TESIS DE DOCTORADO

STUDY FOR THE IDENTIFICATION OF PSYCHOPHYSIOLOGICAL MARKERS OF HEALTHY AGING AND MILD COGNITIVE IMPAIRMENT

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AUTORIZACIÓN DOS DIRECTORES DA TESE

**"Study for the identification of psychophysiological markers of
healthy aging and mild cognitive impairment"**

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"Study for the identification of psychophysiological markers of healthy aging and mild cognitive impairment"

Dña. Kenia Shaily Correa Jaraba

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ASPECTOS ÉTICOS DE LA TESIS

"Study for the identification of psychophysiological markers of healthy aging and mild cognitive impairment"

El proyecto de investigación en el que se engloba la presente tesis doctoral, fue aprobado por el Comité Ético de Investigación Clínica de Galicia (Xunta de Galicia, España) y el estudio fue realizado de acuerdo con las normas éticas establecidas en la declaración de Helsinki de 1964.

Dado que se trata de un proyecto de longitudinal, los códigos de los informes favorables de la Red Gallega de Comités de Ética de Investigación que ocurrieron en el tiempo, son los siguientes: 2006/042; 2007/259; 2010/075; 2013/553; 2017/498.
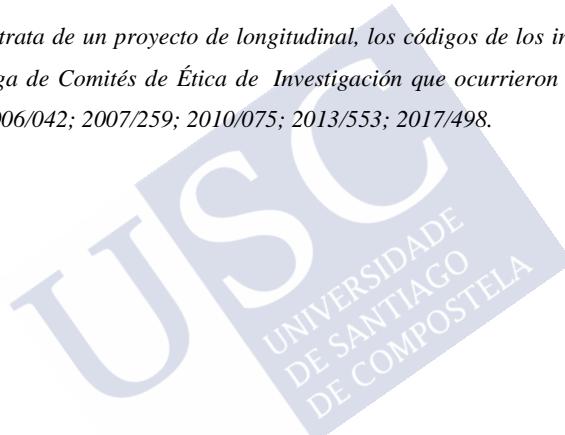
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"Everyone you meet is fighting a battle you know nothing about. Be kind. Always."
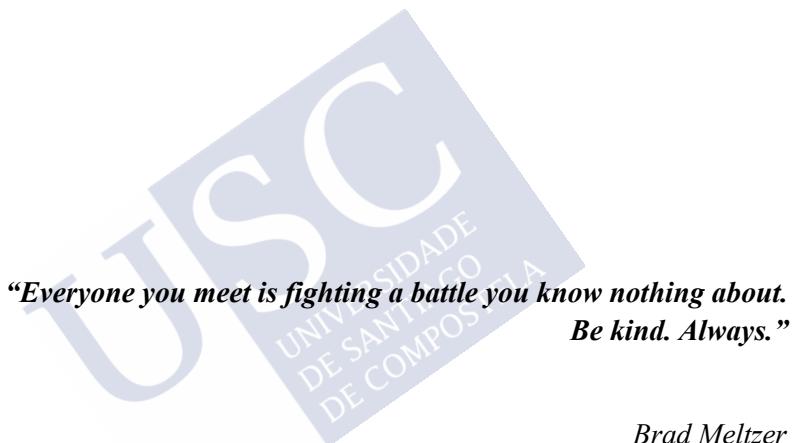
Brad Meltzer

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GLOSSARY OF ABBREVIATIONS

AA: Alzheimer's association

Aβ: Amyloid beta

AD: Alzheimer's disease

ADHD: Attention deficit-hyperactivity disorder

APOE: Apolipoprotein E

AUC: Area under the curve

A-V: Auditory-visual

A-V task: Auditory-visual distraction-attention task

CG: Control group

CRN: Correct-related negativity

CSF: Cerebrospinal fluid

D: Deviant

D: Discrepante

D-E: Discrepante *menos* estándar

DCL: Deterioro cognitivo ligero

> DCLa: Deterioro cognitivo ligero amnésico

> DCLau: Deterioro cognitivo ligero amnésico unidominio

> DCLam: Deterioro cognitivo ligero amnésico multidominio

> DCLnau: Deterioro cognitivo ligero no amnésico unidominio

> DCLnam: Deterioro cognitivo ligero no amnésico multidominio

D-S: Deviant *minus* standard

E: Estándar

EA: Enfermedad de Alzheimer

EEG: Electroencephalogram; Electroencefalografía

e-P3a: Early-P3a

ERPs: Event-related potentials

IIE: Intervalo interestímulo

ISI: Interstimulus interval

l-P3a: Late-P3a

MCI: Mild cognitive impairment

> aMCI: Amnestic mild cognitive impairment

> naMCI: Non-amnestic mild cognitive impairment

sdaMCI: Single-domain amnestic mild cognitive impairment

mdaMCI: Multi-domain amnestic mild cognitive impairment

sdnaMCI: Single-domain non-amnestic mild cognitive impairment

mdnaMCI: Multiple-domain non-amnestic mild cognitive impairment

MMN: Mismatch negativity

MRI: Magnetic resonance imaging

N: Novedoso

N: Novel

N-E: Novedoso *menos* estándar

N-S: Novel *minus* standard

NIA: The national institute on aging

NMDA: N-methyl-D-aspartate

parietalRP: Parietal response positivity

PEs: Potenciales evocados

PET: Positron emission tomography

postRFP: Post-response frontal positivity

preRFP: Pre-response frontal positivity

PSW: Positive slow wave

rLRP: Response-locked lateralized readiness potential

RMf: Resonancia magnética funcional

RON: Reorienting negativity

RT: Reaction time

S: Standard

sLRP: Stimulus-locked lateralized readiness potential

STAC: Scaffolding theory of aging and cognition

TR: Tiempo de reacción
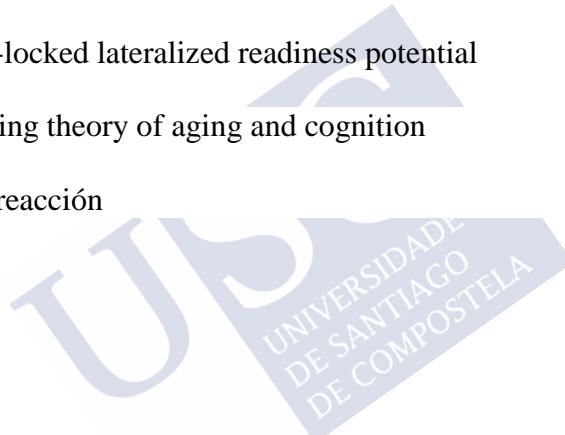
1. INTRODUCTION

The proportion of elderly people in the population has increased significantly in recent decades as a result of the increased life expectancy and low birth rates in developed countries (Bloom & Luca, 2016). As a consequence, there is also an increase in the incidence of aging-associated diseases, which affect many organs and systems, particularly the nervous system (Murman, 2015; Niccoli & Partridge, 2012).

The prevalence of diseases that damage the brain and affect cognition increases greatly with advancing age. These include cardiovascular disease and diabetes as well as neurodegenerative diseases such as multiple sclerosis, Parkinson's disease, frontotemporal dementia, and Alzheimer's disease (AD) (Feinkohl, Price, Strachan, & Frier, 2015; Leritz, McGlinchey, Kellison, Rudolph, & Milberg, 2011; Murman, 2015).

The different types of dementia are the most common cause of significant cognitive decline in older adults (Murman, 2015), with approximately 44.4 million people affected worldwide in 2013. This number is expected to reach 75.6 million by 2030 and 135.5 million by 2050, with the increase mainly occurring in developing countries (Chang, Patel, & Schulz, 2015). AD is the most common form of dementia, followed by vascular dementia and Lewy body dementia (Sonnen et al., 2007). AD is regarded as a progressive, unremitting and neurodegenerative disease with a relatively long asymptomatic premorbid period (Caselli et al., 2004). The average duration of illness is 8–10 years, but the clinical symptomatic phases are preceded by preclinical and prodromal stages that typically extend over two decades (Masters et al., 2015). AD has a profound impact on the quality of life of the patients, their families and caregivers, as well as a

strong economic impact (Sosa-Ortiz, Acosta-Castillo, & Prince, 2012; Vellone, Piras, Talucci, & Cohen, 2008; Wimo, Jönsson, Bond, Prince, & Winblad, 2013).

Accurate and early diagnosis of AD is a major public health concern. Although cognitive symptoms may not be obvious, the premorbid period is characterized by abnormal accumulation of plaques of amyloid beta-protein (Aβ) in extracellular spaces and blood vessel walls, as well as aggregation of the microtubule tau protein in neurofibrillary tangles in neurons (Buerger et al., 2006; Masters et al., 2015). These alterations are particularly evident in brain areas such as the hippocampus and entorhinal cortex (Angulo et al., 2017), which are crucial for the functional cooperation of distant brain regions (Delbeuck, Van der Linden, & Collette, 2003; Drzezga et al., 2011).

Currently, the only way of conclusively diagnosing AD is by post-mortem inspection of the anatomopathological alterations in the brain (Herrup, 2010; Pietrzak, Czarnecka, Mikiciuk-Olasik, & Szymanski, 2018). However, as AD begins years, and possibly even decades, before the onset of clinical symptoms (Ritchie, Ritchie, Yaffe, Skoog, & Scarmeas, 2015; Sperling et al., 2011), AD research has (logically) focused on the reliable detection of early signs that precede the functional and cognitive impairment characterizing the disease (Poil et al., 2013). Early stage identification may help in the development of effective interventions to prevent AD from occurring, slow down AD progression once it occurs and to provide better care and support for patients, their families, and caregivers. However, normal aging is also characterized by a slow decline of cognitive functions, and it can therefore be difficult to disentangle normal cognitive aging from very early stage AD (Poil et al., 2013).

For patients who develop AD, the onset of cognitive decline is subtle and difficult to determine (Murman, 2015). Clinically, most patients first develop mild cognitive impairment (MCI), a condition defined as a transitional state between healthy aging and the clinical onset of dementia (Albert et al., 2011; Petersen et al., 1999).

1.1. MILD COGNITIVE IMPAIRMENT (MCI)

1.1.1. Definition and diagnostic criteria

MCI is a syndrome characterized by objective evidence of cognitive decline, with no notable impairment in the performance of daily activities. As mentioned above, it is considered an intermediate stage between the cognitive changes associated with healthy aging and early clinical features of dementia (Petersen, 2004; Petersen et al., 1999, 2001, 2009, 2014; Winblad et al., 2004).

Petersen et al. (1999) initially proposed five criteria for the diagnosis of MCI: (1) subjective reports of memory complaints, (2) objective memory disorder, (3) normal activities of daily living, (4) normal general cognitive functioning, and (5) absence of dementia. However, later research led to the proposal of more expansive criteria for MCI, including cognitive domains other than memory, and MCI was thereafter considered a prodromal state of different types of dementia (Petersen et al., 2001, 2009; Winblad et al., 2004).

Beyond discussions on the nosological status of MCI, four MCI subtypes are currently recognized (see Figure 1) on the basis of (1) the presence (amnestic MCI: aMCI) or absence (non-amnestic MCI: naMCI) of memory impairment, and (2) the number of cognitive domains affected, as impairment of either single or multiple cognitive domains may occur in both subtypes (aMCI *versus* naMCI) (Petersen et al., 2001, 2009; Winblad et al., 2004):

1) Single-domain amnestic MCI (sdaMCI), with normal general cognitive performance and only memory impairment.
2) Multiple-domain amnestic MCI (mdaMCI), with memory impairment and impairment in other additional cognitive domains.
3) Single-domain non-amnestic MCI (sdnaMCI), characterized by preserved memory but an overt decline in another cognitive domain; and

4) Multiple-domain non-amnestic MCI (mdnaMCI), characterized by preserved memory but with evidence of decline in several cognitive domains.
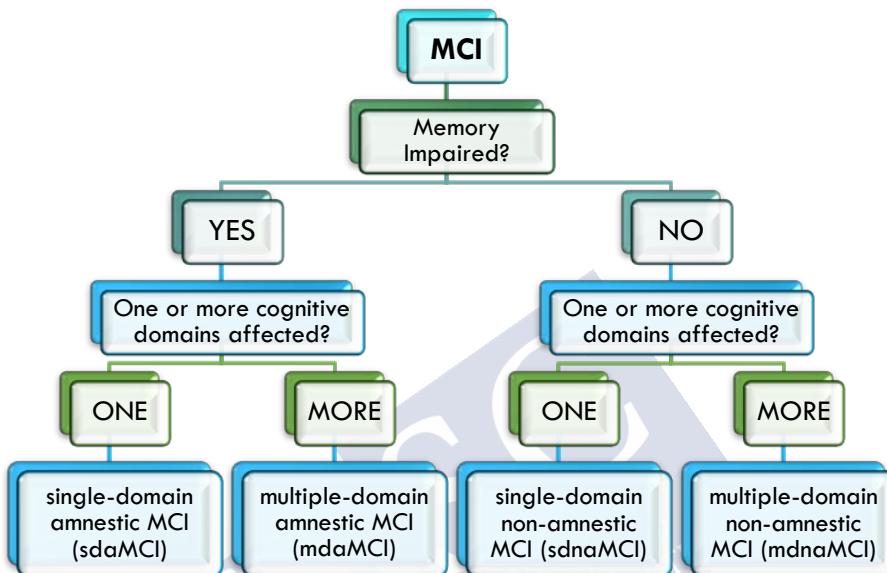
Figure 1. Classification of mild cognitive impairment (MCI).

People with aMCI are usually characterized by some impairment of episodic memory (the capacity to consciously remember past experiences, Tulving, 2002) and other markers that in some way predict the criteria that characterize AD, such as cholinergic dysfunction, white matter lesions, reduced volume of the hippocampus, parahippocampal gyrus and cingulate cortex, abnormal accumulation of tau (tangles) and Aβ protein (plaques), and the presence of one or two ε4 alleles of the apolipoprotein E (APOE) gene (Albert et al., 2011; Gauthier et al., 2006; Plancher, Tirard, Gyselinck, Nicolas, & Piolino, 2012; Richter et al., 2017).

In 2011, the National Institute on Aging (NIA) and the Alzheimer's Association (AA) convened work groups to revise the

diagnostic criteria for the symptomatic predementia stage of AD, referring to it as "MCI due to AD" (Albert et al., 2011). Two sets of criteria were established for the diagnosis: first, a set of core clinical criteria, similar to those previously proposed by other researchers, such as Petersen et al. (1999, 2001) and Winblad et al. (2004), and a second set of criteria that include the use of biomarkers based on cerebrospinal fluid (CSF) measurements and neuroimaging techniques, although the authors point out several of the limitations still existing in the interpretation and use of these criteria (for a review see Albert et al., 2011 and Petersen, 2016).

1.1.2. Prevalence of MCI and rate of conversion to Alzheimer's disease (AD)

Data on the prevalence of MCI are inconsistent, probably due to the use of different diagnostic criteria and sampling methods and to the methodological variation across studies. Available evidence indicates that between 12% and 18% of adults aged over 60 years, without dementia, are affected by MCI (Petersen, 2016), with the amnestic subtype being the most common.

