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The importance of age in the search for ERP biomarkers of aMCI

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ABSTRACT

Alzheimer's Disease (AD) has become a major health issue in recent decades, and there is now growing interest in amnestic mild cognitive impairment (aMCI), an intermediate stage between healthy aging and dementia, usually AD. Event-related brain potential (ERP) studies have sometimes failed to detect differences between aMCI and control participants in the Go-P3 (or P3b, related to target classification processes in a variety of tasks) and NoGo-P3 (related to response inhibition processes, mainly in Go/NoGo tasks) ERP components. The aim of the present study was to evaluate whether the age factor, which is not usually taken into account in ERP studies, modulates group differences in these components. With this aim, we divided two groups of volunteer participants, 34 subjects with aMCI (51–87 years) and 31 controls (52–86 years), into two age subgroups: 69 years or less and 70 years or more. We recorded brain activity while the participants performed a distraction-attention auditory-visual (AV) task. Task performance was poorer in the older than in the younger group, and aMCI participants produced fewer correct responses than the matched controls; but no interactions of the age and group factors on performance were found. On the other hand, Go-P3 and NoGo-N2 latencies were longer in aMCI participants than in controls only in the younger subgroup. Thus, the younger aMCI participants categorized the Go stimuli in working memory and processed the NoGo stimuli (which required response inhibition) slower than the corresponding controls. Finally, the combination of the number of hits, Go-P3 latency and NoGo-N2 latency yielded acceptable sensitivity and specificity scores (0.70 and 0.92, respectively) as regards distinguishing aMCI participants aged 69 years or less from the age-matched controls. The findings indicate age should be taken into account in the search for aMCI biomarkers.

1. Introduction

The world's population is aging, owing to decreased birth rates and increased life expectancy (Park & Reuter-Lorenz, 2009). The accelerated increase in aging is accompanied by an increase in the prevalence of neurodegenerative diseases.

Alzheimer's Disease (AD) is the most common form of dementia and is becoming increasingly more prevalent (Andreasen & Blennow, 2005; Bennys, Rondouin, Benattar, Gabelle, & Touchon, 2011), at great cost to affected individuals and their families and to society as a whole (Park & Reuter-Lorenz, 2009). The prevalence and incidence rates of AD increases exponentially with age, with the most notable rise from 70 years on, as the late-onset form of AD accounts for more of the 95% of affected (Reitz, Brayne, & Mayeux, 2011).

However, most AD patients experience some memory decline before reaching the clinical threshold for the diagnosis of AD (Petersen et al., 2001). The state in which there is greater memory loss than expected for normal aging, but which does not affect daily living and does not meet the criteria for AD, is termed amnestic Mild Cognitive Impairment (aMCI; Petersen et al., 2001, 2009). Individuals with aMCI show an increased risk of developing AD relative to healthy aging: longitudinal studies have revealed that aMCI patients have an 80% chance of developing AD within 6 years of diagnosis (Petersen et al., 2001, 2009, 1999). The prevalence of MCI at present is difficult to calculate, as it depends on the precise diagnostic criteria (Ward, Arrighi, Michels, & Cedarbaum, 2012). Despite this, as AD increases doubles every 5 years after age 65 (Jones, Bruns, & Petersen, 2017), it is worthy to evaluate adults with aMCI from several years before that age.

Characterization of aMCI is important to enable correct diagnosis and prognosis, thus increasing the probability of clinical intervention before brain damage becomes irreversible (Bredesen, 2014). The search for aMCI markers has therefore received a great deal of attention in the last two decades. Useful biomarkers should be able to detect the neuropathology and must be validated in neuropathologically confirmed cases. In addition, biomarkers should also be precise, reliable, non-invasive, simple to obtain and inexpensive (Thies, Truschke, Morrison-Bogorad, & Hodes, 1998). Although several aMCI biomarkers have been proposed (Albert et al., 2011), they are expensive (e.g. functional

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magnetic resonance imaging) and/or invasive (e.g. positron emission tomography, cerebrospinal fluid measures) and have either not been validated (Jack et al., 2011) or show limited sensitivity and specificity (DeKosky & Marek, 2003; Reitz & Mayeux, 2014; Reitz et al., 2011).

The event-related brain potentials (ERP) technique is a suitable tool for use in the search for biomarkers, as it is non-invasive and relatively inexpensive, and has already shown to be useful in the search for biomarkers of aMCI and AD (e.g. Cespón, Galdo-Álvarez, & Díaz, 2013; Cespón, Galdo-Álvarez, & Díaz, 2015; Cespón, Galdo-Álvarez, Pereiro, & Díaz, 2015; Correa-Jaraba, Lindín, & Díaz, 2018; Lindín, Correa, Zurrón, & Díaz, 2013; for reviews, see Jackson & Snyder, 2008; Vecchio & Määttä, 2011).

