogorad, & Hodes, 1998). The biomarkers indicated by Albert et al (2011) for MCI are expensive (functional magnetic resonance [fMRI]), and invasive (positron emission tomography [PET] or cerebrospinal fluid [CSF] measures), and have not been standardized yet (Jack et al., 2011). They do not consider other techniques, as electroencephalogram (quantitative electroencephalogram [qEEG] or event-related potentials [ERPs]), which have shown to be useful in the search for MCI and AD biomarkers (Cespón, Galdo-Álvarez, & Díaz, 2015a, 2013a; Jackson & Snyder, 2008; Lindín, Correa, Zurrón, & Díaz, 2013; Vecchio & Määttä, 2011).

The EEG is a non-invasive, comfortable, and low-cost technique. ERPs are voltage fluctuations in an ongoing EEG that reflect brain activity and are time locked to sensory, motor or cognitive events (Friedman, Cycowicz, & Gaeta, 2001). When event-related EEG epochs are averaged, the resulting waveform comprises a series of positive and negative deflections of voltage, which are considered components of brain activity that have a (relatively) stable time relationship with an event, such as evaluation and categorization of a target stimulus or the preparation and execution of a motor response (Luck, 2005). Thus, ERPs show high temporal resolution (in the order of milliseconds), ideal for the study of psychological processes, as brain processing happens in that temporal order. This technique allows us to capture serial or even parallel processes and it has shown its usefulness for studying healthy aging (e. g. Buján, Lindín, & Díaz, 2010; Cespón, Galdo-Álvarez, & Díaz, 2013b; Galdo-

Alvarez, Lindín, & Díaz, 2009a, 2009b; Pinal, Zurrón, Díaz, & Sauseng, 2015; Pinal, Zurrón, & Díaz, 2014), MCI and EA (e.g. Bennys, Portet, Touchon, & Rondouin, 2007; Bennys, Rondouin, Benattar, Gabelle, & Touchon, 2011; Cespón et al., 2013a, 2015a, 2015b; Friedman, 2008; Saito et al., 2001; West, Schwarb, & Johnson, 2010).

ERPs IN AD AND MCI.

Different ERP components have been evaluated regarding different cognitive processes, with the aim of identifying AD and MCI biomarkers. This doctoral thesis will be focused in cognitive processes related to attention and response emission.

Voluntary target processing in AD and MCI: N2b and P3b components.

The electrophysiological correlates of the processes related to the voluntary processing of the attended target stimulus are the N2b and the P3b ERP components. Both components have been classically elicited by an attended stimulus using the classical *oddball* paradigm, where the participants must attend to one type of infrequent stimulus (target) while ignoring another type of frequent stimulus (standard; Amenedo & Díaz, 1998a; Polich, 1996; Ravden & Polich, 1998). But these components can also be elicited using a *Go/NoGo* task (Falkenstein, 2006), where participants are required to respond by pressing a button to one (usually more frequent, i.e. prepotent) stimulus (Go condition), while inhibiting the response to another (usually infrequent) stimulus (NoGo condition). EEG recordings of participants while performing *Go/NoGo* tasks have revealed different components of the ERPs produced in response to the Go and NoGo conditions.

Hence, two ERP components have been identified in relation to the stimulus in the Go condition of a *Go/NoGo* task, as well as in the *oddball* paradigm, and others (for a review, see Patel & Azzam, 2005): 1) the Go-N2 component (or N2b), a negative wave observed between 200 and 300 ms (Beste, Willemssen, Saft, & Falkenstein, 2010) with maximal amplitude at central locations (Amenedo & Díaz, 1998a, 1998b; Papaliagkas et al., 2011), and 2) the Go-P3 (or P3b) component, a positive wave observed between 300 and 600 ms (Li et al., 2010; Schmiedt-Fehr & Basar-Eroglu, 2011) with maximal amplitude in parietal locations in the young (Bennys et al., 2007; Kutas, Iragui, & Hillyard, 1994; Polich, 2004).

N2b is classically considered as an indicator of controlled detection of a change in stimulation and its active evaluation in working memory (WM; Bennys et al., 2007; Papaliagkas et al., 2011; Ritter, Simson, Vaughan, & Friedman, 1979). P3b is associated with the context-updating of mental representations when a target stimulus occurs and which matches the mental representation of the task-relevant stimulus (Donchin & Coles, 1988; Polich, 2004).

Both the P3b and N2b components have proven to be sensitive to AD (Díaz & Amenedo, 2001; Howe, Bani-Fatemi, & De Luca, 2014; Howe, 2014). The P3b latency is usually longer in AD patients than in controls in studies that used an *oddball* task (Bennys et al., 2007; Frodl et al., 2002; Gironell, García-Sánchez, Estévez-González, Boltes, & Kulisevsky, 2005; Golob & Starr, 2000; Golob, Irimajiri, & Starr, 2007; Lai, Lin, Liou, & Liu, 2010; Parra, Ascencio, Urquina, Manes, & Ibáñez, 2012; Vaitkevicius, Kaubrys, & Audronyte, 2015; van Deursen, Vuurman, Smits, Verhey, & Riedel, 2009), and a Sternberg memory search paradigm (Phillips, Chertkow, Leblanc, Pim, & Murtha, 2004).

Results regarding P3b amplitude are less consistent: although some of the previously cited studies found lower P3b amplitudes in AD than in control participants (e. g. Bennys et al., 2007; Frodl et al., 2002; Parra et al., 2012; Phillips et al., 2004; Saito et al., 2001; van Deursen et al., 2009), others did not observe any differences (e. g. Gironell et al., 2005; Golob & Starr, 2000; Golob et al., 2007; Lai et al., 2010; Vaitkevicius et al., 2015).

The only study that used a *Go/NoGo* task to assess P3b in AD failed to find any differences in P3b latency compared with control participants, but P3b amplitude was lower in the AD than in the Control participants, showing a decline in P3b neural generators, or maybe a deficit of early sensory processing that may cause P3 abnormality, according to the authors (Saito et al., 2001).

Although the N2b is a much less studied component, some studies also did evaluate it in AD patients during an *oddball* task. Some of them found longer N2b latencies in the AD than in the control group (e. g. Bennys et al., 2007; Vaitkevicius et al., 2015), while others failed to find any differences (e. g. Lai et al., 2010; Saito et al., 2001; van Deursen et al., 2009). On the other hand, N2b amplitudes do not usually show differences between both groups (e. g. Bennys et al., 2007; Howe, 2014; Lai et al., 2010; Saito et al., 2001; Vaitkevicius et al., 2015; van Deursen et

al., 2009). To our knowledge, there are no studies that evaluated the N2b in AD patients using a *Go/NoGo* task.

The N2b and P3b components have also been studied in MCI adults with *oddball* tasks, with the aim of detecting early indicators of cognitive decline by evaluating ERP parameters. The results obtained for N2b parameters in such studies were contradictory. In some of these studies, the N2b latency was longer in elderly participants with MCI than in elderly controls (Bennys et al., 2007; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008; Papaliagkas et al., 2011), whereas in other studies no differences were observed between groups (Golob, Johnson, & Starr, 2002; Lai et al., 2010; van Deursen et al., 2009). For the N2b amplitude, several studies did not find any differences between elderly participants with MCI and elderly controls (Golob et al., 2002; Lai et al., 2010; van Deursen et al., 2009), whereas other studies found that the amplitude of the N2b was larger in MCI adults than in control adults (Papaliagkas et al., 2008, 2011).

In relation to P3b, most studies have reported longer latencies in elderly adults with MCI than in healthy elderly controls (Bennys et al., 2007; Golob et al., 2002, 2007; Lai et al., 2010; Li et al., 2010; Papaliagkas et al., 2008; van Deursen et al., 2009), although no such differences were observed in other studies (Frodl et al., 2002; Gironell et al., 2005). In relation to the P3b amplitude, some studies did not find any differences between the two groups (Frodl et al., 2002; Gironell et al., 2005; Golob et al., 2002; Lai et al., 2010; Papaliagkas et al., 2008; van Deursen et al., 2009), whereas other studies reported a lower P3b amplitude in the MCI group than in the control group (Bennys et al., 2007; Li et al., 2010).

The discrepancies in the results of the above-cited studies may be due to different factors, such as the different criteria used for including and excluding participants, in relation to the use of drugs that may affect the task performance and the types of tests used to diagnose the participants.

To our knowledge, there are no studies that evaluated the N2b and P3b ERP components using a *Go/NoGo* task in MCI samples. In addition to the N2b and P3b, classically obtained with *oddball* tasks, a *Go/NoGo* task allows the identification and evaluation of other ERP components, as those related to response inhibition.

Response inhibition in AD and MCI: NoGo-N2 and NoGo-P3 components.

In the NoGo condition of a *Go/NoGo* task, the NoGo-N2 component has been recognized as a negative wave observed at between 200 and 350 ms (Hämmerer, Li, Müller, & Lindenberger, 2010), with maximal amplitude at frontal and central locations, preferentially right (Falkenstein, Hoormann, & Hohnsbein, 2002). Although the functional significance of the component is still a matter of controversy, several authors have suggested that NoGo-N2 is a correlate of the decision to inhibit a motor response (Beste et al., 2010; Bokura, Yamaguchi, & Kobayashi, 2001; Dong, Yang, Hu, & Jiang, 2009).

In contrast, other authors consider the component as a correlate of detection of a conflict between the requirement of a task (e.g., non-emission of a response to a particular stimulus) and the preparation involved in executing the response (Donkers & van Boxtel, 2004; Nieuwenhuis, Yeung, van den Wildenberg, & Ridderinkhof, 2003; Randall & Smith, 2011). Recent studies consider that both of these hypotheses are complementary (Kropotov, Ponomarev, Hollup, & Mueller, 2011; Schmiedt-Fehr & Basar-Eroglu, 2011).

Another component has also been identified in the NoGo condition: the NoGo-P3 component, which is a positive wave that appears between 300 and 500 ms, with maximal amplitudes at midline frontocentral locations (Falkenstein et al., 2002). Although it was classically considered that NoGo-P3 is a correlate of response inhibition (Bokura et al., 2001; Falkenstein et al., 2002), recent studies suggest that NoGo-P3 may play an important role in the post-response stage, reflecting processes of evaluation or monitoring of inhibition, error detection and preparation of future trials (Beste et al., 2010; Schmiedt-Fehr & Basar-Eroglu, 2011).

In the aforementioned only ERP study that used a *Go/NoGo* task with AD participants, the P3 amplitude was lower in elderly AD patients than in healthy elderly controls, both in the Go and NoGo conditions, whereas the P3 latency did not differ between the two groups (Saito et al., 2001). This was interpreted by the authors as a possible decline in the common P3b and NoGo-P3 generators. Moreover, some studies that used neuropsychological tests report deficits in executive function during initial (Grober et al., 2008) and prodromic (Chen et al., 2001; Grober et al., 2008) stages of AD. However, in a behavioral study with a *Go/NoGo* task, no differences in execution were observed between healthy adults and those with MCI (Zhang, Han, Verhaeghen, & Nilsson, 2007).

To our knowledge, only Saito et al. (2001) evaluated ERPs in the NoGo condition in AD patients, using the *Go/NoGo* paradigm, or using other paradigms that allow the study of response inhibition processes (e.g. the *stop-signal* task), and there are no studies involving MCI participants.

Motor processing in AD and MCI: the stimulus-locked and response-locked lateralized readiness potentials (sLRP and rLRP).

Other processes that can be studied when overt responses are required, are motor processes related to the selection and programming of the response. The lateralized readiness potential (LRP) is computed from the ERP recorded above the hand areas of the motor cortices of both hemispheres (Lehle, Cohen, Sangals, Sommer, & Stürmer, 2011; Vallesi & Stuss, 2010). This component consist of two different subcomponents: 1) the stimulus-locked LRP (sLRP) whose onset is the point at which motor activity in the brain begins to favor making one of two possible responses, indexing response selection, and 2) the response-locked LRP (rLRP) reflects processes of motor programming and execution required to execute the given response (Masaki, Wild-Wall, Sangals, & Sommer, 2004; Roggeveen, Prime, & Ward, 2007).

Using both hands to make responses allows computing the sLRP and the rLRP, making possible to obtain the differences between scalp measures from contralateral and ipsilateral activation of the motor cortex.

Recently, Cespón et al. (2013a, 2015b) evaluated the rLRP with a stimulus-response compatibility (*SRC*) task in aMCI adults, where participants usually have to respond to one characteristic of the stimulus (e. g. color), while ignoring another, sometimes incompatible with the appropriate response (e. g. direction). The authors found that aMCI adults showed lower rLRP amplitudes than healthy age-matched controls, evidencing a decline in the motor cortex in aMCI participants, without differences between those aMCI adults with and without impairments in other cognitive functions (multiple-domain aMCI and single-domain aMCI participants, respectively). In addition, these authors obtained high sensitivity and specificity values (≥ 0.82) for rLRP amplitude for discriminating aMCI from control adults (Cespón et al., 2013a, 2015b), showing that the rLRP might be an useful biomarker for aMCI diagnosis.

To our knowkedge, the LRP has never been evaluated in AD patients, and only Cespón et al. (2013a, 2015b) evaluated the rLRP in MCI participants, while the sLRP has never been evaluated in these participants. Besides, these components were never studied using a *Go/NoGo* task in AD or MCI participants.

Summary: ERPs in AD and MCI.

The N2b and P3b components have previously been evaluated in MCI and AD participants using *oddball* tasks, but results are inconclusive. In addition, these components have never been assessed using a *Go/NoGo* task in MCI participants. Similarly, the NoGo-N2 and NoGo-P3 components have never been evaluated in MCI participants (with a *Go/NoGo* task or any other similar paradigm), and only Saito et al. (2001) evaluated the NoGo-P3 and P3b components in AD patients using a *Go/NoGo* task. Finally, the sLRP and rLRP have never been evaluated in AD or MCI until Cespón et al. (2013a, 2015b) recently evaluated the rLRP in MCI participants using a *SRC* task.

In view of the scarcity or even the non-existence of ERP studies involving *Go/NoGo* tasks in MCI patients, an auditory-visual distraction-attention task (A-V task), based on the task designed by Escera et al. (1998), was designed.

THE AUDITORY-VISUAL DISTRACTION-ATTENTION TASK.

For the evaluation of the processes described above, the auditory-visual distraction-attention task (A-V task) seems to be an ideal tool. It involved a passive *oddball* task and a *Go/NoGo* task, allowing the evaluation of the N2b, P3b, NoGo-N2, NoGo-P3, sLRP and rLRP components, and therefore the associated cognitive processes.

The task designed for our studies included an auditory passive *oddball* task and a visual active three-stimulus *Go/NoGo* task. Participants were presented with 500 pairs of auditory-visual stimuli, divided into 2 blocks with a short rest between each block. Each pair consisted of a visual stimulus (200 ms duration) preceded by an auditory stimulus (150 ms duration), separated by an interval of 300 ms (SOA), and with an interval of 2 s between each pair (see Figure 1). Participants were asked to attend to the visual stimuli and to ignore the auditory stimuli.

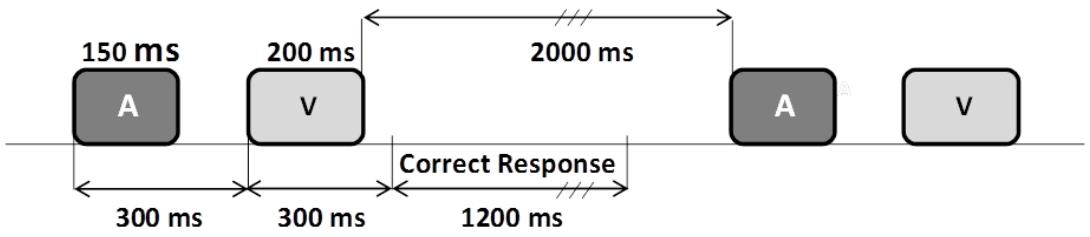


Figure 1: Schematic representation of the present distraction-attention auditory-visual task

The attended visual stimuli were numbers (2, 4, 6, 8), letters (a, e, c, u) and triangles (pointing upwards, downwards, or to the right or left). Participants were instructed to respond to numbers (33%) and to letters (33%), by pressing a button (Go stimuli; target) with their left hand for one type of stimulus and with the right hand for the other type (the response hand was counter-balanced among participants), and to inhibit their responses to triangles (34%; NoGo stimuli).

The non-attended auditory stimuli comprised 3 types of sounds presented binaurally via headphones at 75 dB SPL; 70% were standard stimuli (1000 Hz pure tones), 15% were deviant stimuli (2000 Hz pure tones), and 15% were novel stimuli (which differed each time, e.g., glass crashing).

Previous studies using the A-V task with young participants.

The A-V task used in previous studies (e. g. Escera et al., 1998; Escera, Yago, & Alho, 2001; Polo et al., 2003; SanMiguel, Morgan, Klein, Linden, & Escera, 2010; Yago, Corral, & Escera, 2001) always included a passive auditory *oddball* task and an active visual classification task. The passive auditory task usually comprehends standard stimuli (pure tones) that appear in a large percentage of trials (between 75% and 90%), deviant stimuli (generally pure tones slightly different from the former), and/or novel stimuli (different environmental sounds) that appear in the remaining trials.

The active visual task habitually consisted in a simple 2 stimulus classification task, where the participants must press a different button for each stimulus type. Different visual stimuli have been used previously, such as odd and even numbers (Andrés, Parmentier, & Escera, 2006; Escera et al., 1998, 2001; Escera, Corral, & Yago, 2002; Escera, Yago, Corral, Corbera, & Nuñez, 2003; Parmentier, Elford, Escera, Andres, & Miguel, 2008; Parmentier & Andrés, 2010; Parmentier, Elsley, & Ljungberg, 2010; Yago, Corral, et al., 2001), numbers and letters (Alho, Escera, Díaz, Yago, & Serra, 1997; Polo, Newton, Rogers, Escera, & Butler, 2002; Polo et al., 2003; Yago, Corral, et al., 2001; Yago, Escera, Alho, & Giard, 2001; Yago, Escera, Alho, Giard, & Serra-Grabulosa, 2003), or simple clothes and animal drawings (Wetzel, Schröger, & Widmann, 2013; Wetzel, Widmann, & Schröger, 2011).

The most common outcome of the task is related to performance, in young participants: when a novel sound precedes the visual target (Novel condition) reaction times (RTs) to the latter are longer than when the preceding sound is a standard tone (Standard condition; Barceló, Escera, Corral, & Periáñez, 2006; Cortiñas et al., 2008; Escera et al., 1998, 2001, 2003; Parmentier, 2008; Parmentier et al., 2008, 2010; Parmentier, Elsley, Andrés, & Barceló, 2011; Polo et al., 2003; Wetzel et al., 2013; Yago et al., 2003).

