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Event-related brain potential indexes provide evidence for some decline in healthy people with subjective memory complaints during target evaluation and response inhibition processing

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ABSTRACT

In the preclinical stage of the Alzheimer's disease (AD) continuum, subjects report subjective memory complaints (SMCs), although with the absence of any objective decline, and have a higher risk of progressing to dementia than the general population. Early identification of this stage therefore constitutes a major focus of current AD research, to enable early intervention. In this study, healthy adult participants with high and low SMCs (HSMCs and LSMCs) performed a Go/NoGo task during electroencephalogram (EEG) recording. Relative to LSMC participants, HSMC participants performed the task slower (longer reaction times) and showed changes in the event-related potential (ERP) components associated with response preparation (lower readiness potential -RP- amplitude in the Go condition), and also related to response inhibition processes (lower N2-P3 amplitude in the NoGo condition). In addition, HSMC participants showed lower Go-N2 and NoGo-N2 peak-to-baseline amplitudes, however these results seem to be influenced by a negative tendency overlapping stimulus-related waveforms. The declines observed in this study are mostly consistent with those observed in aMCI participants, supporting the notion of the AD continuum regarding SMC state.

1. Introduction

Alzheimer's Disease (AD) has become a major health and social issue in the last few decades due to population aging. However, there are currently no effective treatments that can reverse or at least halt the progress of this neurodegenerative disease, and efforts are increasingly focused on prevention. AD is defined as a continuum that ranges from healthy aging to dementia, with two intermediate stages in which disease biomarkers such as β-amyloid and p-tau are detected: a preclinical, asymptomatic stage, and a prodromal stage with mild symptoms (Albert et al., 2011; Jack et al., 2011; 2018;; McKhann et al., 2011; Sperling et al., 2011). The prodromal stage between healthy cognitive aging and dementia due to AD was initially designated amnestic Mild Cognitive Impairment (aMCI) and was defined as a syndrome that comprises subjective and objective memory impairment (with or without impairment in other cognitive domains, referred to respectively as multi-domain and single-domain MCI) that does not affect basic activities of daily living (Petersen et al., 2014). In addition, an earlier manifestation of AD has been identified: subjects who report a subjective impression of memory impairment, while their cognitive performance in neuropsychological tests is normal according to sex, age and education norms (Jonker, Jonker, & Schmand, 2000; Reisberg & Gauthier, 2008; Stewart, 2012). This condition is referred to as Subjective Memory Complaints (SMCs) or Subjective Memory Impairment (SMI).

In accordance with the continuum concept (Jack et al., 2018), adults with SMCs have an increased risk of progression to MCI and dementia due to AD, relative to the general population (Dickerson, Sperling, Hyman, Albert, & Blacker, 2007; Jessen et al., 2010, 2014; 2011;; Rönnlund, Sundström, Adolfsson, & Nilsson, 2015). In fact, these adults exhibit early AD pathology, with greater temporal and frontal brain atrophy (Jessen et al., 2006; Jung et al., 2016; Scheef et al., 2012; Toledo et al., 2015) as well as a higher prevalence of pathophysiological AD markers than people who do not report SMCs (Visser et al., 2009). Hence, identification of biomarkers in adults with SMCs may be valuable for the preclinical characterization of early stages of AD, several years before the disease causes dementia.

Despite the fact that episodic memory is the hallmark for the AD continuum, extensive literature indicates that also other cognitive

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domains show impairments in prodromal and preclinical stages of this condition, including language (e. g. Amaefule et al., 2021; Eyigoz, Mathur, Santamaria, Cecchi, & Naylor, 2020; Jester et al., 2020), attention and executive function (e. g. Amaefule et al., 2021; Jester et al., 2020), working memory (e. g. Amaefule et al., 2021; Jiang et al., 2020) or visuospatial abilities (e. g. Amaefule et al., 2021; Jester et al., 2020). The event-related potential (ERP) technique has previously demonstrated its potential usefulness to search for biomarkers of MCI and dementia due to AD, in studies evaluating brain electrical activity associated with several cognitive domains (Cespón, Galdo-Álvarez, & Díaz, 2013, 2015; Cespón, Galdo-Álvarez, Pereiro, & Díaz, 2015; Correa-Jaraba, Lindín, & Díaz, 2018; Lindín, Correa, Zurrón, & Díaz, 2013; for reviews, see Jackson & Snyder, 2008; Paitel, Samii, & Nielson, 2021; Vecchio & Määttä, 2011; Zurrón, Lindín, Cespón, Cid-Fernández, Galdo-álvarez, Ramos-Goicoa, & Díaz, 2018).

In previous studies involving the search for aMCI biomarkers, we used the ERP technique in combination with a distraction-attention auditory-visual task (AV task), formed by auditory-visual stimuli pairs. In this task, participants are asked to ignore auditory stimuli while performing a visual task of the Go/NoGo type. The Go stimuli in this task were letters and numbers (33% each), while NoGo stimuli were triangles (34%). Usually, reaction times (RTs) are significantly longer in aMCI participants than in healthy controls (Cid-Fernández et al., 2014; 2017a; 2017b). In addition, the number of correct responses is usually lower in aMCI participants than in their control counterparts (Cid-Fernández, Lindín, & Díaz, 2014), especially in those with multi-domain aMCI (mdaMCI; Cid-Fernández et al., 2017a; 2017b;; Correa-Jaraba et al., 2018). In fact, the number of hits has proven to be a potential marker for distinguishing between different aMCI subtypes and between these and healthy control participants (Cid-Fernández et al., 2017a; 2017b).

In the Go condition of this visual Go/NoGo task, at least two ERP components related to the target detection and its conscious evaluation and classification are usually observed. First, the Go-N2 (N2b) component is a negative wave that peaks around the 200–300 ms interval after target presentation in young people (Hämmerer, Li, Müller, & Lindenberger, 2010) and amplitudes are maximal at central scalp locations (Amenedo & Díaz, 1998a, 1998b). This component has been interpreted as an index of detection and evaluation of target stimuli, and as a reflection of the selective attention processes coming into action (Amenedo & Díaz, 1998b; Bennys, Portet, Touchon, & Rondouin, 2007), and to our knowledge has never been compared between adults with SMCs.

In addition, the Go-P3 (P3b) component is a positive wave that typically appears in the 300–700 ms post-stimulus interval, with parietal maximal amplitudes in young participants (Coles & Rugg, 1996; Donchin & Coles, 1988; Kutas, Iragui, & Hillyard, 1994), and seems to index context updating in working memory (Donchin & Coles, 1988; Vogel & Luck, 2002), or to reflect a function that bridges perceptual with response processing, with the reactivation of the stimulus–response (S-R) link (Verleger, Hamann, Asanowicz, & Śmigasiewicz, 2015; Verleger, Jaśkowski, & Wascher, 2005). This component was previously evaluated in adults with HSMCs and LSMCs using a Simon paradigm, and any group differences between them were observed in P300 latency or amplitude (Cespón, Galdo-Álvarez, & Díaz, 2018).

Both components have been widely evaluated in aMCI adults by using the oddball paradigm (where these components are usually named N2b and P3b, or N200 and P300). In most studies, no differences between aMCI and control participants have been observed for the N2b amplitudes (e.g. Golob, Johnson, & Starr, 2002; López Zunini et al., 2016; although see Papaliagkas, Kimiskidis, Tsolaki, & Anogianakis, 2008), and the P3b amplitude was usually larger in control than in aMCI participants (e. g. Bennys et al., 2007; Golob, Irimajiri, & Starr, 2007; Li et al., 2010; Papadaniil et al., 2016; Parra et al., 2012). Furthermore, longer latencies were observed in aMCI adults than in healthy adults for N2b (Bennys et al., 2007; López Zunini et al., 2016; Missonnier et al., 2007; Papaliagkas et al., 2008; 2011) and P3b (Li et al., 2010; Parra et al., 2012).

However, in previous studies evaluating N2 and P3 in the Go/NoGo paradigm of the A-V task, the Go-P3 parameters did not usually distinguish between aMCI and control participants (Cid-Fernández et al., 2014; 2017a). When the age factor was considered, longer Go-P3 (P3b) latencies were observed in aMCI participants aged 51–69 years than in their control counterparts (Cid-Fernández, Lindín, & Díaz, 2019). On the other hand, the Go-N2 amplitude was consistently able to distinguish between aMCI and control participants (Cid-Fernández et al., 2014; 2017a) (smaller amplitude in the former participants), while the latency only differentiated aMCI participants from controls when the former were divided into multidomain (mdaMCI) and single-domain (sdaMCI) subtypes, as N2b latency was longer in mdaMCI participants than sdaMCI and control participants (Cid-Fernández, Lindín, & Díaz, 2017a). The aforementioned finding indicated that the Go-N2 latency is only sensitive to the most advanced stages of aMCI.