In previous studies involving the search for biomarkers of aMCI, we used the ERP technique to record the brain activity of participants while they performed a distraction-attention auditory-visual (AV) task (Cid-Fernández, Lindín, & Díaz, 2017; Cid-Fernández, Lindín, & Díaz, 2017; Cid-Fernández, Lindín, & Díaz, 2014; Lindín et al., 2013). In this task, participants are presented with pairs of auditory-visual stimuli, and they are asked to attend to the visual stimuli (making a Go/NoGo task) and to ignore the auditory stimuli (consisting of a passive oddball task with three stimuli: standard, deviant and novel). The following ERP components associated with the processing of visual stimuli (preceded by standard auditory stimuli) were identified and evaluated: (1) N2b (Go-N2) and P3b (Go-P3), in response to Go visual stimuli, and (2) NoGo-N2 and NoGo-P3, in response to NoGo visual stimuli. The Go-N2 and NoGo-N2 amplitudes were smaller in aMCI than in control participants, indicating deficits in the evaluation of target stimuli in working memory (WM) and in response inhibition processes, respectively, in participants with aMCI. No differences were observed between the groups in relation to the Go- and NoGo-P3 components, or in Go- and NoGo-N2 latencies (Cid-Fernández et al., 2014b, 2017a; Mudar et al., 2016).

Go-P3 (or P3b) is a widely studied ERP component, typically maximal at parietal electrodes in young adults, with latencies of 300–700 ms after stimulus presentation. The stimuli that elicit this ERP component are attended stimuli that require a response, e.g. the target stimuli of an *oddball* task, or the *Go* stimuli of a *Go/NoGo* task. Go-P3 is typically interpreted as a correlate of context updating (when a target stimulus is presented) or of stimulus classification in working memory (Coles & Rugg, 1996; Donchin & Coles, 1988; Kutas, Iragui, & Hillyard, 1994). Most studies using an oddball task have reported longer P3b latencies in aMCI patients than in healthy controls (e. g. Bennys, Portet, Touchon, & Rondouin, 2007; Lai, Lin, Liou, & Liu, 2010; Li et al., 2010; Papadaniil et al., 2016; Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008; Parra, Ascencio, Urquina, Manes, & Ibáñez, 2012), although other studies did not observe any differences (Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2011). Regarding the P3b amplitude, most studies did not reveal differences between groups (e. g. Bennys et al., 2007; Golob, Irimajiri, & Starr, 2007; Lai et al., 2010; Papadaniil et al., 2016; Papaliagkas et al., 2008, 2011), although in some studies this parameter was significantly smaller in aMCI patients than in healthy controls (Li et al., 2010; Parra et al., 2012).

On the other hand, the NoGo-P3 component peaks around the 300–500 latency window at central electrodes after presentation of a *NoGo* stimulus that requires a prepotent response to be withheld. This has been interpreted as an index of response inhibition processes (Bokura, Yamaguchi, & Kobayashi, 2001; Jackson, Jackson, & Roberts, 1999; Nakata, Sakamoto, Inui, Hoshiyama, & Kakigi, 2009). Studies evaluating the NoGo-P3 parameters have generally not found any differences between MCI participants and controls (2017a, Cid-Fernández, Lindín, & Díaz, 2014; Mudar et al., 2016). However, López Zunini et al. (2016) observed smaller NoGo-P3 amplitudes in aMCI than in control participants, interpreting this result as an indicator of impaired motor response inhibition processes in aMCI.

In two previous ERP studies carried out in our laboratory, differences between aMCI participants and healthy controls were observed, but only when the sample was split into different age groups. Lindín et al. (2013) used the AV task and analyzed the mismatch negativity (MMN), a component related to automatic and pre-attentive processing of stimuli (Näätänen, Paavilainen, Rinne, & Alho, 2007). The MMN amplitude was smaller in the aMCI than in the control participants, but only in the group aged 50–64 years and not in older participants (Lindín et al., 2013). In addition, in a Stroop task study, Ramos-Goicoa, Galdo-Álvarez, Díaz, and Zurrón, (2016) observed longer P3b latency in aMCI than in healthy participants, but only in the younger subgroup (64 years old or less). Altogether these results show that some important effects (and potential aMCI biomarkers) may be masked when the age factor is not taken into account in the analyses. Indeed, Ramos-Goicoa et al. (2016) suggested that the age factor may have some influence in the mixed results found in the literature regarding P3b latency.