This is also true for the Deviant condition compared with the Standard condition in young (Alho et al., 1997; Escera et al., 2001, 2002; Polo et al., 2003; Wetzel et al., 2013; Yago, Escera, et al., 2001), although some studies failed to find such difference (Escera et al., 1998; Polo et al., 2002; Yago et al., 2003). These longer RTs in the distractor condition indicate that these sounds are able to activate the attentional cerebral network underlying the orienting response, temporarily disengaging attention from the relevant visual task (Escera et al., 1998; Yago et al., 2003), and they are the behavioral correlates of the so-called “attention capture effect”, “distraction effect”, or “involuntary orienting of attention” (Parmentier et al., 2008; Wetzel et al., 2013; Yago, Corral, et al., 2001).

On the contrary, SanMiguel et al. (2010) found longer RTs in the Standard than in the Novel condition, and they interpreted this finding as a facilitation effect produced by the novel stimuli. It is worth noting that their task is the one of the most different variations of the A-V task, involving faces as visual stimuli.

The A-V distraction-attention task has also been used with the aim of studying the ERP components related to attentional processes in young participants triggered

by the unattended auditory stimuli, such as (1) the automatic detection of a disruption in a stable environment (MMN; Alho et al., 1997; Escera et al., 1998, 2001, 2002; Polo et al., 2002, 2003; SanMiguel et al., 2010; Yago, Corral, et al., 2001; Yago, Escera, et al., 2001; Yago et al., 2003), (2) the orientation of the focus of attention towards the auditory irrelevant stimulus and its evaluation and categorization in WM (P3a; Alho et al., 1997; Barcelo et al., 2006; Escera et al., 1998, 2001, 2003; Polo et al., 2003; SanMiguel et al., 2010; Wetzel et al., 2013; Yago, Corral, et al., 2001; Yago et al., 2003), and (3) the reorientation of the focus of attention towards the relevant attended visual stimuli (RON; Polo et al., 2003; SanMiguel et al., 2010; Yago, Corral, et al., 2001).

The correlates of the voluntary processing of the attended visual targets (the N2b and P3b components) have been studied within this task to a lesser extent. Only four studies expressly identified visual ERP components in young participants (Escera et al., 1998, 2001; Polo et al., 2002; SanMiguel et al., 2010), and from these, only Escera et al. (1998) and SanMiguel et al. (2010) evaluated differences between conditions on the P3b amplitude. SanMiguel et al. (2010) found an enhancement in P3b amplitude in the Novel condition, interpreted by the authors as a neural correlate of a facilitation effect, also reflected in shorter RTs. Escera et al. (1998) also observed an enhancement in P3b and N2b amplitudes in the Novel condition, but with longer RTs, although these results were not discussed in this study.

The studies that previously used variations of the A-V task usually required making a different overt response for each of the two types of visual stimuli, being both *Go* conditions. Only one study included a *NoGo* condition (Alho et al., 1997), in which the instructions were to withhold the response. This condition allows studying the electroencephalographic activity related to those executive control processes involved in response inhibition: the NoGo-N2 and NoGo-P3 components. Although Alho et al. (1997) identified the NoGo-P3 component (but not the NoGoN2 component) using a modified version of the A-V task, they did not analyze it statistically.

In addition, all the previously mentioned studies that used this task required two responses using two different buttons, but participants were only required making each response with a different hand in a few (thus allowing to compute the LRP; Barceló et al., 2006; Wetzel et al., 2013, 2011). Despite this, the LRP was not evaluated in any of these studies.

Previous studies using the A-V task with old participants.

Two studies used the A-V task with elderly participants (Andrés et al., 2006; Parmentier & Andrés, 2010). Both studies observed longer RTs (in response to visual stimuli) in both young and elderly participants in the Novel than in the Standard condition. But, while Parmentier and Andrés (2010) did not observe significant differences between age groups, Andrés et al. (2006) found a significantly stronger distraction effect in the elderly group. The last result was interpreted as reflecting a decline in frontal or anterior attentional networks in the older groups, in which filtering of irrelevant information must be accomplished (Andrés et al., 2006).

There are no studies with this task that evaluated any ERP component (N2b, P3b, NoGo-N2, NoGo-P3, LRP, nor others) in elderly participants.

Although any study used the A-V task to assess age-related effects on ERPs, aging is usually associated to latency increases of N2b and P3b, and amplitude decreases of P3b in many different types of tasks (for reviews, see Patel & Azzam, 2005; Polich, 2012). Several studies using a variety of *Go/NoGo* tasks also found that both the NoGo-N2 and the NoGo-P3 show age-related impairments, with reduced amplitudes and longer latencies in the elderly (Beste et al., 2010; Czigler, Csibra, & Ambró, 1996; Hämmerer et al., 2010; Vallesi, Stuss, McIntosh, & Picton, 2009).

Some studies evaluated age-related effects on the LRP using different tasks, but none of them employed any variation of a *Go/NoGo* task. Both sLRP and rLRP consistently show age-related decreases in amplitude, but it is still not clear if this is due to compensation strategies (Cespón et al., 2013b; Wild-Wall, Falkenstein, & Hohnsbein, 2008) or due to deficits in the motor cortex (Roggeveen et al., 2007; Yordanova, Kolev, Hohnsbein, & Falkenstein, 2004) in the elderly. In addition, the rLRP onset latency consistently shows an age-related slowing (Roggeveen et al., 2007; Wild-Wall et al., 2008; Yordanova et al., 2004), while results regarding the sLRP onset latency are contradictory (Cespón et al., 2013b; Kolev, Falkenstein, & Yordanova, 2006; Roggeveen et al., 2007; Wild-Wall et al., 2008; Yordanova et al., 2004).

Besides, the interaction effects between aging and the capture of attention on these components are still unknown.

RESPONSE-RELATED DIRECT BRAIN ACTIVITY: preRFP, CRN, postRFP, parietalRP.

In a task that requires making overt responses, it is possible to evaluate other response-related processes and their ERP correlates, different from those indexed by the LRP. This has never been made with the A-V task, and the literature about these components is really scarce.

At frontal electrodes, the ERP components that usually appear when the responses are mainly stimulus-driven are a positive wave preceding the response (pre-response frontal positivity, preRFP), followed by a negative wave (correct-related negativity, CRN) and then another positive wave just after the response (post-response frontal positivity, postRFP). At parietal electrodes, a positive wave (parietal response positivity, parietalRP) appears concomitant to the response (and to the CRN).

The CRN is the most studied of these response-related components and has been previously associated to response conflict detection and response monitoring processes (Bartholow et al., 2005; Czernochowski, Nessler, & Friedman, 2010; Eppinger, Kray, Mecklinger, & John, 2007; Friedman, Nessler, Cycowicz, & Horton, 2009; Friedman, Nessler, Johnson, Ritter, & Bersick, 2008; Pietschmann, Simon, Endrass, & Kathmann, 2008), although the functional significance of this component is still not clear (Aarts, De Houwer, & Pourtois, 2013; Luu, Collins, & Tucker, 2000; Roger, Bénar, Vidal, Hasbroucq, & Burle, 2010). Some studies evaluated the preRFP, also linking it to response monitoring processes (Nessler, Friedman, Johnson, & Bersick, 2007) or to the upregulation of cognitive control (Friedman et al., 2009), but its functional significance is not yet clear. Finally, the processes reflected by the postRFP and the parietalRP are still unknown.

The processes indexed by the CRN have previously shown to be impaired in healthy aging (Eppinger et al., 2007; Friedman et al., 2008; Schreiber, Pietschmann, Kathmann, & Endrass, 2011) but only at certain levels of task difficulty (Czernochowski et al., 2010), and also in AD (Mathalon et al., 2003). Age-related deficits have also been found regarding the preRFP (Friedman et al., 2009; Nessler et al., 2007). Cespón et al. (2015b) failed to find differences between MCI participants (including amnestic and non-amnestic subtypes) and healthy controls in the CRN parameters, possibly because the task difficulty was not sufficient. On the other

hand, the preRFP showed to be a good biomarker for the mdaMCI subtype, with high values of sensitivity and specificity (Cespón et al., 2015b).

The limited data regarding these response-related components (specially the preRFP, postRFP, and parietalRP) encouraged us to study them more deeply to be able to better characterize these quite unknown processes in young, but also in healthy aging and, in the future, in MCI.

AIMS AND HYPOTHESIS.

In summary, the main aims of the present research were (1) to study the modulation of aging on the ERP correlates of voluntary attention, motor processing and other response-related processes, using samples of young, middle-aged and old participants, and (2) to test if changes in the ERP correlates of the previously mentioned processes, and also of response inhibitory processes, might be optimal aMCI biomarkers.

This work divides into two main parts: (1) two studies aimed to characterize the electrical brain activity associated with the visual stimulus processing and the response-related processing in the A-V task, in healthy middle-aged and old participants (compared to young participants); and (2) two subsequent studies aimed to characterize the same electrical brain activity in adults with aMCI (compared to healthy controls), in order to search for aMCI biomarkers.

Firstly, we aimed to assess age-related differences in performance and in brain electrical activity associated with attention and WM processes related to target stimuli processing and motor execution. In addition, we were also interested in how the attentional capture might affect these processes in a different way in young and older participants. Therefore, **Study 1** examined the differences between young, middle-aged and old participants in the amplitude and latency of the N2b and P3b components (related to target evaluation in WM), in the amplitude and onset latency of the sLRP and rLRP (related to motor selection and programming) and in execution. **Study 1** also aimed to evaluate the differences in these behavioral and ERP parameters between the Novel and Standard conditions, and the possible interactions of the aging and attention-capture effects.

In **Study 1** we expected to find (1) an age-related decrease in the percentage of hits as well as a slowing of the RT and of the latencies of the ERPs components

evaluated, (2) an attentional capture effect in the three age groups (longer RTs, a decrease in the percentage of hits, longer N2b and P3b latencies, and longer sLRP onset latencies in the Novel than in the Standard condition), that would possibly be more pronounced with aging.

Secondly, we were interested in evaluating age-related differences in brain electrical activity associated with response control and evaluation processes, as well as the effects of the attentional capture on them. Hence, **Study 2** focuses on examining the differences between young, middle-aged and old participants, as well as the attention-capture effects, in the amplitude and latency of the ERP correlates of these processes (preRFP and CRN components), and also explores these effects in two relatively unknown ERP components (parietalRP and postRFP). In addition, we also aimed to evaluate whether the timing of these ERP components (including the classic P3b component) was the same in the three age groups, by means of inter-peak latencies, with the purpose of determining if information processing in elderly is made in a more parallel or rather in a more sequential way (with respect to young adults).

In **Study 2** we expected to (1) identify the CRN, preRFP, postRFP and parietalRP components in the three age groups (Young, Middle-aged, and Old), (2) find an age-related slowing in behavior and in the latencies of the ERP components evaluated, (3) observe an attentional capture effect on behavioral and ERP measures in the three age groups, probably larger in the Middle-aged and/or Old groups than in the Young group, and (4) find longer inter-peak latencies with advancing age.

Finally, in order to search for aMCI biomarkers, a sample of aMCI participants was evaluated and compared with a sample of healthy control adults, with the aim of studying ERP correlates of (1) target evaluation and categorization in WM (N2b and P3b; **Study 3**), (2) response inhibition processes (NoGoN2 and NoGoP3; **Study 3**), and (3) motor selection and programming/execution processes (sLRP and rLRP; **Study 4**). Performance of aMCI and healthy control adults was also evaluated in both studies.

In **Study 3**, we expected to find (1) a greater number of errors in execution and a slowing down of the RT in the participants with aMCI relative to healthy participants, (2) ERP indices of the deficits in evaluation and categorization of the target stimuli for which a motor response was required (smaller amplitude and longer latencies for Go-N2 and Go-P3), and (3) deficits in the executive control (smaller amplitudes and

longer latencies for NoGo-N2 and NoGo-P3), in the adults with aMCI relative to the control adults.

Regarding **Study 4**, we expected to find (1) longer RTs in both aMCI groups (perhaps differing in accordance with the severity of the impairment: mdaMCI > sdaMCI > control), (2) fewer correct responses in the mdaMCI group, possibly associated with dysfunctional executive processes, (3) smaller rLRP amplitudes in both aMCI subtypes than in the Control group and no group differences in the rLRP onset latency, (4) for the sLRP amplitude, similar group differences as in the rLRP, as both subcomponents are derived from activity originating from the primary motor cortex, and (5) group differences in the sLRP latency, as in **Study 3** we found delayed RTs for the aMCI participants relative to control participants, with no between-group differences in the N2b and P3b latencies.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

STUDY 1 (Estudio 1)

EFFECTS OF AGING AND INVOLUNTARY CAPTURE OF ATTENTION ON EVENT-RELATED POTENTIALS ASSOCIATED WITH THE PROCESSING OF AND THE RESPONSE TO A TARGET STIMULUS

Cid-Fernández, Lindín, & Díaz (2014a)
Frontiers in Human Neuroscience, 8 (Article 745)
doi: 10.3389/fnhum.2014.00745

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

RESUMEN

El objetivo principal del presente estudio fue evaluar si el envejecimiento modula el efecto de la captura involuntaria de la atención, producida por estímulos novedosos, en la ejecución y en los potenciales evocados (PEs) asociados con el procesamiento del estímulo objetivo (componentes N2b y P3b) y los procesos de selección (sLRP) y preparación (rLRP) de la respuesta. Setenta y siete participantes realizaron una tarea auditivo-visual de distracción-atención, los cuales fueron divididos en 3 grupos de edad (Jóvenes: 21-29 años, Mediana Edad: 51-64 años, Mayores: 65-84 años). Se pidió a los participantes que atendieran a los estímulos visuales y que ignoraran los estímulos auditivos. El aumento de la edad se asoció con mayor tiempo de reacción (TR), mayor tiempo de evaluación y categorización del estímulo objetivo en la memoria de trabajo (mayores latencias de N2b y P3b) y mayor tiempo de selección y preparación de la respuesta (mayor latencia de inicio del sLRP y del rLRP, respectivamente). En la condición Novedosa, con respecto a la Estándar, se observó, en los 3 grupos de edad: (1) un efecto de distracción, reflejado en un enlentecimiento de los TRs, de la categorización del estímulo en la memoria de trabajo (mayor latencia de P3b), y de la selección de la respuesta (mayor latencia de inicio del sLRP); (2) un efecto de facilitación en la preparación de la respuesta (latencia de inicio más tardía del rLRP), y (3) un aumento del *arousal* (mayores amplitudes de todos los PEs evaluados, excepto la amplitud de N2b en el grupo Mayores). También se observó un efecto de distracción en los procesos de evaluación del estímulo (mayor latencia de N2b), aunque solo en los grupos Mediana Edad y Mayores, indicando que la captura atencional enlentece el proceso de evaluación del estímulo en la memoria de trabajo desde edades tempranas (de los 50 años en adelante, sin diferencias entre Mediana Edad y Mayores), pero no en participantes jóvenes.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

STUDY 2 (Estudio 2)

INFORMATION PROCESSING BECOMES SLOWER AND PREDOMINANTLY SERIAL IN AGING: CHARACTERIZATION OF RESPONSE-RELATED BRAIN POTENTIALS IN AN AUDITORY-VISUAL DISTRACTION-ATTENTION TASK

Cid-Fernández S, Lindín M, Díaz F (2015a)
Under review in *Biological Psychology*

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

RESUMEN

El objetivo de este estudio fue evaluar los efectos de la edad y de la captura de la atención provocada por estímulos auditivos novedosos, en la conducta (tiempo de reacción [TR], respuestas correctas) y en los componentes de los potenciales evocados relacionados con la respuesta (preRFP, CRN, postRFP, parietalRP) a estímulos visuales objetivo. Veintidós adultos jóvenes, 27 de mediana edad y 24 mayores realizaron una tarea auditivo-visual de distracción-atención. Los TRs y latencias de preRFP, postRFP y parietalRP fueron mayores en los adultos mayores y de mediana edad que en los adultos jóvenes, reflejando el ya conocido enlentecimiento del procesamiento y la ejecución relacionado con el incremento de la edad. Las latencias inter-pico (P3b-preRFP, preRFP-parietalRP, parietalRP-postRFP) también fueron mayores en los participantes de mediana edad y mayores que en los jóvenes, indicando que existe una tendencia relacionada con el incremento de la edad hacia un procesamiento más serial (en detrimento del procesamiento en paralelo) de la información, y que preRFP, CRN, postRFP y parietalRP representan procesos cognitivos diferentes de aquéllos reflejados por el componente P3b relacionado con el procesamiento del estímulo. Finalmente, se observó un efecto de la distracción en la ejecución (con mayores tiempos de reacción y menor porcentaje de respuestas correctas en la condición Novedosa con respecto a la condición Estándar) en los 3 grupos y en la latencia de postRFP (con mayores latencias en la condición Novedosa que en la condición Estándar) pero sólo en el grupo de mediana edad.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

STUDY 3 (Estudio 3)

EFFECTS OF AMNESTIC MILD COGNITIVE IMPAIRMENT ON N2 AND P3 GO/NOGO ERP COMPONENTS

Cid-Fernández, Lindín, & Díaz (2014b)
Journal of Alzheimer's Disease (JAD), 38, 295-306
doi: 10.3233/JAD-130677

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

RESUMEN

Aunque muchos estudios con potenciales evocados han demostrado un deterioro en la atención y la función ejecutiva (en especial en el control inhibitorio) en el envejecimiento sano y en la Enfermedad de Alzheimer (EA), estudios similares evaluando el efecto del deterioro cognitivo ligero (DCL) son escasos. En el presente estudio, evaluamos cómo el declive cognitivo asociado con el DCL amnésico (DCLa) afecta a estos procesos, analizando los componentes N2 y P3 de los potenciales evocados (PEs) durante la respuesta (*Go*) y la inhibición de la respuesta (*NoGo*) ante diferentes estímulos. Los PEs se analizaron en 63 adultos sanos control y en 30 adultos con DCLa (con edades entre los 50 y los 87 años) mientras realizaban una tarea *Go/NoGo* auditivo-visual de distracción-atención. Los adultos con DCLa mostraron peor ejecución (mayores tiempos de reacción y menos respuestas correctas) y menores amplitudes de los componentes Go-N2 y NoGo-N2 que los adultos control, mientras que las amplitudes de P3 y las latencias de N2 y P3 no mostraron diferencias entre grupos. Estos resultados muestran que el DCLa se asocia con declives en la función ejecutiva y en la evaluación de los estímulos en la memoria de trabajo.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

STUDY 4 (Estudio 4)

STIMULUS-LOCKED LATERALIZED READINESS POTENTIAL AND PERFORMANCE: USEFUL MARKERS FOR DIFFERENTIATING BETWEEN AMNESTIC SUBTYPES OF MILD COGNITIVE IMPAIRMENT

Cid-Fernández, Lindín, & Díaz (2015)

The Journal of Prevention of Alzheimer's Disease (JPAD), in press

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

RESUMEN

Los hallazgos de estudios previos en los que se midieron potenciales evocados (PEs) relacionados con la evaluación del estímulo, no explicaron totalmente el declive conductual que se observa en el deterioro cognitivo ligero amnésico (DCLa). En el presente estudio se evaluaron PEs motores, con el objetivo de proporcionar explicaciones complementarias e identificar biomarcadores del DCLa. Diecinueve adultos sanos control (52-81 años), 21 con DCLa unidominio (DCLau; 51-87 años) y 12 DCLa multidominio (DCLam; 62-85 años) participaron en este estudio. Se evaluaron los tiempos de reacción (TRs), el porcentaje de respuestas correctas, y los potenciales de preparación lateralizados relacionados con el estímulo y la respuesta (sLRP y rLRP, índices de la selección y preparación de la respuesta, respectivamente).