In addition, in the NoGo condition of the visual Go/NoGo paradigm in the AV task, two additional components can be observed at fronto-central locations: the NoGo-N2, which usually peaks in the 200–400 ms interval after stimulus presentation, and the NoGo-P3, which follows the NoGo-N2 and usually peaks in the 300–700 ms interval (Falkenstein, Hoormann, & Hohnsbein, 2002; Jodo & Kayama, 1992; Pfefferbaum & Ford, 1988; Vallesi, Stuss, McIntosh, & Picton, 2009). These components have been associated with response inhibition processes (e. g. Bokura, Yamaguchi, & Kobayashi, 2001; Bruin & Wijers, 2002; Smith, Johnstone, & Barry, 2007), but have also been associated with conflict monitoring (Donkers & van Boxtel, 2004; Nieuwenhuis, Yeung, & Cohen, 2004; Smith, Smith, Provost, & Heathcote, 2010). However, some authors have reported that the NoGo-P3 seems to reflect evaluation processes that monitor the results of the previous inhibition (Beste, Willemssen, Saft, & Falkenstein, 2010; Schmiedt-Fehr & Basar-Eroglu, 2011). For a comprehensive review of the ERP components identified in Go/NoGo tasks, see Huster, Enriquez-Geppert, Lavallee, Falkenstein, and Herrmann (2013).

To our knowledge, the NoGo-N2 and -P3 have never been compared between adults with HSMCs and LSMCs, and have scarcely been studied in participants with aMCI. In some studies using the A-V task, a lower amplitude of the NoGo-N2 component was observed in aMCI than in control adults (Cid-Fernández et al., 2014; 2017a), while another study using a semantic Go/NoGo task failed to detect between-group differences in this parameter (Mudar et al., 2016). However, although Mudar et al. (2016) observed a longer NoGo-N2 latency in the aMCI adults than in control adults, in a previous study using the A-V task, we only observed such differences in latency between aMCI and control adult participants aged between 51 and 69 years (Cid-Fernández et al., 2019). On the other hand, no differences between aMCI and control participants were observed for the NoGo-P3 component, in studies using either an A-V task (Cid-Fernández et al., 2014; 2017a; 2019) or a semantic Go/NoGo task (Mudar et al., 2016).

Therefore, considering previous results obtained with the A-V task in aMCI participants, and because adults with SMCs have an increased risk of progression to MCI and dementia due to AD, in the present study we evaluated the performance and the aforementioned ERP components in healthy adults with high SMCs (HSMCs) relative to healthy adults with low SMCs (LSMCs). Our specific aims were: (1) to evaluate whether adults with HSMCs show differences in the brain electrical activity associated with target stimuli processing and/or in response inhibition processes, relative to adults with LSMCs, and (2) to determine whether the observed differences distinguish between the two groups with good sensitivity and specificity.

Considering the SMC-MCI-dementia continuum and the findings for aMCI adults when Go- and NoGo-N2 and -P3 components were evaluated in the A-V task, we expected to record lower Go-N2 and NoGo-N2 amplitudes in the HSMC participants than in their LSMC counterparts. We did not expect to find between-group differences in Go-N2 or NoGo-N2 latencies, nor in amplitudes or latencies of the Go-P3 or NoGo-P3

components, in line with previous findings (see above). In addition, we expected to observe shorter RTs in the adults with LSMCs than in those with HSMCs, but not to observe between-group differences in the number of hits. Those parameters that were expected to show group differences were also expected to be good neurocognitive and behavioural markers of HSMC (vs. LSMC). As the stimulus-related activity may be influenced by motor activity, anticipatory preparation of neural resources and/or motor activity, a negative slow wave that resembles a Contingent Negative Variation (CNV; Brunia & Van Boxtel, 2001) and the Bereitschaftspotential (Kornhuber & Deecke, 1965) or Readiness Potential (RP; Vaughan, Costa, & Ritter, 1968) was also identified and evaluated in the response-related waveforms.

2. Materials and methods

2.1. Participants

Twenty-eight healthy volunteers, aged between 52 and 81 years, were recruited from Primary Care Health Centres in Santiago de Compostela, Galicia (Spain). These participants were part of a larger sample that reported memory complaints (for a more extensive description of the global sample see Juncos-Rabadán, Facal, Lojo-Seoane, & Pereiro, 2013). Within this larger sample, those that reported memory complaints in the absence of any objective cognitive decline were divided into three SMC groups (low, medium and high SMCs) according to the scores obtained in a standardized memory complaints questionnaire (Benedet Álvarez & Seisdedos, 1996), using the 33rd and 67th percentiles as cut-off points. Thus, the LSMC group was composed in the present study by those participants with SMC scores below the 33rd percentile (scored 15 or below), while the HSMC group was composed by participants with scores between the 67th and the 100th percentile (scored 20 or above). In the present study, 14 participants were included in the LSMC group (9 women, age range: 52–81 years old), and 14 participants were included in the HSMC group (9 women, 53–74 years old). The groups were matched according to age, sex and level of education (see Table 1).

Each participant underwent exhaustive neuropsychological evaluation to ensure that they performed within normal parameters and that memory deficits were not objectively observed in a standardized neuropsychological assessment. The following tests were used: 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 and long-delay recall with semantic cues; 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). All participants also performed the Spanish version of the Yesavage geriatric depression scale (Yesavage et al., 1983) in order to exclude depression as an explanation for the SMCs: subjects with scores of more than 10 in the depression screening were not included in the study. The demographic and neuropsychological measures of the participants are summarized in Table 1.

Table 1
Means (and standard deviations) for the main socio-demographic data and for the neuropsychological tests performed by participants.

	LSMC	HSMC	p = *
Age	66.5 (10.0)	65.1 (6.7)	N.S.
Sex	9 W/5M	9 W/5M	
Years of education	9.9 (5.1)	8.2 (3.4)	N.S.
Vocabulary WAIS	50.8 (14.9)	48.5 (14.2)	N.S.
MMSE	28.4 (1.3)	27.3 (1.5)	**0.027**
IADL	7.7 (0.9)	7.1 (1.1)	N.S.
GDS	2.5 (1.3)	3.2 (1.4)	N.S.
SMC	13.1 (1.5)	22.9 (3.4)	**< 0.001**
CAMCOG			
Orientation	9.7 (0.5)	9.4 (0.8)	N.S.
Language	25.4 (2.3)	24.5 (2.5)	N.S.
Attention	7.2 (1.5)	7.3 (1.6)	N.S.
Praxis	10.6 (1.4)	11.1 (0.9)	N.S.
Perception	6.3 (1.6)	7.2 (1.4)	N.S.
Executive function	16.4 (6.3)	16.6 (4.1)	N.S.
CVLT			
Short-term free recall	10.4 (3.1)	9.6 (1.3)	N.S.
Short-term cued recall	11.3 (2.9)	10.4 (2.4)	N.S.
Long-term free recall	11.1 (3.4)	10.8 (2.2)	N.S.
Long-term cued recall	11.5 (2.8)	11.1 (2.3)	N.S.

LSMC: low subjective memory complaint; HSMC: high subjective memory complaint; N.S.: not significant; WAIS: Weschler's adult Intelligence Scale; MMSE: Mini-mental State Examination; IADL: Instrumental Activities of Daily Living Scale; GDS: Geriatric Depression Scale; SMC: subjective memory complaint; CAMCOG: Cambridge Cognitive Examination; CVLT: California Verbal Learning Test.

* ANOVA (Group), significance level < 0.05.

All participants had normal audition and normal or corrected-to-normal vision. They 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. All were right-handed, as assessed by the Edinburgh inventory (Oldfield, 1971). Participants underwent psychophysiological evaluation immediately after the neuropsychological 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). The anonymity of all participants in the project was carefully and strictly preserved according to national and EU legislation.

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, which were of three types (standard tone: 1000 Hz, 70%; deviant tone: 2000 Hz, 15%; novel sounds, 15%). They were asked to respond by pressing one of two different buttons to target visual stimuli (Go stimuli), i.e. one button with one hand if the visual stimulus was a letter (a, e, c, u; 33%), another button with the other hand if it was a number (2, 4, 6, 8; 33%), and to withhold their responses if the stimulus was a triangle (pointing upwards, downwards, or to the right or left, 34%; NoGo stimuli). The task procedure is summarized in Cid-Fernández et al., 2017a (see their Fig. 1). In addition, participants were instructed to fix their eyes in the centre of the screen and to maintain their head as still as possible, in order to reduce artefacts.