The Mayo Clinic Study of Aging found that the prevalence of MCI increases with age (Petersen et al., 2010). Additionally, some studies suggest that female gender may be an important risk factor for the development of AD and aMCI (Gao et al., 2018; Mielke, Vemuri, & Rocca, 2014). Furthermore, some additional risk factors include lower educational level, APOE ε4 genotype, and vascular risk factors (Petersen, 2011, 2016; Petersen et al., 2010; Tampi, Tampi, Chandran, Ghori, & Durning, 2015).

Petersen (2011) also suggested that the aMCI subtype is more common than the naMCI subtype, with respective prevalence rates of 11.1% and 4.9%. Moreover, non-amnestic subtypes have been found to be at a greater risk to developing types of dementia other than those related to AD, such as vascular dementia, frontotemporal dementia and Lewy body dementia (Howe, 2014; Roberts & Knopman, 2013;

Vos et al., 2013), while people with the aMCI subtype display symptoms that indicate possible progression to AD, but that do not interfere with daily living (Dubois & Albert, 2004; Fisk & Rockwood, 2005; Petersen, 2004; Petersen et al., 2014).

There are some discrepancies regarding the rate of conversion from MCI to AD (for a review see Michaud, Su, Siahpush, & Murman, 2017). In some studies, the annual conversion rate of MCI to AD has been reported to be between 10 and 15% (Morris et al., 2001), while other studies have reported higher conversion rates of between 30 and 40% (Brambati et al., 2009; Geslani, Tierney, Herrmann, & Szalai, 2005). This discrepancy may due to several factors, such as the diagnostic criteria used and the different follow-up periods. Furthermore, not all subjects with MCI will develop AD or dementia; some will remain stable or even return to normal cognition (Michaud et al., 2017; Roberts et al., 2014).

Additionally, several follow-up studies have demonstrated that individuals with the mdaMCI subtype have a more elevated risk of conversion to AD, with an annual conversion rate of approximately 30%, than those individuals with sdaMCI subtype, with a conversion rate of 9% (Fischer et al., 2007; Michaud et al., 2017; Mitchell, Arnold, Dawson, Nestor, & Hodges, 2009; Tabert et al., 2006).

1.1.3. Event-related potentials (ERPs) as a tool for identifying MCI biomarkers

The current diagnostic criteria for MCI include the presence of biomarkers (Albert et al., 2011; Petersen, 2016). Jack et al. (2011) defines biomarkers as parameters (physiological, biochemical, anatomic) that can be measured in vivo and that reflect specific features of disease-related pathophysiological processes. The identification of MCI biomarkers could help clinicians to make objective diagnoses, thus allowing early or pre-symptomatic identification of AD, aiding treatment decisions, monitoring disease

progress, and providing opportunities for preventing the disease via population screening (Henry et al., 2013).

The Working Group on Molecular and Biochemical Markers of AD (1998) specified that an ideal biomarker should be able to detect the neuropathology and must be validated in neuropathologically confirmed cases, but that it also should be precise, reliable, reproducible, non-invasive, simple to perform and inexpensive. The biomarkers proposed by Albert et al. (2011) for detecting MCI require the application of invasive and/or relatively expensive methods (e.g. lumbar puncture to obtain cerebrospinal fluid [CSF] for analysis, positron emission tomography [PET], and magnetic resonance imaging [MRI]), which, moreover, have not yet been standardized for use in routine clinical practice (Jack et al., 2011; Petersen, 2016). However, these authors do not contemplate other techniques, such as the event-related brain potential (ERP) technique, which has been shown to be useful in the search for MCI biomarkers (Cespón, Galdo-Álvarez, & Díaz, 2015; Cid-Fernández, Lindín, & Díaz, 2014a, 2017a, 2017b; for a review, see Jackson & Snyder, 2008; Vecchio & Määttä, 2011).

The ERP technique is non-invasive, simple to apply and inexpensive (Rossini et al., 2006). ERPs are voltage fluctuations in an ongoing electroencephalogram (EEG) that are time locked to sensory, motor or cognitive events (e.g. the presentation of an image or sound) and reflect coordinated neural network activity in the brain (Friedman, Cycowicz, & Gaeta, 2001; Hua-Hall, 2016). When event-related EEG epochs are averaged, the resulting averaged waveform consists of a sequence of positive and negative voltage deflections, which are considered components of changes in brain electrical activity that have a (relatively) stable temporal relationship with an event (Luck, 2005). Moreover, this technique has a high temporal resolution and enables the study of neurophysiological correlates of different stages of information processing. For example, it enables study of sensory-perceptive and pre-attentive processes, the integrity of which is essential for the efficient functioning of higher-level processes and

thus for the final performance. The ERP technique is therefore an ideal candidate for use in the search for psychophysiological markers of MCI, although it has a lower spatial resolution than other techniques such as MRI and PET (Luck, 2005).

With the aim of identifying aMCI psychophysiological markers, changes in ERP components associated with the involuntary capture of attention provoked by irrelevant auditory stimuli were compared in aMCI adults and healthy adults in the research reported in this doctoral thesis.

1.2. INVOLUNTARY CAPTURE AND REORIENTING OF ATTENTION

The ability to distinguish relevant and irrelevant information is essential in daily living and is a prerequisite for flexible adapted behaviour. Voluntary attention allows us to perform tasks successfully by selecting relevant stimuli from among the abundant sensory information that we receive (Horváth, Czigler, Birkás, Winkler, & Gervai, 2009). On the other hand, involuntary attention is engaged when new, potentially relevant events appear outside of the actual attentional focus (Escera, Corral, & Yago, 2002). Normal functioning of the cognitive system is characterized by equilibrium between these two processes (Escera et al., 2002), and its efficacy is reflected in the reaction time (RT) costs associated with processing task-relevant information (Berti, 2013). The magnitude of the RT cost is commonly considered a measure of the degree of distraction caused by irrelevant information (Berti, 2013; Berti & Schröger, 2004), and it is assumed that the effectiveness of the balance between task demands and processing distracting information is reflected by a smaller distraction effect (Berti, 2013). However, this balance may be altered in aging (Horváth et al., 2009).

Some authors have noted a decline in the selective promotion of relevant stimuli and inhibition of irrelevant stimuli in older adults, who are thus particularly susceptible to the distraction effect (Hasher,

Lusitg, & Zacks, 2007; Weeks & Hasher, 2014). For example, the presentation of irrelevant distracting stimuli may have a greater impact on task performance in older adults than in young adults, as the older adults are less able to control their attention and thus prevent being distracted by the irrelevant stimuli. This may result in delayed RT, decreased reading comprehension, disrupted problem solving and reduced memory for target information (Andrés, Parmentier, & Escera, 2006; Getzmann, Gajewski, & Falkenstein, 2013; Kramer & Madden, 2008). Greater sensitivity to distraction in old people has been related to lowered efficiency of inhibitory processes as a consequence of a decline in frontal lobe cognitive function (Hasher et al., 2007; Span, Ridderinkhof, & van der Molen, 2004).

In addition, some authors also suggest that adults with MCI display difficulties in inhibiting distractor stimuli and attention/task-switching, with worse overall performance relative to healthy adults, as reflected by longer RTs and fewer correct responses (Aurtenetxe et al., 2016; Wang et al., 2013; Wylie, Ridderinkhof, Eckerle, & Manning, 2007). However, other authors conclude that the most sensitive aspect of attentional control is the capacity to resist distraction and rapidly switch attention, and that the ability to sustain attention also deteriorates in AD (Perry, Watson, & Hodges, 2000).

For characterization of aMCI, we believe that understanding the changes that occur in the electrical activity of the brain associated with the controlled processing of the relevant stimuli in a task is important. But we also consider of great interest to evaluate the activity associated with the automatic and involuntary processing of irrelevant stimuli, given that involuntary attention to irrelevant stimuli can greatly affect processing of the relevant stimuli and thus the final performance (Berti, 2012, 2013).

To explain the brain mechanisms underlying the process of involuntary capture of attention by unexpected events, but also the subsequent attentional reorientation to the relevant task, some authors have proposed a neurocognitive model based on the results of ERP

studies (Berti, 2008, 2013; Berti, Roeber, & Schröger, 2004; Escera, Alho, Schröger, & Winkler, 2000; Escera, Alho, Winkler, & Näätänen, 1998; Hölig & Berti, 2010; Horváth, Roeber, Bendixen, & Schröger, 2008). This model suggests that, in the auditory domain, rare and unexpected variations in the acoustic environment (including so-called deviant or novel stimuli) relative to the preceding stimuli, elicit the Mismatch Negativity (MMN), and when the detected change is of sufficient magnitude, this also generates the P3a component (Berti, 2013; Berti, Vossel, & Gamer, 2017; Escera & Corral, 2007), thus reflecting the automatic processing of the change in the level of the sensory system (MMN) (Berti, 2013; Näätänen, 1990; Näätänen et al., 2012) and the subsequent involuntary orienting of attention to the detected change (P3a) (Berti, 2013; Berti et al., 2017; Friedman et al., 2001).

Moreover, in situations in which the change is irrelevant, but reorientation of attention to the task at hand is required, a subsequent late negativity can be observed, the so-called Reorienting Negativity (RON) (Berti, 2013; Hölig & Berti, 2010; Schröger, Giard, & Wolff, 2000; Schröger & Wolff, 1998). In the following section, these ERP components will be explained in detail.

1.2.1. ERP correlates of involuntary capture and reorienting of attention

1.2.1.1. Auditory MMN

MMN was first described for the auditory modality (Näätänen, Gaillard, & Mantysalo, 1978), but has also been reported for other sensory modalities (for a review see Näätänen, Paavilainen, Rinne, & Alho, 2007). Auditory MMN, on which we will focus, is a negative wave commonly derived by subtracting the ERP waveform evoked by a standard stimulus from that evoked by a deviant stimulus in passive oddball tasks, which do not require the participant's attention (Näätänen et al., 2007; Paavilainen, 2013). It is elicited when a frequent repetitive (standard) stimulus is occasionally replaced by a

deviant stimulus, differing in tonal frequency, intensity, duration or location (Näätänen et al., 2007; Paavilainen, 2013) or by a novel stimulus (Escera & Corral, 2007). The changes in auditory stimulation can even be complex and abstract, such as language grammar and musical syntax violations (Näätänen et al., 2007).

The MMN latency appears between 150 and 250 ms from stimulus onset (with the peak latency slightly varying depending on the specific experimental paradigm, see Näätänen, Jacobsen, & Winkler, 2005), and its amplitude is maximal at fronto-central sites (reversing polarity at mastoid electrodes). MMN is clearly separable from the sensory N1(Näätänen, Kujala, & Winkler, 2011), but may temporally overlap with this component (Horváth et al., 2008; Kujala, Tervaniemi, & Schröger, 2007; Näätänen, Kujala, & Winkler, 2011).

MMN is considered a correlate of pre-attentive processes, which are triggered when the sensory input does not match the echoic memory representation of a prevalent standard stimulus. Therefore, auditory MMN is an objective index of auditory discrimination, specifically the automatic detection of changes in the acoustic environment, and an indirect measure of the accuracy of the neural representation of a standard stimulus (Näätänen et al., 2007). Alternatively, MMN is also considered to mirror the "prediction error", which is the difference between the expected sensory input (as predicted from the previous input) and the actual sensory input (Garrido, Kilner, Stephan, & Friston, 2009; Winkler & Czigler, 2012).

Among the neural generators of MMN, the bilateral supra-temporal cortices and frontal cortex (predominantly right) have been consistently identified (Näätänen et al., 2007). It has been suggested that the supratemporal component is involved in the automatic detection of auditory change and maintenance of the sensory memory trace, while the frontal component is related to the involuntary attention switch caused by auditory change (Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen et al., 2007; Paavilainen, 2013; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000).

Because MMN is elicited in the absence of direct control of voluntary attention and is independent of fluctuations in motivation, it is particularly useful for investigation in older and/or clinical populations in which prolonged sustained attention tasks are difficult to perform (Näätänen, Pakarinen, Rinne, & Takegata, 2004). MMN has also been proposed as an index of the cognitive decline occurring in a large number of different neurological and neuropsychiatric diseases (Näätänen et al., 2012; Näätänen, Kujala, Kreegipuu, et al., 2011; Näätänen, Sussman, Salisbury, & Shafer, 2014). Regardless of their different aetiologies and symptomatology, most of these disabilities share a functional deficiency in the auditory-frontal cortex network of auditory discrimination (Ruzzoli, Pirulli, Mazza, Miniussi, & Brignani, 2016).

1.2.1.2. P3a component

In the auditory domain, the P3a component (or novelty-P3; Courchesne, Hillyard, & Galambos, 1975; Escera et al., 2000; Squires, Squires, & Hillyard, 1975) is elicited when attention is drawn towards the appearance of infrequent, unexpected (novel and/or deviant) stimuli among regular (standard) stimuli; in other words, when the neural representation of the stimulus environment changes or is updated (Escera et al., 2000; Escera & Corral, 2007; Friedman et al., 2001; Polich, 2007). This response, which reflects involuntary shifts of attention, is considered an electrophysiological correlate of the orienting response and, presumably, of distractibility (Berti et al., 2017; Escera et al., 2000; Escera & Corral, 2007; Friedman et al., 2001; Polich, 2007). It has been distinguished from the P3b ERP component by a shorter peak latency, a more frontally oriented scalp topography and different elicitation conditions (Escera et al., 2000; Squires et al., 1975).

The P3a component is a positive wave that is identified at approximately 300 ms from deviation onset (Friedman et al., 2001; Horváth et al., 2009). Generation of P3a seems to involve a broad network of cortical regions, including the prefrontal cortex, cingulate

gyrus and hippocampus (Alho et al., 1998; Baudena, Halgren, Heit, & Clarke, 1995; Halgren et al., 1995; Knight, Scabini, Woods, & Clayworth, 1989). According to Polich (2007), P3a is associated with activation of the dopaminergic system, while Schomaker and Meeter (2015) claim that the locus-coeruleus norepinephrine system also plays a role in eliciting P3a.

Different studies suggest that P3a may reflect transient activation in the neural network involved in a variety of cognitive tasks that demand continual updating of task-set information for selection of goal-directed actions (Barcelo, Escera, Corral, & Periáñez, 2006; Escera & Corral, 2007). It has also been argued that rather than reflecting the switch itself, the P3a component may have a functional role in the initial unhitching of the focus of attention from the current information in order to prepare for switching attention (Berti, 2008).

It has also been suggested that P3a is not an unitary process, as it has been shown to comprise two different phases in response to deviant (Yago, Escera, Alho, & Giard, 2001) and novel sounds in young participants (Escera et al., 1998; Escera, Yago, & Alho, 2001): an early phase (with latencies of about 220-320 ms post-stimulus) that may reflect violation of the regularity of an established environment model, provoked by a novel stimulus; and a late phase (with latencies of about 300-400 ms post-stimulus) that may reflect orienting of attention toward the irrelevant novel stimulus, because its amplitude increased when these stimuli could act as warning signals for consecutive relevant visual stimuli, relative to conditions where they did not act in this way (in a passive oddball task) (Escera et al., 1998, 2001).