Los participantes con DCLam mostraron mayores TRs que los adultos control, y menos respuestas correctas que los adultos control y DCLau. Además, el grupo DCLam mostró menores amplitudes del sLRP que los participantes control, y el grupo DCLau mostró mayores latencias a pico del sLRP respecto a los grupos DCLam y Control. Así, los grupos Control y DCLau no mostraron diferencias en relación al TR o las respuestas correctas, aunque las latencias a pico del sLRP fueron mayores en el grupo DCLau (sensibilidad y especificidad > .72), lo que podría ser reflejo de mecanismos compensatorios, o un indicador temprano de un declive en el control motor, en este grupo diagnóstico.

La combinación del número de respuestas correctas con los TRs discriminó a los adultos con DCLam de los adultos control con una sensibilidad y especificidad mayor al .82, y la combinación de la latencia a pico del sLRP con el número de respuestas correctas discriminó a los adultos con DCLam de los adultos con DCLau con una sensibilidad de 1 y una especificidad de .88.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

GENERAL DISCUSSION

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

AGE AND ATTENTION-CAPTURE EFFECTS IN THE A-V TASK.

Studies 1 and 2 evaluated aging and attention-capture effects, and their interactions, on behavioral parameters and on ERP components related to 1) the evaluation and categorization of the target stimuli (N2b and P3b), 2) the selection and preparation of the response to the target stimulus (sLRP and rLRP), and 3) cognitive control processes involved in the response (preRFP and CRN), and in the late integration processes related to decisions about the correctness of the response (postRFP and parietalFP).

Insights on behavioral age-related modulations (Studies 1 and 2).

In Studies 1 and 2, while the percentage of hits did not show group effects, longer RTs were observed in both groups of older participants (Middle-aged and Old) than in the Young group. In study 2, RTs were even able to distinguish between old and middle-aged participants in the Standard condition (with longer RTs in the former). These results are consistent with the findings of several studies demonstrating an age-related increase in RTs in a variety of cognitive tasks (Band & Kok, 2000; Salthouse, 2000).

However, the percentage of hits did not show an age-group effect, neither in Study 1 or in Study 2, replicating previous results obtained with very similar tasks (Andrés et al., 2006; Parmentier & Andrés, 2010), probably because the percentage of hits is close to 100% for all three age groups, in both Studies.

Therefore, the behavioral results suggest an age-related slowing in response speed, with maintenance of accuracy levels.

Effects of the capture of attention on performance in young and older participants (Studies 1 and 2).

As expected, a distraction effect was observed in all three age groups, as the RTs were longer when the visual target stimulus was preceded by a novel auditory stimulus than when it was preceded by a standard auditory stimulus. This result is consistent with previous findings of studies using a similar distraction-attention task with young (Andrés et al., 2006; Escera et al., 1998, 2001; Parmentier & Andrés, 2010) and old participants (Andrés et al., 2006; Parmentier & Andrés, 2010), showing

that RTs are suitable for assessing the distraction produced by the involuntary capture of attention (provoked by novel stimuli) on a relevant task, in which the attention is voluntarily dedicated to the target stimuli (Escera et al., 1998, 2001).

Habitually, older adults are more likely to encode and process distractors than younger adults, and they have difficulties in resisting the entrance of distractors in the focus of attention and in disengaging from distracting information (for a review, see Lindenberger & Mayr, 2014). Despite this, we found no age-related differences in the behavioral distraction effect. This might be due to the predictive value of the distractors: although auditory irrelevant stimuli do not predict the kind of visual stimuli that will appear, they predict the exact moment of the appearance. For this reason, auditory stimuli might receive some attention from all the participants, provoking a lack of behavioral differences among groups regarding the Condition effect, as found in a previous study using a very similar task (Parmentier & Andrés, 2010).

A distraction effect on the hit rates was also observed in Study 2. In all three age groups, higher percentage of correct responses were also found when the visual target was preceded by the standard relative to the novel auditory stimulus, showing that the involuntary capture of attention from the relevant task, provoked by the novel auditory stimulus, produced a decline in execution levels. Hit rates do not usually discriminate between Novel and Standard conditions in auditory-visual distraction-attention tasks in young (Escera et al., 1998, 2001, 2003; Parmentier et al., 2008, 2010, 2011; Polo et al., 2003), although the same trend as in Study 2 is observed in all studies reporting such data, including the present Study 1.

Insights on N2b, P3b, sLRP and rLRP age-related modulations (Study 1).

Although there are no previous studies that evaluated ERP in aging with the A-V task, aging is usually associated with latency increases of N2b and P3b, and amplitude decreases of P3b (Patel & Azzam, 2005; Polich, 2012).

In Study 1, the N2b and P3b latencies were longer in the Middle-aged and Old groups (with no differences between them) than in the Young group, in accordance with previous studies using *oddball* or *Go/NoGo* tasks (Amenedo & Díaz, 1998a, 1998b; Ashford, Coburn, Rose, & Bayley, 2011; Czigler, Pató, Poszet, & Balázs, 2006; Gaál, Csuhaj, & Molnár, 2007; Juckel et al., 2012; Schiff et al., 2008; Schmiedt-Fehr

& Basar-Eroglu, 2011). Lower speed of information processing is one of the hallmarks of cognitive aging (Salthouse, 1996, 2000), and our results specifically showed an age-related slowing in the evaluation and the categorization of the target stimuli from middle-age onwards.

The N2b amplitude was larger in middle-aged and old participants than in young participants, which is also consistent with previous findings (Anderer, Semlitsch, & Saletu, 1996; Czigler et al., 2006; Friedman, Simpson, & Hamberger, 1993; Iragui, Kutas, Mitchiner, & Hillyard, 1993; Schmiedt-Fehr & Basar-Eroglu, 2011). Given that the number of correct responses did not discriminate among groups, this may indicate that healthy older people must assign more attentional resources to the evaluation of target stimuli than young participants, probably as compensatory mechanism for correct performance.

Moreover, the N2b amplitude did not differentiate between middle-aged and old participants, and was maximal at central locations in both groups, whereas it showed a more frontal distribution in the Young group. Accordingly, some authors have reported age-related amplitude reductions at anterior scalp areas (Anderer et al., 1996; Enoki, Sanada, Yoshinaga, Oka, & Ohtahara, 1993; Iragui et al., 1993), or a change to a more posterior scalp distribution (Friedman et al., 1993).

Our findings support age-related changes in neural networks facilitating enhanced allocation of processing resources for evaluation of relevant stimuli in WM. These changes appear to begin relatively early in middle age and remain fairly stable from 50 onwards.

The P3b amplitude was larger in the Young than in the Middle-aged and Old groups, at parietal and central locations, which is also consistent with previous findings (Amenedo & Díaz, 1998a; Ashford et al., 2011; Czigler et al., 2006; Hämmerer et al., 2010; Juckel et al., 2012; O'Connell et al., 2012; Schmiedt-Fehr & Basar-Eroglu, 2011). In the Young group, a graded distribution pattern was observed for P3b amplitude (Pz > Cz > Fz), in consonance with previous reports (Czigler et al., 2006; Gaál et al., 2007; Kutas et al., 1994). In the Middle-aged and Old groups, P3b amplitude distribution was more homogeneous across electrode sites (Amenedo & Díaz, 1998a; Anderer, Saletu, Semlitsch, & Pascual-Marqui, 2003; Kutas et al., 1994), which may reflect the need to engage frontal structures related to WM processing (Fabiani & Friedman, 1995).

In the Middle-aged and Old groups, the relative under-recruitment of task-related brain networks (Schmiedt-Fehr & Basar-Eroglu, 2011), possibly due to a decline in the activity of the posterior cortex (Amenedo & Díaz, 1998a; Ashford et al., 2011; Schiff et al., 2008) and/or to a decline in cholinergic neurotransmission (Schiff et al., 2008; Schmiedt-Fehr & Basar-Eroglu, 2011), seem to be accompanied by an over-recruitment of frontal networks. This may reflect the need to engage, as a compensatory mechanism, frontal structures related to WM processing (Fabiani & Friedman, 1995), in accordance with the well-known PASA model (Davis et al., 2008).

In addition, the sLRP onset latency was longer for the middle-aged and old participants than for the young participants. This is consistent with previous studies that used different tasks (Cespón et al., 2013b; Wild-Wall et al., 2008) although other researchers did not find such differences (Kolev et al., 2006; Roggeveen et al., 2007; Yordanova et al., 2004).

The time of preparation of the response (indexed by the rLRP onset latency) was also longer in the Middle-aged and Old groups (as the onset latency occurred earlier, with no differences between them) than in the Young group, as in previous studies (Cespón et al., 2013b; Roggeveen et al., 2007; Wild-Wall et al., 2008; Yordanova et al., 2004).

Hence, these results provide additional support to the idea that age-related slowing affects both the selection (sLRP) and preparation (rLRP) of the motor response. In the case of the sLRP, this may be due to slower transmission of information from visual to motor areas, that might contribute to a deficit in stimulus-response mapping, which in turn impairs response selection (Wild-Wall et al., 2008). The rLRP result, may be due to either the need for a longer activation of the motor cortex in old and middle-aged participants to enable response execution (Cespón et al., 2013b; Kolev et al., 2006), or to an age-related strategy to emphasize response accuracy (Osman et al., 2000).

Effects of the capture of attention on the N2b, P3b, sLRP and rLRP components in young and older participants (Study 1).

The N2b and P3b latencies, and the sLRP onset latencies were longer in the Novel than in the Standard condition. This may indicate that the non-attended auditory novel stimulus eventually captured attention provoking a distraction effect

reflected in a slowing down of visual target evaluation and categorization processes in WM, as well as of the response selection processes. Aging did not modulate this distraction effect for P3b or sLRP. Nevertheless, the N2b latency was significantly longer in the Novel than in the Standard condition only in the Old and Middle-aged groups. So, the unattended novel stimulation affected the active evaluation in WM of the attended target stimuli (N2b), both in middle-aged and old participants, delaying this process, but it was not observed in young adults.

Interestingly, the rLRP onset latency was earlier in the Standard condition than in the Novel condition in all three age groups. This may indicate that the unattended novel stimulus caused some sort of facilitation effect that resulted in a reduction of the time needed to plan and execute the motor response.

The N2b (in Young and Middle-aged), P3b, sLRP, and rLRP (in the three age groups) amplitudes were larger in the Novel than in the Standard condition. In the Escera et al.'s (1998) study (only with young participants) the authors observed similar results for N2b and P3b amplitudes, accompanied by longer RTs in the Novel than in the Standard condition (as an index of the distraction effect), although these results were not further discussed. On the other hand, SanMiguel et al. (2010) also found larger P3b amplitudes, but with shorter RTs, in the Novel than in the Standard condition. They interpreted these results as indexes of a facilitation effect produced by the novel stimulation.

We consider that the larger amplitudes of the ERP components observed in the Novel than in the Standard condition may indicate that the novel stimuli acted as activating signals, causing an enhanced arousal (Polich and Kok, 1995; Ashford et al., 2011).

The larger P3b amplitude obtained in the Novel condition may reflect the response of the neuromodulatory locus coeruleus-norepinephrine (LC-NE) system in information processing (i.e., potentiation of the response to motivationally significant events, as there is evidence that suggests a high degree of regional specificity of NE innervation that is broadly consistent with the regional specificity of P3b activity (for a review, see Nieuwenhuis, Aston-Jones, & Cohen, 2005).

The LC-NE system might also affect N2b and LRP amplitudes. Although there are no studies that assessed this issue directly, there is some evidence that the LC-NE system is involved in motor control (Benarroch, 2009). In addition, the anterior cingulate (ACC) and the dorsolateral prefrontal cortices, proposed as N2b generators

(Folstein & Van Petten, 2008; Potts & Tucker, 2001), seem to be connected up to the LC, linking circuits involved in cognitive processing with the LC-NE system (Aston-Jones & Cohen, 2005). Interestingly, the Old group did not show larger N2b amplitude in the Novel than in the Standard condition. Noradrenergic function seems to be enhanced in older relative to young adults (Elrod et al., 1997; Raskind, Peskind, Holmes, & Goldstein, 1999), which might mask the differences between both conditions (Novel vs. Standard) in this age group.

Insights on preRFP, CRN, postRFP and parietalRP age-related modulations (Study 2).

The CRN showed no age-related differences in amplitude or latency. CRN latencies were very little studied in old samples, but the same result was found in the few studies available (Falkenstein, Hoormann, & Hohnsbein, 2001; Kolev, Falkenstein, & Yordanova, 2005).

On the other hand, data on the CRN amplitude are variable, although it seems that age effects can only be found when certain levels of difficulty are exceeded (Czernochowski et al., 2010), which may not have occurred with this task. It therefore seems that response monitoring processes (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Falkenstein, Hoormann, Christ, & Hohnsbein, 2000; Gehring & Knight, 2000; Vidal, Hasbroucq, Grapperon, & Bonnet, 2000) or affective/motivational reactions to the response (Aarts et al., 2013; Luu et al., 2000; Tucker, Hartry-Speiser, McDougal, Luu, & Degrandpre, 1999) or the default processes present after every behaviorally relevant response (Roger et al., 2010) are not modulated by aging in this auditory-visual distraction-attention task.

Unlike CRN latencies, the preRFP, postRFP and parietalRP latencies showed an age-related increase that started in the middle-aged and remained relatively stable during further aging. Furthermore, parietalRP amplitudes were lower in both older groups than in young participants, suggesting a decline in resource allocation during the process indicated by this component from middle-age onwards. There is not yet sufficient evidence to indicate the functional meaning of these positive waves (Johnson, Barnhardt, & Zhu, 2005; Johnson, Henkell, Simon, & Zhu, 2008), apart from the fact that all three seem to be quite different components.

Information processing becomes more serial in aging (Study 2).

In the Standard condition, the fP3b-preRFP inter-peak latency was longer in the old than in the young participants. This suggests that these two positive components dissociate significantly in time relatively late in aging. The comparison of the preRFP-parietalRP inter-peak latency between groups showed that the latency was significantly longer in the old and middle-aged participants than in the young participants, in both conditions (Novel and Standard). The same trend was observed for the parietalRP-postRFP inter-peak latency.

Thus, while the response-related complex coincides almost exactly in time and shape with the stimulus-related P3b in the young participants, in both of the older groups the whole stimulus and response-related complex clearly dissociates into subcomponents in the order: P3b, preRFP, parietalRP, postRFP (with the CRN peaking at about the same time as parietalRP). This may influence the behavioral results, since the stimulus- and response-related processing seems to be more predominantly serial in middle-aged and old adults than in young adults, with more time required between processes to produce acceptable performance levels. Therefore, speed would be traded for accuracy in aging regarding the processes indicated by these components.

Effects of the capture of attention on the preRFP, CRN, postRFP, parietalRP components in young and older participants (Study 2).

CRN amplitudes were larger when a novel auditory stimulus preceded the visual target stimuli than when it was preceded by a standard stimulus. However, this effect was only significant in the young and middle-aged participants. There is some evidence indicating the ACC as a main CRN generator and the DLPFC as a critical area for modulating the CRN signal (Botvinick et al., 2001; Braver, Barch, Gray, Molfese, & Snyder, 2001; Carter et al., 2000; Cohen, Botvinick, & Carter, 2000; MacDonald, Cohen, Stenger, & Carter, 2000). Moreover, these areas seem to be connected to the locus coeruleus, linking circuits involved in cognitive processing with the neuromodulatory LC-NE system (Aston-Jones & Cohen, 2005).

Thus, the enhanced CRN amplitude in the Novel condition may indicate that the novel stimuli acted as activating signals, causing enhanced arousal (Ashford et al., 2011; Polich & Kok, 1995) and reflecting the response of the LC-NE system in

information processing, i.e. potentiation of the response to motivationally significant events (Nieuwenhuis et al., 2005). As already mentioned, the CRN amplitudes were not larger in the Novel condition than in the Standard condition in the old participants. As for N2b amplitude, the noradrenergic function enhancement that older relative to young adults experience (Elrod et al., 1997; Raskind et al., 1999; Wang et al., 2013), may mask the differences between both conditions (Novel vs. Standard) in this age group. Enhanced amplitudes in the Novel than in the Standard condition were also found for the parietalRP component in all three age groups. However, as this component has scarcely been studied there is no evidence about how it is generated that would allow us to associate the parietalRP component and the LC-NE system.

The preRFP and postRFP amplitudes were not affected by the involuntary capture of attention in any way, nor were the CRN, parietalRP and preRFP latencies. However, the postRFP latency was longer in the Novel than in the Standard condition, although only for the Middle-aged group. Thus, postRFP showed a distraction effect related to the novel irrelevant auditory stimulation in middle-aged, but not in young or old participants. In fact, the opposite pattern was observed in the young participants, while there were no differences in postRFP latencies between conditions in the old participants.

Although the lack of information regarding the functional significance of the postRFP component makes it difficult to explain these effects, it is well known that the brain adapts and reorganizes in response to the neural insults associated with aging through the strengthening of existing connections, formation of new connections, and disuse of connections that have become weak or faulty, in an effort to maintain cognitive behavior (Goh & Park, 2009; Park & Reuter-Lorenz, 2009). Thus, the findings might be explained by such reorganization, as at an early stage of aging (middle-aged participants) the network that generates the postRFP might become sensitive to the distraction effect, and as a result of the neural reorganization the sensitivity to this effect may disappear at a later stage (old participants), yielding an absence of any distraction effect.

Functional significance of the response-related P3 complex (preRFP, postRFP, parietalRP, Study 2).