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 filter 0.01–100 Hz), and the electrode impedance was maintained below 10

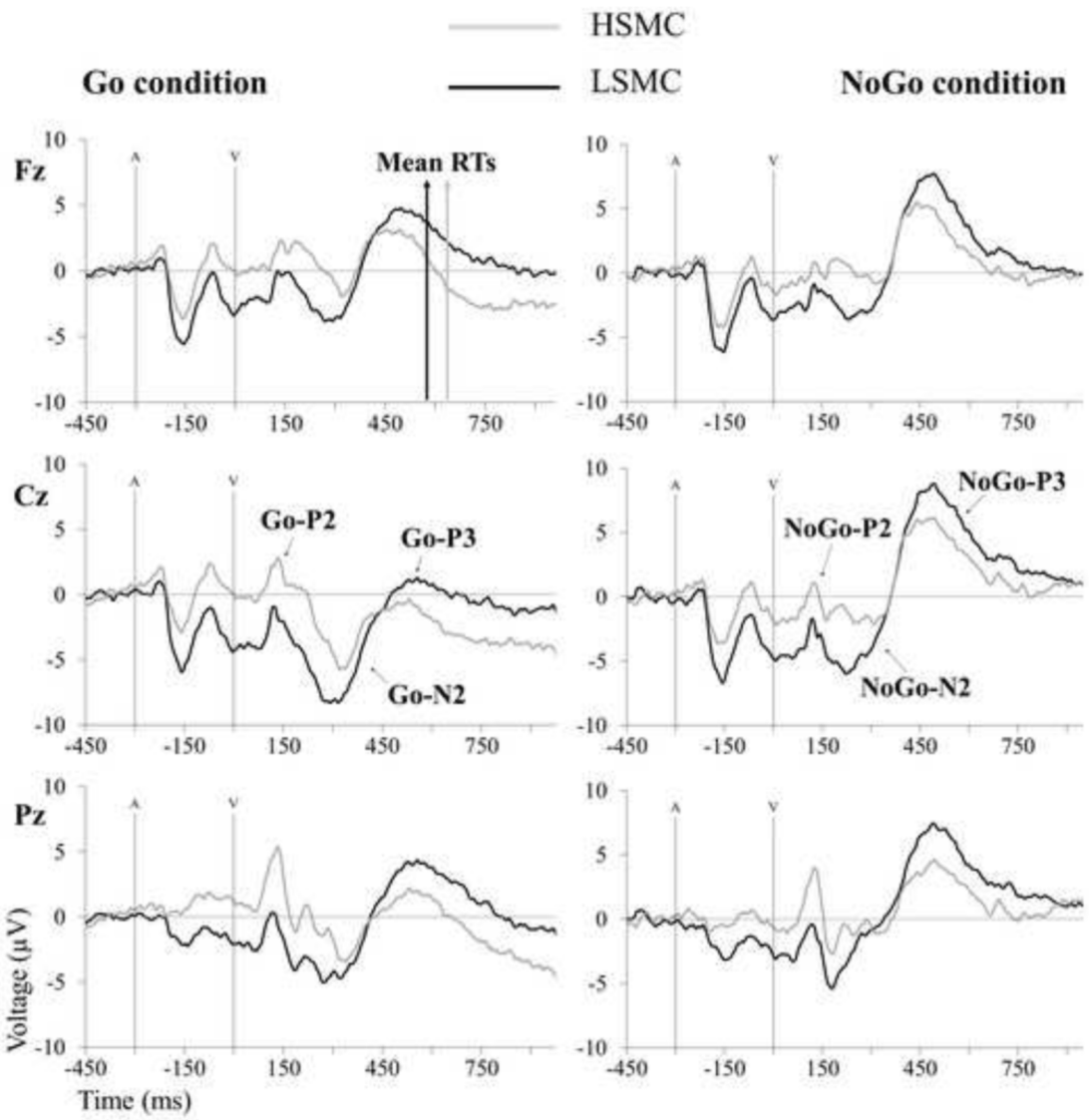

Fig. 1. Stimulus-locked event-related potentials. Grand-average event-related brain potential waveforms elicited in the HSMC (grey line) and LSMC (black line) groups, for the Go and NoGo conditions at the Fz, Cz and Pz electrode locations. The arrows pointing upwards represent the mean RT for the HSMC (grey arrow) and LSMC (black arrow) groups.

kΩ. Once the signal was stored, it was passed through a digital bandpass filter (0.1 to 30 Hz; 12 dB/octave slope), and ocular artefacts were corrected by independent component analysis (Infomax algorithm, implemented in Brain Vision Analyzer v. 2.1; Lee, Girolami, & Sejnowski, 1999).

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 of the standard auditory- visual stimuli pairs with either correctly executed or inhibited responses were evaluated. All epochs were corrected to the mean voltage of the first 150 ms of each epoch (pre-stimulus baseline), 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.

Given the negative tendency observed in the stimulus-locked ERP waveforms of LSMC group compared to the HSMC group ones, starting right after the presentation of the auditory stimuli, we also extracted and averaged response-locked epochs of 1500 ms (-1100 ms pre-response) for the Go condition, with the aim of verifying whether processes associated to motor preparation might be modulating the stimulus-related brain activity.

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 evaluated stimulus-locked ERP components were measured in latency windows relative to the onset of the visual stimuli (see Fig. 1): 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. The peak-to-baseline amplitudes (in microvolts) and peak latencies (in milliseconds) of the Go- and NoGo-N2 and -P3 components recorded at the midline electrode where the amplitude was maximal (Go-N2, NoGo-N2 and NoGo-P3 at Cz; Go-P3 at Pz) were evaluated. The P2-N2 and N2-P3 peak-to-peak amplitudes (at Cz) in each condition (Go- and NoGo) were also evaluated, and for this, the Go- and NoGo-P2 peak amplitude was also measured at Cz, in the 180 to 250 ms interval.

The ERP waveforms of the LSMC participants seemed to be overlapped with a slow negativity (i.e. a Contingent Negative Variation, CNV) that made them sustainedly more negative than the ERP waveforms of the HSMC participants, from the presentation of the auditory stimuli. In consequence, we also measured mean amplitudes (at Cz) in the interval between the onset of auditory and visual stimulus (-300 to 0 ms, with respect to the onset of the visual stimulus; A-V interval) in both conditions (Go and NoGo), with the aim to determine the magnitude of the differences between the ERP waveforms of the two groups previously to visual stimulus presentation.

Given that the stimulus-locked ERP components may be influenced not only by an overlapping CNV, but also by other ERPs related to response preparation, a negative component that resembles a *Bereitschaftspotential* (Kornhuber & Deecke, 1965) or Readiness Potential (RP; Vaughan et al., 1968) was identified and evaluated in the response-locked ERP waveforms of the Go condition (see Fig. 2). We evaluated the mean amplitude (at Cz) of the RP in 300 ms temporal windows, in the range where differences between groups were observable (see Fig. 2; W1: −900 to −600 ms, W2: −600 to −300 ms, and W3: −300 to 0 ms).

2.5. Statistical analysis

One-factor analysis of variance (ANOVA), with the between-subject factor *Group* (two levels: HSMC, LSMC) was applied to the RTs, Hits, amplitudes and latencies of the Go-N2 and -P3 and the NoGo-N2 and -P3 components, P2-N2 and N2-P3 peak-to-peak amplitudes in each condition (Go and NoGo), the mean amplitudes of the A-V interval in each condition, and the RP component in the three evaluated temporal windows. Differences were considered significant at $p \leq 0.05$. Partial eta squared (η_p^2) values are reported as estimates of effect size (Richardson, 2011).

Receiver operating characteristic (ROC) curves were also constructed for those ERP and behavioural parameters in which the Group factor exerted a significant effect. An area under the curve (AUC) of 1.0 corresponds to a perfect prediction, whereas a value of 0.5 indicates a useless model. The optimal sensitivity and specificity values were chosen by ensuring that equal importance was given to both parameters. Hence, we chose the higher sensitivity value that corresponded to the higher specificity value among the possibilities, in other words, the combination of specificity and sensitivity values that added up resulted in the higher value possible from the possible combinations.

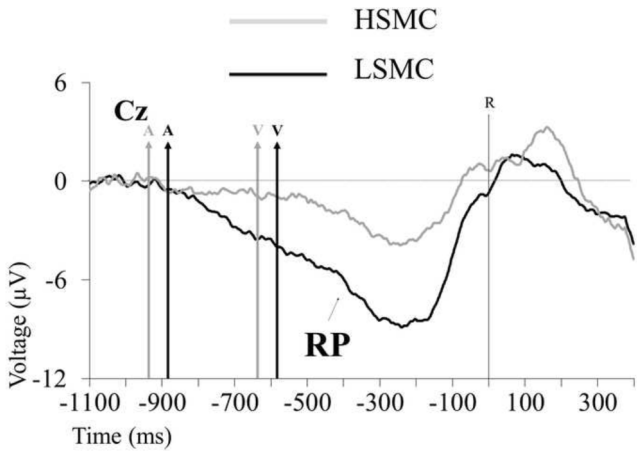

Fig. 2. Response-locked event-related potentials. Grand-average event-related brain potential waveforms elicited in the HSMC (grey line) and LSMC (black line) groups, for the Go condition at the Cz electrode location. Grey and black arrows represent the mean time of appearance of the auditory (A) and visual (V) stimuli for the HSMC and LSMC groups, respectively.