These two phases of P3a have also been observed in middle-aged adults (Mager et al., 2005), and in response to novel visual stimuli in young and old adults (Czigler, Pató, Poszet, & Balázs, 2006). Mager et al. (2005) observed an early P3a phase (mean peak latency: 266 ms post-stimulus) and a consecutive P3a phase (mean

peak latency: 330 ms post-stimulus) in response to novel auditory stimuli, in young and middle-aged adults; nevertheless, the latter phase could not be identified in all participants and was not evaluated.

1.2.1.3. Reorienting negativity (RON)

It has been argued that the ability to retrieve task-relevant information after distraction is enabled by reorientation of the attentional focus, which is reflected in the ERP component known as Reorienting Negativity (RON), discovered by Schröger and Wolff (1998). In the auditory modality, RON follows P3a when the participants are engaged in a primary task while the standard and distracter (deviant or novel) sounds are presented. RON is a negative wave with a fronto-central distribution and latencies of about 400–600 ms from the onset of the distracter sound.

Because RON was observed after distraction only in situations when reorientation was required for the task at hand, it was interpreted as a correlate of the reallocation of the attention toward the relevant task and compensation for the distraction, when active reorienting is necessary for accomplishing the task (Berti & Schroger, 2003; Escera & Corral, 2007; Escera et al., 2001; Hölig & Berti, 2010; Schröger et al., 2000; Schröger & Wolff, 1998). The neural origin of RON is associated with a widespread neural network, including frontal areas (Schröger et al., 2000; Wetzel & Schröger, 2014).

Berti and Schroger (2003) studied RON responses during a high and low working memory load condition, in an auditory distraction paradigm in healthy young adults. For the task, participants were required to discriminate between short and long tones and indicate the duration of the tone by pressing a button. During the high working memory load, the participants had to postpone their response until the next tone was presented. The distracting deviant stimuli were task-irrelevant frequency changes. The results showed that the RON amplitude and also the behavioural distraction effect were reduced with an increase in task load. The authors suggested that working

memory exerts some control over involuntary attention and that after distraction by task-irrelevant information, reallocation of the focus of attention to the relevant information in working memory is needed to perform the task at hand. It has also been suggested that RON may reflect a more general preparation or evaluation process after a distracting event has been detected (Berti, 2008).

1.2.2. Changes in auditory MMN, P3a and RON associated with aging and MCI

Some ERP studies have shown a decline in the controlled processing of information (such as the evaluation of stimuli in working memory) in healthy aging (Finnigan, O'Connell, Cummins, Broughton, & Robertson, 2011; Friedman, Nessler, & Johnson, 2007) and in adults with aMCI relative to healthy adults (Bennys, Portet, Touchon, & Rondouin, 2007; Golob, Irimajiri, & Starr, 2007; Lai, Lin, Liou, & Liu, 2010; Missonnier et al., 2007; Parra, Ascencio, Urquina, Manes, & Ibáñez, 2012), and this deficit is more evident in aMCI adults who progress to AD than in those who do not develop AD (Golob et al., 2007; Missonnier et al., 2007).

However, ERP studies related to the automatic and involuntary processing of unattended infrequent stimuli (MMN) in adults with MCI are scarce, and the results are inconclusive. Furthermore, to our knowledge, there were no published studies (prior to our research) evaluating the ERPs associated with the orienting response towards unattended infrequent stimuli (P3a) or with the reorientation of attention towards the relevant stimuli (RON) in MCI.

1.2.2.1. MMN, aging and MCI

The MMN component is probably the most widely studied ERP component in healthy and clinical populations, in relation to automatic and pre-attentive processing of stimuli. Some studies have shown that the MMN amplitude decreases significantly with age in healthy adults, regardless of the type of change between the standard

and deviant stimuli, such as variations in stimulus duration (Cooper, Todd, McGill, & Michie, 2006; Nowak et al., 2016; Pekkonen et al., 1996) or tonal frequency (Cooper et al., 2006; Czigler, Csibra, & Csontos, 1992; Gaeta, Friedman, Ritter, & Cheng, 1998). The same results are obtained when novel rather than deviant stimuli are presented (Gaeta et al., 1998). This has also been observed with long interstimulus intervals (ISIs) (4.5 s. or more; Czigler et al., 1992; Pekkonen et al., 1996), but not with short ISIs (2.4 s. or less; Amenedo & Díaz, 1998; Pekkonen et al., 1996; Raggi, Tasca, Rundo, & Ferri, 2013; but also see Cooper et al., 2006; Czigler et al., 1992; Gaeta et al., 1998).

Two possible explanations for age-related changes in MMN amplitude have been proposed: (i) the sensory memory trace may be poorer or more degraded in older than in younger subjects, reflecting an inaccurate representation of standard stimuli by the brain, and/or (ii) poorer performance of comparator mechanisms, which become less sensitive with increasing age for differences between deviant and standard stimuli (Gaeta et al., 1998). Other studies (Alain & Woods, 1999; Kisley, Davalos, Engleman, Guinther, & Davis, 2005) have also found that a diminished MMN amplitude may partly result from an enhanced N1 amplitude to task-irrelevant stimulation in elderly people (for a review, see Tomé, Barbosa, Nowak, & Marques-Teixeira, 2015). This was interpreted in terms of declined inhibitory control related to age-related dysfunction of the prefrontal cortex (Chao & Knight, 1997; Kisley et al., 2005).

In a rather less consistent manner, the latency of MMN also increases with age (Cooper et al., 2006; Czigler et al., 1992; Gaeta et al., 1998; Pekkonen et al., 1996), suggesting that old adults take longer than younger adults to process stimulus deviance (Cooper et al., 2006). However, in other studies, use of an auditory distraction paradigm did not reveal any age-related changes in the MMN parameters in comparisons between young and middle-aged adults (Mager et al., 2005) and young and old adults (Horváth et al., 2009).

In studies with AD patients, changes in MMN have been observed under some task conditions. For ISIs of 1.3 s. or less, no significant differences between control adults and adults with AD were observed in the MMN amplitude elicited by changes in tonal frequency (Baldeweg & Hirsch, 2015; Brønnick, Nordby, Larsen, & Aarsland, 2010; Gaeta, Friedman, Ritter, & Cheng, 1999; Kazmerski, Friedman, & Ritter, 1997; Pekkonen, Jousmäki, Könönen, Reinikainen, & Partanen, 1994) or by presentation of novel stimuli (Gaeta et al., 1999; Kazmerski et al., 1997). However, in AD patients, the MMN amplitude was significantly smaller for an ISI of 3 s than for the shorter ISI condition (1 s.), while in control adults the MMN amplitude was stable across both ISIs (Pekkonen et al., 1994). These results were considered evidence that sensory memory traces decay faster in AD patients than in healthy controls, although auditory discrimination was not affected (Pekkonen et al., 1994).

If AD patients show changes in MMN relative to control adults, it is possible that similar changes can be observed in adults with aMCI. However, studies investigating MMN in older adults with aMCI are scarce.

Mowszowski and colleagues (Mowszowski et al., 2012), investigated the effect of MCI on MMN parameters in a sample of 14 healthy adults and 28 adults with MCI, in a passive oddball task in which the standard and deviant stimuli differed in duration (standard: 50 ms, deviant: 100 ms). In the MCI group, all participants showed impairment in several cognitive domains. Of these, half were of the mdaMCI subtype and the other half of the mdnaMCI subtype. The authors found no differences between the MCI and control groups in MMN amplitude or latency, or between the mdaMCI and mdnaMCI subtypes, at frontocentral locations. However, they did observe that at mastoid locations, the MMN amplitude was smaller in the MCI group than in the healthy control group, which was considered to reflect impairment of the early stages of the information processing in the MCI group.

The study by Mowszowski et al. (2012) provided some interesting results, but also had some limitations. Thus, the differences in MMN amplitude between MCI and control adults were obtained at mastoid electrodes, but not at the frontocentral locations, where MMN is typically identified and analyzed. Moreover, the analysis did not take into account the possible effects of interactions between the Age and Group factors, although previous studies have reported age effects on MMN amplitude to changes in stimuli duration (Cooper et al., 2006; Gaeta et al., 1998; Pekkonen et al., 1996). Moreover, the MCI group was heterogeneous, as it included both amnestic and non-amnestic multidomain MCI patients.

1.2.2.2. P3a, aging and MCI

Age-related changes are often observed in parameters of the P3a component. It has typically been observed that in comparison with young adults, older adults show longer latencies and smaller amplitudes at the maximum peak of this component (Berti, Grunwald, & Schröger, 2013; Fabiani & Friedman, 1995; Horváth et al., 2009; Mager et al., 2005; Nowak et al., 2016; Polich, 1997) or in the two phases identified (Czigler et al., 2006). These results were interpreted as evidence of age-related slowing and decline of the orienting response toward stimulation changes, respectively (Fabiani & Friedman, 1995; Friedman & Simpson, 1994; Pontifex, Hillman, & Polich, 2009). As frontal areas are involved in generating the P3a component (Daffner et al., 2000; Knight, 1984), some authors have considered that the decline in P3a (decreased amplitudes and increased peak latencies) in aging may reflect impaired frontal functions (Fabiani & Friedman, 1995; Friedman & Simpson, 1994; Polich, 2007).

Fabiani and Friedman (1995) also reported aging effects regarding variations in the distribution of the P3a peak: thus, while in young adults P3a showed a more frontal distribution than P3b, in older adults the frontal focus was observed in both P3b and P3a. This was attributed to impairment of the process of updating the information in working memory and an inhibitory deficit in the orientation towards

stimuli that should no longer be perceived as new, showing that the frontal functions are compromised in older adults. In addition, there is evidence that P3a is habituated to the repetition of novel stimuli in younger adults, but not in older adults (Friedman et al., 1998; Friedman & Simpson, 1994; Weisz & Czigler, 2006), suggesting impairment of the inhibitory processes in elderly people (Alperin, Mott, Holcomb, & Daffner, 2014; Friedman et al., 1998; Weisz & Czigler, 2006).

On the other hand, the P3a component also shows changes in several psychiatric and neurological disorders (Gumenyuk et al., 2005; Kaipio et al., 1999, 2000; Lepistö et al., 2004; Polo et al., 2003); however, the findings of the few studies evaluating P3a in AD are to some extent inconsistent. Thus, some authors have observed that the P3a latency is longer in patients with AD than in healthy controls, suggesting delayed orientation to the deviant stimuli in the former (Frodl et al., 2002; Juckel et al., 2008). However, other authors have observed a smaller P3a amplitude in subjects with mild AD than in healthy controls (Cecchi et al., 2015), a finding that is consistent with the decline in attention and executive function observed in the former during neuropsychological testing (Baudic et al., 2006; Cecchi et al., 2015). Yet other authors did not observe any difference in the P3a component parameters between AD patients and controls (Yamaguchi, Tsuchiya, Yamagata, Toyoda, & Kobayashi, 2000).

If patients with AD show changes in P3a parameters relative to control adults, it is possible that similar changes can be observed in adults with aMCI. However, we are not aware of the existence of any published studies, prior to our research, investigating the P3a component in older adults with MCI.

1.2.2.3. RON and aging

Studies of the effect of aging on RON showed longer latencies in older than in young adults (Getzmann et al., 2013; Horváth et al., 2009), which was considered evidence of age-related

slowing in the reorienting of attention to the relevant stimuli after distraction. On the contrary, findings on the effect of age on RON amplitude are not consistent. Thus, some studies have observed smaller RON amplitudes in middle-aged (Mager et al., 2005) and old adults (Getzmann et al., 2013) than in young adults, which was considered evidence of a less efficient attentional shift mechanism in aging (Getzmann et al., 2013). However, in another study (Berti et al., 2013), no differences were found between young and middle-aged adults (59–66 years old), and the authors suggested that the RON amplitude is not a stable predictor of the distraction effect, which is assumed to reflect different aspects of attentional control.

On the other hand, the magnitude of the RT cost is usually considered a measure of the degree of distraction by irrelevant information (Berti et al., 2004, 2013; Wetzel, Widmann, & Schröger, 2012). Some studies show that elderly adults are more easily distracted than young adults by task irrelevant stimuli, as indicated by a greater increase in RTs to the task relevant stimuli when irrelevant stimuli capture their attention (Andrés et al., 2006; Parmentier & Andrés, 2010; although, see Cid-Fernández, Lindín, & Díaz, 2014b, 2016). Hence, as the behavioural distraction effect is functionally connected particularly with P3a and RON (Berti et al., 2004, 2013; Hölig & Berti, 2010), this behavioural deterioration in aging, when present, may be due both to greater involuntary capture of attention and also impaired reallocation of processing resources to the relevant task.

In relation to changes in the parameters of RON in clinical populations, some authors indicate that this component is affected in diseases such as schizophrenia spectrum disorders and attention deficit-hyperactivity disorder (ADHD) (Higuchi et al., 2014; Oja et al., 2016); however, we are not aware of the existence of any published studies evaluating RON parameters in people with AD or MCI.

In summary, the MMN/P3a/RON complex has been shown to be a psychophysiological index of the cascade of three main processes involved in involuntary attention (i.e. automatic detection, orienting of attention, and reorienting of attention), following irrelevant and unexpected (deviant and/or novel) stimuli (Berti, 2008, 2013; Berti & Schröger, 2004; Escera & Corral, 2007; Horváth et al., 2008). However, the ERP studies that have evaluated these processes in healthy aging are inconclusive and those evaluating the same in adults with MCI are scarce or non-existent.

We therefore believe that it is important to carry out studies in a healthy population and to compare different age ranges (young adults, middle-aged adults and older adults), to enable observation of the effects of healthy aging on the parameters (amplitude and latency) of these components. On the other hand, as the MMN and P3a components have been shown to be sensitive tools for assessing cognitive impairment in patients with AD (Cecchi et al., 2015; Frodl et al., 2002; Juckel et al., 2008; Pekkonen et al., 1994), and that people with aMCI are more likely than the general population to convert to AD (Dubois & Albert, 2004; Fisk & Rockwood, 2005; Petersen et al., 2014), we consider that studies that enable us to evaluate whether both components also different in people with aMCI relative to healthy elderly controls are of particular interest.

With the aim of carrying out such studies, an auditory-visual distraction-attention task (A-V task), based on the task designed by Escera et al. (1998), was implemented. This task will be explained in the next section.

1.3. THE AUDITORY-VISUAL DISTRACTION-ATTENTION TASK

The auditory-visual distraction-attention task (A-V task), designed by Escera et al. (1998), has been used in different studies for optimal evaluation of the MMM/P3a/RON complex in young participants (Alho, Escera, Díaz, Yago, & Serra, 1997; Escera et al.,

1998, 2001, 2002; Polo et al., 2003; Yago, Corral, & Escera, 2001; Yago, Escera, et al., 2001; Yago, Escera, Alho, Giard, & Serra-Grabulosa, 2003).