Verleger et al. (2005) proposed that a response-related complex (with certain similarities with the observed in the present Study 2) obtained with a *Simon* task in young participants might be a response-related part of P3b. According to these authors, P3b must reflect a function that bridges perceptual processing with response, as (1) other authors have previously identified stimulus- and response-related subcomponents of P3 (Falkenstein, Hohnsbein, & Hoormann, 1994; Hohnsbein, Falkenstein, Hoormann, & Blanke, 1991; Rösler, Borgstedt, & Sojka, 1985); (2) the P3b wave has often been associated with "decision making", which implies a direct link between the perceptions (stimulus) and the alternatives to be decided upon (responses); and (3) P3b is similar in stimulus- and response-related waveforms (obtained with a *Simon* task) when superimposed, and is therefore not more closely related to stimulus than to response or vice versa (Verleger, Jaśkowski, & Wascher, 2005).

Our data provides some support for this view, as in the young participants both the stimulus-related P3b component and the response-related complex were quite similar in shape and timing (Study 2). Furthermore, the response-related positive waves showed effects in common with the P3b component obtained in a similar sample (with young, middle-aged and old participants) undertaking this task (see Study 1): 1) the amplitude of the parietalRP, such as the amplitude of the parietal P3b, was significantly larger in the Novel condition than in Standard condition, while the preRFP or postRFP, such as the frontal P3b amplitude, did not appear to be affected by condition; 2) the amplitude of the parietalRP, such as the parietal P3b amplitude, was significantly larger in the young than in middle-aged and old participants, but the preRFP or postRFP, such as the frontal P3b amplitude, did not appear to be affected by age; and 3) the latencies of preRFP, parietalRP and postRFP, such as frontal and parietal P3b latencies, were significantly longer in middle-aged and old participants than in the young participants.

Nevertheless, the parietal P3b latency showed a condition effect in all three age groups (it was longer in the Novel than in the Standard condition) at the Pz electrode site in Study 1, while the parietalRP latency did not show any such effect in Study 2. Furthermore, the ERP waveforms showed that the P3b and the response-related complex are more variable in shape and timing in the middle-aged and old participants than in the young participants. Thus, our results do not seem to fully

support Verleger et al.'s hypothesis, as the response-related complex does not always behave as the classic stimulus-related P3b component, making it difficult to maintain the same functional interpretation for both.

Following the considerations of Verleger et al. (2005), it is possible that 1) the response-related complex (preRFP, parietalRP, postRFP) is the response-related part of the P3 complex, and 2) all the subcomponents of the P3 complex (stimulus-P3b, preRFP, parietalRP and postRFP), and the related cognitive processes, occur more serially in aging than in young participants. The previously mentioned differences between response-related components and the stimulus-related P3b would be appropriately explained in the framework of this theory: if the four putative P3 positive waves are subcomponents of a general process that reflects "decision and integration", each subcomponent may behave in a different way (as Verleger and colleagues established), indicating different subprocesses, all related to the final decision and integration processes.

Nevertheless, we consider that treating these positive waves as parts of P3b is confusing, as the well-established functional meaning of the P3b may lead to misunderstandings when interpreting the response-related complex, considering that both complexes will not have the same functional meaning. Our data show that these components may be related to different (although maybe connected) processes.

Very little is known about the preRFP, parietalRP, and postRFP components. The preRFP component was associated with the implementation of cognitive control involved in the response (Friedman et al., 2009; O'Connell et al., 2007). The specific functional significance of the parietalRP and the postRFP is still not clear, although we consider that both positive waves may reflect integration of previous processing because of their long latencies. We tentatively propose that the parietalRP component may indicate a general context closure, when processing of the decisions about the response and the stimuli processing are integrated. In a similar way, the postRFP may reflect integration of all the previous processing with response monitoring processes, possibly also with some processing aimed at the preparation for a new trial. However, more data are required to clearly establish the functional significance of these components.

AMNESTIC MCI EFFECTS AND BIOMARKERS IN THE A-V TASK.

Studies 3 and 4 evaluated aMCI modulations on behavioral parameters and on ERPs related to the evaluation and categorization of the target stimulus (N2b and P3b), to response inhibition (NoGo-N2 and NoGo-P3), and to the selection and preparation of the response to the target stimulus (sLRP and rLRP).

Insights on behavioral MCI modulations (Studies 3 and 4).

Behavioral data obtained in Studies 3 and 4 generally supported our initial hypothesis, as adults with aMCI performed less well than healthy controls, with significantly longer RT, as found in other studies (Golob et al., 2002; Missonnier et al., 2007; Wylie, Ridderinkhof, Eckerle, & Manning, 2007), and fewer correct responses. These results reflect deficits in aMCI participants in accuracy and a lengthening of overt responses, showing that this task is consistently able to capture the effects of aMCI on behavioral measures. In addition, differences between sdaMCI, mdaMCI and healthy control participants were also evaluated in Study 4: mdaMCI participants showed longer RTs than control participants, while sdaMCI and control adults showed more correct responses than mdaMCI adults, evidencing a larger behavioral decline in mdaMCI than sdaMCI participants.

In previous studies using a variety of cognitive tasks, the RT and percentage of hits did not always distinguish between aMCI and healthy control participants (e.g. Frodl et al., 2002; Phillips et al., 2004; Staffen et al., 2012); however, some studies reported longer RTs (e.g. Golob et al., 2002, 2007; Wylie et al., 2007) and more errors (e.g. Cespón et al., 2015a, 2015b) in aMCI than in control participants.

Study 3 did not evaluate differences between sdaMCI and mdaMCI participants in RT and correct responses, but in Study 4 these parameters proved to be useful tools for identifying both subtypes of aMCI.

Potential Behavioral MCI markers.

The RT proved to be a potential mdaMCI marker, as this parameter distinguished mdaMCI from control participants with acceptable sensitivity (.73) and specificity (.79) scores, and it also distinguished mdaMCI from sdaMCI and control participants together (sensitivity = .73, specificity = .65).

The percentage of hits also seems to be a potentially good marker (with high sensitivity and specificity scores) for discriminating mdaMCI from control participants (sensitivity: .73; specificity: .90), mdaMCI from sdaMCI participants (sensitivity: .82 and specificity: .81), and mdaMCI from sdaMCI and control participants together (sensitivity: .73 and specificity: .88).

Insights on N2b, P3b, NoGoN2 and NoGoP3 MCI modulations (Study 3).

Go condition.

In accordance with the underlying hypothesis, the Go-N2 (or N2b) amplitude was larger in the Control group than in the aMCI group at central locations. As N2b is a correlate of the allocation of processing resources to the controlled detection and the evaluation of the target stimulus in WM (Amenedo & Díaz, 1998a; Bennys et al., 2007; Papaliagkas et al., 2011), this result may reflect aMCI-related deficits in the mobilization of these resources.

This contrasts with the findings of studies that reported no differences between groups (Golob et al., 2002; Lai et al., 2010; van Deursen et al., 2009) and those that reported larger N2b amplitudes in the MCI than in the control participants (Papaliagkas et al., 2008). The above-cited studies used a classic *oddball* task. However, in the present study we used a complex distraction–attention task, in which visual stimuli, relevant to the task, were preceded by an auditory distractor that had to be ignored. Furthermore, the *Go* visual stimuli were of two types (letters and numbers) and the participants were required to respond to these with different hands. The greater complexity and difficulty of the task used in the present study may have revealed the deficits in the aMCI group in processes involved in evaluating and comparing the target stimulus in the WM, of which the Go-N2 is a correlate.

No differences were observed in the Go-P3 (or P3b) amplitude between aMCI and control adults. This shows that both groups were equally able to mobilize the attentional resources necessary for categorization of the stimuli and updating the context in the WM (Coles & Rugg, 1996; Gironell et al., 2005).

Some previous studies comparing the P3b amplitude between healthy and MCI participants did not find any differences between groups (Golob et al., 2002; Lai et al., 2010; Papaliagkas et al., 2008; van Deursen et al., 2009), while others observed lower amplitudes in the MCI than in the Control group (Bennys et al., 2007; Li et al.,

2010). These differences were interpreted as a loss of the ability of the first group to access attentional resources (Bennys et al., 2007). The discrepancies in the results, even among studies that used similar auditory *oddball* tasks, may be largely due to differences in the criteria used for inclusion of participants in the MCI group.

Contrary to our working hypothesis, we did not observe significant differences in the Go-N2 and Go-P3 latencies between the aMCI and control adults.

The absence of group differences obtained for Go-N2 latencies are consistent with those of previous studies (Golob et al., 2002; Lai et al., 2010; van Deursen et al., 2009), but differ from those of other studies that report a longer latency of this component in MCI adults relative to healthy elderly controls (Bennys et al., 2007; Papaliagkas et al., 2008, 2011). The lack of differences in the Go-P3 latency between the groups in the present study is consistent with the results obtained by Gironell et al. (2005), but contrasts with the findings of most other studies, in which longer Go-P3 latencies were observed in MCI than in control adults (Bennys et al., 2007; Golob et al., 2002, 2007; Lai et al., 2010; Li et al., 2010; Papaliagkas et al., 2008; van Deursen et al., 2009).

In the present study, the lack of differences in the Go-N2 and Go-P3 latencies between the groups indicates that the cognitive decline in the aMCI group does not affect the time taken for evaluation and categorization of the visual *Go* stimuli in the WM. Some studies have shown that the behavioral slowing observed in healthy aging does not appear to be due to delays in stimulus processing or response selection, but to a prolongation of the central generation of the response (Falkenstein, Yordanova, & Kolev, 2006; Yordanova et al., 2004). It can therefore be hypothesized that the lengthening of the RT in the adults with aMCI, relative to healthy controls, may be due to a slowing down of the processes involved in generating the motor response and not only of the evaluation and categorization of the stimuli.

NoGo condition.

As far as we know, this is the first study that has evaluated NoGo-N2 comparing healthy adults and adults with aMCI. The NoGo-N2 amplitude was larger in the Control than in the aMCI group. This component appears to reflect two sequential processes: conflict detection between responding and not responding, and the decision to inhibit the response (for a review, see Falkenstein, 2006). The lower

amplitude of the NoGo-N2 in the aMCI group may reflect deficits in the neural network responsible for inhibitory control, which may include areas proposed as generators of the NoGo-N2, such as the ACC (Bokura et al., 2001; Nieuwenhuis et al., 2003), the inferior frontal and the orbitofrontal cortices (Bokura et al., 2001). Neuroimaging studies would probably support this hypothesis as previous such studies have revealed atrophy in the ACC and the orbitofrontal region in MCI adults (Chen et al., 2001; Twamley, Ropacki, & Bondi, 2006).

Contrary to our hypothesis, we did not observe any differences in the NoGo-N2 latency or in the latency or amplitude of NoGo-P3 between the aMCI and control adults. The lack of differences in the NoGo-N2 latency may indicate that the adults with aMCI are not affected in relation to the speed of detection and controlling the response conflict (Bekker, Kenemans, & Verbaten, 2004; Donkers & van Boxtel, 2004; Nieuwenhuis et al., 2003) or initiating the response inhibition (Beste et al., 2010; Bokura et al., 2001; Dong et al., 2009). Moreover, the lack of differences in the latency and amplitude of the NoGo-P3 component between groups may indicate that the final stage of response inhibition (Donkers & van Boxtel, 2004; Falkenstein et al., 2002; Randall & Smith, 2011) or the process of monitoring the preceding response and preparing future responses (Beste et al., 2010; Schmiedt-Fehr & Basar-Eroglu, 2011) were spared in the aMCI group.

Topographical analysis (Go and NoGo conditions).

Besides, in Study 3 we observed topographical differences in the frontal source of activity for the Go-N2 and Go-P3 between the groups, with a bilateral frontal source of activity in the Control group and a right-lateralized source in the aMCI group. This difference may be related to differences in compensatory recruitment of the frontal areas in both groups and may indicate a possible ceiling effect of the compensation in the aMCI group. The CSD maps did not reveal any differences between groups in the topographic distribution of the N2 and P3 components in the *NoGo* condition.

Insights on sLRP and rLRP MCI modulations (Study 4).

Regarding the sLRP and rLRP components, no between-group differences were found for onset latencies, as also observed in previous studies that used *SRC* (*Simon*

type) tasks (Cespón et al., 2013a, 2015b). However, the sLRP peak latency was longer in the sdaMCI participants than in the control participants (with intermediate scores, but more similar to controls, for the mdaMCI group). This finding may be related to the higher percentage of hits obtained by the sdaMCI participants relative to the mdaMCI participants. Thus, the sdaMCI participants take more time in selecting the appropriate response than controls, while they maintain good levels of accuracy, similar to control participants. On the contrary, the mdaMCI participants (in accordance with impairments of executive functions) take almost the same time as control participants for response selection, but at the expense of accuracy.

In Study 4, the sLRP amplitude was lower in mdaMCI participants than in control participants (with intermediate values for sdaMCI adults), supporting the idea of aMCI-related deficits in the motor cortex (Tsutsumi et al., 2012). On the other hand, no significant between-group differences in rLRP amplitude were observed, in contrast with previous findings that observed lower amplitudes in aMCI than in control participants (Cespón et al., 2013a, 2015b), although our data showed a similar trend.

The combined results for sLRP and rLRP support previous findings using the TMS technique that observed aMCI-related deficits in the motor cortex (Tsutsumi et al., 2012). Regarding rLRP amplitudes, the discrepancies between the results of the present and previous studies (Cespón et al., 2013a, 2015b) may be due to the different characteristics of the tasks. This is mainly because *SRC* tasks are specifically conceived to study inhibitory control processes related to response interference (Lu & Proctor, 1995), while the AV task explores attention to the visual target stimuli and the possible effects of the auditory distractor stimuli on this process.

Potential LRP MCI biomarkers.

The sLRP peak latency proved to be a potential biomarker for the sdaMCI state, being able to distinguish (with acceptable sensitivity and specificity values) the sdaMCI group from the Control group (sensitivity = .76, specificity = .73) and from mdaMCI participants (sensitivity = .81, specificity = .67) and from both the control and mdaMCI participants together (sensitivity = .76, specificity = .72).

On the other hand, the sLRP amplitude proved to be a potential biomarker of mdaMCI, distinguishing this group from the Control group with a sensitivity of .67 and a specificity of .79.

Combinations of markers (Study 4).

Finally, the combination of potential markers (when appropriate) detected in Study 4 yielded better results than each of the individual parameters (see Table 2 in Study 4). Hence, the best marker for (a) distinguishing mdaMCI participants from control participants only (sensitivity = .82, specificity = .90) and from sdaMCI and control participants altogether (sensitivity = .82, specificity = .85) was the combination of RTs and percentage of hits; and (b) distinguishing between mdaMCI and sdaMCI groups (sensitivity = 1.00, specificity = .88) was the combination of sLRP peak latency and percentage of hits.

CONCLUSIONS

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

1. Normal aging was associated with slower RTs, but not with differences in the percentage of hits. The results supported the idea of a progressive age-related slowing in response execution in order to maintain task accuracy. In addition, aging was associated with a slowing of target stimulus processing (longer N2b and P3b latencies) and the associated selection and preparation of the corresponding motor response (longer sLRP and rLRP onset latencies).

2. Four relatively unknown response-related ERP components were identified, in direct ERP traces, in young, middle-aged and old healthy adults: CRN, preRFP, postRFP, and parietalRP. The preRFP, postRFP, and parietalRP latencies slowed significantly in aging, evidencing an age-related slowing in the implementation of cognitive control processes involved in the response (preRFP), and in the late integration processes involved in decisions about the correctness of the response (postRFP and parietalFP). In addition, the inter-peak latencies evaluated (P3b-preRFP, preRFP-parietalRP and parietalRP-postRFP) were also longer in the old and middle-aged than in the young participants, supporting the hypothesis of an age-related tendency to more predominantly serial information processing.

3. The response-related potential complex (CRN, preRFP, postRFP, and parietalRP) seems to reflect different (although perhaps related) processing stages from those indicated by the classical stimulus-related P3b component, as both are affected by experimental manipulations in different ways, and their morphology and timing are substantially different in young, middle-aged, and old participants.

4. The involuntary capture of attention triggered by novel irrelevant auditory stimuli, relative to the standard irrelevant auditory stimuli, on processes related to the evaluation and categorization of the visual stimuli and to response selection and preparation, was assessed for the first time in middle-aged and old participants. This capture of attention was associated with a distraction effect in all three healthy age groups under study (Young, Middle-aged and Old), with longer RT, more time for stimulus categorization in WM (longer P3b latencies), and more time for selection of the motor response (longer sLRP onset latency). A facilitation effect on response prrogramming (earlier rLRP onset latency) and an increase in the global arousal (larger amplitudes of all ERP components evaluated, except for N2b amplitude in the Old group) were also observed in the Novel condition.

5. The distraction effect was also found in both older groups (Middle-aged and Old) regarding stimulus evaluation processes in WM (longer N2b latency in the Novel than in the Standard condition), but it was not observed for the Young group. This

result reflects an age-related modulation of the distraction effect on the evaluation of target stimuli in WM, with a slowing of the evaluation process that seems to affect people from 50 years onwards, without differences between middle-aged and older adults. In addition, the latency of the postRFP component also showed a distraction effect, but only in the Middle-aged group. This type of distraction effect may be due to age-related changes in the activated networks that generate this component, in order to maintain acceptable levels of cognitive performance.

6. Regarding aMCI studies, the N2b and NoGo-N2 amplitudes were lower in aMCI than in control adults, also reflecting an aMCI-related deficit in target stimulus evaluation and in the inhibitory control of the response, respectively. In addition, aMCI participants showed poorer execution (longer RTs and less correct responses).

7. The mdaMCI participants showed behavioral and neurocognitive decline relative to the sdaMCI and Control groups, reflected in a decrease of response accuracy and an increase of RTs, as well as in a decrease of neural resources available for response selection (sLRP), respectively. The RTs and levels of accuracy were similar in sdaMCI and control participants, but at the expense of a specific lengthening in the time required for selecting the appropriate response in the former (longer sLRP peak latency), which may be interpreted as a sign of compensatory mechanisms or an early indication of a decline in motor control.

8. Several potential aMCI markers were identified. The best single parameter for differentiating the sdaMCI participants from mdaMCI participants only and from mdaMCI and control participants together was the sLRP peak latency, with sensitivity and specificity scores higher than .67.

9. The best combination of markers for discriminating mdaMCI participants from control participants only and from sdaMCI and control participants together was the RTs and the percentage of hits, with sensitivity and specificity values above .82. The best combination of parameters for discriminating sdaMCI from mdaMCI participants was composed by the sLRP peak latency and the percentage of hits, with sensitivity and specificity scores of 1.00 and .88, respectively.