In line with this observation, the age ranges of the mentioned studies differ considerably: while the participants of the study that observed group differences in P3b latency are the youngest (younger subgroups age range = 51–64 years old; Ramos-Goicoa et al., 2016) those of studies that did not find such differences were quite (Mudar et al., 2016; age range = 54–86 years old; aMCI mean age = 68.5 years old; control mean age = 65.4 years old) or much (López Zunini et al., 2016; aMCI mean age = 75.6 years old; control mean age = 72.4 years old) older. On the other hand, only the study that used the eldest sample was able to observe differences regarding P3b amplitude, as this parameter was larger in the control than in the aMCI group (López Zunini et al., 2016).

In the present study, we used the AV task to evaluate (1) possible differences between control (healthy) participants and aMCI participants in task performance (reaction time -RT- and number of correct responses), in the Go-N2 and -P3 ERP components (in response to visual stimuli that required a response), and in the NoGo-N2 and -P3 ERP components (in response to visual stimuli that required to withhold a prepotent response); and (2) whether these differences are modulated by age. For this purpose, two age subgroups were established for statistical comparison: participants aged 69 years or less and participants 70 years or more. We tested whether the Age factor interacts with the Group factor (aMCI *vs* controls), to clarify whether important group effects on the parameters of the aforementioned ERP components may be overlooked.

According to previous reports, we expected to find differences between groups in the behavioural measures, with poorer performance in the aMCI than in the control participants (longer RT and fewer correct responses). By contrast, we did not expect to find any general group differences in the Go- and NoGo-P3 latencies, and only expected to find longer Go-P3 latencies in the aMCI than in the control participants in the younger subgroups, in accordance with Ramos-Goicoa et al. (2016). In addition, we did not expect to find group differences for the Go-P3 amplitude, in the global sample or in either of the age subgroups. Finally, we were also expecting to find some age-dependent differences between groups for the Go-N2 (or N2b) and NoGo-N2 latencies, as (1) in previous studies using the A-V task we failed to observe any group differences regarding these parameters, and (2) it seems that there are significant changes in the N200 subcomponents in MCI adults compared to healthy adults across studies, despite some contradictions between results (for a review see Howe, 2014).

2. Materials and methods

2.1. Participants

Sixty-five volunteers were recruited from Primary Care Health Centers in Santiago de Compostela, Galicia (Spain), after being referred to our research group by their general practitioners (GPs). The participants had no history of clinical stroke, traumatic brain injury, motor-sensory deficits or alcohol or drug abuse/dependence, and they were not diagnosed with any significant medical or psychiatric illnesses.

Each participant then underwent the following neuropsychological tests: 1) the Spanish version of the Mini-Mental State Examination (MMSE; Lobo et al., 1999); 2) the Spanish version of the Californian Verbal Learning Test (CVLT; Benedet Álvarez & Alexandre, 1998), which assesses short-delay free recall, short-delay recall with semantic cues, and long-delay free recall; 3) the Spanish version of the Cambridge Cognitive Examination (CAMCOG-R), which assesses deterioration in specific domains, such as language, attention-calculation, praxis, perception and executive functioning (Huppert et al., 1996); and (4) the Spanish version of the Lawton-Brody Instrumental Activities of Daily Living (IADL) scale (Vergara et al., 2012).

Participants were classified into two groups: Control (31 subjects, aged between 52 and 86 years, with normal cognitive functioning) and aMCI (34 subjects aged between 51 and 87 years). The aMCI participants met the general criteria for MCI outlined by Albert et al. (2011) and the criteria for aMCI proposed by Petersen (2004). Thus, all aMCI participants fulfilled the following criteria: 1) memory complaints corroborated by an informant; 2) performance of less than 1.5 SDs below age norms in the CVLT; 3) no significant impact on activities of daily living; and 4) no dementia. For a more extensive description of the global samples, see Juncos-Rabadán, Facal, Lojo-Seoane, and Pereiro (2013). The aMCI and control participants were matched according to age and level of education.

In order to evaluate whether the age factor modulates the differences between the groups, two subgroups were established in each group: 69 years or less and 70 years or more. In each age subgroup, aMCI and control participants were also matched according to age and level of education. The demographic and neuropsychological measures of the participants are summarized in Table 1, together with the differences between groups, calculated by the corresponding analysis.

To control for the effects of depression, volunteers with scores of more than 10 in depression screening (Geriatric Depression Scale; Yesavage et al., 1983) were not included in the study. All participants had normal audition and normal or corrected-to-normal vision. All were right-handed, as assessed by the Edinburgh inventory (Oldfield, 1971). Right after the neuropsychological evaluation, participants underwent the psychophysiological evaluation.

In addition, all participants gave their written informed consent prior to taking part in the study. The research project was approved by the Galician Clinical Research Ethics Committee (Xunta de Galicia, Spain). The study was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki (Lynöe, Sandlund, Dahlqvist, & Jacobsson, 1991).