The task designed for our studies involves an auditory passive oddball task and a visual active three-stimulus Go/NoGo task, enabling evaluation of the processes related to the involuntary processing of irrelevant and unexpected auditory stimuli and the effect of these distracting stimuli on the main task being performed in response to the visual stimuli. In other studies by our research group, the A-V task has been used with the aim of evaluating the ERP components related to voluntary processing of the attended visual stimuli in healthy participants (young and old) and adults with aMCI (Cid-Fernández et al., 2014a, 2014b, 2016, 2017a, 2017b).

The task consists of the presentation of 500 auditory-visual (A-V) pairs of stimuli (divided in two blocks). Each pair includes an auditory stimulus (150 ms duration) followed by a visual stimulus (200 ms duration), separated by an interval of 300 ms (onset-to-onset), and with a 2-second interval between each pair (onset-to-onset). Participants are instructed to pay attention to the visual stimuli and ignore the auditory stimuli. See diagram of the task procedure in Figure 2.

The unattended auditory stimuli, of intensity 75 dB SPL, are presented binaurally, via headphones, and three types were used: 70% standard stimuli (tone bursts, 1000 Hz), 15% deviant stimuli (tone bursts, 2000 Hz), and 15% novel stimuli (different each time, e.g. glass crashing, phone ringing). Three types of attended visual stimuli were also presented: numbers (2, 4, 6, and 8) with a presentation probability of 33%, letters (a, c, e, and u) with a presentation probability of 33%, and triangles (pointing right, left, upward or downward) with a presentation probability of 34%. Participants were instructed to ignore the auditory stimuli and to respond (Go condition) to the numbers and the letters by pressing two different buttons, each with a different hand (the buttons were counterbalanced among

participants), and to inhibit their responses to triangles (NoGo condition).
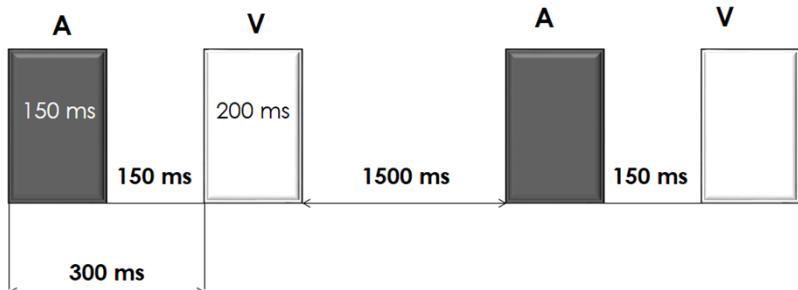
Figure 2. Schematic representation of the auditory-visual distraction-attention task.

The A-V task used in previous studies (see Escera et al., 1998, 2001; Polo et al., 2003; SanMiguel, Morgan, Klein, Linden, & Escera, 2010; Yago, Corral, et al., 2001) always included a passive auditory oddball task and an active visual classification task. The passive auditory task usually comprises standard stimuli (pure tones) that appear in high proportion of trials (between 75% and 90%), deviant stimuli (generally pure tones slightly different from the former), and/or novel stimuli (different rare natural environmental sounds) that appear in the remaining trials. The active visual task habitually consisted of a simple 2-stimulus classification task, in which the participants had to press a different button for each stimulus type. Different visual stimuli have been used, and in the original version of the task, subjects were instructed to classify digits into odd and even categories (Escera et al., 1998, 2001, 2002; Escera, Yago, Corral, Corbera, & Nuñez, 2003; Yago, Corral, et al., 2001), while in other versions of the A-V distraction paradigm, the task was modified to classify digits vs. letters (Alho et al., 1997; Polo et al., 2003; Yago, Escera, et al., 2001; Yago et al., 2003) or to include more complex visual stimuli and decisions, such as classifying drawings into animate (animals) or inanimate (objects) categories (Gumenyuk, Korzyukov,

Alho, Escera, & Näätanen, 2004), or deciding whether two natural pictures presented simultaneously were equal or different (Dominguez-Borrás, Garcia-Garcia, & Escera, 2008).

In young participants, RTs were longer when a novel sound preceded the visual target (Novel condition) than when the preceding sound was a standard tone (Standard condition) (Barcelo et al., 2006; Cortiñas et al., 2008; Escera et al., 1998, 2001, 2003; Parmentier, 2008; Parmentier, Elford, Escera, Andrés, & Miguel, 2008; Parmentier, Elsley, Andrés, & Barceló, 2011; Parmentier, Elsley, & Ljungberg, 2010; Polo et al., 2003; Wetzel, Schröger, & Widmann, 2013; Yago et al., 2003). This result has also been observed for the deviant condition relative to the standard condition (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 did not observe any such difference between conditions (Escera et al., 1998; Yago et al., 2003).

The longer RTs in the distractor (Deviant and/or Novel) conditions were considered evidence that these auditory stimuli 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). The longer RTs were considered behavioural correlates of the distraction effect and the involuntary orienting of attention (Parmentier et al., 2008; Wetzel et al., 2013; Yago, Escera, et al., 2001). Moreover, some authors established that the distraction effect is larger to novel than deviant sounds in young participants, at both behavioural and electrophysiological levels (Berti, 2012; Escera et al., 1998, 2001).

Using the A-V task with young participants, Escera et al. (1998) found that MMN peaked earlier and P3a showed larger amplitude in response to novel sounds than to deviant tones and that the RT was longer for visual targets following novel auditory stimuli than for visual targets following deviant auditory stimuli. Berti (2012), who used a similar task with young participants, reported that P3a and RON components showed larger amplitudes in response to novel than

to deviant stimuli, suggesting that rare environmental sounds are more effective than deviant signals in triggering attentional switching and resulting in clear behavioural distraction effects.

On the other hand, in some studies in which the A-V task was used with older adults (Andrés et al., 2006; Parmentier & Andrés, 2010), it was found that RTs in response to visual stimuli were longer when the visual stimuli followed novel sounds than when they followed standard stimuli (distraction effect), in young and old participants. Parmentier and Andrés (2010) did not observe significant differences between age groups for the size of distraction effect; however, Andrés et al. (2006) found a significantly stronger distraction effect in the elderly group, which 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).

Additionally, two studies (Cid-Fernández et al., 2014b, 2016), in which the same task as used in the present thesis was applied, evaluated the effects of aging and the involuntary capture of attention provoked by irrelevant novel relative to standard auditory stimuli (Novel and Standard conditions) on RTs, percentage of hits, the N2b and P3b ERP components, the stimulus-locked lateralized readiness potential (sLRP) and response-locked lateralized readiness potential (rLRP), and other response-related ERP components (pre-response frontal positivity [preRFP]; correct-related negativity [CRN]; post-response frontal positivity [postRFP]; and parietal response positivity [parietalRP]), all of which were measured in relation to the response to Go visual stimuli in three different age groups (young, middle-aged and old adults). The results indicated age-related slowing of performance (longer RTs) and of all the ERP components evaluated (except CRN), with no significant differences between the middle-aged and old participants. The age-related slowing of processing affected the stimuli stimulus evaluation and categorization in working memory (N2b and P3b latencies, respectively), selection and preparation of the motor response (sLRP and rLRP onset latencies,

respectively), and also upregulation of cognitive control (preRFP) and the relatively unknown response-related processes indicated by postRFP and parietalRP.

In addition, in the novel relative to the standard condition, the three age groups showed distraction effects on performance (longer RTs), Go visual stimulus categorization (longer P3b latencies) and motor response selection (longer sLRP onset latency); and a facilitation effect on response preparation (later rLRP onset latency). However, the distracting effect provoked by deviant stimuli relative to the standard and novel stimuli was not evaluated in the three different age groups.

The A-V task has also been used to assess the distracting effects in a range of clinical populations, including attention deficit-hyperactivity disorder (ADHD) (Gumenyuk et al., 2005), closed-head-injured patients (Polo, Newton, Rogers, Escera, & Butler, 2002), chronic alcoholics (Polo et al., 2003) and schizophrenics (Cortiñas et al., 2008). Moreover, two studies using an A-V task have evaluated differences in performance between control, sdaMCI and mdaMCI participants (Cid-Fernández et al., 2017a, 2017b). The authors observed longer RT and fewer hits in mdaMCI participants than in control (Cid-Fernández et al., 2017a, 2017b) and sdaMCI (Cid-Fernández et al., 2017b) participants. In addition to poorer execution, the mdaMCI participants also showed neurocognitive decline relative to the sdaMCI and/or Control groups, as the sdaMCI showed 1) lower sLRP amplitudes than the control participants, interpreted as decline in motor control (Cid-Fernández et al., 2017b), and 2) longer Go-N2 latencies than the Control group, with the sdaMCI participants showing intermediate values (more similar to those of the Control group). The authors suggested that the mdaMCI participants need more time for the conscious evaluation of the target stimulus than the healthy controls (Cid-Fernández et al., 2017a). On the other hand, both the mdaMCI and sdaMCI participants showed lower NoGo-N2 amplitudes than the control participants, which was interpreted as a deficit in response conflict monitoring and/or inhibition processes in

both aMCI subgroups (Cid-Fernández et al., 2017a). The authors also observed that the sdaMCI participants showed a late positive slow wave (PSW) that did not appear in most of the mdaMCI and control participants, which they interpreted as a possible compensatory mechanism allowing sdaMCI participants to maintain acceptable execution levels (Cid-Fernández et al., 2017a). In addition, Cid-Fernández et al. (2017b) also observed that the sdaMCI group showed longer sLRP peak latencies than the control participants, although they did not differ in relation to RTs or hits, which was interpreted as a sign of compensatory mechanisms, as mentioned above, or early indication of a decline in motor control.

However, no studies with A-V tasks have evaluated the MMN, P3a or RON components in response to auditory stimuli in participants with aMCI. The limited data regarding these components in MCI encouraged us to study these in more detail (concretely the MMN and P3a) to better characterize the cognitive processes in adults with aMCI.

1.4. AIMS AND HYPOTHESIS

The main aims of the present doctoral thesis, using the A-V task, were as follows:

(1) To evaluate the effects of healthy aging and the capture of attention (and their interaction) on the ERP components associated with the automatic detection of changes in the acoustic environment (MMN), the orienting response (P3a component) toward irrelevant unexpected auditory stimuli, and the reorienting of attention to relevant visual stimuli (RON).

(2) To compare the MMN and P3a components in healthy adults and adults with aMCI, in order to determine whether changes in the parameters (amplitude and latency) of both components can be considered sensitive and specific biomarkers of aMCI.

This thesis is divided into two main parts: (1) The aim of **Study 1** was to characterize MMN, P3a and RON components in healthy middle-aged and old participants (relative to young participants); and (2) The aims of **Studies 2** and **3** were to characterise the MMN and P3a components in adults with aMCI (relative to healthy controls), in order to search for aMCI biomarkers.

Firstly, in **Study 1**, the participants were divided into three age groups: (1) Young, 21–29 years old; (2) Middle-aged, 51–64 years old; and (3) Old, 65–81 years old. The participants performed the A-V task described in the previous section, in which they were asked to attend to visual stimuli (Go, NoGo) and to ignore auditory stimuli (S: standard, D: deviant, N: novel). The specific aims of this study were to investigate the effects of aging and the capture of attention provoked by novel and deviant auditory stimuli on the parameters of MMN, P3a and RON components, as well as on the RTs in response to Go visual stimuli. In other studies, we have evaluated the effect of the involuntary capture of attention provoked by novel auditory stimuli relative to standard stimuli on the RTs, using an identical task with a similar sample (Cid-Fernández et al., 2014b, 2016). In **Study 1,** we also tested for significant differences between the Deviant *versus* Novel conditions, and Deviant *versus* Standard conditions. In addition, the ERP components were identified in the deviant *minus* standard (D-S) and novel *minus* standard (N-S) difference waveforms (N-S and D-S conditions). Finally, two consecutive different phases were identified in the interval of the P3a component, which were denominated early-P3a (e-P3a) and late-P3a (l-P3a).

Regarding the aging effect, we expected to find longer RTs in the Old and Middle-aged groups than in the Young group, and possibly longer RTs in the Old than in the Middle-aged group. ERP latencies were expected to change in a similar way. Furthermore, we expected to observe smaller amplitudes of the ERP components in the Old and Middle-aged groups relative to the Young group.

Regarding attention capture, we expected to find longer RTs in the Novel (auditory novel – visual Go) than in the Standard condition (auditory standard – visual Go) (distraction effect), with intermediate values in the Deviant condition (auditory deviant – visual Go). Furthermore, we expected to observe age-related differences in the magnitude of this distraction effect, which would be larger in the Old group and decrease in the order old > middle-aged > young adults. In addition, we expected to find larger amplitudes and shorter latencies of MMN, e-P3, and l-P3a in the N-S than in D-S condition, because the difference between novel sounds and standard tones was greater than the difference between deviant and standard tones, increasing pre-attentive and attentive capture. Moreover, we also expected to find larger amplitudes and longer latencies of the RON component in the N-S than in D-S condition, because the greater capture of attention in the former should delay the reorientation of attention toward the visual stimuli and make it more difficult.

In **Study 2**, the MMN component, identified in the D-S and N-S difference waveforms, was studied in healthy adults and adults with aMCI. The participants undertook the study task at two times separated by an interval of between 18 and 24 months. The specific aims of this study were: (1) to determine any differences in MMN parameters between healthy adults and adults with aMCI, in a first evaluation; (2) to evaluate whether such differences are modulated by age, by dividing each group in two age subgroups (50–64 years and 65 years and over); (3) to determine whether the differences between healthy and aMCI adults for the MMN parameters are maintained in a second evaluation, conducted 18–24 months after the first evaluation; and (4) to evaluate whether MMN changes associated with aMCI are sensitive and specific biomarkers of this syndrome.

We expected to observe smaller amplitude of MMN in adults with aMCI than in healthy adults, as result of the addition of the cognitive impairment and the aging that characterizes the former. In the second evaluation, we expected to observe a reduction in the MMN amplitude in both groups, relative to the first evaluation, as a consequence of

aging, with the change being more accentuated in adults with aMCI than in healthy adults.

Finally, **Study 3** was designed to investigate the effects of aMCI on the P3a component, recorded in response to irrelevant novel auditory stimuli. The P3a component was identified in the N-S difference waveforms. Participants were classified into three groups: Control, sdaMCI and mdaMCI.

The specific aims of this study were to identify and characterize the phases of P3a (e-P3a and l-P3a) in both subtypes of aMCI (sdaMCI and mdaMCI) and the controls. As patients with AD showed changes in P3a parameters relative to controls, we expected to find similar changes in aMCI, such as longer latencies and smaller amplitudes in participants with aMCI than in healthy controls, especially in the mdaMCI group. This was also expected as the rate of conversion to AD is considerably greater when memory deficits are associated with other cognitive deficits (mdaMCI) than when they are isolated (sdaMCI), suggesting that mdaMCI may represent a more advanced prodromal stage of AD. We also aimed to determine whether changes in these ERP parameters may be sensitive and specific biomarkers of sdaMCI and mdaMCI.