CONCLUSIONES

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

1. El envejecimiento se asoció a tiempos de reacción más lentos, aunque el porcentaje de aciertos no difirió significativamente entre grupos de edad. Los resultados apoyan la idea de que existe un enlentecimiento progresivo de la ejecución relacionado con la edad, con el fin de mantener la precisión. Además, el envejecimiento se asoció con un enlentecimiento del procesamiento del estímulo *target* (mayores latencias de N2b y P3b) y de la selección y preparación de la respuesta motora correspondiente (mayores latencias *onset* de sLRP y rLRP).

2. Se identificaron cuatro componentes de los PEs relacionados con la respuesta, relativamente desconocidos, en los trazados directos, en adultos jóvenes, de mediana edad y mayores: CRN, preRFP, postRFP, and parietalRP. Las latencias de preRFP, postRFP y parietalRP aumentaron significativamente con el envejecimiento, poniendo en evidencia un progresivo enlentecimiento relacionado con la edad en la implementación de los procesos de control cognitivo implicados en la respuesta (preRFP), y de los procesos tardíos de integración implicados en las decisiones sobre el grado de corrección de la respuesta (postRFP y parietalRP). Además, las latencias interpico evaluadas (P3b-preRFP, preRFP-parietalRP y parietalRP-postRFP) también fueron mayores en los participantes mayores y de mediana edad que en los jóvenes, apoyando la hipótesis de que existe una tendencia relacionada con la edad hacia un procesamiento más serial.

3. El complejo relacionado con la respuesta parece reflejar etapas diferentes de procesamiento (aunque tal vez relacionadas) de las indicadas por el clásico componente P3b relacionado con el estímulo, ya que ambas se ven afectadas de forma diferente por las manipulaciones experimentales, y su morfología y latencia son considerablemente diferentes en participantes jóvenes, de mediana edad y mayores.

4. Por primera vez se ha evaluado cómo influye la captura involuntaria de la atención producida por los estímulos auditivos novedosos irrelevantes (con respecto a los estímulos auditivos estándar irrelevantes), en procesos relacionados con la evaluación y categorización de los estímulos visuales y con la selección y preparación de la respuesta. Esta captura de la atención se asoció con un efecto de la distracción en los tres grupos bajo estudio (Jóvenes, Mediana edad y Mayores), con mayores TRs, mayor tiempo de categorización del estímulo en la memoria de trabajo (mayores latencias de P3b), y mayor tiempo de selección de la respuesta (mayor latencia *onset* del sLRP). En la condición Novedosa también se observó un efecto de facilitación en la preparación de la respuesta (latencia *onset* del rLRP más temprana) y un aumento

del *arousal* global (amplitudes mayores de todos los componentes de los PEs analizados, excepto la amplitud de N2b en el grupo Mayores).

5. El efecto de distracción se observó también en los dos grupos de mayor edad (Mediana edad y Mayores), en cuanto a los procesos de evaluación del estímulo en memoria de trabajo (mayor latencia de N2b en la condición Novedosa que en la condición Estándar), pero no se observó en el grupo Jóvenes. Este resultado refleja una modulación relacionada con la edad del efecto de distracción en la evaluación del estímulo *target* en memoria de trabajo, con un enlentecimiento del proceso que parece afectar a personas de 50 años en adelante, sin diferencias entre adultos de mediana edad y mayores. Además, la latencia de la onda postRFP también mostró un efecto de la distracción, pero solo en el grupo Mediana edad. Este tipo de efecto de la distracción podría deberse a cambios relacionados con la edad en las redes neurales que generan este componente, con el fin de mantener niveles aceptables de ejecución cognitiva.

6. En cuanto a los estudios con DCLa, las amplitudes de N2b y NoGo-N2 fueron menores en los adultos DCLa que en los adultos control, reflejando un déficit en la evaluación del estímulo *target* y en el control inhibitorio de la respuesta, respectivamente.

7. Los participantes DCLam mostraron un déficit conductual y neurocognitivo con respecto a los grupos DCLau y Control, reflejado en las respuestas correctas y en los TRs, al igual que en los recursos neurales disponibles para la selección de la respuesta (sLRP), respectivamente. Los TRs y el porcentaje de respuestas correctas fueron similares en los participantes DCLau y Control, aunque a expensas de un enlentecimiento específico en el tiempo requerido para seleccionar la respuesta apropiada en los primeros, lo que podría interpretarse como un signo de mecanismos compensatorios o un indicador temprano de un declive en el control motor.

8. Se identificaron varios marcadores potenciales del DCLa. El mejor biomarcador para diferenciar a los participantes DCLau solo de los participantes DCLam, y de los DCLam y los control en conjunto, fue la latencia a pico del sLRP, con una sensibilidad y especificidad mayores de .67.

9. La mejor combinación de marcadores para discriminar a los participantes DCLam de los control únicamente, y de los DCLau y los control en conjunto, fue la combinación del TR y el porcentaje de respuestas correctas, con una sensibilidad y especificidad por encima de .82. El mejor parámetro para discriminar a los

participantes DCLau de DCLam fue la combinación de la latencia a pico del sLRP y el porcentaje de respuestas correctas, con unos valores de sensibilidad y especificidad de 1.00 y .88, respectivamente.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

FUTURE STUDIES

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

The first study that will complement the studies that are included in this doctoral thesis is an ongoing study that evaluates the CRN, preRFP, postRFP and parietalRP in aMCI participants. Considering that the different aMCI subtypes are related to differences in probability of evolving to AD (Petersen & Negash, 2008), this new study will also investigate the possibility of distinguishing specific electrophysiological correlates for each aMCI subtype.

Another ongoing study, derived from a research stay in the University of Edinburgh, is searching for MCI biomarkers (including amnestic and non-amnestic subtypes) with this task, using functional connectivity analysis in EEG (classic coherence measures, and measures of the imaginary part of coherence), based on graph theories (Reijneveld, Ponten, Berendse, & Stam, 2007; Stam & Reijneveld, 2007). Graph theoretical analysis usually starts with the construction of a network consisting of vertices that are linked by edges. The vertices stand for elementary units, such as cortical areas or channels, while the edges represent associations between vertices. Regarding the associations, there are many choices, for instance, coherence measures. Various properties can be calculated from the constructed network, such as clustering coefficient (the most elementary measures of local segregation), path length (an index reflecting the overall integration of the network), and efficiency (computed as the average of the inverse of the distance matrix). These properties might provide potential MCI biomarkers.

In addition, as the studies presented here were performed in the frame of a longitudinal project, future investigations will focus on results obtained from a second evaluation using the A-V task, in order to study the evolution of the participants and evaluate the predictive value of ERP parameters for the progression from MCI to dementia, especially AD.

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

REFERENCES

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

Aarts, K., De Houwer, J., & Pourtois, G. (2013). Erroneous and correct actions have a different affective valence: evidence from ERPs. *Emotion (Washington, D.C.)*, *13*(5), 960–73. doi:10.1037/a0032808

Albert, M. S., DeKosky, S. T., Dickson, D., Dubois, B., Feldman, H. H., Fox, N. C., … Phelps, C. H. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *7*(3), 270–279. doi:10.1016/j.jalz.2011.03.008

Alho, K., Escera, C., Díaz, R., Yago, E., & Serra, J. M. (1997). *Effects of involuntary auditory attention on visual task performance and brain activity. Neuroreport* (Vol. 8). doi:10.1097/00001756-199710200-00010

Amenedo, E., & Díaz, F. (1998a). Aging-related changes in processing of non-target and target stimuli during an auditory oddball task. *Biological Psychology*, *48*(3), 235–267. doi:10.1016/S0301-0511(98)00040-4

Amenedo, E., & Díaz, F. (1998b). Automatic and effortful processes in auditory memory reflected by event-related potentials. Age-related findings. *Electroencephalography and Clinical Neurophysiology*, *108*(4), 361–9. doi:10.1016/S0168-5597(98)00007-0

Anderer, P., Saletu, B., Semlitsch, H. V, & Pascual-Marqui, R. D. (2003). Non-invasive localization of P300 sources in normal aging and age-associated memory impairment. *Neurobiology of Aging*, *24*(3), 463–79. doi:10.1016/S0197-4580(02)00058-1

Anderer, P., Semlitsch, H. V, & Saletu, B. (1996). Multichannel auditory event-related brain potentials: effects of normal aging on the scalp distribution of N1, P2, N2 and P300 latencies and amplitudes. *Electroencephalography and Clinical Neurophysiology*, *99*(5), 458–472. doi:10.1016/S0013-4694(96)96518-9

Andrés, P., Parmentier, F. B. R., & Escera, C. (2006). The effect of age on involuntary capture of attention by irrelevant sounds: a test of the frontal hypothesis of aging. *Neuropsychologia*, *44*(12), 2564–2568. doi:10.1016/j.neuropsychologia.2006.05.005

Ashford, J. W., Coburn, K. L., Rose, T. L., & Bayley, P. J. (2011). P300 energy loss in aging and Alzheimer's disease. *Journal of Alzheimers Disease JAD*, *26 Suppl 3*, 229–38. doi:10.3233/JAD-2011-0061

Aston-Jones, G., & Cohen, J. D. (2005). Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. *Journal of Comparative Neurology*, *493*(1), 99–110. doi:10.1002/cne.20723

Band, G. P., & Kok, A. (2000). Age effects on response monitoring in a mental-rotation task. *Biological Psychology*, *51*(2-3), 201–21. doi:10.1016/S0301-0511(99)00038-1

Barcelo, F., Escera, C., Corral, M. J., & Periáñez, J. A. (2006). Task switching and novelty processing activate a common neural network for cognitive control.

Journal of Cognitive Neuroscience, *18*(10), 1734–48. doi:10.1162/jocn.2006.18.10.1734

Bartholow, B. D., Pearson, M. A., Dickter, C. L., Sher, K. J., Fabiani, M., & Gratton, G. (2005). Strategic control and medial frontal negativity: Beyond errors and response conflict. *Psychophysiology*, *42*(1), 33–42. doi:10.1111/j.1469-8986.2005.00258.x

Bekker, E. M., Kenemans, J. L., & Verbaten, M. N. (2004). Electrophysiological correlates of attention, inhibition, sensitivity and bias in a continuous performance task. *Clinical Neurophysiology*, *115*(9), 2001–13. doi:10.1016/j.clinph.2004.04.008

Benarroch, E. E. (2009). The locus ceruleus norepinephrine system: functional organization and potential clinical significance. *Neurology*, *73*(20), 1699–1704. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/19917994

Bennys, K., Portet, F., Touchon, J., & Rondouin, G. (2007). Diagnostic value of event-related evoked potentials N200 and P300 subcomponents in early diagnosis of Alzheimer's disease and mild cognitive impairment. *Journal of Clinical Neurophysiology*, *24*(5), 405–412. doi:10.1097/WNP.0b013e31815068d5

Bennys, K., Rondouin, G., Benattar, E., Gabelle, A., & Touchon, J. (2011). Can Event-Related Potential Predict the Progression of Mild Cognitive Impairment? *Journal of Clinical Neurophysiology*, *5*(6), 625–32. doi:10.1097/WNP.0b013e31823cc2d3

Bernard, J. A., & Seidler, R. D. (2012). Evidence for motor cortex dedifferentiation in older adults. *Neurobiology of Aging*, *33*(9), 1890–9. doi:10.1016/j.neurobiolaging.2011.06.021

Beste, C., Willemssen, R., Saft, C., & Falkenstein, M. (2010). Response inhibition subprocesses and dopaminergic pathways: basal ganglia disease effects. *Neuropsychologia*, *48*(2), 366–73. doi:10.1016/j.neuropsychologia.2009.09.023

Bokura, H., Yamaguchi, S., & Kobayashi, S. (2001). Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clinical Neurophysiology*, *112*(12), 2224–32. doi:10.1016/S1388-2457(01)00691-5

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. doi:10.1037/0033-295X.108.3.624

Braver, T. S., Barch, D. M., Gray, J. R., Molfese, D. L., & Snyder, A. (2001). Anterior cingulate cortex and response conflict: effects of frequency, inhibition and errors. *Cerebral Cortex (New York, N.Y. : 1991)*, *11*(9), 825–36. doi:10.1093/cercor/11.9.825

Buján, A., Lindín, M., & Díaz, F. (2010). The effect of aging on movement related cortical potentials during a face naming task. *International Journal of Psychophysiology*, *78*(2), 169–78. doi:10.1016/j.ijpsycho.2010.07.006

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 (New York, N.Y. : 1991)*, *14*(4), 364–75. doi:10.1093/cercor/bhg133

Carter, C. S., Macdonald, A. M., Botvinick, M., Ross, L. L., Stenger, V. A., Noll, D., & Cohen, J. D. (2000). Parsing executive processes: strategic vs. evaluative functions of the anterior cingulate cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(4), 1944–1948. doi:10.1073/pnas.97.4.1944

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2013b). Age-related changes in ERP correlates of visuospatial and motor processes. *Psychophysiology*, *50*(8), 743–57. doi:10.1111/psyp.12063

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2013a). Electrophysiological correlates of amnestic mild cognitive impairment in a simon task. *PloS One*, *8*(12), e81506. doi:10.1371/journal.pone.0081506

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2015a). Inhibition deficit in the spatial tendency of the response in multipledomain amnestic mild cognitive impairment. An event-related potential study. *Frontiers in Aging Neuroscience*. doi:10.3389/fnagi.2015.00068

Cespón, J., Galdo-Álvarez, S., Pereiro, A. X., & Díaz, F. (2015b). Differences between Mild Cognitive Impairment Subtypes as Indicated by Event-Related Potential Correlates of Cognitive and Motor Processes in a Simon Task. *Journal of Alzheimers Disease JAD*, *43*, 631–647. doi:10.3233/JAD-132774

Chen, P., Ratcliff, G., Belle, S. H., Cauley, J. A., DeKosky, S. T., & Ganguli, M. (2001). Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. *Archives of General Psychiatry*, *58*(9), 853–8. doi:10.1001/archpsyc.58.9.853

Cid-Fernández, S., Lindín, M., & Díaz, F. (2014a). Effects of aging and involuntary capture of attention on event-related potentials associated with the processing of and the response to a target stimulus. *Frontiers in Human Neuroscience*, *8*(745). doi:10.3389/fnhum.2014.00745

Cid-Fernández, S., Lindín, M., & Díaz, F. (2014b). Effects of Amnestic Mild Cognitive Impairment on N2 and P3 Go/NoGo ERP Components. *Journal of Alzheimers Disease JAD*, *38*, 295–306. doi:10.3233/JAD-130677

Cid-Fernández, S., Lindín, M., & Díaz, F. (2015b). Stimulus-locked lateralized readiness potential and performance: useful markers for differentiating between amnestic subtypes of mild cognitive impairment. *The Journal of Prevention of Alzheimer's Disease (JPAD)*, *in press*.

Cohen, J. D., Botvinick, M., & Carter, C. S. (2000). Anterior cingulate and prefrontal cortex: who's in control? *Nature Neuroscience*. doi:10.1038/74783

Cohen, J. E. (2003). Human population: the next half century. *Science (New York, N.Y.)*, *302*(5648), 1172–1175. doi:10.1126/science.1088665

Coles, M. G. H., & Rugg, M. D. (1996). Event-related brain potentials: an introduction. (M. D. Rugg & M. G. H. Coles, Eds.)*Electrophysiology of the Mind*

Event Related Brain Potentials and Cognition. Oxford University Press. doi:10.1093/acprof:oso/9780198524168.003.0001

Cortiñas, M., Corral, M. J., Garrido, G., Garolera, M., Pajares, M., & Escera, C. (2008). Reduced novelty-P3 associated with increased behavioral distractibility in schizophrenia. *Biological Psychology*, *78*(3), 253–60. doi:10.1016/j.biopsycho.2008.03.011

Czernochowski, D., Nessler, D., & Friedman, D. (2010). On why not to rush older adults - Relying on reactive cognitive control can effectively reduce errors at the expense of slowed responses. *Psychophysiology*, *47*(4), 637–646. doi:10.1111/j.1469-8986.2009.00973.x

Czigler, I., Csibra, G., & Ambró, A. (1996). Aging, stimulus identification and the effect of probability: an event-related potential study. *Biological Psychology*, *43*(1), 27–40. doi:10.1016/0301-0511(95)05173-2

Czigler, I., Pató, L., Poszet, E., & Balázs, L. (2006). Age and novelty: event-related potentials to visual stimuli within an auditory oddball--visual detection task. *International Journal of Psychophysiology*, *62*(2), 290–9. doi:10.1016/j.ijpsycho.2006.05.008

Davis, S. W., Dennis, N. A., Daselaar, S. M., Fleck, M. S., & Cabeza, R. (2008). Que PASA? The posterior-anterior shift in aging. *Cerebral Cortex (New York, N.Y.: 1991)*, *18*(5), 1201–1209. doi:10.1093/cercor/bhm155

Díaz, F., & Amenedo, E. (2001). Demencia senil: Enfermedad de Alzheimer. In M. A. Simón & E. Amenedo (Eds.), *Manual de Psicofisiología Clínica* (pp. 155–196). Madrid: Pirámide.

Donchin, E., & Coles, M. G. H. (1988). Is the P300 component a manifestation of context updating? *Behavioral and Brain Sciences*, *11*(3), 357–374. doi:10.1017/S0140525X00058027

Dong, G., Yang, L., Hu, Y., & Jiang, Y. (2009). Is N2 associated with successful suppression of behavior responses in impulse control processes? *NeuroReport*, *20*(6), 537–542. doi:10.1097/WNR.0b013e3283271e9b

Donkers, F. C., & van Boxtel, G. J. (2004). The N2 in go/no-go tasks reflects conflict monitoring not response inhibition. *Brain and Cognition*, *56*(2), 165–176. doi:10.1016/j.bandc.2004.04.005

Elrod, R., Peskind, E. R., DiGiacomo, L., Brodkin, K. I., Veith, R. C., & Raskind, M. A. (1997). Effects of Alzheimer's disease severity on cerebrospinal fluid norepinephrine concentration. *The American Journal of Psychiatry*, *154*(1), 25–30.

