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Research Report

Can a failure in the error-monitoring system explain unawareness of memory deficits in Alzheimer's disease?



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ABSTRACT

Unawareness of memory deficits is an early manifestation in patients with Alzheimer's disease (AD), which often delays diagnosis. This intriguing behavior constitutes a form of anosognosia, whose neural mechanisms remain largely unknown. We hypothesized that anosognosia may depend on a critical synaptic failure in the error-monitoring system, which would prevent AD patients from being aware of their own memory impairment. To investigate, we measured event-related potentials (ERPs) evoked by erroneous responses during a word memory recognition task in two groups of amyloid positive individuals with only subjective memory complaints at study entry: those who progressed to AD within the five-year study period (PROG group), and those who remained cognitively normal (CTRL group). A significant reduction in the amplitude of the positivity error (Pe), an ERP related to

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Memory deficits
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error awareness, was observed in the PROG group at the time of AD diagnosis (*vs* study entry) in intra-group analysis, as well as when compared with the CTRL group in inter-group analysis, based on the last EEG acquisition for all subjects. Importantly, at the time of AD diagnosis, the PROG group exhibited clinical signs of anosognosia, overestimating their cognitive abilities, as evidenced by the discrepancy scores obtained from caregiver/informant *vs* participant reports on the cognitive subscale of the Healthy Aging Brain Care Monitor. To our knowledge, this is the first study to reveal the emergence of a failure in the error-monitoring system during a word memory recognition task at the early stages of AD. This finding, along with the decline of awareness for cognitive impairment observed in the PROG group, strongly suggests that a synaptic dysfunction in the error-monitoring system may be the critical neural mechanism at the origin of unawareness of deficits in AD.

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1. Introduction

Error monitoring is critical for normal functioning in daily life (Vidal et al., 2020). It is usually defined as the ability to detect and evaluate an error in order to adjust behavior, avoid previous mistakes, and improve learning (Ullsperger, Danielmeier, & Jocham, 2014; Ullsperger, Fischer, Nigbur & Endrass, 2014). There is evidence, though scarce, that this system is impaired in Alzheimer's disease (AD) (Dodson et al., 2011; Mathalon et al., 2003). For instance, even when AD patients have comparable memory performance to an age-matched control group, they seem unable to distinguish between correct and erroneous memory recognition responses in contrast to the control group (Dodson et al., 2011). This is particularly relevant because it suggests an inability of AD patients to be aware of their errors as a consequence of a failure in the error-monitoring system rather than a consequence of their typical memory impairment. Notably, it is well-known that unawareness of memory deficits is often an early manifestation of AD (Bastin et al., 2021) that can delay its diagnosis, as well as therapeutic interventions, further increasing the burden of care (Starkstein, 2014). This behavior constitutes a manifestation of anosognosia (Starkstein, 2014), with growing evidence suggesting that it may predict clinical progression to advanced stages of AD (Munro et al., 2018; Therriault et al., 2018). However, although memory and executive impairments have been proposed as plausible mechanisms underlying anosognosia in neurodegenerative conditions (Agnew & Morris, 1998; Rosen, 2011; Morris & Mograbi, 2013), there is still a lack of evidence supporting the neural mechanistic cascade at the origin of this intriguing behavior.

Here, we hypothesized that anosognosia for memory deficits in AD patients may critically depend on a synaptic failure in the error-monitoring system from the early stages of the disease. Our rationale is that an inability to distinguish correct from erroneous responses in a word memory recognition task would suggest a form of anosognosia, and we postulated that such an inability to be aware that an error was committed (and not the memory deficit *per se*) might be corroborated by

significant changes in the amplitude of the error-related negativity (ERN) and/or the error positivity (Pe) – two event-related potentials (ERPs) that are well-established neural signatures of the error-monitoring system (Falkenstein et al., 1991; Gehring et al., 1993) – from preclinical to early stages of AD. Of note, we tested our hypothesis on a memory task because anosognosia is prone to deficits (or errors) (Leicht et al., 2010) and memory deficits are primordial in typical AD (Dubois et al., 2014). Nevertheless, our rationale implies that such a synaptic failure in the error-monitoring system might be the critical neural mechanism for the emergence of anosognosia for any type of deficits (cognitive, such as memory or executive, or even motor, as in the case of anosognosia for hemiplegia; see Saj et al., 2014), therefore extending this hypothesis to other neurological disorders in which anosognosia frequently occurs (see details of our rationale in Andrade et al., 2023).

The ERN is a negative deflection that peaks approximately 50–150 ms after the commission of an error (e.g., after an erroneous response in tasks that require the recognition of a stimulus), whereas the Pe is a positive deflection following the ERN in a time window between 150 and 550 ms after an erroneous response. The earlier process of error detection is presumably implicit, whereas the later process of error awareness is considered explicit (Ullsperger, Danielmeier et al., 2014; Ullsperger, Fischer et al., 2014). Accordingly, ERP results indicate that the Pe is associated with error awareness (Nieuwenhuis et al., 2001; O'Connell et al., 2007; Boldt & Yeung, 2015), while the ERN is likely to reflect the activation of a more generic, preconscious system of error detection (Falkenstein et al., 1991; Gehring et al., 1993) or conflict monitoring (Scheffers & Coles, 2000; van Veen & Carter, 2002; Yeung et al., 2004), with additional evidence showing that the ERN is not always necessary for the emergence of the Pe and error awareness (Di Gregorio et al., 2018). Some authors have further divided the Pe into an early (appearing until 400 ms after the ERN) and late subcomponents, suggesting that only the latter is modulated by error awareness (Endrass et al., 2007).