The performance (RTs and hits) to Go visual stimuli were also evaluated with the aim of determining whether both aMCI subtypes modulate the effects of involuntary capture of attention provoked by novel stimuli on both measures.

2. STUDIES

2.1 STUDY 1 (ESTUDIO 1): Involuntary capture and voluntary reorienting of attention decline in middle-aged and old participants.

http://journal.frontiersin.org/article/10.3389/fnhum.2016.00129/full

2.2. STUDY 2 (ESTUDIO 2): Mismatch Negativity (MMN) amplitude as a biomarker of sensory memory deficit in amnestic mild cognitive impairment.

http://journal.frontiersin.org/article/10.3389/fnagi.2013.00079/full

2.3. STUDY 3 (ESTUDIO 3): Increased amplitude of the P3a ERP component as a neurocognitive marker for differentiating amnestic subtypes of mild cognitive impairment.

https://www.frontiersin.org/articles/10.3389/fnagi.2018.00019/full

3. GENERAL DISCUSSION

3.1. INVOLUNTARY CAPTURE AND VOLUNTARY REORIENTING OF ATTENTION IN HEALTHY AGING

Study 1 of this doctoral thesis evaluated the effects of aging and the involuntary capture of attention, and their interactions, on RTs to Go visual stimuli and on ERP components associated with 1) the automatic detection of unattended infrequent deviant and novel auditory stimuli (Mismatch Negativity, MMN), 2) the orienting of attention to these stimuli (P3a component), and 3) the reorienting of attention to the relevant visual task (Reorienting Negativity, RON). These measures were compared among three groups of participants: Young (21-29 years old), Middle-aged (51-64 years old), and Old (65–81 years old).

3.1.1. Performance: effects of age and the involuntary capture of attention

In **Study 1**, we observed an age-related slowing of RT, which was significantly longer in the middle-aged and old adults than in young adults for the three auditory conditions (Standard, Deviant, and Novel) that preceded Go visual stimuli. This result supports the well documented age-related slowing (increases in RTs) observed in a variety of cognitive tasks (Salthouse, 2000), and it is consistent with the findings of two previous studies that used the same task and a similar sample (Cid-Fernández et al., 2014b, 2016).

Additionally, as expected, a distraction effect was observed in all three age groups, with no interaction between the distraction effect and age factor. Specifically, the RTs were significantly longer when the visual Go stimuli were preceded by novel auditory stimuli than

when they were preceded by standard and/or deviant auditory stimuli. This result is partly consistent with those of previous studies in which a similar task was used with young participants (Escera et al., 1998, 2001; Polo et al., 2003). Such studies usually report a gradual change, in which RTs are longer in the Novel than in the Deviant and Standard conditions, and longer in the Deviant than in the Standard condition. The greater distraction effect produced by the novel irrelevant stimuli (relative to the deviant stimuli) on responses to the visual stimuli supports the possibility that a novel event in the acoustic environment temporarily engages the subject's attention during performance of a visual task (Berti, 2012, 2013; Polo et al., 2003). There is also some evidence to suggest that semantic analysis can identify novel irrelevant stimuli that are not words, but have a conceptual meaning (e.g. environmental sounds, the ringing of a telephone) (Orgs, Lange, Dombrowski, & Heil, 2007); thus, novel sounds bring about a contextual change, making selection of appropriate response to relevant visual tasks relatively difficult and slowing the RT (Parmentier, 2008). In this line, **Study 1** showed that RTs are suitable for assessing the distraction effect in young, middle-aged and old adults.

On the other hand, in **Study 1**, we did not observe any differences in RT between the Standard and Deviant conditions, which is consistent with the findings of Yago, Corral, et al. (2001). These authors used a similar task and six different deviant tones, which differed in frequency from the standard tone by 5, 10, 15, 20, 40, and 80%. They did not observe any differences in RT between the Standard and Deviant conditions for the 15% frequency deviance condition or higher; in fact, they observed longer RT in the Deviant than in the Standard condition for a deviance in frequency of around 10%, in accordance with other studies (Escera et al., 1998, 2001; Polo et al., 2003; Yago, Escera, et al., 2001; Yago et al., 2003). Yago, Corral, et al. (2001) concluded that behavioural distraction is only observed when an optimal range of cerebral activation is reached; once the critical interval of distracting deviance is surpassed, the greater activation of the brain network underlying involuntary control

of attention may reflect a compensatory effect that would prevent behavioural distraction from being manifested. This may be what was observed in the present study, as the Deviant condition differed in frequency from the Standard condition by 100%.

3.1.2. ERPs: aged-related modulations and effects of the involuntary capture of attention.

In **Study 1**, we observed that the MMN amplitude did not differ significantly between the three age groups. These results are similar to those of other studies using short inter-stimulus intervals (ISIs), in which no differences in MMN amplitude were observed on comparing young and middle-aged adults (Amenedo & Díaz, 1998; Gunter, Jackson, & Mulder, 1996; Mager et al., 2005; Pekkonen et al., 1996; Raggi et al., 2013; but also see Czigler et al., 1992; Gaeta et al., 1998) or comparing young, middle-aged, and old adults (Amenedo & Díaz, 1998; Ruzzoli, Pirulli, Brignani, Maioli, & Miniussi, 2012).

However, the MMN latency in the N-S condition was significantly longer in the middle-aged and old participants than in the young participants. This finding is consistent with previous research findings (Bertoli, Smurzynski, & Probst, 2002; Verleger, Neukäter, Kömpf, & Vieregge, 1991). As MMN latency is considered a correlate of the time necessary for detection of the acoustic change in echoic memory (Amenedo & Díaz, 1998; Tiitinen, May, Reinikainen, & Näätänen, 1994), the results of **Study 1** suggest an age-related slowing in this process from age 50 years.

Subsequent to MMN, the P3a component was identified in all three age groups, which indicates that involuntary switching of attention to novel and deviant stimuli occurs in aging (Fabiani & Friedman, 1995; Gaeta et al., 1998). We observed that the P3a component comprised two consecutive phases in all three age groups: an early phase (e-P3a) and a late phase (l-P3a). Both phases showed maximum amplitude at the Cz electrode site (Cz > Fz and Pz electrode

sites). The e-P3a phase showed a fronto-central distribution, while the distribution of l-P3a phase was parieto-central.

These findings are partly consistent with those reported by Escera et al. (1998, 2001) who, using a similar task, identified two phases of P3a in response to novel auditory stimuli in young people: (1) an early phase with central distribution and with latencies of about 220–320 ms, and (2) a late phase with right frontal distribution and peaking between 300 and 400 ms. The amplitude of the late P3a phase increased when the novel irrelevant stimuli acted as warning signals for consecutive relevant visual stimuli, relative to conditions where they did not act in this way (in a passive oddball task). This led the authors to propose that this subcomponent may reflect orienting of attention toward the irrelevant stimulation. Escera et al. (1998, 2001) also suggested that the right frontal scalp distribution of the late P3a component may reflect the activity of right frontal areas involved in reorientation. They also indicated that the early P3a phase might not reflect orientation toward the stimulation because the amplitude did not increase when it acted as a warning signal. This early subcomponent was thus considered an index of a violation of regularity of an established environment model produced by novel stimulation.

Some studies have found differences for the frontal and parietal part of the P3a component (without identifying two different peaks in the time window of P3a; for a review, see Friedman et al., 2001). As P3a showed greater habituation at frontal than at parietal locations (Courchesne et al., 1975; Friedman & Simpson, 1994; Knight, 1984), and as habituation is an important feature of the orienting response (Öhman, 1992; Siddle, 1991), the frontal subcomponent was therefore interpreted as an index of processes related to orienting towards the stimulus (Cycowicz & Friedman, 1997; Friedman et al., 1998), while the posterior part of P3a was interpreted as possibly reflecting categorization processes (Courchesne et al., 1975; Knight, Grabowecky, & Scabini, 1995), because it had features in common

with the P3b component elicited in response to target stimuli (Friedman et al., 2001).

We consider that the scalp distribution of the two phases of P3a, identified in **Study 1** may be consistent with the aforementioned hypothesis. We therefore suggest that e-P3a may be a correlate of the effective orienting response and that l-P3a may be a correlate of subsequent evaluation of the infrequent unexpected novel or deviant stimuli. Our proposal regarding the functional significance of the P3a complex is consistent with previous studies suggesting that this component indicates evaluation of the contextual novelty of unexpected sounds (for a review, see Escera & Corral, 2007).

Regarding the effects of aging, we observed that the e-P3a amplitude (but not the l-P3a amplitude) was significantly larger and that the e-P3a latency was significantly shorter in young than in the middle-aged and old adults, in the N-S difference ERP waveform. Similar results were observed for the D-S difference waveform, except that the e-P3a amplitude was not significantly different in young and middle-aged participants. These results suggest a decline and slowing of the orientation to the non-attended infrequent stimulation (deviant or novel) in aging and is consistent with the findings of some studies in which larger amplitudes and shorter latencies of P3a were observed in young than in old adults (Fabiani & Friedman, 1995; Friedman & Simpson, 1994).

Moreover, as frontal areas are involved in genesis of the P3a component (Daffner et al., 2000; Halgren et al., 1995; Knight, 1984), some authors have considered that the decline of P3a in aging reflects impaired frontal functions (Friedman et al., 1998; Friedman & Simpson, 1994). Therefore, the presence of smaller e-P3a amplitudes in the Middle-aged and Old groups may indicate that some frontal lobe mechanisms become less sensitive during middle age, with no significant changes thereafter. In addition, the latency of l-P3a was longer in middle-aged and old than in young adults, which may indicate age-related slowing of the auditory stimuli evaluation.

A decline was also observed in the speed of attentional reorienting from middle-age, reflected in significantly longer latencies of the RON component in middle-aged and old participants than in young participants. This finding is consistent with those of some studies comparing young and old adults (Getzmann et al., 2013; Horváth et al., 2009).

The findings of **Study 1** also showed significantly larger e-P3a and l-P3a amplitudes in the N-S than in the D-S difference waveforms, in all three age groups. This finding may indicate that novel sounds cause greater involuntary capture of attention than deviant tones, as reflected by greater orienting of attention to (larger e-P3a amplitude) and a greater allocation of processing resources (larger l-P3a amplitude) in the subsequent evaluation of the novel stimuli.

In addition, the MMN and e-P3a latencies were significantly shorter in the N-S than in the D-S condition in young participants, possibly indicating that the novel auditory stimuli provoked faster automatic detection of auditory changes and faster orienting of attention, respectively, than the deviant stimuli in this group. In the Middle-aged group, the novel auditory stimuli also led to faster automatic detection of changes than the deviant stimuli (as reflected by a shorter MMN latency in the N-S than in the D-S trace); however, the orienting of attention did not differ between conditions.

In the old participants, e-P3a latency was significantly shorter in the D-S than in the N-S condition, and there were no differences between conditions for MMN latency. The finding on P3a latency was unexpected. To our knowledge, no studies have compared N-S and D-S difference for MMN, P3a, and RON components in the three different age groups. However, the brain is known to adapt and reorganize in response to the neural insults associated with aging, through the strengthening of existing connections, the formation of new connections and the disuse of weak or faulty connections, in an effort to maintain cognitive behaviour (Goh & Park, 2009; Park &

Reuter-Lorenz, 2009). Therefore, we suggest that the results obtained for e-P3a latency in the old participants relative to young participants, comparing the N-S *versus* D-S difference waveforms, may reflect the use of different processing strategies in both age groups for irrelevant stimulus processing, as result of the neural reorganization that takes place during healthy aging. However, this hypothesis must be tested in future studies.

In summary, novel environmental sounds were observed to be more effective than deviant sounds for triggering attentional switching and cause clear behavioural distraction effects in young, middle-aged and old adults. This finding is partly consistent with those of Berti (2012), who used a similar task with young participants and reported that the P3a and RON components showed more pronounced amplitudes for novel than deviant stimuli. Nevertheless, we did not find any statistically significant differences between N-S and D-S for the RON component, although the same trend was observed for the amplitude.

3.2. INVOLUNTARY CAPTURE OF ATTENTION IN AMNESTIC MILD COGNITIVE IMPAIRMENT (aMCI). IDENTIFICATION OF BIOMARKERS

In this second part of the discussion, the results obtained in **Studies 2** and **3** comparing the performance and the ERP components between control adults and aMCI adults, including the different aMCI subtypes (sdaMCI and mdaMCI), will be discussed. We will first discuss the effects of aMCI on the MMN component (**Study 2**) and then discuss the effects of aMCI (differentiating adults with sdaMCI and mdaMCI) on the behavioural parameters and the P3a component (**Study 3**).

3.2.1. MMN and aMCI

In **Study 2**, two evaluations were carried out, with an interval of between 18 and 24 months. In the first evaluation, the Control group

(CG) comprised 30 adults, and the aMCI group comprised 26 adults; in addition, two age subgroups (50–64 years and 65 years and over) in each group were considered for the analysis, with the aim of evaluating whether the differences between healthy adults and adults with aMCI are modulated by age. In the second evaluation, the CG comprised 9 adults and the aMCI group comprised 7 adults, whose initial diagnosis was maintained at the second evaluation.

In the first evaluation, the MMN latency (measured in the N-S difference) was significantly shorter in the aMCI group than in the CG. However, in the second evaluation, no significant differences were found for this parameter on comparing adults with aMCI and healthy adults, which may be due to the fact that the sample size was smaller at the second evaluation. The result of the first evaluation was initially intriguing because no significant differences in MMN latencies had been observed in previous MMN studies comparing AD patients and healthy control subjects (Brønnick et al., 2010; Gaeta et al., 1999; Kazmerski et al., 1997) or in the only previous study (prior to **Study 2**), in which an MCI group was compared with a Control group (Mowszowski et al., 2012). Interestingly, Mowszowski et al. (2012) also observed slightly shorter (but non-significant) MMN latencies (measured at Fz and Cz electrodes) in the MCI than in the controls (see Table 2, page 214, of the cited study). Although the shorter MMN latency in the aMCI group than in the CG, in the first evaluation of our study, must be considered with caution, we tentatively speculated that in the former, this may reflect earlier closure of the comparison (in echoic memory) of each novel stimulus with the stored model of a standard stimulus, indicating deterioration of echoic memory in aMCI adults.

In a recent study, Gao et al. (2018) also found that the auditory MMN latency was significantly shorter in participants with aMCI (71.28 years old) than in healthy controls (69.93 years old). In addition, the P3a component was also identified in all participants, but no significant differences were found between the Control and aMCI groups. The authors used a passive auditory oddball task comprising a

sequence of 224 (80%) 1000 Hz standard tones, 28 (10%) 1050 Hz deviant tones, and 28 (10%) novel stimuli, and the tones were presented while participants watched a silent video of a comedy film; at the end of the task, the participants were asked to relate the storyline of the film. MMN was analyzed by subtracting ERP waveforms induced only by the novel auditory stimuli from those of the standard auditory stimuli. The authors suggested that their findings may indicate a frontal cortex compensatory mechanism in aMCI, because some studies have reported an increase in activity in the prefrontal cortex in MCI group (Browndyke et al., 2013), as well as increased functional connectivity between the right prefrontal regions and other cerebral regions (Bai et al., 2009).