Enoki, H., Sanada, S., Yoshinaga, H., Oka, E., & Ohtahara, S. (1993). The effects of age on the N200 component of the auditory event-related potentials. *Brain Research. Cognitive Brain Research*, *1*(3), 161–167. doi:10.1016/0926-6410(93)90023-X

Eppinger, B., Kray, J., Mecklinger, A., & John, O. (2007). Age differences in task switching and response monitoring: Evidence from ERPs. *Biological Psychology*, *75*(1), 52–67. doi:10.1016/j.biopsycho.2006.12.001

Escera, C., Alho, K., Winkler, I., & Näätänen, R. (1998). Neural mechanisms of involuntary attention to acoustic novelty and change. *Journal of Cognitive Neuroscience*, *10*(5), 590–604. doi:10.1162/089892998562997

Escera, C., Corral, M. J., & Yago, E. (2002). An electrophysiological and behavioral investigation of involuntary attention towards auditory frequency, duration and intensity changes. *Cognitive Brain Research*, *14*(3), 325–32. doi:10.1016/S0926-6410(02)00135-0

Escera, C., Yago, E., & Alho, K. (2001). Electrical responses reveal the temporal dynamics of brain events during involuntary attention switching. *The European Journal of Neuroscience*, *14*(5), 877–883. doi:10.1016/j.neulet.2009.04.053

Escera, C., Yago, E., Corral, M.-J., Corbera, S., & Nuñez, M. I. (2003). Attention capture by auditory significant stimuli: semantic analysis follows attention switching. *The European Journal of Neuroscience*, *18*(8), 2408–2412. doi:10.1046/j.1460-9568.2003.02937.x

Fabiani, M., & Friedman, D. (1995). Changes in brain activity patterns in aging: the novelty oddball. *Psychophysiology*, *32*(6), 579–594. doi:10.1111/j.1469-8986.1995.tb01234.x

Falkenstein, M. (2006). Inhibition, conflict and the Nogo-N2. *Clinical Neurophysiology*, *117*(8), 1638–40. doi:10.1016/j.clinph.2006.05.002

Falkenstein, M., Hohnsbein, J., & Hoormann, J. (1994). Time Pressure Effects on Late Components of the Event-Related Potential (Erp). *Journal of Psychophysiology*, *8*(1), 22–30. Retrieved from http://psycnet.apa.org/psycinfo/1995-00785-001

Falkenstein, M., Hoormann, J., Christ, S., & Hohnsbein, J. (2000). ERP components on reaction errors and their functional significance: A tutorial. *Biological Psychology*, *51*(2-3), 87–107. doi:10.1016/S0301-0511(99)00031-9

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2001). Changes of error-related ERPs with age. *Experimental Brain Research*, *138*(2), 258–262. doi:10.1007/s002210100712

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. doi:10.1027//0269-8803.16.3.167

Falkenstein, M., Yordanova, J., & Kolev, V. (2006). Effects of aging on slowing of motor-response generation. *International Journal of Psychophysiology*, *59*(1), 22–9. doi:10.1016/j.ijpsycho.2005.08.004

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. doi:10.1111/j.1469-8986.2007.00602.x

Friedman, D. (2008). The components of aging. In S. J. Luck & E. S. Kappenman (Eds.), *The Oxford Handbook of Event-Related Potential Components* (pp. 513–537). New York: Oxford University Press.

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 and Biobehavioural Reviews*, *25*, 355–373. doi:10.1016/S0149-7634(01)00019-7

Friedman, D., Nessler, D., Cycowicz, Y. M., & Horton, C. (2009). Development of and change in cognitive control: a comparison of children, young adults, and older adults. *Cognitive, Affective & Behavioral Neuroscience*, *9*(1), 91–102. doi:10.3758/CABN.9.1.91

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, Neuropsychology and Cognition*, *15*(1), 95–128. doi:10.1080/13825580701533769

Friedman, D., Simpson, G., & Hamberger, M. (1993). Age-related changes in scalp topography to novel and target stimuli. *Psychophysiology*, *30*(4), 383–96. doi:10.1111/j.1469-8986.1993.tb02060.x

Frodl, T., Hampel, H., Juckel, G., Bürger, K., Padberg, F., Engel, R. R., … Hegerl, U. (2002). *Value of event-related P300 subcomponents in the clinical diagnosis of mild cognitive impairment and Alzheimer's Disease. Psychophysiology* (Vol. 39). Wiley Online Library. doi:10.1017/S0048577202010260

Gaál, Z. A., Csuhaj, R., & Molnár, M. (2007). Age-dependent changes of auditory evoked potentials--effect of task difficulty. *Biological Psychology*, *76*(3), 196–208. doi:10.1016/j.biopsycho.2007.07.009

Galdo-Alvarez, S., Lindín, M., & Díaz, F. (2009a). Age-related prefrontal over-recruitment in semantic memory retrieval: Evidence from successful face naming and the tip-of-the-tongue state. *Biological Psychology*, *82*(1), 89–96. doi:doi:10.1016/j.biopsycho.2009.06.003

Galdo-Alvarez, S., Lindín, M., & Díaz, F. (2009b). The effect of age on event-related potentials (ERP) associated with face naming and with the tip-of-the-tongue (TOT) state. *Biological Psychology*, *81*(1), 14–23. doi:10.1016/j.biopsycho.2009.01.002

Ganguli, M., Dodge, H. H., Shen, C., & DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology*, *63*(1), 115–21. doi:10.1212/01.WNL.0000132523.27540.81

Gauthier, S., Reisberg, B., Zaudig, M., Petersen, R. C., Ritchie, K., Broich, K., … De Leon, M. (2006). Mild cognitive impairment. *Lancet*, *367*, 1262–1270. doi:10.1016/S0140-6736(06)68542-5

Gehring, W. J., & Knight, R. T. (2000). Prefrontal-cingulate interactions in action monitoring. *Nature Neuroscience*, *3*(5), 516–520. doi:10.1038/74899

Gironell, A., García-Sánchez, C., Estévez-González, A., Boltes, A., & Kulisevsky, J. (2005). Usefulness of p300 in subjective memory complaints: a prospective

study. *Journal of Clinical Neurophysiology*, *22*(4), 279–284. doi:10.1097/01.WNP.0000173559.60113.AB

Goh, J. O. S., & Park, D. C. (2009). Neuroplasticity and cognitive aging: the scaffolding theory of aging and cognition. *Restorative Neurology and Neuroscience*, *27*(5), 391–403. doi:10.3233/RNN-2009-0493

Golob, E. J., Irimajiri, R., & Starr, A. (2007). Auditory cortical activity in amnestic mild cognitive impairment: relationship to subtype and conversion to dementia. *Brain: A Journal of Neurology*, *130*(Pt 3), 740–752. doi:10.1093/brain/awl375

Golob, E. J., Johnson, J. K., & Starr, A. (2002). Auditory event-related potentials during target detection are abnormal in mild cognitive impairment. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *113*, 151–61. doi:10.1016/S1388-2457(01)00713-1

Golob, E. J., & Starr, A. (2000). Effects of stimulus sequence on event-related potentials and reaction time during target detection in Alzheimer's disease. *Clinical Neurophysiology*, *111*(8), 1438–1449. doi:10.1016/S1388-2457(00)00332-1

Grober, E., Hall, C. B., Lipton, R. B., Zonderman, A. B., Resnick, S. M., & Kawas, C. (2008). Memory impairment, executive dysfunction, and intellectual decline in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society JINS*, *14*(2), 266–278. doi:10.1017/S1355617708080302

Gutchess, A. H., Welsh, R. C., Hedden, T., Bangert, A., Minear, M., Liu, L. L., & Park, D. C. (2005). Aging and the neural correlates of successful picture encoding: frontal activations compensate for decreased medial-temporal activity. *Journal of Cognitive Neuroscience*, *17*(1), 84–96. doi:10.1162/0898929052880048

Hämmerer, D., Li, S., Müller, V., & Lindenberger, U. (2010). An electrophysiological study of response conflict processing across the lifespan: assessing the roles of conflict monitoring, cue utilization, response anticipation, and response suppression. *Neuropsychologia*, *48*(11), 3305–16. doi:10.1016/j.neuropsychologia.2010.07.014

Hebert, L. E., Scherr, P. A., Bienias, J. L., Bennett, D. A., & Evans, D. A. (2003). Alzheimer disease in the US population: prevalence estimates using the 2000 census. *Archives of Neurology*, *60*(8), 1119–22. doi:10.1001/archneur.60.8.1119

Hohnsbein, J., Falkenstein, M., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. I. Simple and choice reaction tasks. *Electroencephalography and Clinical Neurophysiology*, *78*(6), 438–446. doi:10.1016/0013-4694(91)90061-8

Howe, A. S. (2014). Meta-analysis of the endogenous N200 latency event-related potential subcomponent in patients with Alzheimer's disease and mild cognitive impairment. *Clinical Neurophysiology*, *125*(6), 1145–51. doi:10.1016/j.clinph.2013.10.019

Howe, A. S., Bani-Fatemi, A., & De Luca, V. (2014). The clinical utility of the auditory P300 latency subcomponent event-related potential in preclinical

diagnosis of patients with mild cognitive impairment and Alzheimer's disease. *Brain and Cognition*, *86*(1), 64–74. doi:10.1016/j.bandc.2014.01.015

Iragui, V. J., Kutas, M., Mitchiner, M. R., & Hillyard, S. A. (1993). Effects of aging on event-related brain potentials and reaction times in an auditory oddball task. *Psychophysiology*, *30*(1), 10–22. doi:10.1111/j.1469-8986.1993.tb03200.x

Jack, C. R., Albert, M. S., Knopman, D. S., Mckhann, G. M., Sperling, R. A., Carrillo, M. C., … Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging and the Alzheimer ' s Association workgroup on diagnostic guidelines for Alzheimer ' s disease. *Alzheimer's & Dementia*, *7*, 257–62. doi:10.1016/j.jalz.2011.03.004

Jackson, C. E., & Snyder, P. J. (2008). Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, *4*(1 Suppl 1), 137–43. doi:10.1016/j.jalz.2007.10.008

Johnson, R., Barnhardt, J., & Zhu, J. (2005). Differential effects of practice on the executive processes used for truthful and deceptive responses: An event-related brain potential study. *Cognitive Brain Research*, *24*(3), 386–404. doi:10.1016/j.cogbrainres.2005.02.011

Johnson, R., Henkell, H., Simon, E., & Zhu, J. (2008). The self in conflict: The role of executive processes during truthful and deceptive responses about attitudes. *NeuroImage*, *39*(1), 469–482. doi:10.1016/j.neuroimage.2007.08.032

Juckel, G., Karch, S., Kawohl, W., Kirsch, V., Jäger, L., Leicht, G., … Mulert, C. (2012). Age effects on the P300 potential and the corresponding fMRI BOLD-signal. *NeuroImage*, *60*(4), 2027–34. doi:10.1016/j.neuroimage.2012.02.019

Kolev, V., Falkenstein, M., & Yordanova, J. (2005). Aging and Error Processing. *Journal of Psychophysiology*. doi:10.1027/0269-8803.19.4.289

Kolev, V., Falkenstein, M., & Yordanova, J. (2006). Motor-response generation as a source of aging-related behavioural slowing in choice-reaction tasks. *Neurobiology of Aging*, *27*(11), 1719–30. doi:10.1016/j.neurobiolaging.2005.09.027

Kropotov, J. D., Ponomarev, V. A., Hollup, S., & Mueller, A. (2011). Dissociating action inhibition, conflict monitoring and sensory mismatch into independent components of event related potentials in GO/NOGO task. *NeuroImage*, *57*(2), 565–575. doi:10.1016/j.neuroimage.2011.04.060

Kutas, M., Iragui, V., & Hillyard, S. A. (1994). Effects of aging on event-related brain potentials (ERPs) in a visual detection task. *Electroencephalography and Clinical Neurophysiology*, *92*(2), 126–39. doi:10.1016/0168-5597(94)90053-1

Lai, C., Lin, R., Liou, L., & Liu, C. (2010). The role of event-related potentials in cognitive decline in Alzheimer's disease. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *121*(2), 194–9. doi:10.1016/j.clinph.2009.11.001

Lehle, C., Cohen, A., Sangals, J., Sommer, W., & Stürmer, B. (2011). Differential dynamics of spatial and non-spatial stimulus-response compatibility effects: a dual task LRP study. *Acta Psychologica*, *136*(1), 42–51. doi:10.1016/j.actpsy.2010.09.013

Lenzi, D., Serra, L., Perri, R., Pantano, P., Lenzi, G. L., Paulesu, E., … Macaluso, E. (2011). Single domain amnestic MCI: A multiple cognitive domains fMRI investigation. *Neurobiology of Aging*, *32*(9), 1542–57. doi:10.1016/j.neurobiolaging.2009.09.006

Li, X., Shao, X., Wang, N., Wang, T., Chen, G., & Zhou, H. (2010). Correlation of auditory event-related potentials and magnetic resonance spectroscopy measures in mild cognitive impairment. *Brain Research*, *1346*, 204–212. doi:10.1016/j.brainres.2010.04.078

Lindenberger, U., & Mayr, U. (2014). Cognitive aging: Is there a dark side to environmental support? *Trends in Cognitive Sciences*. doi:10.1016/j.tics.2013.10.006

Lindín, M., Correa, K., Zurrón, M., & Díaz, F. (2013). Mismatch negativity (MMN) amplitude as a biomarker of sensory memory deficit in amnestic mild cognitive impairment. *Frontiers in Aging Neuroscience*, *5*, 79. doi:10.3389/fnagi.2013.00079

Lu, C., & Proctor, R. W. (1995). The influence of irrelevant location information on performance: A review of the Simon and spatial Stroop effects. *Psychonomic Bulletin & Review*. doi:10.3758/BF03210959

Luck, S. J. (2005). Ten Simple Rules for Designing and Interpreting ERP Experiments. In T. C. Handy (Ed.), *Event-related potentials: a methods handbook* (pp. 17–32). Cambridge, Mass.: MIT Press.

Lustig, C., Snyder, A. Z., Bhakta, M., O'Brien, K. C., McAvoy, M., Raichle, M. E., … Buckner, R. L. (2003). Functional deactivations: change with age and dementia of the Alzheimer type. *Proceedings of the National Academy of Sciences of the United States of America*, *100*(24), 14504–9. doi:10.1073/pnas.2235925100

Luu, P., Collins, P., & Tucker, D. M. (2000). Mood, personality, and self-monitoring: negative affect and emotionality in relation to frontal lobe mechanisms of error monitoring. *Journal of Experimental Psychology. General*, *129*(1), 43–60. doi:10.1037/0096-3445.129.1.43

MacDonald, A. W., Cohen, J. D., Stenger, V. A., & Carter, C. S. (2000). Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. *Science (New York, N.Y.)*, *288*(5472), 1835–1838. doi:10.1126/science.288.5472.1835

Masaki, H., Wild-Wall, N., Sangals, J., & Sommer, W. (2004). The functional locus of the lateralized readiness potential. *Psychophysiology*, *41*(2), 220–30. doi:10.1111/j.1469-8986.2004.00150.x

Mathalon, D. H., Bennett, A., Askari, N., Gray, E. M., Rosenbloom, M. J., & Ford, J. M. (2003). Response-monitoring dysfunction in aging and Alzheimer's disease: An

event-related potential study. *Neurobiology of Aging*, *24*(5), 675–85. doi:10.1016/S0197-4580(02)00154-9

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., … Phelps, C. H. (2011). The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's and Dementia*. doi:10.1016/j.jalz.2011.03.005

Missonnier, P., Deiber, M.-P., Gold, G., Herrmann, F. R., Millet, P., Michon, a, … Giannakopoulos, P. (2007). Working memory load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment. *Neuroscience*, *150*(2), 346–56. doi:10.1016/j.neuroscience.2007.09.009

Mitchell, J., Arnold, R., Dawson, K., Nestor, P. J., & Hodges, J. R. (2009). Outcome in subgroups of mild cognitive impairment (MCI) is highly predictable using a simple algorithm. *Journal of Neurology*, *256*(9), 1500–9. doi:10.1007/s00415-009-5152-0

Nessler, D., Friedman, D., Johnson, R., & Bersick, M. (2007). ERPs suggest that age affects cognitive control but not response conflict detection. *Neurobiology of Aging*, *28*(11), 1769–1782. doi:10.1016/j.neurobiolaging.2006.07.011

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus-norepinephrine system. *Psychological Bulletin*, *131*(4), 510–532. doi:10.1037/0033-2909.131.4.510

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*(1), 17–26. doi:10.3758/CABN.3.1.17

O'Connell, R. G., Balsters, J. H., Kilcullen, S. M., Campbell, W., Bokde, A. W., Lai, R., … Robertson, I. H. (2012). A simultaneous ERP/fMRI investigation of the P300 aging effect. *Neurobiology of Aging*, *33*(10), 2248–61. doi:10.1016/j.neurobiolaging.2011.12.021

O'Connell, R. G., Dockree, P. M., Bellgrove, M. A., Kelly, S. P., Hester, R., Garavan, H., … Foxe, J. J. (2007). The role of cingulate cortex in the detection of errors with and without awareness: A high-density electrical mapping study. *European Journal of Neuroscience*, *25*(8), 2571–2579. doi:10.1111/j.1460-9568.2007.05477.x

Osman, A., Lou, L., Muller-Gethmann, H., Rinkenauer, G., Mattes, S., & Ulrich, R. (2000). Mechanisms of speed-accuracy tradeoff: evidence from covert motor processes. *Biological Psychology*, *51*(2-3), 173–99. doi:10.1016/S0301-0511(99)00045-9

Papaliagkas, V. T., Anogianakis, G., Tsolaki, M. N., Koliakos, G., & Kimiskidis, V. K. (2009). Progression of mild cognitive impairment to Alzheimer's disease: improved diagnostic value of the combined use of N200 latency and beta-amyloid(1-42) levels. *Dementia and Geriatric Cognitive Disorders*, *28*(1), 30–35. doi:10.1159/000229023

Papaliagkas, V. T., Kimiskidis, V. K., Tsolaki, M. N., & Anogianakis, G. (2008). Usefulness of event-related potentials in the assessment of mild cognitive impairment. *BMC Neuroscience*, *9*, 107. doi:10.1186/1471-2202-9-107

Papaliagkas, V. T., Kimiskidis, V. K., Tsolaki, M. N., & Anogianakis, G. (2011). Cognitive event-related potentials: longitudinal changes in mild cognitive impairment. *Clinical Neurophysiology*, *122*(7), 1322–6. doi:10.1016/j.clinph.2010.12.036

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(35), 13091–5. doi:10.1073/pnas.0405148101

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*, 173–196. doi:10.1146/annurev.psych.59.103006.093656

Park, D. C., & Reuter-Lorenz, P. A. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annual Review of Psychology*, *60*(1), 173–196. doi:10.1146/annurev.psych.59.103006.093656

Parmentier, F. B. R. (2008). Towards a cognitive model of distraction by auditory novelty: The role of involuntary attention capture and semantic processing. *Cognition*, *109*(3), 345–62. doi:10.1016/j.cognition.2008.09.005