Source localization studies have found that both the ERN and Pe are generated by the anterior cingulate cortex (ACC),

with contributions from a more caudal region in the case of the ERN (Dehaene et al., 1994; O'Connell et al., 2007), and a more rostral region in the ACC as well as the posterior cingulate cortex (PCC) in the case of the Pe (O'Connell et al., 2007; Vocat et al., 2008). A prominent theory holds that ACC activity in response to errors might reflect a reinforcement learning process whereby subjects learn to associate actions with negative outcomes in order to improve goal-oriented behavior on the next occurrence (Holroyd & Coles, 2002). Interestingly, there is evidence that healthy elderly may be particularly affected by β -amyloid pathology in regions that ultimately develop heavy β -amyloid loads in AD patients, including the PCC and the ACC, as well as the precuneus and the medial orbitofrontal cortex (see Chételat et al., 2013, for a review). Yet, although β -amyloid deposition in the brain confers a high risk for AD, the percentage of individuals with positive biomarkers who will progress to symptomatic clinical conditions remains unknown (Dubois et al., 2014).

In parallel to these ERP components of error-monitoring, there is consistent evidence of equivalent evoked potentials occurring after correct responses (Vidal et al., 2000). These ERPs, called correct-related negativity (CRN) and correct positivity (Pc), have a similar topography and presumably the same brain origin as those evoked by errors (Roger et al., 2010), suggesting that both CRN and Pc could be associated with brain processes identical to those implicated in the emergence of ERN and Pe, respectively, regardless of the related outcomes.

The main goal of this study was to assess the integrity of the error-monitoring system in individuals at risk of developing AD while performing a word memory recognition task during an EEG session. Specifically, we investigated whether a synaptic failure in the error-monitoring system, as reflected by the ERN and the Pe amplitudes in that task could distinguish subjects who progressed to AD at some point over the five-year study period (PROG group) from those who remained cognitively normal (CTRL group). We predicted that subjects of the PROG group would have a difficulty in distinguishing erroneous from correct responses, which would suggest an inability to monitor their errors (that is, in the case of this study, errors or deficits in a memory recognition task). Last, to further evaluate whether these subjects were unaware of their decline in a broader cognitive domain, we used the Healthy Aging Brain Care Monitor (HABC-M) questionnaire (Monahan et al., 2014). The study was based on the INSIGHT-preAD cohort, an observational, longitudinal cohort of elderly subjects, who were cognitively normal at study entry despite subjective memory complaints (Dubois et al., 2018).

2. Materials and methods

In this section, we report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. The INSIGHT-preAD study data are available at <https://www.gaaindata.org/partner/INSIGHT-preAD>. In accordance with the study sponsor's ethical conditions, access rights are

subject to specific requests. For further details, please see *Data availability* below.

2.1. Participants

Participants were a subpopulation of the INSIGHT-preAD cohort (Dubois et al., 2018). The overall inclusion criteria for this cohort were: participants aged 70–85 years with subjective memory complaints but unimpaired cognition and memory (as indicated by: Mini-Mental State Examination [MMSE; Folstein et al., 1975] score ≥ 27 , Clinical Dementia Rating [CDR; Morris, 1993] score 0, and Free and Cued Selective Reminding Test [FCSRT; Grober & Buschke, 1987] total recall score ≥ 41). Importantly, there is evidence that the amnesic syndrome identified by the FCSRT can distinguish patients at an early stage of AD from mild cognitive impairment non-converters (Sarazin et al., 2007), as well as AD from non-AD dementias (Grober et al., 2010). Memory complaints were defined as follows: subjects answered “YES” to both questions «Are you complaining about your memory?» and «Is it a constant complaint that has lasted for more than six months?». The exclusion criteria were: a history of neurological or psychiatric diseases, including depressive disorders, or other relevant medical comorbidities. One study-partner for each subject also took part in the study. The protocol was approved by the local ethics committee of the Pitié-Salpêtrière University Hospital and conducted according to the Declaration of Helsinki. All participants signed an informed consent form, given and explained to them two weeks before enrolment.