By contrast, in a study using also a passive auditory oddball task, Ji, Zhang, Zhang, He and Lu (2015), observed longer auditory MMN latency in adults with aMCI (65.81 years old) than in healthy adults (66.21 years old). MMN was evoked by deviant stimuli, which differed from the standard stimuli in tonal frequency and intensity (standard tone: 85%, 1000 Hz, 85 dB; deviant tone: 15%, 2000 Hz, 90 dB). The authors thus suggested that MMN latency could be used as a biomarker of aMCI; and they established that the discrepancy between their and our (**Study 2**) findings may be due to differences in the sample. In addition, they concluded that further studies should be carried out to clarify whether the MMN latency can act as a fairly sensitive and specific psychophysiological biomarker for the identification of adults with aMCI.

Regarding the MMN amplitude, in the first evaluation, this parameter was significantly larger in the CG than in the aMCI group, only for the middle-aged subgroup (50–64 years). In the middle-age aMCI adults, this may indicate some impairment of the automatic mechanism for detecting disparities, when the novel stimuli are presented. This mechanism depends on maintaining an echoic memory trace of the standard stimulus, with which each novel (or deviant) stimulus is automatically compared. Näätänen et al. (2012) suggested that MMN deficits may be at least partly explained

by dysfunction of the N-methyl-D-aspartate (NMDA) receptor system, which usually binds to the neurotransmitter glutamate. Consequently, reduced MMN in aMCI adults may signify a more general functional deficiency involving glutamatergic dysfunction, as suggested by Mowszowski et al. (2012). The ROC curves showed that MMN amplitude could be considered a possible biomarker of aMCI in middle-aged adults, discriminating between the two groups (CG *versus* aMCI) with a sensitivity of 0.70 and specificity of 0.66 (area under the curve, AUC: 0.76).

For adults 65 years old or more, there were no differences in MMN amplitude between the control and aMCI adults in the first evaluation. This is probably due to a significant age-related decrease in MMN amplitude in the CG, as also found by Gaeta et al. (1998), while in the aMCI group, the MMN amplitude did not differ between the two age subgroups (middle-aged *versus* old). Thus, the lack of differences in MMN amplitude between the CG and the aMCI group for the subgroup of older adults (65 years and over) may be due to an age-related decline in the mechanism of echoic memory trace maintenance and/or the pre-attentional mechanism involved in the automatic detection of differences in the acoustic environment, which may mask the effects of aMCI on the parameter. This finding is also consistent with those of subsequent studies (Gao et al., 2018; Ji et al., 2015), in which no differences were found between aMCI and CG adults for the MMN amplitude, in participants all of whom were more than 65 years old.

Our results therefore indicated that seems important to consider the age factor in the search for biomarkers of aMCI. This finding was later supported by other studies. For example, in a recent study using the same A-V task, Cid-Fernández, Lindín and Díaz (2019) also divided two groups of participants (subjects with aMCI and controls), into two age subgroups: 69 years or less and 70 years or more, and found differences in the ERP components in relation to the diagnosis and age: the latencies of Go-P3 (or P3b, related to target classification processes in a variety of tasks) and NoGo-N2 (related to response

inhibition processes, mainly in Go/NoGo tasks) were longer in aMCI participants than in controls, but only in the younger subgroup (69 years or less), and there were no group differences between the older (70 years or more). The authors suggested that their results may reflect a decline in aMCI that becomes evident early on in aging and intriguingly disappears at later stages.

Furthermore, the MMN amplitude was significantly larger in the middle-aged than in the older control adults. However, in **Study 1** of the present research, this MMN parameter did not differ significantly between healthy middle-aged and older adults. This discrepancy may be explained by the variability among participants, as the same trend was observed in **Study 1**.

In the MMN temporal interval, CSD maps revealed a centroparietal source in the middle-aged adults with aMCI, but not in the middle-aged control adults, which we consider consistent with the significant between-group differences (control and aMCI adults) for MMN amplitude. Moreover, in accordance with the observed effects of aging on the MMN amplitude in the CG, this source was also observed in the older control adults (65 years and over). Within the framework of the Scaffolding Theory of Aging and Cognition (STAC) proposed by Park and Reuter-Lorenz (2009), we believe that the said source may reflect a brain that is adapting, through neural scaffolding, to the functional and structural changes that appear either due to aMCI in middle-aged adults or to healthy aging.

The ERP results of the **Study 2** are partly consistent with those reported by Mowszowski et al. (2012) for the MMN amplitude evoked by deviant stimuli, which differed from the standard stimuli in duration (standard: 50 ms, deviant: 100 ms). These authors observed a larger MMN amplitude in healthy adults than in a MCI group (for an age range of 50–90 years in both groups), although only at mastoid locations, where MMN shows polarity reversal, but not at the frontocentral locations, where the amplitude of this negative component is maximal. The authors considered that this result reflects

the inefficiency of information processing in an early pre-attentional stage in the MCI group.

Our results are also consistent with those reported by Pekkonen et al. (1994) for AD patients and healthy controls. These authors observed a significant decrease in MMN amplitude in the AD group, when the ISI used in the task changed from 1 s. to 3 s., which was interpreted as a weakening of echoic memory trace in people with AD with increasing ISI. In **Study 2**, in which we used the A-V distraction-attention task, the interval between the irrelevant auditory stimuli was 1.85 s. and relevant visual stimuli between auditory stimuli were also presented, so that the combination of both factors may also have affected the maintenance of echoic memory trace of standard auditory stimuli in aMCI participants, but not in CG participants.

In a second evaluation of **Study 2**, which was conducted between 18 and 24 months after the first and in which the parameters of MMN (in the N-S difference waveforms) were compared in a subsample of participants, the MMN amplitude was again significantly larger in the CG than in the aMCI group. The MMN amplitude discriminated between the two groups with 0.71 sensitivity and 0.78 specificity (AUC: 0.82, in ROC curves), indicating that this parameter may even be considered a possible biomarker of aMCI. On the other hand, the MMN amplitude was also significantly smaller in the second than in the first evaluation in the group with aMCI, while it did not differ significantly between evaluations in the CG. This finding may indicate progressive impairment in aMCI adults of the neural mechanisms involved in the maintenance of sensory trace and/or the pre-attentive mechanisms for automatic detection of changes in the acoustic environment. These findings highlight the importance of longitudinal studies to determine (1) the evolution of deficits detected in a first evaluation in participants with aMCI, and (2) the diagnostic and prognostic value of psychophysiological markers.

3.2.2. P3a and aMCI

The main aim of **Study 3** of this doctoral thesis was to evaluate the effects of sdaMCI and mdaMCI on the P3a component, identified in the N-S difference waveforms. In addition, the RTs and hits in response to the Go visual stimuli following the novel and standard auditory stimuli were also evaluated, with the aim of studying whether both aMCI subtypes modulate the effects of involuntary capture of attention provoked by novel stimuli.

The percentage of hits was significantly lower in participants with mdaMCI than in the healthy controls and sdaMCI participants. This result is consistent with those obtained by Cid-Fernández et al. (2017a, 2017b), who used an identical A-V distraction-attention task. These authors observed a lower percentage of hits in mdaMCI participants than in control (Cid-Fernández et al., 2017a, 2017b) and sdaMCI (Cid-Fernández et al., 2017b) participants, indicating a behavioural decline in the mdaMCI participants relative to the sdaMCI and control participants. However, in **Study 3**, no differences were observed between the groups in relation to the RT, while Cid-Fernández et al. (2017a, 2017b) observed longer RTs in mdaMCI participants than in control participants, with the RT in the sdaMCI participants being fairly similar to those in the Control group.

On the other hand, RTs were longer in response to Go visual stimuli when these stimuli followed novel auditory stimuli (Novel condition) relative to when the visual stimuli followed standard auditory stimuli (Standard condition). This finding, which was observed in all three groups under study, suggests that the novel stimuli triggered a distraction effect. This effect was also observed in our **Study 1** and other studies (Cid-Fernández et al., 2014b, 2016; Escera et al., 1998, 2001) in which healthy participants, including young, middle-aged and old adults, performed the A-V task.

In accordance with the results of **Study 1**, two consecutive phases of P3a (e-P3a and l-P3a) were observed in the three groups evaluated

(sdaMCI, mdaMCI and Controls). These phases showed the same topographical distributions as those observed in young, middle-age and old adults: e-P3a showed fronto-central distribution and l-P3a showed parieto-central distribution. We considered again that e-P3a may indicate the effective orienting response and that l-P3a may indicate subsequent evaluation of the novel infrequent unexpected stimuli. In both studies (**1** and **3**), the late phase of P3a showed similar distribution and latencies to those of the P3b component. We therefore suggest that these ERP components may be identical, although further studies should be carried out to explore this possibility.

The findings of **Study 3** revealed significant differences between the three groups of participants in the e-P3a and l-P3a amplitudes; however, they did not reveal differences between groups for the latencies. The e-P3a amplitude was significantly larger in mdaMCI than in sdaMCI participants, and the l-P3a amplitude was significantly larger in mdaMCI than in sdaMCI and control participants, indicating greater involuntary capture of attention to unattended novel auditory stimuli and allocation of more attentional resources for the subsequent evaluation of these stimuli, respectively, in mdaMCI participants. Moreover, e-P3a and l-P3a amplitudes discriminated the groups of participants with moderate to high values of sensitivity and specificity (sensitivity about 0.73-0.91; specificity about 0.68-0.79; for more details see Table 3, page 73 of this thesis), indicating that increases in these parameters may be considered optimal neurocognitive markers of mdaMCI in the clinical setting. However, additional studies with larger samples of participants must be carried out to confirm our results and also to evaluate the clinical usefulness of changes in e-P3a and l-P3a amplitudes for identifying aMCI subtypes.

Gao et al. (2018) also identified the P3a component in participants with aMCI and in healthy controls, but did not observe any significant differences between both groups for this ERP component, suggesting that the discrepancy between their results and ours (**Study 3**) may be due to methodological differences, such as the task used, size and type of sample.

There were no differences between the sdaMCI group and the CG for e-P3a or l-P3a, which leads us to assume that when the two subtypes of aMCI (sdaMCI and mdaMCI) are not distinguished, possible differences between healthy aging and aging with aMCI may be masked. This assumption is supported by the findings of previous ERP studies in which other (Cespón et al., 2015) or similar (Cid-Fernández et al., 2017a, 2017b) cognitive tasks were used. These studies revealed behavioural and neurocognitive decline in mdaMCI participants relative to the sdaMCI and control participants. Specifically, a decrease in the allocation of attentional resources to target stimuli was observed in mdaMCI participants relative to healthy controls, with no difference between controls and sdaMCI participants (Cespón et al., 2015; Cid-Fernández et al., 2017a, 2017b), as well as deficits in executive processes in mdaMCI relative to sdaMCI and control adults (Cespón et al., 2015). Studies using neuroimaging techniques or histopathological analysis also supported the need to distinguish the two aMCI subtypes, as adults with mdaMCI showed a different type of brain damage than those with sdaMCI, e.g. a more widespread white matter degeneration (Li et al., 2013; Liu et al., 2017) and higher Aβ deposition (for a review see Ong et al., 2013).

Additionally, several follow-up studies revealed a higher annual conversion rate to AD in individuals with mdaMCI (30% - 40%) than in individuals with sdaMCI (9%) (Caffarra, Ghetti, Concari, & Venneri, 2008; Fischer et al., 2007; Michaud et al., 2017; Tabert et al., 2006). The larger e-P3a and l-P3a amplitudes observed in the mdaMCI group than in the sdaMCI group may also represent optimal markers of possible progression to AD; however, this assumption would be better addressed in a longitudinal study comparing aMCI subtypes.

Finally, as mentioned at the beginning of this thesis, although some authors have observed a smaller P3a amplitude in subjects with mild AD than in healthy controls (Cecchi et al., 2015), other authors did not find any difference in this component between both groups (Yamaguchi et al., 2000). The results of **Study 3** are partly in

accordance with the findings for AD, because we observed significant differences between the mdaMCI group and the sdaMCI and/or Control groups, but with significantly larger e-P3a and l-P3a amplitudes in the mdaMCI group. In addition, we did not observe any differences between the sdaMCI and Control groups in the e-P3a or l-P3a parameters. Reports of the effects on P3a of AD and other types of dementia are scarce, and the findings are to some extent inconsistent. The discrepancies between the results of the present and previous studies with AD patients may stem from variations in the methods used, e.g. related to different task characteristics. Further studies should be carried out to explore this possibility.

4. CONCLUSIONS

Effect of healthy aging and capture of attention (and their interaction) on task performance and on the MMN, P3a and RON ERP components.

1. RTs were longer in middle-aged and old adults than in the young adults, in response to relevant visual stimuli, independent of the type of irrelevant auditory stimuli (standard, deviant or novel) that preceded the visual stimuli, indicating an age-related slowing of task performance.

2. A distraction effect on task performance was observed in young, middle-aged and old adults, as the RTs were significantly longer when the visual Go stimuli were preceded by novel auditory stimuli than they were preceded by standard and/or deviant auditory stimuli.

3. In the novel *minus* standard (N-S) and the deviant *minus* standard (D-S) difference waveforms, the MMN, P3a and RON components were identified in young, middle-aged and old adults. The P3a component comprised two consecutive phases: an early phase (e-P3a) with fronto-central distribution, and a late phase (l-P3a) with parieto-central distribution.

4. The automatic detection of novel auditory stimuli was slower (longer MMN) in middle-aged and old adults than in young adults.

5. The e-P3a amplitude was significantly smaller and the e-P3a latency was significantly longer in the middle-aged and old adults than in young adults, which may reflect, respectively, a

decline in the allocation of processing resources and slowing of the orienting response to the non-attended infrequent stimulation, from middle age onwards.

6. The l-P3a and RON latencies were significantly longer in middle-aged and old adults than in young adults, which may indicate, respectively, slowed evaluation of irrelevant auditory stimuli and slower reorienting to relevant visual stimuli, from middle age onwards.

7. For the first time, the ERP components (measured in the N-S and D-S difference waveforms), associated with the involuntary capture of attention, was compared among young, middle-aged and old adults.

   7.1 Novel sounds provoked significantly faster automatic detection of auditory changes (reflected by a shorter MMN latency in N-S than in D-S trace) in young and middle-aged adults.

   7.2 In all three age groups, e-P3a and l-P3a amplitudes were significantly larger in the N-S than in the D-S difference waveforms, which may indicate greater allocation of processing resources in the orienting response to, and the subsequent evaluation of, novel sounds compared to deviant tones. In addition, although the e-P3a latency was shorter in the N-S than in the D-S difference waveforms in young participants, indicating that the novel auditory stimuli provoked a faster orienting of attention in these participants, it was shorter in the D-S than in the N-S in old participants, which may reflect the use of different processing strategies in old adults for irrelevant stimulus processing, as result of the neural reorganization that takes place during healthy aging.