Parmentier, F. B. R., & Andrés, P. (2010). The involuntary capture of attention by sound: novelty and postnovelty distraction in young and older adults. *Experimental Psychology*, *57*(1), 68–76. doi:10.1027/1618-3169/a000009

Parmentier, F. B. R., Elsley, J. V, Andrés, P., & Barceló, F. (2011). Why are auditory novels distracting? Contrasting the roles of novelty, violation of expectation and stimulus change. *Cognition*, *119*(3), 374–380. doi:10.1016/j.cognition.2011.02.001

Parmentier, F. B. R., Elsley, J. V, & Ljungberg, J. K. (2010). Behavioral distraction by auditory novelty is not only about novelty: the role of the distracter's informational value. *Cognition*, *115*(3), 504–511. doi:10.1016/j.cognition.2010.03.002

Parmentier, F., Elford, G., Escera, C., Andres, P., & Miguel, I. (2008). The cognitive locus of distraction by acoustic novelty in the cross-modal oddball task. *Cognition*, *106*(1), 408–432. doi:10.1016/j.cognition.2007.03.008

Parra, M. A., Ascencio, L. L., Urquina, H. F., Manes, F., & Ibáñez, A. M. (2012). P300 and neuropsychological assessment in mild cognitive impairment and alzheimer dementia. *Frontiers in Neurology*, *3 DEC*. doi:10.3389/fneur.2012.00172

Patel, S. H., & Azzam, P. N. (2005). Characterization of N200 and P300: selected studies of the Event-Related Potential. *International Journal of Medical Sciences*, *2*(4), 147–154. doi:10.7150/ijms.2.147

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*(6), 1021–32. doi:10.1162/jocn.2007.19.6.1021

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine*, *256*(3), 183–94. doi:10.1111/j.1365-2796.2004.01388.x

Petersen, R. C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., & Fratiglioni, L. (2014). Mild cognitive impairment: A concept in evolution. *Journal of Internal Medicine*, *275*(3), 214–228. doi:10.1111/joim.12190

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V, … Winblad, B. (2001). Current concepts in mild cognitive impairment. *Archives of Neurology*, *58*(12), 1985–1992. doi:10-1001/pubs.Arch Neurol

Petersen, R. C., & Negash, S. (2008). Mild cognitive impairment: an overview. *CNS Spectrums*, *13*(1), 45–53. doi:10.1017/S1092852900016151

Petersen, R. C., Roberts, R. O., Knopman, D. S., Boeve, B. F., Geda, Y. E., Ivnik, R. J., … Jack, C. R. (2009). Mild cognitive impairment: ten years later. *Archives of Neurology*, *66*(12), 1447–55. doi:10.1001/archneurol.2009.266

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnick, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild Cognitive Impairment: Clinical Characterization and Outcome. *Archives of Neurology*, *56*(3), 303–308. doi:10.1001/archneur.56.3.303

Phillips, N. A., Chertkow, H., Leblanc, M. M., Pim, H., & Murtha, S. (2004). Functional and anatomical memory indices in patients with or at risk for Alzheimer's disease. *Journal of the International Neuropsychological Society : JINS*, *10*(2), 200–210. doi:10.10170S1355617704102063

Pietschmann, M., Simon, K., Endrass, T., & Kathmann, N. (2008). Changes of performance monitoring with learning in older and younger adults. *Psychophysiology*, *45*(4), 559–568. doi:10.1111/j.1469-8986.2008.00651.x

Pinal, D., Zurrón, M., & Díaz, F. (2014). Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. *Frontiers in Human Neuroscience*, *8*, 165. doi:10.3389/fnhum.2014.00165.

Pinal, D., Zurrón, M., Díaz, F., & Sauseng, P. (2015). Stuck in default mode: inefficient cross-frequency synchronization may lead to age-related short-term memory decline. *Neurobiology of Aging*, *36*(4), 1611–8. doi:10.1016/j.neurobiolaging.2015.01.009

Polich, J. (1996). Meta-analysis of P300 normative aging studies. *Psychophysiology*, *33*(4), 334–53. doi:10.1111/j.1469-8986.1996.tb01058.x

Polich, J. (2004). Clinical application of the P300 event-related brain potential. *Physical Medicine and Rehabilitation Clinics of North America*, *15*(1), 133–161. doi:10.1016/S1047-9651(03)00109-8

Polich, J. (2012). Neuropsychology of P300. In E. S. Kappenman & S. J. Luck (Eds.), *The Oxford Handbook of Event-Related Potential ComponentsHandbook of*

event-related potential components (Oxford Uni., pp. 159–188). Oxford University Press. doi:10.1093/oxfordhb/9780195374148.013.0089

Polich, J., & Kok, A. (1995). Cognitive and biological determinants of P300: an integrative review. *Biological Psychology*, *41*(2), 103–46. doi:10.1016/0301-0511(95)05130-9

Polo, M. D., Escera, C., Yago, E., Alho, K., Gual, A., & Grau, C. (2003). Electrophysiological evidence of abnormal activation of the cerebral network of involuntary attention in alcoholism. *Clinical Neurophysiology*, *114*(1), 134–146. doi:10.1016/S1388-2457(02)00336-X

Polo, M. D., Newton, P., Rogers, D., Escera, C., & Butler, S. (2002). ERPs and behavioural indices of long-term preattentive and attentive deficits after closed head injury. *Neuropsychologia*, *40*(13), 2350–59. doi:10.1016/S0028-3932(02)00127-6

Potts, G. F., & Tucker, D. M. (2001). Frontal evaluation and posterior representation in target detection. *Cognitive Brain Research*, *11*(1), 147–56. doi:10.1016/S0926-6410(00)00075-6

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*, *122*(12), 2400–2407. doi:10.1016/j.clinph.2011.05.012

Raskind, M. A., Peskind, E. R., Holmes, C., & Goldstein, D. S. (1999). Patterns of cerebrospinal fluid catechols support increased central noradrenergic responsiveness in aging and Alzheimer's disease. *Biological Psychiatry*, *46*(6), 756–765. doi:10.1016/S0006-3223(99)00008-6

Ravden, D., & Polich, J. (1998). Habituation of P300 from visual stimuli. *International Journal of Psychophysiology*, *30*(3), 359–65. doi:10.1016/S0167-8760(98)00039-7

Reijneveld, J. C., Ponten, S. C., Berendse, H. W., & Stam, C. J. (2007). The application of graph theoretical analysis to complex networks in the brain. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *118*(11), 2317–2331. doi:10.1016/j.clinph.2007.08.010

Reuter-Lorenz, P. A., & Park, D. C. (2014). How Does it STAC Up? Revisiting the Scaffolding Theory of Aging and Cognition. *Neuropsychology Review*, *24*, 355–70. doi:10.1007/s11065-014-9270-9

Ritter, W., Simson, R., Vaughan, H. G., & Friedman, D. (1979). A brain event related to the making of a sensory discrimination. *Science*, *203*(4387), 1358–1361. doi:10.1126/science.424760

Roger, C., Bénar, C. G., Vidal, F., Hasbroucq, T., & Burle, B. (2010). Rostral Cingulate Zone and correct response monitoring: ICA and source localization evidences for the unicity of correct- and error-negativities. *NeuroImage*, *51*(1), 391–403. doi:10.1016/j.neuroimage.2010.02.005

Roggeveen, A. B., Prime, D. J., & Ward, L. M. (2007). Lateralized readiness potentials reveal motor slowing in the aging brain. *The Journals of Gerontology Series B Psychological Sciences and Social Sciences*, *62*(2), 78–84. doi:10.1093/geronb/62.2.P78

Rösler, F., Borgstedt, J., & Sojka, B. (1985). When perceptual or motor sets are changed: Effects of updating demands on structure and energy of P300. *Acta Psychologica*, *60*(2-3), 293–321. doi:10.1016/0001-6918(85)90059-9

Saito, H., Yamazaki, H., Matsuoka, H., Matsumoto, K., Numachi, Y., Yoshida, S., … Sato, M. (2001). Visual event-related potential in mild dementia of the Alzheimer's type. *Psychiatry and Clinical Neurosciences*, *55*, 365–371. doi:10.1046/j.1440-1819.2001.00876.x

Salthouse, T. a. (1996). The processing-speed theory of adult age differences in cognition. *Psychological Review*, *103*(3), 403–428. doi:10.1037/0033-295X.103.3.403

Salthouse, T. A. (2000). Aging and measures of processing speed. *Biological Psychology*, *54*(1-3), 35–54. doi:10.1016/S0301-0511(00)00052-1

SanMiguel, I., Morgan, H. M., Klein, C., Linden, D., & Escera, C. (2010). On the functional significance of Novelty-P3: facilitation by unexpected novel sounds. *Biological Psychology*, *83*(2), 143–152. doi:10.1016/j.biopsycho.2009.11.012

Schiff, S., Valenti, P., Andrea, P., Lot, M., Bisiacchi, P., Gatta, A., & Amodio, P. (2008). The effect of aging on auditory components of event-related brain potentials. *Clinical Neurophysiology*, *119*(8), 1795–802. doi:10.1016/j.clinph.2008.04.007

Schmiedt-Fehr, C., & Basar-Eroglu, C. (2011). Event-related delta and theta brain oscillations reflect age-related changes in both a general and a specific neuronal inhibitory mechanism. *Clinical Neurophysiology*, *122*(6), 1156–1167. doi:10.1016/j.clinph.2010.10.045

Schreiber, M., Pietschmann, M., Kathmann, N., & Endrass, T. (2011). ERP correlates of performance monitoring in elderly. *Brain and Cognition*, *76*(1), 131–139. doi:10.1016/j.bandc.2011.02.003

Staffen, W., Ladurner, G., Höller, Y., Bergmann, J., Aichhorn, M., Golaszewski, S., & Kronbichler, M. (2012). Brain activation disturbance for target detection in patients with mild cognitive impairment: An fMRI study. *Neurobiology of Aging*, *33*(5). doi:10.1016/j.neurobiolaging.2011.09.002

Stam, C. J., & Reijneveld, J. C. (2007). Graph theoretical analysis of complex networks in the brain. *Nonlinear Biomedical Physics*, *1*(1), 3. doi:10.1186/1753-4631-1-3

Thies, B., Truschke, E., Morrison-Bogorad, M., & Hodes, R. J. (1998). Consensus report of the Working Group on: molecular and biochemical markers of Alzheimer's disease. *Neurobiology of Aging*. doi:10.1016/S0197-4580(98)00022-0

Tsutsumi, R., Hanajima, R., Hamada, M., Shirota, Y., Matsumoto, H., Terao, Y., … Ugawa, Y. (2012). Reduced interhemispheric inhibition in mild cognitive

impairment. *Experimental Brain Research*, *218*(1), 21–26. doi:10.1007/s00221-011-2997-0

Tsutsumi, R., Hanajima, R., Hamada, M., Shirota, Y., Matsumoto, H., Terao, Y., … Ugawa, Y. (2012). Reduced interhemispheric inhibition in mild cognitive impairment. *Experimental Brain Research. Experimentelle Hirnforschung. Expérimentation Cérébrale*, *218*(1), 21–6. doi:10.1007/s00221-011-2997-0

Tucker, D. M., Hartry-Speiser, A., McDougal, L., Luu, P., & Degrandpre, D. (1999). Mood and spatial memory: Emotion and right hemisphere contribution to spatial cognition. *Biological Psychology*, *50*(2), 103–125. doi:10.1016/S0301-0511(99)00005-8

Twamley, E. W., Ropacki, S. A. L., & Bondi, M. W. (2006). Neuropsychological and neuroimaging changes in preclinical Alzheimer's disease. *Journal of the International Neuropsychological Society JINS*, *12*(5), 707–735. doi:10.1044/nnsld13.4.12

Vaitkevicius, A., Kaubrys, G., & Audronyte, E. (2015). Distinctive Effect of Donepezil Treatment on P300 and N200 Subcomponents of Auditory Event-Related Evoked Potentials in Alzheimer Disease Patients. *Medical*, *21*, 1920–27. doi:10.12659/MSM.894940

Vallesi, A., & Stuss, D. T. (2010). Excessive sub-threshold motor preparation for non-target stimuli in normal aging. *NeuroImage*, *50*(3), 1251–1257. doi:10.1016/j.neuroimage.2010.01.022

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), 577–586. doi:10.1016/j.neuropsychologia.2008.10.018

Valls-Pedret, C., Molinuevo, J.-L., & Rami, L. (2010). Diagnóstico precoz de la enfermedad de Alzheimer: fase prodrómica y preclínica. *Rev Neurol*, *51*, 471–480. Retrieved from http://www.revneurol.com/sec/resumen.php?or=pubmed&id=2010501#

Van Deursen, J. A., Vuurman, E. F. P. M., Smits, L. L., Verhey, F. R. J., & Riedel, W. J. (2009). Response speed, contingent negative variation and P300 in Alzheimer's disease and MCI. *Brain and Cognition*, *69*(3), 592–9. doi:10.1016/j.bandc.2008.12.007

Vecchio, F., & Määttä, S. (2011). The use of auditory event-related potentials in Alzheimer's disease diagnosis. *International Journal of Alzheimers Disease*, *2011*(653173). doi:10.4061/2011/653173

Verleger, R., Jaśkowski, P., & Wascher, E. (2005). Evidence for an Integrative Role of P3b in Linking Reaction to Perception. *Journal of Psychophysiology*. doi:10.1027/0269-8803.19.3.165

Vidal, F., Hasbroucq, T., Grapperon, J., & Bonnet, M. (2000). Is the "error negativity" specific to errors? *Biological Psychology*, *51*(2-3), 109–128. doi:10.1016/S0301-0511(99)00032-0

Vos, S. J. B., Van Rossum, I. A., Verhey, F., Knol, D. L., Soininen, H., Wahlund, L. O., … Visser, P. J. (2013). Prediction of Alzheimer disease in subjects with amnestic and nonamnestic MCI. *Neurology*, *80*(12), 1124–1132. doi:10.1212/WNL.0b013e318288690c

Voss, M. W., Erickson, K. I., Chaddock, L., Prakash, R. S., Colcombe, S. J., Morris, K. S., … Kramer, A. F. (2008). Dedifferentiation in the visual cortex: An fMRI investigation of individual differences in older adults. *Brain Research*, *1244*, 121–31. doi:10.1016/j.brainres.2008.09.051

Wang, L. Y., Murphy, R. R., Hanscom, B., Li, G., Millard, S. P., Petrie, E. C., … Peskind, E. R. (2013). Cerebrospinal fluid norepinephrine and cognition in subjects across the adult age span. *Neurobiology of Aging*, *34*(10), 2287–92. doi:10.1016/j.neurobiolaging.2013.04.007

West, R., Schwarb, H., & Johnson, B. N. (2010). The influence of age and individual differences in executive function on stimulus processing in the oddball task. *Cortex*, *46*(4), 550–563. doi:10.1016/j.cortex.2009.08.001

Wetzel, N., Schröger, E., & Widmann, A. (2013). The dissociation between the P3a event-related potential and behavioral distraction. *Psychophysiology*, *50*(9), 920–30. doi:10.1111/psyp.12072

Wetzel, N., Widmann, A., & Schröger, E. (2011). Distraction and facilitation-two faces of the same coin? *Journal of Experimental Psychology: Human Perception and Performance*, *38*(3), 664–74. doi:10.1037/a0025856

Wild-Wall, N., Falkenstein, M., & Hohnsbein, J. (2008). Flanker interference in young and older participants as reflected in event-related potentials. *Brain Research*, *1211*, 72–84. doi:10.1016/j.brainres.2008.03.025

Wylie, S. A., Ridderinkhof, K. R., Eckerle, M. K., & Manning, C. A. (2007). Inefficient response inhibition in individuals with mild cognitive impairment. *Neuropsychologia*, *45*(7), 1408–19. doi:10.1016/j.neuropsychologia.2006.11.003

Yago, E., Corral, M. J., & Escera, C. (2001). Activation of brain mechanisms of attention switching as a function of auditory frequency change. *Neuroreport*, *12*(18), 4093–7. doi:10.1097/00001756-200112210-00046

Yago, E., Escera, C., Alho, K., & Giard, M. H. (2001). Cerebral mechanisms underlying orienting of attention towards auditory frequency changes. *Neuroreport*, *12*(11), 2583–2587. doi:10.1097/00001756-200108080-00058

Yago, E., Escera, C., Alho, K., Giard, M. H., & Serra-Grabulosa, J. M. (2003). Spatiotemporal dynamics of the auditory novelty-P3 event-related brain potential. *Cognitive Brain Research*, *16*(3), 383–390. doi:10.1016/S0926-6410(03)00052-1

Yordanova, J., Kolev, V., Hohnsbein, J., & Falkenstein, M. (2004). Sensorimotor slowing with ageing is mediated by a functional dysregulation of motor-generation processes: evidence from high-resolution event-related potentials. *Brain: A Journal of Neurology*, *127*(Pt 2), 351–362. doi:10.1093/brain/awh042

Zhang, Y., Han, B., Verhaeghen, P., & Nilsson, L.-G. (2007). Executive functioning in older adults with mild cognitive impairment: MCI has effects on planning, but not on inhibition. *Neuropsychology, Development, and Cognition. Section B, Aging, Neuropsychology and Cognition*, *14*(6), 557–70. doi:10.1080/13825580600788118

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

ANNEX I: RESUMEN

USC
UNIVERSIDADE
DE SANTIAGO
DE COMPOSTELA

El envejecimiento de la población es un problema que afecta a todo el mundo, por lo que su estudio ha ganado importancia en los últimos años, tanto para mejorar la calidad de vida de los mayores, como para reducir el alto coste que conllevan las enfermedades relacionadas con la edad (en especial aquéllas relacionadas con la demencia), dado que los mayores de 85 años muestran un ratio de demencia de alrededor del 50%.

Se ha propuesto que existe un continuo entre el envejecimiento sano y las demencias, pero la mayor parte de los investigadores opinan que si esperamos a que emerja el deterioro funcional (asociado ya a etapas iniciales de la demencia) podría ser demasiado tarde para tratar la enfermedad subyacente. Por esto, se ha puesto gran interés en estas fases pre-demencia con el objetivo de identificar síntomas clínicos de la enfermedad antes de que el deterioro sea evidente.

El concepto de deterioro cognitivo ligero (DCL) pretende identificar este estado intermedio que a menudo es una fase de transición del envejecimiento normal a la demencia. Para establecer un diagnóstico de DCL se requiere que las actividades de la vida diaria se encuentren preservadas, que no exista demencia, y que uno o más dominios cognitivos se encuentren afectados (subtipos unidominio y multidominio, respectivamente). Así, si la memoria es un dominio afectado, se pueden identificar dos subtipos de DCL amnésico (DCLa): DCLa unidominio (DCLau) y DCLa multidominio (DCLam). Si la memoria no es un dominio afectado, pueden ser identificados otros dos subtipos de DCL no amnésico (DCLna): DCLna unidominio (DCLnau) y DCLna multidominio (DCLnam).