We focused our study on two groups of this INSIGHT-preAD cohort (Dubois et al., 2018) identified after five years of follow-up. Both groups presented a brain pathological β -amyloid status evaluated by 18F-florbetapir (AV-45) positron emission tomography (PET) imaging at study entry. The PROG group refers to β -amyloid positive subjects who progressed to AD, according to the diagnostic criteria of Dubois et al. (2014), while the CTRL group refers to β -amyloid positive subjects who did not progress to AD all along the five-year study period. For β -amyloid PET images, standard uptake value ratios were calculated by averaging the mean activity of cortical regions of interest: both left and right precuneus, posterior cingulate, anterior cingulate, and parietal, temporal and orbitofrontal cortex (the reference region was a combination of whole cerebellum and pons). The threshold for normal (amyloid negative) vs abnormal (amyloid positive) uptake was set to .79 (Habert et al., 2018). A second inclusion criterion for the present study was a total recall score of the FCSRT < 47 at study entry and/or at the last study visit to approximately balance the memory performance across subjects of the CTRL group. The above inclusion/exclusion criteria, all manipulations, and all measures in the study were established prior to data analyses. No part of the study procedures or analysis plans was pre-registered prior to the research being conducted.

A total of 88 out of 318 healthy volunteer subjects of the INSIGHT-preAD cohort were β -amyloid positive at study entry. Of these, 19 did not have complete behavioral/EEG data, and 18 had a high FCSRT total recall score (≥ 47) at both study entry and the last study visit. Thus, our remaining sample

comprised 51 individuals, of which 15 progressed to AD within the five years of the study duration (PROG group), and 36 remained cognitively normal (CTRL group). Specifically, subjects of the PROG group were identified on the basis of a persistent cognitive decline on two consecutive neuropsychological evaluations, in agreement with the IWG-2 criteria for Alzheimer's disease (Dubois et al., 2014; for further details, see also Dubois et al., 2018). All had a typical AD profile, with an amnesic syndrome of the hippocampal type (as corroborated by the FCSRT), except one subject who presented a logopenic variant of AD.

We conducted the behavioral and EEG analyses at two time points (M0 and Mdiag/M60), which respectively correspond to the first and last EEG acquisition for subjects in both groups. More precisely, M0 (at month 0) corresponds to study entry and the first EEG acquisition for all subjects, Mdiag corresponds to the last EEG acquisition for subjects in the PROG group (as detailed hereafter), and M60 (at month 60 from study entry) corresponds to the last EEG acquisition for subjects in the CTRL group. Of note, Mdiag coincided with the AD diagnosis visit for nine subjects, or corresponded to a visit within 12 months of this critical time point for five subjects, or within 36 months for one subject. The latter was the only subject who had been taking a cholinesterase inhibitor for nearly two years at the time of Mdiag. Importantly, at this time point, all subjects of the PROG group presented a global CDR score <1.

Descriptive characteristics for these two groups included demographic and clinical data on age, sex, education level (indicated by the scoring adopted by Dubois et al. (2018), covering pre-primary to tertiary levels of education on a scale ranging from 1 to 8; scores ≥ 7 correspond to "high" education levels and scores ≤ 6 indicate "lower or intermediate" education levels), the MMSE, and the total recall score of the FCSRT at M0 and Mdiag/M60, as previously defined.

Data are presented in Table 1 and Supplementary Table 3 as mean \pm standard deviation (SD) and range (minimum and maximum) for numerical variables, and frequency counts and percentages for categorical variables. Wilcoxon–Mann–Whitney test for numerical variables or Fisher's exact test for categorical variables were used to compare the groups at each time point (M0 or Mdiag/M60).

2.2. Assessment of anosognosia with the Healthy Aging Brain Care Monitor

Participants were followed up with the HABC-M (Monahan et al., 2014) every 12 months. This questionnaire helps monitor and manage three key areas: cognition, functional autonomy, behavioral/psychological health, as well as caregiver burden. Specifically, the HABC-M questionnaire asks how often the participant has encountered certain difficulties in those distinct domains over the past two weeks. There are two versions of the HABC-M, one for the patient for self-reporting, and another for the caregiver for both observations of the patient and self-reporting on the caregiver's own status. In this study, we were interested in assessing cognitive deficits, so we focused on the cognitive subscale of the HABC-M, which comprises 6 items (questions) with answers ranging from 0 (never) to 3 (very often) and thus a total score ranging from 0 to 18. By subtracting the HABC-M total cognitive score obtained from the participant (self-report) from that obtained from the caregiver (hetero-report), we computed a discrepancy score reflecting participants' awareness of their cognitive difficulties (i.e., discrepancy score = caregiver hetero-report minus participant self-report). Thus, higher discrepancy scores indicated that the participants overestimated their cognitive abilities, thereby reflecting a lack of awareness in the cognitive domain (i.e., anosognosia). To assess longitudinal effects of anosognosia for cognitive difficulties across groups, we compared the discrepancy scores of the PROG and CTRL groups at times M0 and Mdiag/M60.