2.2. Procedure

The distraction-attention auditory-visual task was adapted from Escera, Alho, Winkler, and Näätänen, (1998). Participants were presented with 500 pairs of auditory-visual (A-V) stimuli. Each pair of stimuli consisted of a visual stimulus (200 ms duration) preceded by an auditory stimulus (150 ms duration), separated by an interval of 300 ms (SOA). Each pair of stimuli was separated by an interval of 2 s. Participants were asked to attend to the visual stimuli and to ignore the auditory stimuli. They should respond pressing one button with one hand if the visual stimulus was a letter, another button with the other hand if it was a number (33% each; Go stimuli), and withhold their responses if it was a triangle (34%; NoGo stimuli). The task procedure is further explained in Cid-Fernández et al. (2017b; see Fig. 1; and 2017b).

2.3. EEG recording

The EEG was recorded via 49 electrodes placed in an elastic cap (Easycap, GmbH), according to the International 10-10 System. All electrodes were referenced to an electrode attached to the tip of the nose, and an electrode positioned at Fpz served as ground. The horizontal electrooculogram (EOG) was recorded via two electrodes placed at the outer canthi of both eyes, whereas the vertical EOG was recorded via two electrodes placed supra and infraorbitally to the right eye. The EEG was continuously digitized at a rate of 500 Hz (bandpass 0.01–100 Hz), and the electrode impedance was maintained below 10 k Ω.

Once the signal was stored, it was passed through a digital 0.1–30 Hz (24 dB/octave slope) bandpass filter, and ocular artefacts were corrected using the Gratton, Coles & Donchin method (Gratton, Coles, & Donchin, 1983).

With the aim of evaluating the ERP components of interest (Go-N2, NoGo-N2, Go-P3 and NoGo-P3 components), the EEG was segmented by extraction of auditory stimulus-locked epochs of 1450 ms (150 ms pre-auditory stimulus). The epochs composed by the standard auditory-target visual pairs with correct responses were evaluated. All epochs were corrected to the mean voltage of the first 150 ms of each epoch, and segments exceeding ± 100 μV were automatically rejected. The epochs were then averaged separately for the Go and NoGo trials (Go and NoGo conditions, respectively), and a minimum of 38 artefact-free epochs were averaged for each condition.

Table 1
Mean values and standard deviations (in parentheses) of the demographical and neuropsychological measures considered.

	C N = 31	aMCI N = 34	p ≤ *	C ≤ 69 y.o. N = 13	aMCI ≤ 69 y.o. N = 17	p ≤ *	C ≥ 70 y.o. N = 18	aMCI ≥ 70 y.o. N = 17	p ≤ *
Age	69.6 (9.5)	69.9 (9.1)	.896	60.1 (5.8)	62.7 (5.6)	.228	76.4 (4.0)	77.1 (5.4)	.675
Years of education	9.1 (5.0)	9.1 (4.5)	.984	9.8 (5.5)	9.7 (4.5)	.947	8.6 (4.6)	8.5 (4.5)	.987
Sex (Women/Men)	22/9	19/15		9/4	8/9		13/5	11/6	
MMSE	28.0 (1.8)	25.7 (2.5)	.001	28.6 (1.2)	26.3 (2.0)	.001	27.6 (2.1)	25.0 (2.8)	.004
CVLT (short-delay free recall)	8.9 (3.1)	3.7 (1.9)	.001	11.2 (2.5)	4.7 (1.4)	.001	7.2 (2.3)	2.6 (1.7)	.001
CVLT (short-delay cued recall)	10.4 (3.2)	5.5 (2.2)	.001	12.6 (1.9)	6.4 (1.7)	.001	8.9 (3.1)	4.5 (2.4)	.001
CVLT (long-delay free recall)	9.8 (3.5)	4.1 (3.1)	.001	12.5 (2.9)	5.3 (2.7)	.001	8.2 (3.0)	2.9 (3.0)	.001
CVLT (long-delay cued recall)	10.6 (3.3)	5.7 (2.7)	.001	12.5 (2.1)	6.5 (1.9)	.001	9.2 (3.4)	5.0 (3.2)	.001
CAMCOG-R (Orientation)	9.4 (0.9)	9.1 (1.0)	.146	9.9 (0.4)	9.4 (0.7)	.056	9.1 (1.1)	8.7 (1.2)	.303
CAMCOG-R (Language)	24.9 (2.1)	24.3 (2.9)	.293	25.8 (2.1)	24.7 (2.4)	.219	24.3 (1.9)	23.8 (3.3)	.579
CAMCOG-R (Attention and Calculation)	7.4 (1.5)	6.4 (2.3)	.036	7.6 (1.6)	6.6 (2.3)	.177	7.2 (1.4)	6.1 (2.3)	.097
CAMCOG-R (Praxis)	10.9 (1.3)	9.9 (2.6)	.058	11.1 (1.3)	9.8 (2.7)	.136	10.7 (1.3)	9.9 (2.5)	.250
CAMCOG-R (Perception)	6.3 (1.5)	6.2 (1.5)	.888	6.5 (1.7)	6.5 (1.4)	.987	6.1 (1.4)	5.9 (1.6)	.737
CAMCOG-R (Executive function)	15.9 (5.2)	14.6 (4.1)	.249	18.6 (6.0)	15.5 (3.9)	.092	13.9 (3.6)	13.7 (4.2)	.823