3. Results

The stimulus-locked ERP waveforms for the Go and NoGo conditions are shown in Fig. 1, and response-locked ERP waveforms for the Go condition are shown in Fig. 2. Voltage and current source density (CSD) maps for the stimulus-related ERP components evaluated are shown in Fig. 3.

3.1. Behavioural measures

The one-factor ANOVA (Group) applied to the RTs revealed a significant effect of the factor ($F(1, 26) = 3.84$, $p = .02$, $\eta_p^2 = 0.178$), as the RT was significantly longer in the HSMC (mean = 639 ms; SD = 60.1) than in the LSMC (mean = 587 ms; SD = 56.0) participants.

The one-factor ANOVA (Group) applied to the number of hits did not reveal any significant effect of the factor (HSMC mean = 219.7; SD = 2.0; LSMC mean = 220.2; SD = 2.1).

3.2. ERP components

The one-factor ANOVAs (Group) did not show any significant effects of the factor for the Go-N2 and NoGo-N2 latencies, for the Go-P3 and NoGo-P3 amplitudes and latencies, for the P2-N2 peak-to-peak amplitude in the Go or NoGo conditions, for the N2-P3 peak-to-peak amplitude in the Go condition, or for the mean amplitude of the RP in W3 (-300 to 0 response-related temporal window).

The one-factor ANOVA (Group) applied to the Go-N2 amplitude at Cz showed a significant effect of the factor ($F(1, 26) = 4.5$, $p = .05$, $\eta_p^2 = 0.139$), as the amplitude was significantly larger in the LSMC (mean = -10.8 μV; SD = 7.7) than in the HSMC (mean = -5.9 μV; SD = 5.2) group.

The one-factor ANOVA (Group) applied to the NoGo-N2 amplitude at Cz showed a significant effect of the factor ($F(1, 26) = 5.7$, $p = .04$, $\eta_p^2 = 0.147$), as the amplitude was significantly larger in the LSMC (mean = -8.1 μV; SD = 6.3) than in the HSMC (mean = -3.4 μV; SD = 5.3) group.

The one-factor ANOVA (Group) applied to the N2-P3 peak-to-peak amplitude at Cz in the NoGo condition showed a significant effect of the factor ($F(1, 26) = 14.8$, $p = .001$, $\eta_p^2 = 0.363$), as the amplitude was significantly larger in the LSMC (mean = 19.1 μV; SD = 5.0) than in the HSMC (mean = 12.4 μV; SD = 4.2) group.

The one-factor ANOVA (Group) applied to the mean amplitude in the A-V interval at Cz in the Go condition showed a significant effect of the factor ($F(1, 26) = 11.2$, $p = .003$, $\eta_p^2 = 0.301$), as this parameter was significantly larger in the LSMC (mean = -2.3 μV; SD = 1.8) than in the HSMC (mean = 0.1 μV; SD = 2.0) group. In addition, the one-factor ANOVA (Group) applied to the mean amplitude in the A-V interval at Cz in the NoGo condition also showed a significant effect of the factor ($F(1, 26) = 9.3$, $p = .005$, $\eta_p^2 = 0.263$), as this parameter was significantly larger in the LSMC (mean = -2.9 μV; SD = 1.7) than in the HSMC (mean = -0.7 μV; SD = 2.0) group.

The one-factor ANOVAs (Group) applied to the RP mean amplitude at Cz showed a significant effect of the factor in W1 (-900 to −600 response-related temporal window) ($F(1, 26) = 7.3$, $p = .01$, $\eta_p^2 = 0.225$), as the amplitude was significantly larger in the LSMC (mean = -1.8 μV; SD = 1.9) than in the HSMC (mean = -0.1 μV; SD = 1.3), and also in W2 (-600 to −300 response-related temporal window) ($F(1, 26) = 5.1$, $p = .03$, $\eta_p^2 = 0.171$), as the amplitude was significantly larger in the LSMC (mean = -4.7 μV; SD = 5.2) than in the HSMC (mean = -0.9 μV; SD = 3.0) group.

3.3. ROC curves

The RT discriminated between groups (HSMC vs. LSMC) with sensitivity and specificity values of 0.75 and 0.58, respectively (AUC = 0.56). In addition, the Go-N2 amplitude yielded a sensitivity value of 0.50 and specificity value of 0.83 (AUC = 0.66). The NoGo-N2 amplitude yielded sensitivity and specificity values of 0.50 and 0.83,

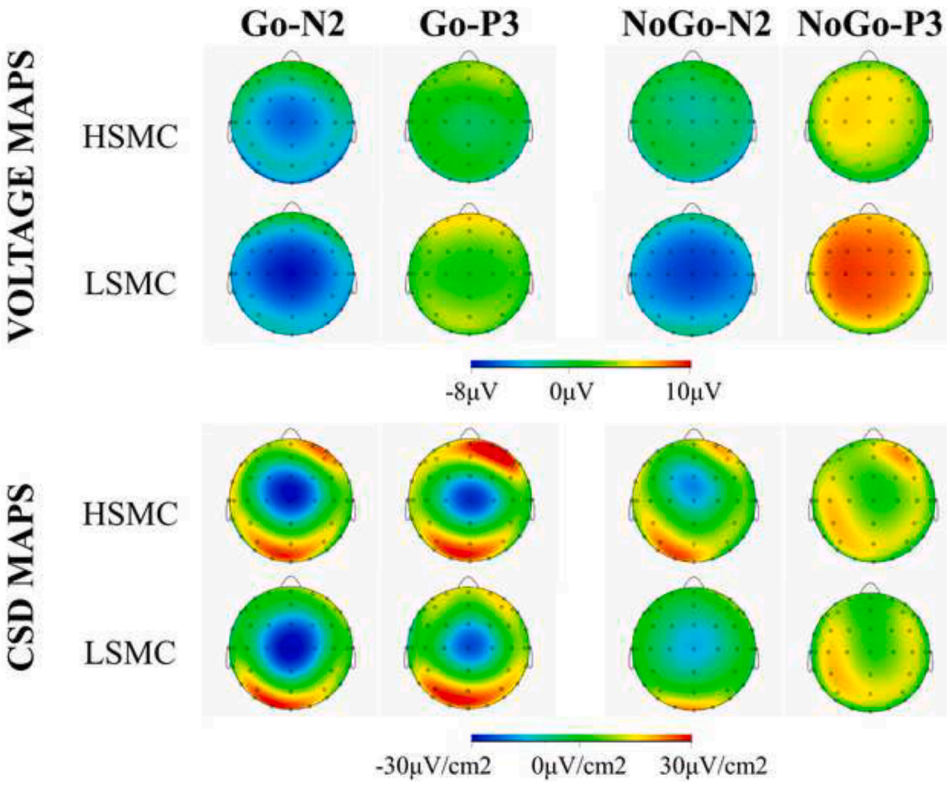

Fig. 3. Voltage (upper panel) and current source density (CSD; lower panel) maps for the maximum peak amplitude of the ERP components evaluated (Go- and NoGo-N2 and Go- and NoGo-P3) in the HSMC and LSMC groups.

respectively (AUC = 0.65). The N2-P3 peak-to-peak amplitude in the NoGo condition yielded a sensitivity value of 0.79 and a specificity value of 0.86 (AUC = 0.86). Finally, the amplitude of the RP component in W1 showed a sensitivity value of 0.75 and a specificity value of 0.77 (AUC = 0.75), while in W2 the values were 0.71 and 0.62, respectively (AUC = 0.71).

4. Discussion

The present study investigated task performance and ERP components associated with detection and evaluation of target stimuli and context updating (Go-N2 and Go-P3 components), as well as with response inhibition and conflict monitoring processes (NoGo-N2 and NoGo-P3 components), in two groups of healthy participants with different levels of subjective memory complaints (SMCs): high (HSMC group) and low (LSMC group). During the EEG recording, participants performed an A-V task in which they were required to attend to the visual Go/NoGo stimuli. Relative to LSMC participants, the HSMC participants were slower when responding to target stimuli in the Go condition (indicated by longer RT), and showed smaller amplitudes of Go-N2, NoGo-N2, N2-P3 in the NoGo condition, the A-V interval in the Go and NoGo conditions, and the RP in the Go condition.