2.3. Experimental design of EEG study

EEG data were collected annually for each participant over a five-year period while the participants performed a cognitive task of memory recognition of words. Stimuli consisted of 16 target words sampled from the FCSRT (Grober & Buschke, 1987), and 64 distractor words that matched the target words in frequency of occurrence and length. Participants were instructed by a neuropsychologist to memorize the study list (target words) between one and 4 h before the EEG session. During the EEG session, they were presented with sequences of these words, and were instructed to indicate which of them

Table 1 – Demographic and neuropsychological characteristics of the PROG and CTRL groups at M0 and Mdiag/M60. p-values were computed using a Wilcoxon–Mann–Whitney test for numerical variables (Age, MMSE, FCSRT) and Fisher's exact test for categorical variables (Gender, Education level). Significant differences are indicated by asterisks: * $p < .001$, ** $0.001 \leq p < .01$, * $0.01 \leq p < .05$.^a Categorization of the education level into "high" and "low or intermediate" education levels are as indicated in Dubois et al. (2018).**

Population Characteristics	M0			Mdiag/M60		
	PROG (n = 15)	CTRL (n = 36)	p-value	PROG (n = 15)	CTRL (n = 36)	p-value
Gender (M/F, % F)	7/8, 53%	14/22, 61%	.76			
Age mean \pm SD (range)	77.5 \pm 3.4 (70–85)	76.3 \pm 3.0 (71–84)	.18	81.7 \pm 3.2 (75–86)	81.3 \pm 3.0 (76–89)	.44
Education level ^a	10/5, 67%	17/19, 47%	.23			
High/Low-Intermediate, % High						
MMSE (maximum 30) mean \pm SD (range)	28.2 \pm .7 (27–29)	28.7 \pm .9 (27–30)	.07	25.9 \pm 3.9 (14–30)	28.5 \pm 1.5 (23–30)	.002**
FCSRT-Total Recall (maximum 48) mean \pm SD (range)	44.7 \pm 2.2 (41–48)	45.9 \pm 1.8 (41–48)	.043*	32.5 \pm 8.7 (10–41)	45.5 \pm 2.2 (40–48)	<.001***

they had previously memorized. Each trial started with a fixation cross, displayed in the center of the screen for 1.5 sec, followed by the presentation of the stimulus (word item) for 2 sec. Then a question prompted the participant to indicate whether the word was one of the target words (yes/no, corresponding to target and distractor words, respectively) by pressing buttons in a two-alternative forced choice design. No feedback was provided to the subjects on their performances. The first question was followed by a second one: “Are you sure of your answer?”. This question also required a binary response (yes/no), which indicated whether subjects were in doubt about their answers. The present study focused only on the subjects' responses to the first question in terms of behavior and EEG potentials evoked by correct or erroneous answers during the described memory task.

The experiment began with a training phase, during which participants performed a short training block to familiarize them with the EEG task setup. The episodic memory test then consisted of four successive blocks of 52 trials each, for a total of 208 trials. These trials presented in pseudorandom order each target word five times and the distractor words as follows: 16 distractors were presented five times, while the remaining 48 were presented only once during the whole experiment (i.e., all four blocks). Experimental blocks were separated by breaks. Stimulus presentation was controlled by E-prime software version 2.0 (Psychology Software Tools, Pittsburgh, PA), with words being displayed in white color on a black screen monitor at 1 m distance from the participant. The episodic memory test lasted about 20 min.

A failure to recognize whether a given word had been presented previously by the neuropsychologist, or not, constituted an error (i.e., either a false recognition of a distractor word or an omission of the recognition of a target word). Participants were not instructed to respond quickly, which could have increased the number of errors (see [Bogacz et al., 2010](#), for a review on the speed-accuracy tradeoff), but were allowed to respond as soon as they were ready, with no upper time limit set for response. Behavioral data in this experiment consisted of the subjects' accuracy (percentage of correct responses over 208 trials per subject) and the time interval between the presentation of the stimulus and their responses (reaction time; RT). Importantly, RT could decrease even after accuracy reached 100%, thus providing valuable behavioral assessment even in situations in which task performance was relatively error free. Both accuracy and RT were then investigated as behavioral clues to memory and learning abilities.

2.4. Signal recording and pre-processing of EEG data

EEG data were acquired with a 256-channel whole-head Geodesic 300 EEG System (Electrical Geodesics, Eugene, OR, USA) at a sampling rate of 250 Hz. Electrooculogram (EOG) data were recorded from electrodes placed above, below, and lateral to each eye. All electrode impedances were kept below 50 k Ω . The initial reference electrode was placed at Cz site. Sensor layout for 256-channel Hydrocel Geodesic Sensor Net is given in Supplementary information.

The Brainstorm software was used for pre-processing ([Tadel et al., 2011](#)). As the channel Cz was of interest for analyzing the ERN and the Pe amplitudes, we first re-

referenced the EEG signals from Cz to the mean of the Left and Right Mastoids channels (CH094/CH190) (cf. [Supplementary Fig. 1](#)). The data were then band-pass filtered between .1 and 40 Hz. Blinks were automatically detected from four pairs of channels (CH018–CH037, CH025–CH032, CH010–CH046, CH033–CH019; cf. [Supplementary Fig. 1](#)). Four steps of blink detection were performed consecutively for each of the pairs previously cited. Blinks detected from a pair of channels are grouped in one series. Based on each blink series, the Signal-Space Projection (SSP) algorithm was applied separately to remove blink artifacts leading to four projectors. The projector on which the artifacts were most clearly detected was retained. After artifact suppression (from SSP), epochs from each trial were extracted in the time interval of [–100 ms, 600 ms] with respect to the button press response time. Individual epochs containing residual blink-related artifact when compared before and after component suppression or high amplitude variation (peak-to-peak > 100 μ V) were detected visually and rejected.