Effect of aMCI on task performance and the MMN and P3a ERP components.

1. The percentage of hits (in response to relevant visual stimuli) was significantly higher in healthy adults and adults with single-domain aMCI (sdaMCI) than in adults with multi-domain aMCI (mdaMCI), independently of the type of irrelevant auditory stimuli (standard, deviant or novel) that preceded the relevant visual stimuli, indicating a decline in the performance in mdaMCI adults, but not in sdaMCI adults, relative to healthy adults.

2. A distraction effect on the performance was observed in healthy and aMCI adults, as the RTs were significantly longer when the visual Go stimuli were preceded by novel auditory stimuli than they were preceded by standard auditory stimuli.

3. The MMN latencies (measured in the N-S difference waveforms) were shorter in adults with aMCI than in control adults, which may reflect premature closure of the automatic comparison between each novel stimulus with the stored model of the standard stimulus, indicating impairment of echoic memory in aMCI.

4. The MMN amplitudes (measured in the N-S difference waveforms) were smaller in middle-aged aMCI adults than in the middle-aged control adults, indicating impairment of the automatic mechanism of change detection in the acoustic environment, when novel stimuli are presented. However, the MMN amplitude did not differ between control and aMCI adults aged 65 and over, possibly reflecting that the effects of aMCI on the MMN amplitude are masked by an age-related decline in the echoic memory trace maintenance and/or the pre-attentional mechanism involved in the automatic detection of acoustic changes.

5. Comparison of the MMN amplitude between two evaluations (separated by between 18 and 24 months) revealed a significant decline in this parameter in aMCI participants in the second evaluation relative to the first, while no significant changes were identified for the MMN amplitude in healthy adults. This finding in aMCI adults may indicate progressive impairment of the neural mechanisms involved in the maintenance of the echoic memory trace and/or the pre-attentive mechanisms for automatic detection of changes in the acoustic environment. These findings also highlight the importance of carrying out longitudinal studies to determine any changes in deficits detected in the initial evaluation of participants with aMCI, as well as the diagnostic and prognostic value of psychophysiological markers

6. The ROC curves for MMN amplitude showed moderate sensitivity and specificity for discriminating between aMCI and control adults. The MMN amplitude could therefore be considered a possible biomarker for discriminating between aMCI and control adults.

7. Adults with mdaMCI showed greater allocation of processing resources in the orienting response to unattended novel auditory stimuli, and the subsequent evaluation of these stimuli, as indicated by respectively a significantly larger e-P3a amplitude (relative to the sdaMCI adults) and larger l-P3a amplitude (relative to the sdaMCI and control adults).

8. The e-P3a and l-P3a amplitudes discriminated the groups (mdaMCI *versus* sdaMCI, Controls) with moderate to high values of sensitivity and specificity.

In summary, MMN and P3a ERP components may be useful psychophysiological markers for diagnosing aMCI and distinguishing between sdaMCI and mdaMCI subtypes, as MMN amplitudes were

smaller in adults with aMCI than in healthy controls, and e-P3a and l-P3a amplitudes were larger in mdaMCI than in sdaMCI and control adults. Furthermore, both components are elicited in the absence of voluntary attention, and they are obtained using a non-invasive, simple and inexpensive technique, which are considered optimal features of early markers of AD.

5. FUTURE STUDIES

Considering the differences in the P3a component between the different aMCI subtypes (sdaMCI and mdaMCI), we believe that a complementary study would enable us to evaluate possible differences between aMCI subtypes in relation to the MMN and RON components.

Studies evaluating exogenous auditory ERP components (e.g. P50) in participants with aMCI (distinguishing aMCI subtypes), would also be of interest to reveal whether MCI adults show perceptual deficits prior to pre-attentional and attentional processes.

In addition, future studies should include follow-up evaluations in both groups (control adults and adults with aMCI) to further assess the effect of healthy aging and the aMCI on the ERP components (MMN, P3a and RON) over time; this would also enable us to identify which aMCI adults progress to AD (or not) and to estimate the diagnostic and prognostic value of these ERP components.

6. RESUMEN

Con el incremento de la esperanza de vida que han experimentado los países desarrollados en los últimos años, se evidencia un importante aumento del porcentaje de personas mayores y con ello un crecimiento exponencial de enfermedades asociadas al envejecimiento, en especial aquéllas relacionadas con la demencia (Murman, 2015; Niccoli & Partridge, 2012). La enfermedad de Alzheimer (EA) es la demencia más común, la cual tiene un profundo impacto en la calidad de vida de las personas afectadas, de sus familias y de los cuidadores, además del impacto económico que esto representa (Sosa-Ortiz et al., 2012; Vellone et al., 2008; Wimo et al., 2013). Una detección precoz de esta enfermedad permitiría la puesta en marcha de programas no sólo farmacológicos sino también psicológicos que permitiesen una demora en su manifestación clínica y una mejor calidad de vida para el paciente y sus cuidadores.

Algunas personas que padecen demencia debida a la EA han mostrado con anterioridad deterioro cognitivo ligero (DCL) (Murman, 2015). El término DCL fue introducido para llenar la brecha existente entre los cambios cognitivos asociados con el envejecimiento normal y el deterioro cognitivo asociado con la demencia (Albert et al., 2011; Petersen et al., 1999). 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 (Petersen, 2004; Petersen et al., 1999, 2001, 2009, 2014; Winblad et al., 2004).

Actualmente se reconocen cuatro grandes tipos de DCL (Petersen et al., 2001, 2009; Winblad et al., 2004): (1) amnésico unidominio (DCLau), con rendimiento cognitivo general normal pero alteraciones en memoria; (2) amnésico multidominio (DCLam) con alteraciones no

sólo en memoria sino en otros dominios cognitivos; (3) no amnésico unidominio (DCLnau), con memoria preservada pero alteración en otro dominio cognitivo; y (4) no amnésico multidominio (DCLnam), con memoria preservada pero déficits en varios dominios cognitivos. Adicionalmente, se ha observado que los tipos amnésicos constituyen un estado de transición entre el envejecimiento normal y la EA, mientras que los tipos no amnésicos preceden normalmente a otras formas de demencia, como demencia frontotemporal, con cuerpos de Lewy, entre otras (Howe, 2014; Roberts & Knopman, 2013; Vos et al., 2013). Además, varios estudios sugieren que las personas con DCLam muestran mayor riesgo de conversión a EA, que aquellas personas con DCLau (Fischer et al., 2007; Michaud et al., 2017; Mitchell et al., 2009; Tabert et al., 2006).

Los datos sobre la prevalencia del DCL son inconsistentes, probablemente debido a la utilización de diferentes criterios de definición, muestreo y métodos de evaluación. Algunos autores señalan que aproximadamente entre un 12% y un 18% de personas mayores de 60 años de edad, sin demencia, presentan DCL, siendo el subtipo amnésico el más común; y señalan, además, que la prevalencia aumenta con la edad (Petersen, 2016). También existen discrepancias en cuanto a las tasas de conversión desde el DCL a la EA, mientras que algunos estudios señalan que la tasa anual de conversión a EA en poblaciones con DCL se encuentra entre el 10% y el 15% (Morris et al., 2001), otros estudios hacen referencia a tasas de conversión más altas, aproximadamente del 30% al 40% (Brambati et al., 2009; Geslani et al., 2005).

La posibilidad de identificar biomarcadores tempranos de la EA, realizando estudios en personas con DCL, se muestra como una alternativa muy sugerente para afrontar la enfermedad desde fases prodrómicas. 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 (Jack et al., 2011). La electroencefalografía (EEG) cumple los requisitos para proporcionar biomarcadores

óptimos, y concretamente la técnica de los potenciales evocados (PEs) se muestra como una candidata idónea para la búsqueda de marcadores psicofisiológicos de diversos procesos patológicos que cursan con afectación encefálica, entre ellos la EA y el DCL.

Uno de los procesos cognitivos que se ha estudiado con un importante éxito utilizando la técnica de PEs es la atención, tanto voluntaria como involuntaria. La atención voluntaria hace referencia a un proceso de control voluntario, a través del cual el individuo dirige su atención a ciertos estímulos relevantes de entre la abundante información sensorial que recibimos (Horváth et al., 2009). Mientras que la atención involuntaria es aquella que se produce ante un evento nuevo, el cual posee ciertas características físicas que atraen hacia sí el foco de la evaluación consciente, aunque el evento sea de carácter irrelevante para la tarea que se estaba ejecutando (Escera et al., 2002). El funcionamiento normal del sistema cognitivo se caracteriza por un equilibrio de estos dos procesos (Escera et al., 2002), sin embargo este balance puede verse alterado durante el envejecimiento sano y el envejecimiento que cursa con DCL.

Desde nuestro punto de vista, para una caracterización del DCL (principalmente de tipo amnésico) resulta muy interesante comprender los cambios que se producen en la actividad eléctrica cerebral asociada al procesamiento controlado de los estímulos relevantes en una tarea, pero también consideramos de gran interés determinar qué sucede con la actividad asociada al procesamiento automático e involuntario de los estímulos que son irrelevantes, ya que la atención involuntaria hacia lo irrelevante puede afectar en gran medida a los procesos de atención voluntaria y de memoria de trabajo, y por ello a la ejecución final.

Para explicar los mecanismos cerebrales que subyacen al proceso de captura involuntaria de la atención por estímulos infrecuentes e inesperados, pero también la posterior reorientación de la atención a la tarea relevante, algunos autores han propuesto un modelo neurocognitivo basado en los resultados de la investigación con PEs

(Berti, 2008, 2013; Berti et al., 2004; Escera et al., 1998, 2000; Hölig & Berti, 2010; Horváth et al., 2008). Este modelo plantea que variaciones infrecuentes e inesperadas en la estimulación auditiva repetitiva activan un mecanismo automático detector de cambios asociado a la generación del potencial de disparidad o *Mismatch Negativity* (componente MMN). Además, cuando el cambio detectado es de suficiente magnitud, se pondría en funcionamiento un generador frontal asociado al componente P3a, considerado un correlato de la respuesta de orientación (Berti, 2013; Berti et al., 2017; Escera & Corral, 2007). Adicionalmente, en situaciones en las que el cambio es irrelevante y se requiere una reorientación de la atención hacia una tarea relevante, se puede observar una negatividad tardía, llamada negatividad de la reorientación o *Reorienting Negativity* (RON) (Berti, 2013; Hölig & Berti, 2010; Schröger et al., 2000; Schröger & Wolff, 1998).

MMN es una onda de polaridad negativa, que presenta un pico máximo de amplitud entre 150 a 250 ms en localizaciones centrales y frontales (Näätänen et al., 2005). La generación de MMN se produce por un proceso de comparación, cuando la entrada auditiva no coincide con la información sensorial codificada actual o prevista en la huella de memoria sensorial (Näätänen et al., 2007). Debido a que MMN se obtiene en ausencia de control directo de la atención voluntaria, y es independiente de las fluctuaciones en la motivación, este componente de los PEs es particularmente útil para la investigación en poblaciones mayores sanas y/o clínicas, en las que resulta difícil realizar tareas largas de atención sostenida. Además, la relación de MMN con la memoria sensorial sugiere que su obtención estandarizada podría utilizarse para la valoración fisiológica de las funciones mnésicas, especialmente en algunos trastornos neurodegenerativos, tales como la EA (Näätänen et al., 2004).

En relación a los cambios en los parámetros (amplitud y latencia) de MMN, asociados al envejecimiento sano y al envejecimiento que cursa con DCL, algunas investigaciones obtuvieron una amplitud de MMN menor en las personas mayores que en jóvenes,

independientemente del tipo de cambio utilizado entre los estímulos estándar y discrepante, como variaciones en la frecuencia tonal o duración y también al presentar estímulos novedosos (Cooper et al., 2006; Czigler et al., 1992; Gaeta et al., 1998; Nowak et al., 2016; Pekkonen et al., 1996). También se ha observado que la amplitud de MMN es menor en adultos mayores respecto a jóvenes con un intervalo interestímulo (IIE) largo (4.5 s. o más: Czigler et al., 1992; Pekkonen et al., 1996)), pero no se observaron diferencias entre ambos grupos con IIE cortos (2.4 s. o menos; Amenedo & Díaz, 1998; Pekkonen et al., 1996; Raggi et al., 2013).

Se han propuesto dos posibles explicaciones para los cambios relacionados con la edad en la amplitud de MMN: 1) un debilitamiento de la huella de memoria ecoica en personas mayores, lo que reflejaría una representación inadecuada en el cerebro de los estímulos estándar y/o 2) un rendimiento deficiente del mecanismo comparador para identificar las diferencias entre el estímulo estándar y discrepante (Gaeta et al., 1998).

De forma menos consistente, se ha observado que la latencia de MMN también aumenta con la edad (Cooper et al., 2006; Czigler et al., 1992; Gaeta et al., 1998; Pekkonen et al., 1996), lo que sugiere que los adultos mayores requieren más tiempo que los jóvenes para procesar estímulos irrelevantes e infrecuentes (Cooper et al., 2006). Sin embargo, otros estudios no han encontrado diferencias en los parámetros de MMN al comparar jóvenes con personas de mediana edad (Mager et al., 2005) y con adultos mayores (Horváth et al., 2009).

En estudios de pacientes con EA, que utilizaron tareas con detección de cambios en la frecuencia tonal, no se encontraron diferencias entre personas mayores sanas y con EA para la amplitud de MMN, cuando el IIE fue corto (1,3 s. o menos; Baldeweg & Hirsch, 2015; Brønnick et al., 2010; Gaeta et al., 1999; Kazmerski et al., 1997; Pekkonen et al., 1994) o ante la presentación de estímulos novedosos (Gaeta et al., 1999; Kazmerski et al., 1997). Por otro lado,

algunos estudios encontraron que en participantes con EA, la amplitud de este componente se redujo significativamente cuando el IIE fue largo (3 s.) respecto a cuando fue corto (1 s.), mientras que en los adultos sanos, la amplitud de MMN permaneció estable entre ambos IIE, evidenciando que el trazo de memoria decae más rápido en pacientes con EA que en mayores sanos de su misma edad (Pekkonen et al., 1994).

Solo un estudio previo al nuestro comparó MMN en mayores sanos y mayores con DCL (Mowszowski et al., 2012), no encontrando diferencias entre grupos para la latencia pero sí una reducción de la amplitud en el segundo grupo respecto al primero, lo que consideraron reflejo de la ineficacia del procesamiento de la información en un estadio pre-atencional temprano en las personas con DCL. Si bien, las diferencias de amplitud fueron observadas en los electrodos situados en localizaciones mastoideas, donde el componente MMN invierte su polaridad, y no en aquellas localizaciones centrales o frontales de línea media en las que esta onda negativa muestra su máxima amplitud.