These findings indicate that in comparison with LSMC participants, the HSMC participants showed behavioural slowing and neurocognitive decline associated with stimuli and response processing. The results for the Go-N2 peak-to-baseline amplitude may indicate that the HSMC adults showed deficits in the allocation of processing resources during the conscious evaluation of the target stimuli (indicated by lower Go-N2 amplitude). However, the slowing of the RTs in the Go condition in the HSMC group cannot be explained by a generalized slowing of stimulus evaluation and classification processes, as neither Go-P3 nor Go-N2 latencies, respectively, differed significantly between groups. In addition to the observed decline in Go-N2 amplitude, the HSMC participants also showed lower NoGo-N2 amplitude, which may indicate that these adults are undergoing a decline in inhibition processes and/or in conflict monitoring processes.

Nonetheless, some slow modulation of the stimulus-locked ERP waveforms in the LSMC group can be observed, as the ERP waveforms were sustainedly more negative than the ERP waveforms of the HSMC group (see Fig. 1). A negative slow wave that resembles a contingent negative variation (CNV) could be overlapping with the ERPs waveforms in the Go and NoGo conditions. In fact, a significant difference in mean amplitudes between both groups was obtained for the amplitude in the Go and NoGo conditions in the interval from the onset of the auditory stimulus to the onset of the visual stimulus (A-V interval), with larger negative amplitude in the LSMC participants.

The CNV is related to orientation (Loveless & Sanford, 1974; McCarthy & Donchin, 1978) and subsequent motor response preparation (Brunia & Van Boxtel, 2001). Thus, for the participants with LSMCs, auditory stimuli may be acting as warning signals that promote the allocation of attentional resources to the perception, evaluation and classification of the visual stimuli, and also probably to motor selection and preparation, in order to identify and respond (in the Go condition) or avoid responding (in the NoGo condition) to the visual stimulus, modulating brain activity during visual stimuli processing (Verleger et al., 2006). This modulation of the processing seem to be diminished in the adults with HSMCs in the present study (evidenced by lower mean amplitude in the A-V interval compared to the LSMC group, both in the Go and NoGo conditions), and might reflect declines in this group in frontal brain areas and in their subcortical inputs (Brunia & Van Boxtel, 2001; Gómez, Marco, & Grau, 2003; Kropotov, Ponomarev, Tereshchenko, Müller, & Jäncke, 2016; Leynes, Allen, & Marsh, 1998; Wild-Wall, Hohnsbein, & Falkenstein, 2007).

Our result is in accordance with previous literature regarding the CNV, as it is generally smaller in older than in younger adults (Sterr & Dean, 2008; Wild-Wall & Falkenstein, 2010), and larger in old adults with good performance than in old adults with worse performance, a result that has been related to higher cognitive reserve in the former

(Gajewski, Falkenstein, Thönes, & Wascher, 2020). The CNV has also shown to be larger in sdaMCI than in mdaMCI adults (and therefore larger in a less severe form of MCI), although this result was only marginally significant in the only study that to our knowledge assessed such differences comparing MCI subtypes (Missonnier et al., 2013). Hence, it seems that the orientation and motor response preparation processes indexed by the CNV may be sensitive to cognitive decline in healthy aging and also in the AD continuum. However, one study failed to find any differences in CNV amplitude between AD dementia, MCI (with the four subtypes altogether) and control participants (van Deursen, Vuurman, Smits, Verhey, & Riedel, 2009).

In addition, when the response-locked ERPs waveforms (depicted in Fig. 2) were considered, differences between both groups (HSMC vs. LSMC) were observed for a negative tendency preceding the Go response, which we identified as the *Bereitschaftspotential* or RP (Kornhuber & Deecke, 1965; Vaughan et al., 1968), a neural correlate of the timing of a future voluntary movement (see Brunia & Van Boxtel, 2001; Di Russo et al., 2017 for reviews). In this study, the RP amplitude was significantly larger in the LSMC group than in the HSMC group from −900 to −300 ms before the response (roughly corresponding to the −300 to 300 ms interval in relation to the visual stimulus presentation, see Fig. 2), evidencing that the adults with HSMCs showed diminished resources allocation in response preparation processes. This result may reflect a decline in the activation of motor brain areas related to the generation of RP, as the supplementary motor area (SMA) and the cingulate motor area (CMA), or of subcortical structures known to be necessary for the bringing out of this slow wave (Brunia & Van Boxtel, 2001; Di Russo et al., 2017). This result is also in accordance with previous literature, as related motor processes (indexed by the lateralized readiness potential, LRP) have been showed to be diminished in aMCI when compared to their control counterparts (Cespón et al., 2013, 2015; Cid-Fernández, Lindín, & Díaz, 2017b).

Hence, both expectation processes indexed by an early CNV overlapping to the stimulus-locked waveforms and response preparation processes indexed by the RP may account to a large extent for the group differences observed in the peak-to-baseline amplitudes of the Go- and NoGo-N2 components. Besides, declines in the neural processes indexed by the stimulus-locked overlapped negative tendency and the RP may explain the slowing of the RTs in the HSMC group: the auditory standard stimuli preceding the visual Go stimuli may lead to increased resource allocation for response preparation in the LSMC adults, facilitating a faster response, while this did not occur (or did to a lower extent) in the HSMC adults.

The results for Go-N2 and NoGo-N2 amplitudes in the present study are consistent with previous findings regarding aMCI adults. In previous studies using the same task, we observed lower Go-N2 and NoGo-N2 amplitudes in aMCI participants than in healthy controls (Cid-Fernández et al., 2014; 2017a). In those studies, a slow negative component related to response preparation may be also influencing their results, as a negative tendency starting after the presentation of the auditory stimulus seems to be modulating brain activity related to the processing of visual stimuli (see Figure 4 in Cid-Fernández et al., 2014 and Fig. 2 in Cid-Fernández et al., 2017a). Either way, the present results showed that these neural changes are not only a correlate of aMCI, but that they precede this condition. This may indicate that these stages (SMC and aMCI) are indeed part of a continuum ranging from healthy aging to dementia (Jack et al., 2018), although more studies are needed in order to confirm this hypothesis.

Furthermore, in order to evaluate ERP amplitude differences between both groups free to a certain degree from the CNV and RP influence, we also evaluated the P2-N2 and N2-P3 peak-to-peak amplitudes. The analysis revealed significant differences between groups for the N2-P3 amplitude in the NoGo condition, being larger in the LSMC than HSMC group. These differences may indicate the existence of some deficits in the HSMC adults (compared to the LSMC adults) in relation to (1) neural processes related to the processing of the NoGo stimulus and to the inhibitory control of the behavioural response (Falkenstein et al., 1999; 2002; see Pires, Leitão, Guerrini, & Simões, 2014 for a review), and (2) the fronto-basal ganglia network thought to be responsible for these processes, that includes the pre-SMA, the inferior frontal cortex and cingulate cortex (see Aron, 2011; Huster et al., 2013; Simmonds, Pekar, & Mostofsky, 2008 for reviews).

Previous literature about NoGo-N2 and –P3 regarding SMCs is absent as far as we know, and extremely scarce regarding MCI participants. Existing studies that evaluated NoGo-N2 and –P3 in MCI participants found smaller amplitudes of NoGo-N2 in aMCI than in control adults using the A-V task (Cid-Fernández et al., 2014; 2017a), while failed to observe any differences regarding NoGo-P3 amplitude using either this task (Cid-Fernández et al., 2014; 2017a; 2019) or a semantic Go/NoGo task (Mudar et al., 2016).

As stated above, group differences for Go- and NoGo-N2 amplitudes in the previous aMCI studies using the A-V task might be modulated by superimposed slow waves that would largely explain these differences. In fact, peak-to-baseline amplitudes were evaluated and the influence of such negativities was not assessed in those studies. Thus, group differences in the N2-P3 complex that are observable in their figures might have gone unnoticed (see Figure 4 in Cid-Fernández et al., 2014, Fig. 2 in Cid-Fernández et al., 2017a; 2017b, Fig. 1 in Cid-Fernández et al., 2019). Mudar et al. (2016) used a semantic Go/NoGo task where differences between aMCI and control participants were not observed in NoGo-P3 amplitude. However, visual inspection of their Fig. 1 leads one to think that N2-P3 peak-to-peak amplitudes might have provided evidence for group differences, as larger amplitudes can be observed in the control than in the aMCI participants, especially in the NoGo condition (Mudar et al., 2016). In any case, more studies comparing NoGo-N2 and –P3 components between participants with HSMCs and LSMCs are necessary to characterize early declines in response inhibition processes.

The ROC curve analyses showed that the amplitudes of Go- and NoGo-N2 components and RTs are not able to distinguish adults with HSMCs from those with LSMCs with sensitivity and specificity values as good as for the comparisons between MCI and control participants stated in our previous studies (Cid-Fernández et al., 2017a; 2019). This is an expectable result, as neurocognitive differences between MCI and healthy controls must be larger than between adults showing high and low SMCs. However, at the present study, the N2-P3 amplitude in the NoGo condition was able to distinguish adults with HSMCs from those with LSMCs with moderate sensitivity (0.79) and specificity (0.86) values. In addition, the mean amplitude in the A-V interval in the Go condition and the initial part of the RP were also able to distinguish between groups with moderate sensitivity and specificity values ($\geq$0.72).