For electrodes Cz and FCz, which were our channels of interest, ERPs were estimated from the averaged epochs after removing the baseline mean activity of each channel in the 100 ms window prior to response. Specifically, the ERN was determined as the mean amplitude within –15/+15 ms around the most negative peak in the time interval from 0 to 150 ms after an erroneous response ([Larson et al., 2007](#)). The Pe was subdivided into two early (Pe1, 150–250 ms; Pe2, 250–350 ms) and two late (Pe3, 350–450 ms; Pe4, 450–550 ms) sub-components, being determined for each subcomponent as the mean amplitude for 100 ms time windows from 150 to 550 ms. The same time intervals were used for their correct-response counterparts, CRN and Pc. For a single participant, ERP components at FCz were instead estimated with a neighboring posterior sensor (CH009) due to noise at FCz.

Importantly, we required a minimum of six artifact-free trials on errors (or correct responses) for a reliable ERP estimation. This is in line with previous findings showing that six to eight error trials are sufficient to achieve adequate consistency for ERN and Pe amplitudes ([Olvet & Hajcak, 2009c](#)). Therefore, given the relatively scarce erroneous responses by some individuals, for EEG data analysis the number of subjects was $n = 9$ at M0 and $n = 15$ at Mdiag for the PROG group, and $n = 10$ at M0 and $n = 9$ at M60 for the CTRL group. The demographic and neuropsychological characteristics of these subsamples are shown in [Supplementary Table 3](#).

2.5. Statistical analyses

All statistical analyses were conducted using R version 3.6.1 ([R Core Team, 2019](#)) and plots were generated with the ggplot2 package (v3.3.2) ([Wickham, 2016](#)). The level of statistical significance was set to $p < .05$ for all tests.

Within and between group differences and changes were examined using linear mixed-effects models (LMMs). Specifically, models were built for each outcome of interest: assessment of anosognosia (discrepancy scores derived from the cognitive HABC-M subscale); behavioral (two models, one for accuracy and the other for RT); and EEG (eight models, for the amplitudes of the ERN/CRN and Pe/Pc components at FCz and Cz electrodes, respectively).

In the assessment of anosognosia, one linear mixed model was fitted to investigate effects of group (PROG; CTRL), time (M0; Mdiag/M60), and their interaction. The model included a random intercept on the subject identifier and covariates for age, gender, and education level at M0. We have specifically introduced gender as a covariate in this model because of previous evidence suggesting a co-effect of gender on caregiver burden (Xiong et al., 2020), which could eventually impact caregivers' estimation of participants' cognitive abilities. Main and interaction effects (“omnibus” test) of the fitted LMMs are reported with Wald χ^2 statistic and degrees of freedom (df); and post hoc pairwise comparisons (including a Benjamini-Hochberg correction of the false discovery rate) on significant main and interaction effects are reported with t-ratio statistic (t) and Kenward-Roger's approximation for the degrees of freedom.

In the behavioral models, the factors Group (PROG, CTRL), Time (M0, Mdiag/M60), and Type of response (Correct, Erroneous) only for RT, were regarded as fixed effects. We further included the interaction terms between these factors as fixed effects.

In the ERP models related to either correct or erroneous responses, fixed effects involved Group (PROG, CTRL), Time (M0, Mdiag/M60), the addition of the two early and two late Pe/Pc subcomponents for the Pe/Pc models, and all the resulting interaction terms. The subject identifier was assigned as a random effect (intercept) to account for the repeated measurements. Age and education level at M0 were also included for covariate adjustments.

All LMMs were fitted using restricted maximum-likelihood estimation (REML) from the function `lmer` in the `lme4` package (v1.1-21) (Bates et al., 2015). Significance for the main effects and all two-way and three-way interactions was assessed based on Type II Wald chi-square tests using the function `Anova` in the `car` package (v3.0-7). Post hoc pairwise comparisons were carried out on significant higher interaction with the `emmeans` package (v1.4.5) allowing the specification of custom contrasts between specific group means of interest to further determine where the differences occurred. *p*-values resulting from the post hoc tests were determined from the t-ratio (t) with Kenward-Roger's approximation for degrees of freedom (df), and after adjustment by the Benjamini and Hochberg false discovery rate procedure to account for the multiplicity of contrasts. Results of the post hoc tests were also reported with the estimated marginal means (i.e., means predicted by the LMMs) and standard errors (SE) of the groups compared using `emmeans`. For the behavioral accuracy model, an arcsine square root transformation was applied to the proportion data prior to modeling as this improved the model assumptions of linearity, normality and constant variance of residuals. Finally, all significant interaction effects were also confirmed with Type III Wald chi-square tests using the function `Anova` in the `car` package (v3.0-7).