C: control group; aMCI: amnestic MCI group; y.o.: years old; MMSE: Mini-Mental State Examination; CVLT: California Verbal Learning Test; CAMCOG-R: Cambridge Cognitive Examination.

* ANOVA (Group), signification level < 0.05.

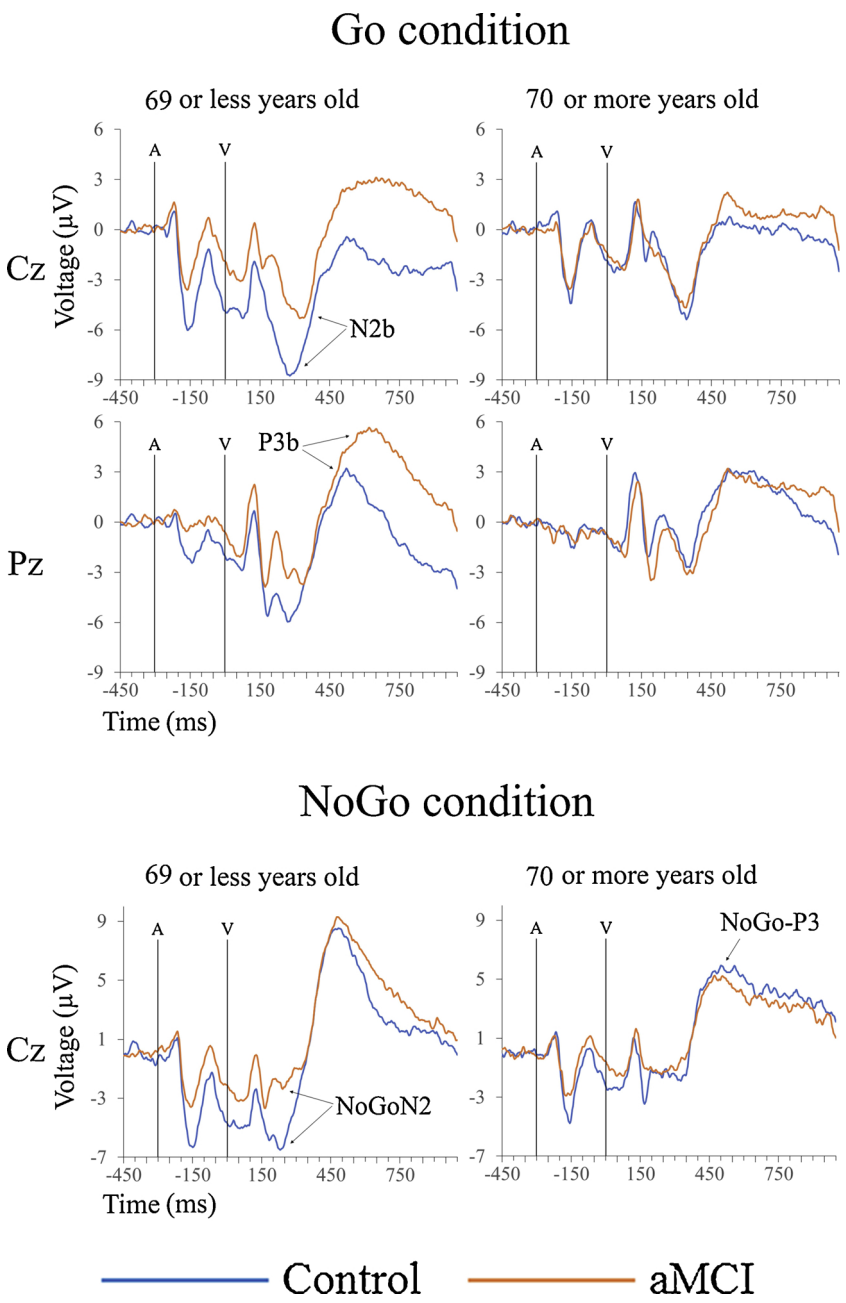

Fig. 1. Grand-average event-related brain potential waveforms for the age subgroups in the control (blue/light grey line) and aMCI (orange/dark grey line) groups, for each condition (Go: upper panel; NoGo: lower panel) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2.4. Data analysis

Reaction times (RTs, between the onset of the visual stimulus and pressing the key) for correct responses and the number of correct responses (Hits) were evaluated in the Go condition.