El componente P3a suele seguir en el registro a MMN, cuando el estímulo infrecuente que lo evoca es bastante diferente del estímulo estándar. P3a es una positividad que se identifica aproximadamente a los 300 ms desde la aparición del estímulo irrelevante, puede ser registrada ante estímulos novedosos y/o discrepantes y muestra una distribución fronto-central (Friedman et al., 2001; Horváth et al., 2009). En general, el componente P3a se ha asociado al procesamiento de la novedad y la orientación involuntaria a cambios en el medio ambiente (Berti et al., 2017; Escera et al., 2000; Escera & Corral, 2007; Friedman et al., 2001; Polich, 2007).

Algunos autores han señalado que P3a presenta dos fases diferenciadas en jóvenes (Escera et al., 1998; Escera et al., 2001;Yago, Escera, et al., 2001): (1) Una fase inicial entre los 220-320 ms, que podría reflejar la violación, por la estimulación novedosa, de un modelo del entorno establecido y mantenido en la corteza de asociación témporo-parietal; y (2) una segunda fase de mayor latencia,

aproximadamente entre los 300-400 ms, que podría constituir una señal de la orientación involuntaria efectiva de la atención hacia la estimulación novedosa desencadenante. Estas dos fases de P3a también se observaron en adultos de mediana edad (Mager et al., 2005), y en respuesta a estímulos visuales novedosos en adultos jóvenes y mayores (Czigler et al., 2006). Mager y colaboradores (2005) observaron una fase temprana y una fase tardía en respuesta a estímulos auditivos novedosos, sin embargo, la fase tardía de P3a no pudo ser identificada en todos los participantes, razón por la cual los autores no la evaluaron.

Con el envejecimiento, P3a ha mostrado en general un aumento en la latencia y una reducción de la amplitud (Berti et al., 2013; Fabiani & Friedman, 1995; Horváth et al., 2009; Mager et al., 2005; Nowak et al., 2016; Polich, 1997). Además, P3a muestra habituación ante la repetición de los estímulos novedosos en jóvenes y no en mayores, como reflejo de que la actividad inhibitoria está comprometida en mayores (Friedman et al., 1998; Friedman & Simpson, 1994; Weisz & Czigler, 2006). Previos a nuestra investigación, no existían estudios publicados que hubieran evaluado P3a en personas con DCL, y existen pocos estudios que hayan evaluado este componente en pacientes con EA, siendo los hallazgos inconsistentes. Algunos autores observaron que los pacientes con EA muestran una latencia de P3a mayor que los controles, sugiriendo una orientación demorada ante los estímulos discrepantes en los primeros (Frodl et al., 2002; Juckel et al., 2008); adicionalmente, algunos autores observaron menor amplitud de P3a en pacientes con EA leve respecto a controles sanos (Cecchi et al., 2015). Sin embargo, otros autores no encontraron diferencias en los parámetros de este componente al comparar adultos sanos y adultos con EA (Yamaguchi et al., 2000).

Por otra parte, tras la distracción generada por un estímulo novedoso y/o discrepante, y el consecuente cambio de la atención, es importante reorientar los procesos cognitivos a la tarea relevante, esta capacidad de reorientación de la atención se refleja en el componente

de los PEs conocido como reorientación o *Reorienting Negativity* (RON). RON es una onda negativa, la cual se observa entre los 400-600 ms después de la presentación del estímulo distractor y muestra una distribución fronto-central. A partir de lo anterior, se ha sugerido que RON refleja la reorientación o reenfoque de la atención a la tarea relevante (Berti & Schroger, 2003; Escera & Corral, 2007; Escera et al., 2001; Hölig & Berti, 2010; Schröger et al., 2000; Schröger & Wolff, 1998).

Los estudios sobre el efecto del envejecimiento en RON muestran latencias más largas en adultos mayores que en adultos jóvenes, lo que fue interpretado como reflejo de un enlenteciendo asociado a la edad en la reorientación de la atención hacia los estímulos relevantes después de la distracción (Getzmann et al., 2013; Horváth et al., 2009). Sin embargo, los resultados sobre el efecto de la edad en la amplitud de RON no son consistentes, mientras que algunos estudios observaron menor amplitud de RON en adultos de mediana edad (Mager et al., 2005) o en adultos mayores (Getzmann et al., 2013) al compararlos con jóvenes, otros no encontraron diferencias entre adultos jóvenes y de mediana edad (Berti et al., 2013). Por otra parte, no tenemos conocimiento de la existencia de estudios publicados que evalúen los parámetros de RON en personas con EA o DCL.

En la presente tesis doctoral, se diseñó una tarea auditivo-visual (A-V) de distracción-atención, basada en la diseñada por Escera et al. (1998) para evaluar los componentes de los potenciales evocados mencionados previamente, y los procesos relacionados con los mismos, en el envejecimiento sano. Esta tarea se había utilizado en diferentes estudios para evaluar de manera óptima estos tres componentes (MMM, P3a y RON) en participantes jóvenes (Alho et al., 1997; Escera et al., 1998, 2001, 2002; Polo et al., 2003; Yago, Corral et al., 2001; Yago, Escera, et al., 2001; Yago et al., 2003).

Por otra parte, dado que los componentes MMN y P3a se han mostrado en algunos estudios como herramientas objetivas y sensibles para evaluar daño cognitivo en pacientes con EA, también

consideramos de especial interés utilizar esta tarea para determinar si ambos componentes muestran cambios en personas con DCL amnésico respecto a mayores sanos.

Esta tarea A-V incluye una tarea oddball pasiva y una tarea Go/NoGo, en la que presenta un par de estímulos en cada ensayo (uno auditivo y uno visual, separados por 300 ms de inicio a inicio). Los estímulos auditivos fueron tonos frecuentes (70%) de 1000 Hz (Estándar), tonos infrecuentes (15%) de 2000 Hz (Discrepantes) y sonidos distintos cada vez (Novedosos, 15%), que era necesario ignorar. Por su parte, los estímulos visuales fueron números (33%) y letras (33%), ante los que había que presionar un botón distinto en cada caso (condición Go), y triángulos (34%) ante los que se debía inhibir la respuesta. En esta tarea, la atención del participante es, en ocasiones, atraída involuntariamente (atención involuntaria) por la presentación de los estímulos auditivos novedosos y discrepantes que preceden a los visuales.

Así, la presente tesis doctoral se divide en dos partes principales: (1) un primer estudio (**Estudio 1**), el cual tuvo como objetivo caracterizar y comparar los componentes MMN, P3a y RON entre participantes jóvenes (edad: 21-29 años), de mediana edad (edad: 51-64 años) y mayores (edad: 65-81 años); y (2) dos estudios (**Estudios 2 y 3**) que tuvieron como objetivo caracterizar los componentes de MMN y P3a en adultos con DCL (en comparación con controles sanos), para buscar posibles biomarcadores del DCL.

En el **Estudio 1**, se observaron mayores tiempos de reacción (TR) ante los estímulos visuales Go en los participantes de mediana edad y lo más mayores que en los jóvenes, un resultado que apoya la existencia de un enlentecimiento progresivo relacionado con el envejecimiento, el cual fue observado en varias tareas cognitivas (Salthouse, 2000). Además, en los tres grupos de edad, se observó un efecto de distracción provocado por los estímulos novedosos, ya que los TR fueron mayores cuando los estímulos visuales Go eran

precedidos por estímulos auditivos novedosos que por estímulos auditivos discrepantes y estándar.

Los componentes de los PEs en el **Estudio 1** fueron identificados en los trazados de la diferencia Novedoso *menos* Estándar (N-E) y Discrepante *menos* Estándar (D-E). Se observó que la latencia de MMN fue significativamente mayor en los adultos de mediana y mayor edad que en los participantes jóvenes en la condición N-E, lo que asociamos a un enlentecimiento en la detección automática de cambios en el entorno acústico. Adicionalmente, en ambos trazados de la diferencia se observó que el componente P3a presentó dos fases consecutivas en los tres grupos de edad: P3a temprana, a la que denominamos e-P3a, la cual podría reflejar la respuesta de orientación hacia la estimulación irrelevante, y P3a tardía, a la que denominamos como l-P3a, la cual podría ser un correlato de la evaluación posterior de los estímulos infrecuentes inesperados novedosos o discrepantes.

Las latencias de e-P3a, l-P3a y RON fueron significativamente mayores en los grupos de Mediana y Mayor edad que en el grupo de Jóvenes (en ambos trazados de la diferencia), indicando un enlentecimiento en la respuesta de orientación, la posterior evaluación de los estímulos auditivos no atendidos y la reorientación de la atención hacia los estímulos visuales relevantes (Go), respectivamente. Adicionalmente, en este estudio observamos que la amplitud de e-P3a fue significativamente menor en los grupos de Mediana y Mayor edad que en Jóvenes en el trazado N-E, con resultados similares para el trazado D-E, aunque en este último no hubo diferencias significativas entre los participantes jóvenes y los de mediana edad. La menor amplitud de e-P3a podría evidenciar un déficit en la respuesta de orientación hacia los estímulos auditivos novedosos y discrepantes irrelevantes.

Por otra parte, en el **Estudio 1**, observamos que los estímulos auditivos novedosos provocaron una detección automática más rápida de cambios en el entorno acústico, que los estímulos auditivos discrepantes, reflejado en una latencia más corta de MMN en el

trazado N-E que en el trazado D-E en los participantes jóvenes y de mediana edad. Además, en los tres grupos de edad, las amplitudes de e-P3a y l-P3a fueron significativamente mayores en N-E que en D-E, lo que podría indicar una mayor asignación de recursos de procesamiento en la respuesta de orientación a los estímulos novedosos, así como en la posterior evaluación de los mismos, que ante los estímulos discrepantes. Además, en los participantes jóvenes la latencia de e-P3a fue más corta en el trazado N-E que en D-E, lo que podría indicar que los estímulos auditivos novedosos provocan una orientación más rápida de la atención en estos participantes, sin embargo, en los participantes de mayor edad, la latencia de este componente fue más corta en D-E que en N-E, lo que podría reflejar el uso de diferentes estrategias de procesamiento de estímulos irrelevantes en los adultos mayores respecto a los jóvenes, como consecuencia de una reorganización neuronal que tiene lugar durante el envejecimiento sano (Goh & Park, 2009; Park & Reuter-Lorenz, 2009).

En el **Estudio 2**, ya centrado en el efecto del DCLa en MMN (medida en el trazado de la diferencia N-E), los participantes de la muestra fueron divididos en dos grupos: grupo Control y grupo con DCLa, los cuales realizaron dos evaluaciones separadas por un intervalo entre 18 y 24 meses. Además, en la primera evaluación cada grupo fue dividido en dos subgrupos de edad (50- 64 años y 65 años o más) para el análisis de los datos obtenidos.

En relación a la amplitud de MMN, observamos que, en la primera evaluación, este parámetro fue significativamente mayor en los participantes controles que en los participantes con DCLa, aunque solo en el grupo de Mediana edad, lo que podría indicar que los adultos con DCLa de mediana edad presentan algún tipo de deterioro en el mecanismo automático para detectar cambios en el entorno acústico. Sin embargo, la amplitud de la MMN no mostró diferencias entre adultos controles y adultos con DCLa con edades superiores a los 65 años, lo que posiblemente podría reflejar que los efectos del DCLa sobre la amplitud de MMN están enmascarados por déficits

relacionados a la edad en el mantenimiento de la huella de memoria ecoica.

En la segunda evaluación, la amplitud de este componente fue de nuevo significativamente mayor en los participantes controles que en los participantes con DCLa. Adicionalmente, los adultos con DCLa mostraron una disminución de la amplitud de MMN en la segunda evaluación respecto a la primera mientras que el grupo de adultos controles no mostraron cambios significativos, evidenciando la sensibilidad de la amplitud de MMN para reflejar el deterioro progresivo de las personas con DCLa.

Por otra parte, las curvas ROC evidenciaron que la amplitud de este componente puede ser un posible marcador psicofisiológico, específico y sensible, para la identificación de adultos con DCLa.

Además, la latencia de MMN fue significativamente más corta en los adultos con DCLa que en los adultos controles, resultado que solo se obtuvo en la primera evaluación, y que podría reflejar un cierre prematuro de la comparación automática entre cada estímulo novedoso con la representación mental del estímulo estándar, evidenciando un deterioro de la memoria ecoica en el DCLa.

Finalmente, el **Estudio 3** de la presente tesis doctoral, examinó los efectos del DCLau y el DCLam sobre el componente P3a de los PEs, razón por la cual los participantes de este estudio fueron divididos en tres grupos: un grupo Control, un grupo formado por participantes con DCLau, y otro grupo de participantes con DCLam. El componente P3a fue identificado en el trazado de la diferencia N-E, observándose dos fases diferenciadas de P3a en los tres grupos (e-P3a y l-P3a). Este hallazgo estaría en concordancia con lo observado en el **Estudio 1** en adultos sanos.

Los hallazgos del **Estudio 3** revelaron diferencias significativas entre los tres grupos de participantes para las amplitudes de e-P3a y l-P3a, sin embargo para las latencias no se observaron diferencias

significativas entre grupos. La amplitud de e-P3a fue significativamente mayor en los adultos con DCLam respecto a los adultos con DCLau, y la amplitud de l-P3a fue significativamente mayor en los adultos con DCLam que en los adultos con DCLau y los controles, lo que podría indicar que los participantes con DCLam presentan una mayor captura involuntaria de la atención hacia los estímulos auditivos novedosos no atendidos y una mayor asignación de recursos atencionales para la evaluación posterior de estos estímulos. Adicionalmente, las amplitudes de e-P3a y l-P3a se mostraron como posibles marcadores neurocognitivos óptimos para distinguir los diferentes grupos evaluados, con una sensibilidad y especificidad de moderada a alta.

Por otra parte, además de analizar el componente P3a, también se analizaron los TR y las respuestas correctas ante los estímulos Go, observando que los participantes con DCLam mostraron peor ejecución (menos respuestas correctas) que los participantes controles y con DCLau. En los tres grupos, los TR fueron significativamente mayores cuando los estímulos Go eran precedidos por estímulos auditivos novedosos (respecto a los estímulos estándar), lo que sugiere que los estímulos novedosos provocaron un efecto de distracción en los tres grupos , resultado que está en concordancia con lo obtenido en el **Estudio 1** en adultos sanos.

En conclusión, los componentes de los PEs MMN y P3a podrían ser marcadores psicofisiológicos útiles para diagnosticar el DCLa y distinguir entre subtipos (DCLau y DCLam), ya que la amplitud de MMN fue menor en adultos con DCLa que en controles sanos, y las amplitudes de e-P3a y l-P3a fueron mayores en adultos con DCLam respecto a adultos controles y con DCLau. Además, ambos componentes se pueden obtener en ausencia de atención voluntaria y mediante una técnica no invasiva, fácil de usar y más económica que otras (por ejemplo la resonancia magnética funcional [RMf]), características consideradas como óptimas para un biomarcador.

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