3. Results

Demographic and neuropsychological characteristics of the PROG and CTRL groups are shown in Table 1. At entry (month M0), there were only minor, if any, cognitive differences

between the groups in the MMSE score and the FCSRT total recall score. By contrast, differences on those neuropsychological tests became highly significant between the groups at Mdiag/M60, which objectively distinguished these groups in terms of cognition.

Clinically, we have therefore observed an insidious cognitive decline of the PROG group and a relatively constant cognitive performance of the CTRL group over time. The demographic characteristics (age, gender and education level) did not differ significantly between groups.

3.1. Unawareness of cognitive deficits

To assess unawareness of cognitive deficits in our subject cohort, we used the cognitive subscale of the HABC-M questionnaire (Monahan et al., 2014). Specifically, high discrepancy scores (that is, caregiver reported higher cognitive deficits than participant) indicated heightened unawareness of cognitive deficits (also see Material and Methods section). A linear mixed model was fitted to investigate effects of group (PROG; CTRL), time (M0; Mdiag/M60), and their interaction.

The statistical model revealed significant longitudinal anosognosia effects only for the PROG group. Specifically, Type II Wald chi-square tests for the fitted models indicated a significant Group main effect, with the PROG group having higher discrepancy scores than the CTRL group ($p = .04$). There was a significant “Group \times Time” interaction effect ($p = .01$), with the PROG group having higher discrepancy scores at Mdiag than at M0 ($p < .05$), which suggests that these individuals overestimated their cognitive abilities, being unaware of their deficits at the time of AD diagnosis (Fig. 1). Further, the discrepancy scores of the CTRL group did not change over time, and were lower than the discrepancy scores of the PROG group at M60/Mdiag, respectively, which suggests that, unlike the PROG group, the CTRL group did not develop signs of anosognosia across the duration of the study.

3.2. Performance on the memory task during the EEG session

We compared the overall performance of the participants on the word memory recognition task in terms of accuracy (percentage of correct responses over 208 trials) and reaction time (RT) during the EEG session. To this end, two linear mixed models (LMMs) were fitted to investigate the effects of group (PROG; CTRL), time (M0; Mdiag/M60), type of response (Correct or Erroneous, only for RT), and all interaction terms. More information on the statistical analyses is provided in the Materials and methods section.

Both LMMs robustly distinguished the evolution of PROG and CTRL groups in terms of accuracy and RT (Figs. 2 and 3, respectively; also see Supplementary Tables 1 and 2 for detailed list of effects). Critically, Type II Wald chi-square tests for the two fitted models indicated a significant “Group \times Time” interaction effect on accuracy ($p < .001$) and RT ($p < .001$). A further investigation of this interaction with pairwise comparisons based on estimated marginal means \pm standard error (SE) revealed that the PROG group was significantly less accurate ($p < .001$) at Mdiag ($78.9 \pm 2.7\%$) than at M0 ($93.4 \pm 1.6\%$), indicating a decrease of accuracy over

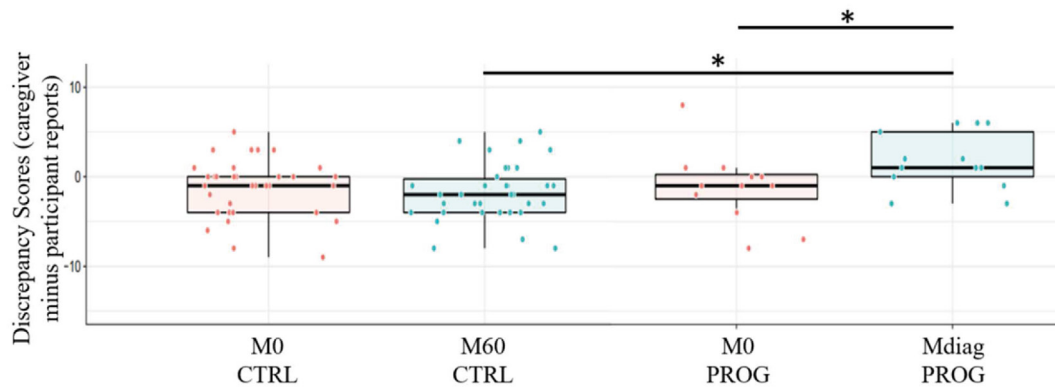


Fig. 1 – Unawareness of cognitive deficits of the PROG and CTRL groups at times M0 and Mdiag/M60. Box plots show the discrepancy between the caregiver and participant reports on the cognitive HABC-M subscale, which is a surrogate of anosognosia (Cacciamani et al., 2017). Significant differences are indicated by asterisks: $*.01 \leq p < .05$.