Se ha observado que los subtipos no amnésicos del DCL experimentan un riesgo mayor de desarrollar demencias distintas de la Enfermedad de Alzheimer (EA), mientras que los subtipos amnésicos sufren un mayor riesgo de desarrollar EA. Diversos estudios han sugerido además que los pacientes con DCL multidominio muestran un riesgo mayor de progresar a demencia que aquéllos con DCL unidominio.

La EA es la forma más común de demencia, y se asocia a un estado de dependencia de alto coste no solo social, sino también económico y psicológico, siendo por lo tanto un problema social y sanitario de primer orden. Por esto, la identificación de personas con DCL posibilitaría enfrentar la enfermedad incluso desde estadios prodrómicos.

Los biomarcadores son parámetros que reflejan características específicas de procesos fisiopatológicos relacionados con una enfermedad, e idealmente deben ser

no invasivos, de uso sencillo y de bajo coste. El EEG cumple los requisitos para proporcionar buenos biomarcadores, y concretamente la técnica de los potenciales evocados (PEs) ha demostrado ser útil en la identificación de biomarcadores de la EA y el DCL. Esta técnica muestra una alta resolución temporal, con lo que permite evaluar la actividad eléctrica cerebral asociada a distintos procesos cognitivos que se producen en rangos temporales del orden de milisegundos.

Los correlatos electrofisiológicos de los procesos relacionados con el procesamiento voluntario del estímulo atendido (objetivo) son los componentes N2b y P3b, clásicamente identificados cuando se emplea el paradigma *oddball* (en el que se debe atender a un estímulo objetivo infrecuente para identificarlo, y no se emite respuesta ante un segundo tipo de estímulo frecuente), aunque pueden elicitarse con otras tareas, como las *Go/NoGo* (se debe responder a un tipo de estímulo frecuente [condición *Go*] mientras se inhibe la respuesta ante otro tipo de estímulo infrecuente [condición *NoGo*]).

En la tarea *Go/NoGo* se han identificado dos componentes de los PEs en relación con el estímulo, en la condición *Go:* el componente N2b (o Go-N2), relacionado clásicamente con la evaluación activa de un cambio en la estimulación en la memoria de trabajo, y el componente P3b (o Go-P3), asociado con la actualización del esquema del contexto representado en la memoria de trabajo, cuando aparece un estímulo que encaja con las representación mental del estímulo relevante para la tarea y no encaja con la del estímulo previo (frecuente o estándar).

Tanto el componente N2b como el P3b han probado ser útiles para diferenciar a pacientes con EA de adultos sanos usando diversas tareas, siendo a menudo sus latencias mayores en el grupo diagnóstico que en el control, aunque los resultados no son concluyentes. Además, mientras algunos estudios han informado de menores amplitudes de P3b en los pacientes con EA que en los adultos sanos (aunque otros no encontraron diferencias entre grupos), la amplitud de N2b no suele mostrar diferencias entre EA y control.

Solo un estudio ha analizado estos componentes usando una tarea *Go/NoGo*, observando menor amplitud de P3b en el grupo con EA, resultado interpretado por los investigadores como evidencia de un declive en los generadores del componente, o un déficit ya en el procesamiento sensorial temprano.

Los componentes N2b y P3b también se han estudiado con tareas *oddball* en participantes con DCL. Los resultados son contradictorios, dado que a menudo las

latencias de ambos componentes son mayores en los adultos con DCL que en los adultos sanos, pero algunos estudios no han encontrado dichas diferencias. En cuanto a la amplitud de N2b, la mayor parte de los estudios no han encontrado diferencias entre grupos, aunque algunos observaron mayores amplitudes en los participantes con DCL que en los participantes del grupo Control. Por último, la amplitud de P3b ha mostrado ser menor en los grupos con DCL que en los adultos sanos, aunque algunos estudios no encontraron diferencias entre grupos.

Las discrepancias entre los resultados mencionados podrían deberse a distintos factores, como los criterios de inclusión y exclusión de los participantes (medicación, tipo de tests utilizados en la evaluación neuropsicológica…).

A nuestro conocimiento, no existe ningún estudio que haya evaluado estos componentes de los PEs en muestras de adultos con DCL con una tarea *Go/NoGo*.

Por otra parte, en la condición *NoGo* de una tarea *Go/NoGo* se han identificado otros dos componentes, NoGo-N2 y NoGo-P3. Aunque su significado funcional aún es tema de debate, ambos componentes se han relacionado con la inhibición de una respuesta prepotente.

Solo un estudio ha evaluado el componente NoGo-P3 en pacientes con EA usando una tarea *Go/NoGo*, encontrando menores amplitudes en los participantes con EA que en los controles sanos, tanto en la condición *Go* como en la condición *NoGo*, mientras que la latencia de P3 no diferenció entre grupos. Los autores interpretaron esto como una posible afectación de los generadores comunes a P3b y NoGo-P3 en la EA. Ningún estudio ha evaluado el componente NoGo-N2 en pacientes con EA, ni los componentes NoGo-P3 y NoGo-N2 en adultos con DCL.

La tarea *Go/NoGo* también permite el estudio de la actividad cortical asociada a la respuesta motora, ya que requiere la emisión de respuestas manifiestas (*vs*. encubiertas). El potencial de preparación lateralizado relacionado con el estímulo (sLRP) y con la respuesta (rLRP), son dos componentes que reflejan procesos de selección y preparación de la respuesta, respectivamente. Recientemente se ha evaluado el rLRP con una tarea de compatibilidad estímulo-repuesta (*SRC*), en las que los participantes debían responder a una característica del estímulo mientras ignoraban otra. La amplitud del rLRP fue menor en los adultos con aMCI que en los mayores sanos, lo que fue considerado por los autores como reflejo de un declive en el control motor en los primeros. Además, este parámetro podría ser un biomarcador

útil para el DCLa, ya que mostró valores de sensibilidad y especificidad por encima de 0,82.

Ni el sLRP ni el rLRP han sido avaluados en pacientes con EA, y ningún otro estudio ha evaluado estos componentes en participantes con DCL utilizando tareas *Go/NoGo* u otras (a excepción de los estudios de Cespón et al. (2013, 2015)).

En el presente trabajo, se diseñó una tarea auditivo-visual de atención-distracción, basada en la diseñada por Escera et al. (1998), para evaluar los componentes mencionados previamente, y por lo tanto los procesos relacionados con los mismos, en adultos con DCLa. Esta tarea incluye una tarea *oddball* pasiva y una tarea *Go/NoGo* activa.

En La tarea A-V se presenta un par de estímulos en cada ensayo (uno auditivo y uno visual, separados por 300 ms). Los estímulos auditivos fueron tonos puros frecuentes de 1000 Hz (Estándar), tonos puros infrecuentes de 2000 Hz (Discrepantes) y sonidos distintos cada vez (Novedosos), que era necesario ignorar. Por su parte, los estímulos visuales fueron números y letras (ante los que había que presionar un botón distinto en cada caso [*Go*]; cada tipo aparece en un 33% de los ensayos) y triángulos (ante los que se debía inhibir la respuesta, apareciendo en un 34% de los ensayos).

Estudios previos utilizaron diversas variaciones de la tarea A-V diseñada por Escera et al. (1998) para estudiar, en participantes jóvenes, la captura atencional producida por los estímulos auditivos novedosos y/o discrepantes irrelevantes (con respecto a los estándar), y cómo esta captura puede afectar a la ejecución de la tarea visual relevante.

El resultado típico de estas tareas consiste en un alargamiento de los tiempos de reacción (TRs) en las condiciones Novedosa (aquélla en la que el estímulo auditivo que precede al visual es de tipo novedoso) y Discrepante (el estímulo auditivo del par auditivo-visual es discrepante) con respecto a la condición Estándar (el estímulo auditio es del tipo estándar). Este aumento del tiempo de reacción se ha calificado como un efecto de la distracción que produce la estimulación auditiva irrelevante novedosa (o discrepante), consecuencia de la orientación involuntaria de la atención hacia esos estímulos.

Los estudios que han investigado estos efectos previamente, no se han centrado en evaluar cómo la captura atencional puede afectar al procesamiento del estímulo visual relevante, más allá de los datos conductuales. Solo dos estudios evaluaron el efecto de la captura atencional sobre la amplitud del componente P3b, y solo uno

sobre la amplitud de N2b, mostrando que ambas son mayores en la condición Novedosa que en la condición Estándar. El significado de estos resultados todavía no están claro.

Además, estos estudios no suelen incluir una condición *NoGo* que permita estudiar los componentes NoGo-N2 y NoGo-P3, con lo que estos componentes nunca fueron evaluados usando esta tarea, y no se conocen estudios que los hayan evaluado en participantes con DCLa en ningún tipo de tarea *Go/NoGo*. De forma similar, los componentes sLRP y rLRP tampoco fueron evaluados en estudios anteriores con esta tarea, y apenas han sido estudiados con otras en adultos con DCLa.

Dos estudios han utilizado la tarea A-V comparando la ejecución de participantes jóvenes con la de participantes mayores sanos, demostrando que en los últimos también se observa un efecto de la captura atencional producida por la estimulación irrelevante novedosa, con respecto a la estándar (mayores TRs en la condición Novedosa que en la condición Estándar). Sin embargo, ningún estudio utilizó esta tarea para evaluar componentes de los PEs en participantes mayores.

Utilizando diferentes tareas, se ha observado que el envejecimiento se asocia con aumentos en las latencias de N2b y P3b y reducciones en la amplitud de P3b. Utilizando diferentes variaciones de la tarea *Go/NoGo*, diversos estudios mostraron que tanto el componente NoGo-N2 como el NoGo-P3 reflejan declives relacionados con la edad, con menores amplitudes y mayores latencias en los participantes mayores.

Algunos estudios evaluaron efectos de la edad en el sLRP y el rLRP, pero ninguno utilizó alguna variación de la tarea *Go/NoGo*. Ambos componentes muestran de forma consistente reducciones en la amplitud relacionados con el envejecimiento, aunque todavía no está claro a qué es debido. Por otra parte, mientras el rLRP muestra un enlentecimiento relacionado con la edad de forma habitual, los resultados en cuanto al sLRP son contradictorios. La interacción de los efectos del envejecimiento sano con la captura atencional en estos componentes es aún desconocida.

Se evaluaron cuatro componentes más, observados en los trazados directos de los PEs en relación con la respuesta, en los participantes adultos sanos (incluyendo grupos de jóvenes, de mediana edad y de mayores). Los componentes CRN y preRFP han sido caracterizados en jóvenes, mayores sanos y adultos con DCLa (aunque nunca utilizando una tarea *Go/NoGo*), y se han relacionado con procesos de control de la

respuesta, aunque su significado funcional todavía no está totalmente claro. Estos procesos han probado estar deteriorados en el envejecimiento normal. Además, el componente preRFP, elicitado con una tarea *SRC*, ha demostrado ser un potencial biomarcador del subtipo DCLam. El componente postRFP habitualmente aparece junto a CRN y preRFP, al igual que el componente parietalRP. Estos componentes han sido descritos únicamente en estudios con participantes jóvenes, pero se desconoce su significado funcional.

La gran escasez de datos en cuanto a estos componentes los convierte en una herramienta muy interesante para estudiar procesos por ahora desconocidos en jóvenes, pero también en el envejecimiento sano y, en el futuro, podrían contribuir a la búsqueda de biomarcadores del DCL.

Así, la presente tesis doctoral tiene como objetivo evaluar los procesos enumerados previamente en una muestra de adultos sanos jóvenes, de mediana edad y mayores. El Estudio 1 examinó las diferencias entre estos 3 grupos en las amplitudes y latencias de los componentes N2b y P3b (relacionados con la evaluación y categorzación del estímulo *target* en la memoria de trabajo), en la amplitud y latencia *onset* de los componentes sLRP y rLRP (relacionados con la selección y preparación motora), y en la ejecución conductual. Además de los efectos de la edad, en el Estudio 1 se pretendía analizar las diferencias en estos parámetros entre las condiciones Novedosa y Estándar, y las posibles interacciones de los efectos de la edad y de la captura de la atención.

De igual forma, en el Estudio 2 se evaluaron los efectos de la edad y la captura atencional en otros procesos relacionados con el control y evaluación de la respuesta. Así, se estudiaron (en participantes jóvenes, de mediana edad y mayores) las amplitudes y latencias de los correlatos neurales de estos procesos (CRN y preRFP), y se exploraron otros dos componentes relativamente desconocidos (parietalRP y postRFP).

Por último, los componentes N2b, P3b, NoGo-N2, NoGo-P3, sLRP y rLRP, así como el TR y las respuestas correctas, fueron analizadas en el Estudio 3 y Estudio 4 en relación al DCLa con el fin de obtener marcadores psicofisiológicos y conductuales de este estado.

Como se esperaba, en los Estudios 1 y 2 del presente trabajo, se observaron mayores TRs en los participantes de mediana edad y mayores con respecto a los jóvenes, sin diferencias entre grupos para el porcentaje de respuestas correctas. Esto

parece indicar que se produce un enlentecimiento de la velocidad de la respuesta mientras se mantienen los niveles de éxito en la ejecución. Estos resultados apoyan la idea de que existe un enlentecimiento progresivo relacionado con la edad, con el fin de mantener la precisión. Además, el envejecimiento se asoció con un enlentecimiento del procesamiento del estímulo *target* (mayores latencias de N2b y P3b) y de la selección y preparación de la respuesta motora correspondiente (mayores latencias *onset* de sLRP y rLRP).

Se identificaron cuatro componentes de los PEs relacionados con la respuesta, relativamente desconocidos, en los trazados directos, en adultos jóvenes, de mediana edad y mayores: CRN, preRFP, postRFP, and parietalRP. Las latencias de preRFP, postRFP y parietalRP aumentaron significativamente con el aumento de la edad, poniendo en evidencia un progresivo enlentecimiento relacionado con la edad en la implementación de los procesos de control cognitivo implicados en la respuesta (preRFP), y de los procesos tardíos de integración implicados en las decisiones sobre el grado de corrección de la respuesta (postRFP y parietalRP).

Además, las latencias interpico evaluadas (P3b-preRFP, preRFP-parietalRP y parietalRP-postRFP) también fueron mayores en los participantes mayores y de mediana edad que en los jóvenes, apoyando la hipótesis de que existe una tendencia relacionada con la edad hacia un procesamiento más serial.

El complejo relacionado con la respuesta parece reflejar etapas diferentes de procesamiento (aunque tal vez relacionadas) de las indicadas por el clásico componente P3b relacionado con el estímulo, ya que ambos se ven afectados de formas diferentes por las manipulaciones experimentales, y su morfología y latencias son considerablemente diferentes en participantes jóvenes, de mediana edad y mayores.

En el presente trabajo, se ha evaluado por primera vez la captura atencional producida por los estímulos auditivos novedosos irrelevantes con respecto a los estímulos auditivos estándar, sobre los potenciales evocados relacionados con el procesamiento del estímulo visual relevante y con la respuesta, en participantes de mediana edad y mayores.

Esta captura de la atención se asoció con un efecto de la distracción en los tres grupos bajo estudio (Jóvenes, Mediana edad y Mayores), con mayores TRs, mayor tiempo de categorización del estímulo en la memoria de trabajo (mayores latencias de P3b), y mayor tiempo de selección de la respuesta (mayor latencia *onset* del

sLRP). En la condición Novedosa también se observó un efecto de facilitación en la preparación de la respuesta (latencia *onset* del rLRP más temprana) y un aumento del *arousal* global (amplitudes mayores de todos los componentes de los PEs analizados, excepto la amplitud de N2b en el grupo Mayores).

El efecto de distracción se observó también en los dos grupos de mayor edad (Mediana edad y Mayores), en cuanto a los procesos de evaluación del estímulo en memoria de trabajo (mayor latencia de N2b en la condición Novedosa que en la condición Estándar), pero no se observó en el grupo Jóvenes. Este resultado refleja una modulación relacionada con la edad del efecto de distracción en la evaluación del estímulo *target* en memoria de trabajo, con un enlentecimiento del proceso que parece afectar a personas de 50 años en adelante, sin diferencias entre adultos de mediana edad y mayores. Además, la latencia de la onda postRFP también mostró un efecto de la distracción, pero solo en el grupo Mediana edad. Este tipo de efecto de la distracción podría deberse a cambios relacionados con la edad en las redes neurales que generan este componente, con el fin de mantener niveles aceptables de ejecución cognitiva.

En cuanto a los estudios con DCLa (estudios 3 y 4 del presente trabajo), los participantes DCLam mostraron un déficit conductual y neurocognitivo con respecto a los grupos DCLau y Control, reflejado en las respuestas correctas y en los TRs, al igual que en los recursos neurales disponibles para la selección de la respuesta, respectivamente. Los TRs y el porcentaje de respuestas correctas fueron similares en los participantes DCLau y Control, aunque a expensas de un enlentecimiento específico en el tiempo requerido para seleccionar la respuesta apropiada en los primeros, lo que podría interpretarse como un signo de mecanismos compensatorios o un indicador temprano de un declive en el control motor.

Además, las amplitudes de N2b y NoGoN2 fueron menores en los adultos DCLa que en los control, reflejando también un déficit en la evaluación del estímulo *target* y en el control inhibitorio de la respuesta, respectivamente.

Se identificaron varios marcadores potenciales. El mejor biomarcador para diferenciar a los participantes DCLau solo de los participantes DCLam, y de los DCLam y los control fue la latencia a pico del sLRP, con una sensibilidad y especificidad mayores de .67.

La mejor combinación de marcadores para discriminar a los participantes DCLam de los control únicamente, y de los DCLau y los control fue la combinación del

TR y el porcentaje de respuestas correctas, con una sensibilidad y especificidad por encima de .82. El mejor parámetro para discriminar a los participantes DCLau de DCLam fue la combinación de la latencia a pico del sLRP y el porcentaje de respuestas correctas, con unos valores de sensibilidad y especificidad de 1.00 y .88, respectivamente.

En estudios futuros se estudiarán, con el objetivo de obtener nuevos biomarcadores del DCL (1) los componentes CRN, preRFP, postRFP y parietalRP en adultos con DCLa, (2) las diferencias entre adultos con aMCI y adultos sanos mediante parámetros de conectividad funcional (basada en las teorías de grafos), y (3) datos procedentes de una segunda evaluación, dado que estos estudios se enmarcan en un proyecto de carácter longitudinal, con el fin de observar la evolución de los participantes y poner a prueba el valor predictivo de los parámetros evaluados en los presentes estudios.