The Go-N2 (in the 250–430 ms interval) and the Go-P3 (in the 450–750 ms interval) components (after the Go visual stimulus), and the NoGo-N2 (in the 200–360 ms interval) and the NoGo-P3 (in the 400–650 ms interval) components (after the NoGo visual stimulus) were also evaluated. The peak amplitudes (in microvolts) and latencies (in milliseconds) of the Go- and NoGo-N2 and -P3 components were evaluated at the midline electrode where the amplitude was maximal (Pz for Go-P3, Cz for Go-N2, NoGo-N2 and NoGo-P3).

2.5. Statistical analysis

Two-factor analysis of variance (ANOVA), with the between-subject factors *Group* (two levels: Control, aMCI) and *Age* (two levels: 69 or less years old and 70 or more years old), was applied to the RTs, Hits and amplitudes and latencies of the Go-N2 and -P3 and the NoGo-N2 and -P3 components. Whenever the ANOVAs revealed significant effects due to the factors or their interactions, post hoc comparisons of the mean values (adjusted to Bonferroni correction) were conducted. Differences were considered significant at $p \leq 0.05$.

Finally, receiver operating characteristic (ROC) curves were constructed for those ERP and behavioral parameters in which the Group factor exerted a significant main effect or interaction. These parameters

Table 2
Number of correct responses (Hits) and reaction times (RT, from the visual stimulus onset to the button press), and amplitudes (in microvolts) and latencies (in milliseconds, from the visual stimulus onset) for P3b and NoGo-P3 components for each age group.

	YOUNGER (≤ 69 years old)		OLDER (≥ 70 years old)	
	CONTROL	aMCI	CONTROL	aMCI
Hits	224.2 (5.2)	215.5 (19.3)	210.1 (21.0)	200.3 (25.7)
RT	605.5 (86.7)	640.6 (64.4)	660.5 (107.3)	679.6 (96.2)
N2b Amp (Cz)	−10.3 (7.0)	−6.4 (4.6)	−6.7 (9.2)	−5.2 (4.8)
N2b Lat (Cz)	583.5 (49.1)	625.8 (33.2)	620.3 (60.8)	630.4 (65.7)
NoGo-N2 Amp (Cz)	−8.0 (6.2)	−4.1 (3.4)	−4.7 (7.2)	−3.6 (3.0)
NoGo-N2 Lat (Cz)	536.2 (22.7)	578.4 (51.4)	598.5 (58.9)	570.0 (64.2)
P3b Amp (Pz)	4.6 (7.4)	7.4 (5.9)	8.4 (9.1)	6.4 (5.7)
P3b Lat (Pz)	528.5 (80.4)	597.4 (87.9)	588.1 (111.1)	547.3 (108.1)
NoGo-P3 Amp (Cz)	10.8 (4.9)	11.0 (4.9)	10.4 (7.2)	11.0 (7.6)
NoGo-P3 Lat (Cz)	477.0 (74.4)	504.4 (53.5)	521.9 (77.2)	501.4 (97.2)

RT: reaction time; Amp: amplitude; Lat: latency.

were also combined by constructing a binary logistic regression model, with the parameters included as the explanatory variables (covariates) and the group of interest as the dependent variable. The predicted probabilities were saved as a new variable and ROC curves were computed. An area under the curve (AUC) of 1.0 corresponds to a perfect prediction, whereas a value of 0.5 indicates a useless model.

3. Results

The RTs, number of hits, and amplitudes and latencies of the Go- and NoGo-N2, and Go- and NoGo-P3 components are summarized in Table 2, and the ERP waveforms evaluated are depicted in Fig. 1.

3.1. Behavioural measures

The two factor ANOVA (Group x Age) applied to the RTs revealed a significant effect of the *Age* factor ($F(1, 59) = 4.2$, $p = .045$), as this parameter was significantly longer in the older (70 or more years old) than in the younger (69 or less years old) participants (see Table 2). There were no other significant effects or interactions regarding the RTs.

The two factor ANOVA (Group x Age) applied to the number of hits also revealed a significant effect of the *Age* factor ($F(1, 59) = 8.6$, $p = .005$), as this parameter was significantly smaller in the older than in the younger participants (see Table 2). In addition, a marginally significant effect of the *Group* factor was observed ($F(1, 59) = 3.4$, $p = .07$), as this parameter was smaller in the aMCI than in the Control group (see Table 2). No significant interaction of the factors was observed.

3.2. ERP components

3.2.1. Go-N2 and NoGo-N2

The two-factor ANOVAs (Group × Age) did not show any significant main effects or interactions of the factors for the Go-N2 amplitude and latency or the NoGo-N2 amplitude at the Cz electrode location.