On the other hand, no group differences were observed for the Go-P3, NoGo-P3 or in NoGo-N2 latencies. This was expected, as in previous studies using the A-V task, we did not observe any differences in these parameters between healthy adults and aMCI participants (Cid-Fernández et al., 2014; 2017a). In addition, we also did not observe any differences between groups in Go-N2 latency and the number of hits in the present study. In previous studies, Go-N2 latency was longer and the number of hits was lower in the mdaMCI group than in the sdaMCI or control groups (Cid-Fernández et al., 2017a). Hence, it seems that the significant slowing in the conscious evaluation of the target stimuli, as well as the poorer accuracy when responding to those stimuli, do not take place until advanced stages of aMCI.

As a limitation of the present study, we recognize that the sample size was relatively small. However, objective classification of two subgroups within the healthy aging participants was possible according to the degree of subjective memory complaints reported. Nonetheless, present results along with previous reports encourage the emphasis on neurocognitive functioning assessment in adults with subjective cognitive complaints.

In summary, relative to participants with LSMCs, those with HSMCs showed a slowing in the RT and lower ERP amplitudes during the

temporal range of Go- and NoGo-N2 ERP components, in response to the visual stimuli. These ERP amplitude differences may be explained, to a great extent, by modulations of ERP components associated with the anticipatory preparation of neural resources (CNV) to be allocated to visual relevant stimuli processing, and with response preparation processes (RP), triggered by the auditory stimulus presentation. Besides, compared to LSMC participants, the participants with HSMCs showed also a decline in these processes, reflected in lower amplitudes of the RP and in the A-V interval. Finally, the participants with HSMCs showed smaller N2-P3 peak-to-peak amplitude in the NoGo condition than the participants with LSMCs, which may evidence incipient deficits in response inhibition processing in the former.

CRediT authorship contribution statement

Cid-Fernández Susana: Investigation, Formal analysis, Visualization, Writing - original draft, Funding acquisition. **Lindín Mónica:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration. **Díaz Fernando:** Conceptualization, Methodology, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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References

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

Amaefule, C. O., Dyrba, M., Wolfsgruber, S., Polcher, A., Schneider, A., Fliessbach, K., … Teipel, S. J. (2021). Association between composite scores of domain-specific cognitive functions and regional patterns of atrophy and functional connectivity in the Alzheimer's disease spectrum. *NeuroImage: Clinical, 29*, Article 102533. https://doi.org/10.1016/j.nicl.2020.102533.

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

Amenedo, E., & Díaz, F. (1998b). Automatic and effortful processes in auditory memory reflected by event-related potentials. Age-related findings. *Electroencephalography and Clinical Neurophysiology, 108*(4), 361–369. https://doi.org/10.1016/S0168-5597(98)00007-0.

Aron, A. R. (2011). From reactive to proactive and selective control: Developing a richer model for stopping inappropriate responses. *Biological Psychiatry, 69*(12), e55–e68. https://doi.org/10.1016/j.biopsych.2010.07.024.

Benedet Álvarez, M. J., & Alexandre, M. A. (1998). Test de aprendizaje verbal españa complutense (M. J. Benedet Álvarez & M. A. Alexandre (eds.)). Madrid: TEA.

Benedet Álvarez, M. J., & Seisdedos, N. (1996). Evaluación Clínica de las Quejas de Memoria en la Vida Cotidiana. Médica Panamericana.

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

Beste, C., Willemssen, R., Saft, C., & Falkenstein, M. (2010). Response inhibition subprocesses and dopaminergic pathways: Basal ganglia disease effects. *Neuropsychologia, 48*(2), 366–373. https://doi.org/10.1016/j.neuropsychologia.2009.09.023.

Bokura, H., Yamaguchi, S., & Kobayashi, S. (2001). Electrophysiological correlates for response inhibition in a Go/NoGo task. *Clinical Neurophysiology, 112*(12), 2224–2232. https://doi.org/10.1016/S1388-2457(01)00691-5.

Bruin, K. J., & Wijers, A. A. (2002). Inhibition, response mode, and stimulus probability: A comparative event-related potential study. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 113*(7), 1172–1182. http://www.sciencedirect.com/science/article/pii/S1388245702001414.

Brunia, C. H. M., & Van Boxtel, G. J. M. (2001). Wait and see. *International Journal of Psychophysiology*. https://doi.org/10.1016/S0167-8760(01)00179-9.

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

Cespón, J., Galdo-Álvarez, S., & Díaz, F. (2015). Inhibition deficit in the spatial tendency of the response in multipledomain amnestic mild cognitive impairment. An event-related potential study. *Frontiers in Aging Neuroscience, 7*(68). https://doi.org/10.3389/fnagi.2015.00068.

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

Cespón, Jesús, Galdo-Álvarez, S., & Díaz, F. (2018). Event-related potentials reveal altered executive control activity in healthy elderly with subjective memory complaints. *Frontiers in Human Neuroscience*. https://doi.org/10.3389/fnhum.2018.00445.

Cid-Fernández, S., Lindín, M., & Díaz, F. (2014). Effects of amnestic mild cognitive impairment on N2 and P3 Go/NoGo ERP components. *Journal of Alzheimers Disease JAD, 38*(2), 295–306. https://doi.org/10.3233/JAD-130677.

Cid-Fernández, S., Lindín, M., & Díaz, F. (2017a). Neurocognitive and behavioral indexes for identifying the amnestic subtypes of mild cognitive impairment. *Journal of Alzheimer's Disease*. https://doi.org/10.3233/JAD-170369.

Cid-Fernández, S., Lindín, M., & Díaz, F. (2017b). Stimulus-locked lateralized readiness potential and performance: useful markers for differentiating between amnestic subtypes of mild cognitive impairment. *The Journal of Prevention of Alzheimer's Disease (JPAD), 4*(1), 21–28. https://doi.org/10.14283/jpad.2016.88.

Cid-Fernández, S., Lindín, M., & Díaz, F. (2019). The importance of age in the search for ERP biomarkers of aMCI. *Biological Psychology, 142*, 108–115. https://doi.org/10.1016/j.biopsycho.2019.01.015.

Coles, M. G. H., & Rugg, M. D. (1996). Event-related brain potentials: An introduction. In M. D. Rugg, & M. G. H. Coles (Eds.), *Electrophysiology of the mind event related brain potentials and cognition* (Vol. 1(6, pp. 1–26). Oxford University Press. https://doi.org/10.1093/acprof:Oso/9780198524168.003.0001.

Correa-Jaraba, K. S., Lindín, M., & Díaz, F. (2018). Increased amplitude of the P3a ERP component as a neurocognitive marker for differentiating amnestic subtypes of mild cognitive impairment. Frontiers in Aging Neuroscience. https://doi.org/doi: 10.3389/fnagi.2018.00019.

Di Russo, F., Berchicci, M., Bozzacchi, C., Perri, R. L., Pitzalis, S., & Spinelli, D. (2017). Beyond the "Bereitschaftspotential": Action preparation behind cognitive functions. *Neuroscience and Biobehavioral Reviews*. https://doi.org/10.1016/j.neubiorev.2017.04.019.

Dickerson, B. C., Sperling, R. A., Hyman, B. T., Albert, M. S., & Blacker, D. (2007). Clinical prediction of Alzheimer disease dementia across the spectrum of mild cognitive impairment. *Archives of General Psychiatry*. https://doi.org/10.1001/archpsyc.64.12.1443.

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

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

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

Eyigoz, E., Mathur, S., Santamaria, M., Cecchi, G., & Naylor, M. (2020). Linguistic markers predict onset of Alzheimer's disease. *EClinicalMedicine, 28*. https://doi.org/10.1016/j.eclinm.2020.100583.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (1999). ERP components in Go/Nogo tasks and their relation to inhibition. *Acta Psychologica, 101*(2–3), 267–291. https://doi.org/10.1027//0269-8803.16.3.167.

Falkenstein, M., Hoormann, J., & Hohnsbein, J. (2002). Inhibition-related ERP components: variation with modality, age, and time-on-task. *Journal of Psychophysiology, 16*(3), 167–175. https://doi.org/10.1027//0269-8803.16.3.167.

Gajewski, P. D., Falkenstein, M., Thönes, S., & Wascher, E. (2020). Stroop task performance across the lifespan: High cognitive reserve in older age is associated with enhanced proactive and reactive interference control. *NeuroImage, 207*, Article 116430. https://doi.org/10.1016/j.neuroimage.2019.116430.

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

Golob, E., Johnson, J., & Starr, A. (2002). Auditory event-related potentials during target detection are abnormal in mild cognitive impairment. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 113*, 151–161. https://doi.org/10.1016/S1388-2457(01)00713-1.