The two-factor ANOVA (Group × Age) applied to the NoGo-N2 latency at Cz showed a significant effect of the *Group* × *Age* interaction ($F(1, 50) = 6.1$, $p = .017$), as this parameter was significantly longer ($p = .004$) in the aMCI than in the control participants, but only in the younger subgroup (69 or less years old), and significantly longer ($p = .039$) in the elder controls (70 or more years old) than in the younger controls (69 or less years old; see Fig. 1).

3.2.2. Go-P3 and NoGo-P3

The two factor ANOVAs (Group × Age) applied to the Go-P3 amplitude at Pz, did not show any significant main effects or interactions.

The two factor ANOVA (Group × Age) applied to the Go-P3 latency at Pz revealed a significant effect of the *Group* × *Age* interaction ($F(1, 54) = 4.5$, $p = .039$), as this parameter was significantly longer in the aMCI than in the control participants, but only in the younger subgroup (≤ 69 years old; $p = .049$; see Fig. 1).

The two factor ANOVAs (Group × Age) applied to the NoGo-P3 amplitude and latency at Cz did not show any significant main effects or interactions of the factors.

3.3. ROC curves

The number of hits discriminated groups (aMCI *versus* controls) with sensitivity and specificity scores of 0.59 and 0.62, respectively (AUC = .68). In addition, the Go-P3 latency (at Pz) showed sensitivity and specificity scores of 0.65 and 0.66, respectively, for distinguishing control and aMCI participants aged ≤ 69 years (AUC = 0.71). For the same comparison (control *versus* aMCI in the younger subgroup), the NoGo-N2 latency (at Cz) showed sensitivity and specificity scores of 0.60 and 0.67, respectively.

The number of hits and Go-P3 latency at Pz were then combined with the aim of distinguishing aMCI participants aged ≤ 69 years from their control counterparts, yielding a sensitivity score of 0.82 and a specificity score of 0.75 (AUC = 0.79). For the same comparison, the combination of NoGo-N2 latency (at Cz) and Go-P3 latency (at Pz) yielded sensitivity and specificity scores of 0.70 and 0.67, respectively, while the combination of NoGo-N2 latency at Cz and the number of hits yielded sensitivity and specificity scores of 0.80 and 0.75, respectively.

Finally, the three parameters (number of hits, NoGo-N2 latency at Cz and Go-P3 latency at Pz) were combined with the aim of distinguishing aMCI from control participants of 69 years-old or less, obtaining a sensitivity score of 0.70 and a specificity score of 0.92.

4. Discussion

The RT was significantly longer and the number of hits significantly lower in the older (≥ 70 years old) than in the younger (≤ 69 years old) participants. In addition, the number of hits was lower in the aMCI than in the Control group (although this effect was only marginally significant). The Go-P3 (or P3b) and the NoGo-N2 latencies were significantly longer in the aMCI than in the control participants, but only in the younger subgroup (≤ 69 years old). In addition, the NoGo-N2 latency was significantly longer in the older than in the younger participants, but only in the control group.

It is generally agreed that older adults react more slowly than younger adults, as demonstrated in a variety of cognitive tasks (Glisky, 2007; Salthouse, 2000). In fact, the slower RT in the older than in the younger participants supports previous findings obtained with the AV task in healthy subjects (Cid-Fernández, Lindín, & Díaz, 2016) and with other tasks in healthy subjects (Lucci et al., 2013) and subjects with aMCI (Ramos-Goicoa et al., 2016). However, the differences between groups in this parameter are not always statistically significant (e.g. Cid-Fernández et al., 2014b; Correa-Jaraba, Cid-Fernández, Lindín, & Díaz, 2016).

Moreover, the older participants provided fewer correct responses than the younger participants. Although a similar tendency was observed in previous studies using the AV task, the differences was not found to be statistically significant (Cid-Fernández et al., 2014b, 2016). The discrepancy in the results of the different studies may be due to the different age cut-off used here (69/70 years old in the present study; 64/65 years old in the previous studies). Besides, it seems that the general increase in RTs across aging studies is usually associated with little or no decrease in accuracy (Ratcliff, Thapar, & McKoon, 2010). In addition, the control participants provided a greater number of correct

responses than the aMCI participants, although the difference was only marginally significant (0.07). This is consistent with the findings of a previous study using the AV task (Cid-Fernández et al., 2014a), where this result was significant.

Regarding the ERP parameters, the aMCI participants showed longer Go-P3 and NoGo-N2 latencies than control participants, but only those in the younger subgroup. This may indicate that the aMCI participants aged 69 years or less old categorized the Go stimuli in the working memory more slowly and were slower regarding early response inhibition processing than their control counterparts. However, this difference was not observed in the participants aged 70 years or more. The latency values show that the evident (and significant) difference between the younger aMCI and control participants disappears in the older subgroups (see Table 2 and Fig. 1).