Gómez, C. M., Marco, J., & Grau, C. (2003). Preparatory visuo-motor cortical network of the contingent negative variation estimated by current density. *NeuroImage*. https://doi.org/10.1016/S1053-8119(03)00295-7.

Hämmerer, D., Li, S., Müller, V., & Lindenberger, U. (2010). An electrophysiological study of response conflict processing across the lifespan: Assessing the roles of conflict monitoring, cue utilization, response anticipation, and response suppression. *Neuropsychologia, 48*(11), 3305–3316. https://doi.org/10.1016/j.neuropsychologia.2010.07.014.

Huppert, F. A., Jorm, A. F., Brayne, C., Girling, D. M., Barkley, C., Beardsall, L., & Paykel, E. S. (1996). Psychometric properties of the CAMCOG and its efficacy in the diagnosis of dementia. *Aging, Neuropsychology, and Cognition: A Journal on Normal and Dysfunctional Development, 3*(3), 201–214. https://doi.org/10.1080/13825589608256624.

Huster, R. J., Enriquez-Geppert, S., Lavallee, C. F., Falkenstein, M., & Herrmann, C. S. (2013). Electroencephalography of response inhibition tasks: Functional networks and cognitive contributions. *International Journal of Psychophysiology, 87*(3), 217–233.

Jack, C. R., Albert, M. S., Knopman, D. S., Mckhann, G. M., Sperling, R. A., Carrillo, M. C., … Phelps, C. H. (2011). Introduction to the recommendations from the National Institute on Aging and the Alzheimer ' s Association workgroup on diagnostic guidelines for Alzheimer ' s disease. *Alzheimer's & Dementia, 7*, 257–262. https://doi.org/10.1016/j.jalz.2011.03.004.

Jack, C. R., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., … Silverberg, N. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's and Dementia*. https://doi.org/10.1016/j.jalz.2018.02.018.

Jackson, C. E., & Snyder, P. J. (2008). Electroencephalography and event-related potentials as biomarkers of mild cognitive impairment and mild Alzheimer's disease. *Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 4*(1 Suppl 1), 137–143. https://doi.org/10.1016/j.jalz.2007.10.008.

Jessen, F., Feyen, L., Freymann, K., Tepest, R., Maier, W., Heun, R., … Scheef, L. (2006). Volume reduction of the entorhinal cortex in subjective memory impairment. *Neurobiology of Aging*. https://doi.org/10.1016/j.neurobiolaging.2005.10.010.

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kölsch, H., … Bickel, H. (2014). Prediction of Dementia by Subjective Memory Impairment. *Arch Gen Psychiatry*. https://doi.org/10.1001/archgenpsychiatry.2010.30.

Jessen, F., Wiese, B., Bachmann, C., Eifflaender-Gorfer, S., Haller, F., Kölsch, H., … Bickel, H. (2010). Prediction of dementia by subjective memory impairment effects of severity and temporal association with cognitive impairment. *Archives of General Psychiatry*. https://doi.org/10.1001/archgenpsychiatry.2010.30.

Jessen, F., Wiese, B., Bickel, H., Eiffländer-Gorfer, S., Fuchs, A., Kaduszkiewicz, H., … van den Bussche, H. (2011). Prediction of dementia in primary care patients. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0016852.

Jester, D. J., Andel, R., Cechová, K., Laczó, J., Lerch, O., Marková, H., … Hort, J. (2020). Cognitive Phenotypes of Older Adults with Subjective Cognitive Decline and Amnestic Mild Cognitive Impairment: The Czech Brain Aging Study. *Journal of the International Neuropsychological Society*. https://doi.org/10.1017/S1355617720001046.

Jiang, Y., Li, J., Schmitt, F. A., Jicha, G. A., Munro, N. B., Zhao, X., … Abner, E. L. (2020). Memory-Related Frontal Brainwaves Predict Transition to Mild Cognitive Impairment in Healthy Older Individuals Five Years Before Diagnosis. *Journal of Alzheimer's Disease*. https://doi.org/10.3233/jad-200931.

Jodo, E., & Kayama, Y. (1992). Relation of a negative ERP component to response inhibition in a Go/No-go task. *Electroencephalography and Clinical Neurophysiology, 82*(6), 477–482. http://www.sciencedirect.com/science/article/B6SYX-482XG41-4K/2/f3a9837d5128d574a050b92a6a41552e.

Jonker, C., Jonker, M. I., & Schmand, B. (2000). Are memory complaints predictive for dementia? A review of clinical and population-based studies. *International Journal of Geriatric Psychiatry.*. https://doi.org/10.1002/1099-1166(200011)15:11<983::AID-GPS238>3.0.CO;2-5.

Juncos-Rabadán, O., Facal, D., Lojo-Seoane, C., & Pereiro, A. X. (2013). Does tip-of-the-tongue for proper names discriminate amnestic mild cognitive impairment? *International Psychogeriatrics / IPA, 25*(4), 627–634. https://doi.org/10.1017/S1041610212002207.

Jung, N. Y., Seo, S. W., Yoo, H., Yang, J. J., Park, S., Kim, Y. J., … Kim, H. J. (2016). Classifying anatomical subtypes of subjective memory impairment. *Neurobiology of Aging*. https://doi.org/10.1016/j.neurobiolaging.2016.08.010.

Kornhuber, H. H., & Deecke, L. (1965). Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. *Pflügers Archiv Für Die Gesamte Physiologie Des Menschen Und Der Tiere*. https://doi.org/10.1007/BF00412364.

Kropotov, J., Ponomarev, V., Tereshchenko, E. P., Müller, A., & Jäncke, L. (2016). Effect of aging on ERP components of cognitive control. *Frontiers in Aging Neuroscience*. https://doi.org/10.3389/fnagi.2016.00069.

Kutas, M., Iragui, V., & Hillyard, S. A. (1994). Effects of aging on event-related brain potentials (ERPs) in a visual detection task. *Electroencephalography and Clinical Neurophysiology, 92*(2), 126–139. https://doi.org/10.1016/0168-5597(94)90053-1.

Lee, T. W., Girolami, M., & Sejnowski, T. J. (1999). Independent component analysis using an extended infomax algorithm for mixed subgaussian and supergaussian sources. *Neural Computation*. https://doi.org/10.1162/089976699300016719.

Leynes, P. A., Allen, J. D., & Marsh, R. L. (1998). Topographic differences in CNV amplitude reflect different preparatory processes. *International Journal of Psychophysiology*. https://doi.org/10.1016/S0167-8760(98)00032-4.

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

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

Lobo, A., Saz, P., Marcos, G., Día, J. L., De La Cámara, C., Ventura, T., … Aznar, S. (1999). Revalidation and standardization of the cognition mini-exam (first Spanish version of the Mini-Mental Status Examination) in the general geriatric population. *Medicina Clinica, 112*(20), 767–774. http://www.ncbi.nlm.nih.gov/pubmed/10422057.

López Zunini, R., Knoefel, F., Lord, C., Dzuali, F., Breau, M., Sweet, L., … Taler, V. (2016). Event-related potentials elicited during working memory are altered in mild cognitive impairment. *International Journal of Psychophysiology, 109*, 1–8. https://doi.org/10.1016/j.ijpsycho.2016.09.012.

Loveless, N. E., & Sanford, A. J. (1974). Slow potential correlates of preparatory set. *Biological Psychology*. https://doi.org/10.1016/0301-0511(74)90005-2.

Lynöe, N., Sandlund, M., Dahlqvist, G., & Jacobsson, L. (1991). Informed consent: Study of quality of information given to participants in a clinical trial. *BMJ British Medical Journal, 303*(6803), 610–613. https://doi.org/10.1136/bmj.303.6803.610.

McCarthy, G., & Donchin, E. (1978). Brain potentials associated with structural and functional visual matching. *Neuropsychologia*. https://doi.org/10.1016/0028-3932(78)90085-4.

McKhann, G. M., Knopman, D. S., Chertkow, H., Hyman, B. T., Jack, C. R., Kawas, C. H., … Phelps, C. H. (2011). *The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. In Alzheimer's and Dementia* (Vol. 7(3,, 263–269.

Missonnier, P, Deiber, M.-P., Gold, G., Herrmann, F. R., Millet, P., Michon, a, Fazio-Costa, L., Ibañez, V., & Giannakopoulos, P. (2007). Working memory load-related electroencephalographic parameters can differentiate progressive from stable mild cognitive impairment. Neuroscience, 150(2), 346–356. https://doi.org/10.1016/j.neuroscience.2007.09.009.

Missonnier, Pascal, Herrmann, F. R., Richiardi, J., Rodriguez, C., Deiber, M. P., Gold, G., & Giannakopoulos, P. (2013). Attention-related potentials allow for a highly accurate discrimination of mild cognitive impairment subtypes. *Neurodegenerative Diseases*. https://doi.org/10.1159/000338815.

Mudar, R. A., Chiang, H.-S., Eroh, J., Nguyen, L. T., Maguire, M. J., Spence, J. S., … Hart, J., Jr. (2016). The Effects of Amnestic Mild Cognitive Impairment on Go/NoGo Semantic Categorization Task Performance and Event-Related Potentials. *Journal of Alzheimers Disease JAD, 50*, 577–590. https://doi.org/10.3233/JAD-150586.

Nieuwenhuis, S., Yeung, N., & Cohen, J. D. (2004). Stimulus modality, perceptual overlap, and the go/no-go N2. *Psychophysiology, 41*(1), 157–160. https://doi.org/10.1046/j.1469-8986.2003.00128.x.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4.

Paitel, E. R., Samii, M. R., & Nielson, K. A. (2021). A systematic review of cognitive event-related potentials in mild cognitive impairment and Alzheimer's disease. *Behavioral Brain Research, 396*, Article 112904, 10.1016/j.bbr.2020.112904.

Papadaniil, C. D., Kosmidou, V. E., Tsolaki, A., Tsolaki, M., Kompatsiaris, I. (Yiannis), & Hadjileontiadis, L. J. (2016). Cognitive MMN and P300 in mild cognitive impairment and Alzheimer's disease: A high density EEG-3D vector field tomography approach. Brain Research. https://doi.org/10.1016/j.brainres.2016.07.043.

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

Papaliagkas, V. T., Kimiskidis, V. K., Tsolaki, M. N., & Anogianakis, G. (2011). Cognitive event-related potentials: Longitudinal changes in mild cognitive impairment. *Clinical Neurophysiology, 122*(7), 1322–1326. https://doi.org/10.1016/j.clinph.2010.12.036.

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

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

Pfefferbaum, A., & Ford, J. M. (1988). ERPs to stimuli requiring response production and inhibition: Effects of age, probability and visual noise. *Electroencephalography and Clinical Neurophysiology, 71*(1), 55–63. http://www.ncbi.nlm.nih.gov/pubmed/2446846.

Pires, L., Leitão, J., Guerrini, C., & Simões, M. R. (2014). Event-Related Brain Potentials in the Study of Inhibition: Cognitive Control, Source Localization and Age-Related Modulations. In Neuropsychology Review. https://doi.org/10.1007/s11065-014-9275-4.

Reisberg, B., & Gauthier, S. (2008). Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. *International Psychogeriatrics*. https://doi.org/10.1017/S1041610207006412.

Richardson, J. T. E. (2011). Eta squared and partial eta squared as measures of effect size in educational research. *Educational Research Review*. https://doi.org/10.1016/j.edurev.2010.12.001.

Rönnlund, M., Sundström, A., Adolfsson, R., & Nilsson, L. G. (2015). Subjective memory impairment in older adults predicts future dementia independent of baseline memory performance: Evidence from the Betula prospective cohort study. *Alzheimer's and Dementia*. https://doi.org/10.1016/j.jalz.2014.11.006.

Scheef, L., Spottke, A., Daerr, M., Joe, A., Striepens, N., Kölsch, H., … Jessen, F. (2012). Glucose metabolism, gray matter structure, and memory decline in subjective memory impairment. *Neurology*. https://doi.org/10.1212/WNL.0b013e31826c1a8d.

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

Simmonds, D. J., Pekar, J. J., & Mostofsky, S. H. (2008). Meta-analysis of Go/No-go tasks demonstrating that fMRI activation associated with response inhibition is task-dependent. *Neuropsychologia, 46*(1), 224–232. https://doi.org/10.1016/j.neuropsychologia.2007.07.015.

Smith, J. L., Johnstone, S. J., & Barry, R. J. (2007). Response priming in the Go/NoGo task: The N2 reflects neither inhibition nor conflict. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology, 118*(2), 343–355. https://doi.org/10.1016/j.clinph.2006.09.027.

Smith, J. L., Smith, E. A., Provost, A. L., & Heathcote, A. (2010). Sequence effects support the conflict theory of N2 and P3 in the Go/NoGo task. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology, 75*(3), 217–226. https://doi.org/10.1016/j.ijpsycho.2009.11.002.

Sperling, R. A., Jack, C. R., Black, S. E., Frosch, M. P., Greenberg, S. M., Hyman, B. T., … Schindler, R. J. (2011). Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimer's and Dementia, 7*(4), 367–385.

Sterr, A., & Dean, P. (2008). Neural correlates of movement preparation in healthy ageing. *European Journal of Neuroscience, 27*(1), 254–260. http://www.ncbi.nlm.nih.gov/pubmed/18184323.

Stewart, R. (2012). Subjective cognitive impairment. *Current Opinion in Psychiatry*. https://doi.org/10.1097/YCO.0b013e3283586fd8.

Toledo, J. B., Bjerke, M., Chen, K., Rozycki, M., Jack, C. R., Weiner, M. W., … Trojanowski, J. Q. (2015). Memory, executive, and multidomain subtle cognitive impairment: Clinical and biomarker findings. *Neurology*. https://doi.org/10.1212/WNL.0000000000001738.

Vallesi, A., Stuss, D. T., McIntosh, A. R., & Picton, T. W. (2009). Age-related differences in processing irrelevant information: Evidence from event-related potentials. *Neuropsychologia, 47*(2), 577–586. https://doi.org/10.1016/j.neuropsychologia.2008.10.018.

van Deursen, J. A., Vuurman, E. F. P. M., Smits, L. L., Verhey, F. R. J., & Riedel, W. J. (2009). Response speed, contingent negative variation and P300 in Alzheimer's disease and MCI. *Brain and Cognition, 69*(3), 592–599. https://doi.org/10.1016/j.bandc.2008.12.007.

Vaughan, H. G., Costa, L. D., & Ritter, W. (1968). Topography of the human motor potential. *Electroencephalography and Clinical Neurophysiology*. https://doi.org/10.1016/0013-4694(68)90080-1.

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

Vergara, I., Bilbao, A., Orive, M., Garcia-Gutierrez, S., Navarro, G., & Quintana, J. (2012). Validation of the Spanish version of the Lawton IADL Scale for its application in elderly people. *Health and Quality of Life Outcomes, 10*(130). https://doi.org/10.1186/1477-7525-10-130.

Verleger, R., Paehge, T., Kolev, V., Yordanova, J., Jaśkowski, P., & Jaskowski, P. (2006). On the relation of movement-related potentials to the go/no-go effect on P3. *Biological Psychology, 73*(3), 298–313. https://doi.org/10.1016/j.biopsycho.2006.05.005.

Verleger, Rolf, Hamann, L. M., Asanowicz, D., & Śmigasiewicz, K. (2015). Testing the S-R link hypothesis of P3b: The oddball effect on S1-evoked P3 gets reduced by increased task relevance of S2. *Biological Psychology*. https://doi.org/10.1016/j.biopsycho.2015.02.010.

Verleger, Rolf, Jaśkowski, P., & Wascher, E. (2005). Evidence for an Integrative Role of P3b in Linking Reaction to Perception. *Journal of Psychophysiology, 19*(3), 165–181. https://doi.org/10.1027/0269-8803.19.3.165.

Visser, P. J., Verhey, F., Knol, D. L., Scheltens, P., Wahlund, L. O., Freund-Levi, Y., … Blennow, K. (2009). Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: A prospective cohort study. *The Lancet Neurology*. https://doi.org/10.1016/S1474-4422(09)70139-5.

Vogel, E. K., & Luck, S. J. (2002). Delayed working memory consolidation during the attentional blink. *Psychonomic Bulletin and Review*. https://doi.org/10.3758/BF03196329.

Wild-Wall, N., & Falkenstein, M. (2010). Age-dependent impairment of auditory processing under spatially focused and divided attention: An electrophysiological study. *Biological Psychology, 83*(1), 27–36. https://doi.org/10.1016/j.biopsycho.2009.09.011.

Wild-Wall, N., Hohnsbein, J., & Falkenstein, M. (2007). Effects of ageing on cognitive task preparation as reflected by event-related potentials. *Clinical Neurophysiology*. https://doi.org/10.1016/j.clinph.2006.09.005.

Yesavage, J. A., Brink, T. L., Rose, T. L., Lum, O., Huang, V., Adey, M., & Leirer, V. O. (1983). Development and validation of a geriatric depression screening scale: A preliminary report. *Journal of Psychiatric Research, 17*(1), 37–49. https://doi.org/10.1016/0022-3956(82)90033-4.

Zurrón, M., Lindín, M., Cespón, J., Cid-Fernández, S., Galdo-álvarez, S., Ramos-Goicoa, M., & Díaz, F. (2018). Effects of mild cognitive impairment on the event-related brain potential components elicited in executive control tasks. In Frontiers in Psychology (Vol. 9, Issue MAY). https://doi.org/10.3389/fpsyg.2018.00842.