These results may be able to explain at least in part the contradictory results reported in other studies regarding Go/NoGo tasks performed by aMCI participants. On one hand, López Zunini et al. (2016) did not find any group differences between aMCI and control participants in the latencies of the NoGo-N2 and Go and NoGo-P3 ERP components. The mean ages of their participants (control, mean age = 72.4 y-o; aMCI, mean age = 75.6 y-o) resemble the mean ages of our elderly subgroup, so it is reasonable that they were not able to capture differences in latencies between control and aMCI participants as those observed in the present study in the younger age subgroup.

On the other hand, Mudar et al. (2016) found group differences in N2 latency (globally, including both Go- and NoGo-N2), as this parameter was longer in the aMCI than in the control group. The mean ages of their groups (control, mean age = 65.4 y-o; aMCI, mean age = 68.5 y-o) are much more alike our younger subgroup, so it is possible that they were able to capture this global effect due to the age of their sample (younger than in López Zunini et al., 2016). However, they did not find differences in Go-P3 latency as those reported in this study, but this might be explained by the different age range of the aMCI adults, as in Mudar et al. (2016) it was slightly higher than in our study (our study = 51 years-old onwards, their study = 57 years-old onwards).

The present results may reflect a decline in aMCI that becomes evident early in aging (slower Go-P3 latency and slower NoGo-N2 latency in younger aMCI relative to younger healthy adults), and intriguingly disappears in later aging stages (absence of differences in Go-P3 and NoGo-N2 latencies between older aMCI relative to older healthy adults). Although we are not able to infer the cause of this pattern from this study, it might reflect a hypothetical compensatory mechanism that would allow the aMCI patients to preserve their speed of stimulus categorization after an early decline. Alternatively, this result might indicate that those adults diagnosed with aMCI at an earlier age may show larger impairments than those diagnosed later in aging. Any of these hypotheses should be tested in future studies.

Ramos-Goicoa et al. (2016) also observed longer Go-P3 latencies in middle-aged aMCI participants than in age-matched controls using a Stroop task and a quite lower cut-off age (64/65 years old; age range of the younger subgroups: 51–64 years old), indicating that regardless of the cause of this effect it seems to be quite robust across tasks in relatively young elderly. Hence, the age factor can mask some interesting effects in the search for aMCI biomarkers, and might account for some of the contradictory results in the literature regarding P3b and other ERP components.

On the other hand, N2 amplitudes did not show any group differences, as in previous studies (López Zunini et al., 2016; Mudar et al., 2016). Using the AV task, a previous study observed lower Go- and NoGo-N2 amplitudes in aMCI than in control participants in the Standard Condition (standard auditory-visual stimuli pairs; Cid-Fernández et al., 2014b), while another study did only observe differences between groups in this condition for Go-N2 amplitude as a marginally significant effect (Cid-Fernández et al., 2017b). In the present study (see Fig. 1 and Table 2), there is a tendency in line with the significant results discussed throughout this article: it seems that Go- and NoGo-N2 amplitude might differ between groups (aMCI and controls) only in the younger subgroup, and therefore might account for the apparently contradictory results regarding these parameters in previous literature. This hypothesis should be tested in future studies using larger samples, where probably would reach significance.

Regarding the ROC curves, the Go-P3 latency, the NoGo-N2 latency and the number of correct responses alone did not yield sensitivity and specificity scores (equal or over 0.70) that would enable groups to be distinguished. The same was true for the combination of the NoGo-N2 and Go-P3 latencies. However, the combination of the Go-P3 latency and the number of hits may be useful for distinguishing aMCI from control participants of age 69 years or less (sensitivity = 0.82 and specificity = 0.75). Similar results were found for the combination of the NoGo-N2 latency and the number of hits (sensitivity = 0.80 and specificity = 0.75), and for the combination of the three parameters (sensitivity = 0.70, specificity = 0.92).

Finally, it is worth noting that the results of the present study might be restricted to cognitive control tasks. More ERP studies evaluating these components, with other tasks and larger samples, would be necessary to draw more general conclusions about the modulations of age in the search of aMCI biomarkers.

5. Conclusions

Task performance was worse in the older old participants ($\geq$70 years old) (longer RTs and less correct responses) than in the younger old participants (50–69 years old). In addition, the aMCI participants processed both the Go and the NoGo stimuli more slowly than the control participants (longer NoGo-N2 and Go-P3 latencies in the former), although only in the younger old subgroup.

In conclusion, aMCI was found to affect NoGo-N2 and Go-P3 latencies in this study because modulation by the age factor on the group effects was taken into account. Hence, it seems important to consider this factor in future studies aiming to search for ERP biomarkers of aMCI.

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