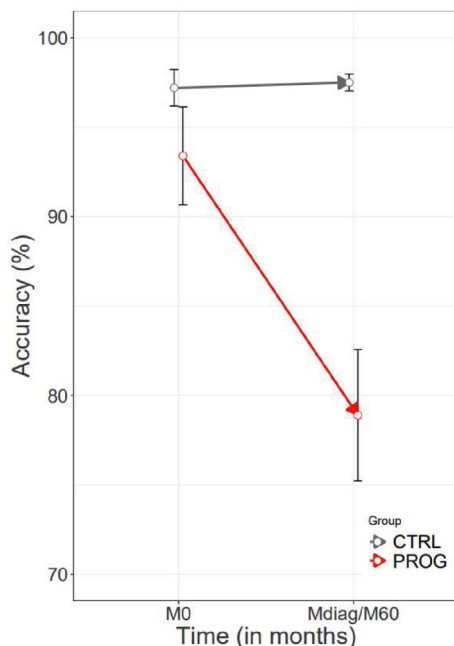


Fig. 2 – Behavioral accuracy of the PROG and CTRL groups on the memory task during the EEG session at times M0 and Mdiag/M60. Plots show percentage of correct responses together with 95% confidence intervals.

time. By contrast, the accuracy of the CTRL group remained high between these two time points. As a result, the two groups ended up differing significantly ($p < .001$) at Mdiag/M60, where the accuracy was worse for the PROG group ($78.9 \pm 2.7\%$) than for the CTRL group ($97.5 \pm .7\%$).

The RT results were consistent with these findings. Specifically, the PROG group had significantly longer RT ($p < .001$) at Mdiag for all responses (correct and erroneous combined, 1380 ± 112 ms) than at M0 (1087 ± 113 ms), which further resulted in the two groups differing significantly ($p < .01$) at Mdiag/M60 regardless of the type of response. This difference became markedly larger due to the fact that the RT of the subjects of the CTRL group decreased significantly ($p < .05$) for all responses (correct and erroneous combined, 1069 ± 72 ms

at M0 vs 933 ± 72 ms at M60) between the two time points (as detailed in [Supplementary Table 1b](#)). Furthermore, we observed that the response times for erroneous responses (1237 ± 66 ms) were significantly larger than those for correct responses (998 ± 65 ms) over both groups and both time points ($p < .001$) (Fig. 3).

Taken together, these results revealed a learning disability emerging in the PROG group from M0 to Mdiag, which clearly contrasted with the subjects of the CTRL group, whose behavioral performance remained relatively unchanged (accuracy) or even improved (reaction time) over time.

3.3. ERP analysis on errors

For ERP analysis, we fitted four LMMs to separately model the two ERP components (ERN and Pe, where the latter was divided into two early and two late subcomponents) at each electrode location (FCz and Cz). The LMMs assessed the effects of group (PROG, CTRL), time (M0, Mdiag/M60), two early and two late subcomponents for Pe, and all the resulting interaction terms. More information on the statistical analyses is provided in the Materials and methods section.

The ERN and Pe responses for the PROG and CTRL groups are shown on [Figs. 4 and 5](#). The LMM results revealed a significant interaction effect of “Group \times Time” on Pe at both FCz ($p < .001$) and Cz ($p < .001$) electrodes, indicating that group differences are time-dependent. There were no significant differences between early and late Pe subcomponents, thus suggesting that both may reflect the same neural mechanism. A detailed description of the LMM results is presented in [Supplementary Tables 4 and 5](#)

From the “Group \times Time” interaction, the following post hoc comparisons on estimated marginal mean amplitudes (\pm SE) showed direct evidence of a failure in the error-monitoring system during a memory task in early stages of AD. Specifically, at Cz electrode, the Pe amplitude decreased significantly from M0 to Mdiag for the PROG group ($2.75 \pm .61$ μ V at M0 vs $.79 \pm .57$ μ V at Mdiag, $p < .001$), whereas the CTRL group showed the inverse pattern of evolution ($.47 \pm .61$ μ V at M0 vs $2.71 \pm .63$ μ V at M60, $p < .001$), as illustrated in [Fig. 4](#). A similar evolution was found at FCz electrode, although with lower Pe amplitudes for both groups:

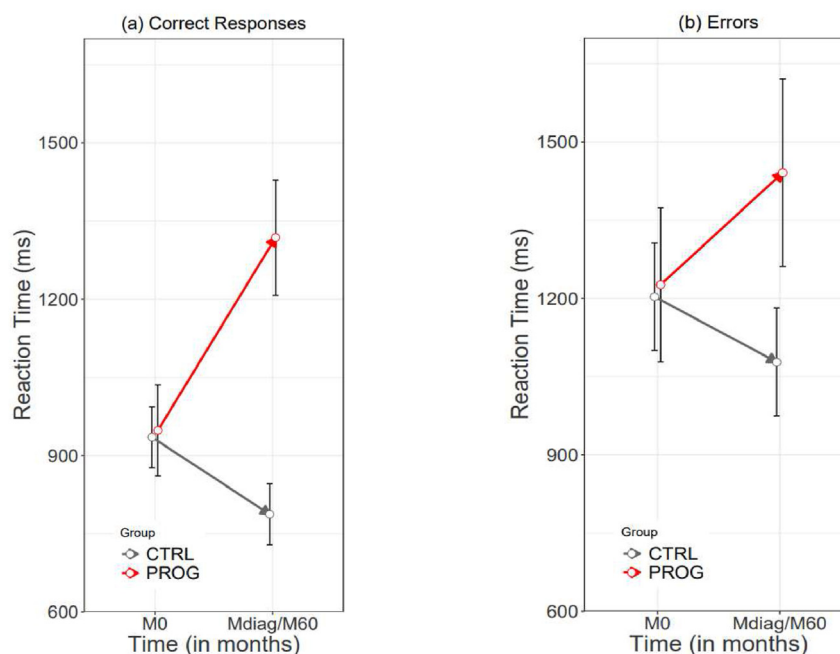


Fig. 3 – Reaction times of the PROG and CTRL groups on the memory task during the EEG session at times M0 and Mdiag/M60. Plots show the mean of reaction times with 95% confidence intervals for (a) correct responses, and (b) errors.

.61 ± .49 μ V at M0 vs .14 ± .45 μ V at Mdiag, $p = .145$, for the PROG group; and $-.31 \pm .48 \mu$ V at M0 vs $1.84 \pm .50 \mu$ V at M60, $p < .001$, for the CTRL group (Fig. 5). Importantly, these results strongly suggest that different phenomena reflected in the Pe amplitude (Orr & Carrasco, 2011) may contribute to distinguishing the two groups between M0 and Mdiag/M60: 1) a lack of awareness for memory impairment (erroneous responses in the memory task) at Mdiag in those subjects who progressed to AD (i.e., the PROG group); and 2) a learning effect, probably resulting from an improved ability to recognize erroneous responses and to adjust one's behavior with the repetition of the task, in those subjects who remained cognitively normal over time (i.e., the CTRL group).

Barplots showing the estimated marginal means and standard errors of ERPs at M0 and Mdiag/M60 for both groups (bottom panel), as estimated from the linear mixed-effects modeling. Significant differences are indicated by asterisks: *** $p < .001$, ** $0.001 \leq p < .01$, * $0.01 \leq p < .05$.

Interestingly, at M0, the Pe amplitude of the PROG group was significantly higher than the Pe amplitude of the CTRL group at Cz electrode (.47 ± .61 μ V at M0 for the CTRL group vs $2.75 \pm .61 \mu$ V at M0 for the PROG group, $p < .05$), further suggesting the existence of a neural compensation mechanism that probably helped the subjects of the PROG group to accurately perform the memory task at entry (that is, up to five years before their AD diagnosis).

At FCz, where the ERN is typically maximal, we observed that the magnitude (absolute value of the amplitude) of the ERN for the CTRL group at M60 was lower than for the PROG group at Mdiag, but it remained only a trend (.54 ± .44 μ V at M60 vs $2.00 \pm .34 \mu$ V at Mdiag, $p = .058$). An additional trend was found for a decrease of the ERN magnitude between M0 and M60 in the CTRL group ($1.85 \pm .42 \mu$ V at M0 vs $.54 \pm .44 \mu$ V at

M60, $p = .073$), while no differences on the ERN were found between these two time points in the PROG group ($1.76 \pm .44 \mu$ V at M0 vs $2.00 \pm .34 \mu$ V at Mdiag, $p = .87$). Details of the post hoc tests are reported in Supplementary Table 4. At Cz electrode, neither a significant effect nor even a trend was found on the ERN (Supplementary Table 5).

3.4. ERP analysis on correct responses

For ERP analysis on correct responses, four separate models were constructed in a similar manner to those based on the erroneous response data for the two respective ERP components (CRN and Pc) within the same time intervals as above, at the FCz and Cz electrodes.

As detailed in Supplementary Tables 6 and 7, Type II Wald chi-square tests for the fitted model indicated a significant effect of “Group × Time” on Pc models at both Cz ($p < .001$) and FCz ($p < .001$) electrodes. No significant effect of the CRN component was found. Post hoc comparisons on the “Group × Time” interaction showed a significant decrease of the Pc amplitude from M0 to Mdiag for the PROG group at Cz ($1.65 \pm .40 \mu$ V at M0 vs $.85 \pm .37 \mu$ V at Mdiag, $p < .01$) and at FCz ($.62 \pm .27 \mu$ V at M0 vs $.19 \pm .24 \mu$ V at Mdiag, $p < .05$). By contrast, the CTRL group showed a significant increase of the Pc amplitude from M0 to M60 at the same fronto-central sites (Cz, $.72 \pm .39 \mu$ V at M0 vs $2.30 \pm .41 \mu$ V at M60, $p < .001$; and FCz, $.19 \pm .27 \mu$ V at M0 vs $1.31 \pm .28 \mu$ V at M60, $p < .001$). Moreover, a significant difference was found between the two groups at Mdiag/M60 also at Cz ($2.30 \pm .41 \mu$ V at M60 vs $.85 \pm .37 \mu$ V at Mdiag, $p < .05$) and at FCz ($1.31 \pm .28 \mu$ V at M60 vs $.19 \pm .24 \mu$ V at Mdiag, $p < .05$). This pattern of evolution was similar to that of the Pe amplitude for the same subsamples of subjects as presented above in the respective subsection.

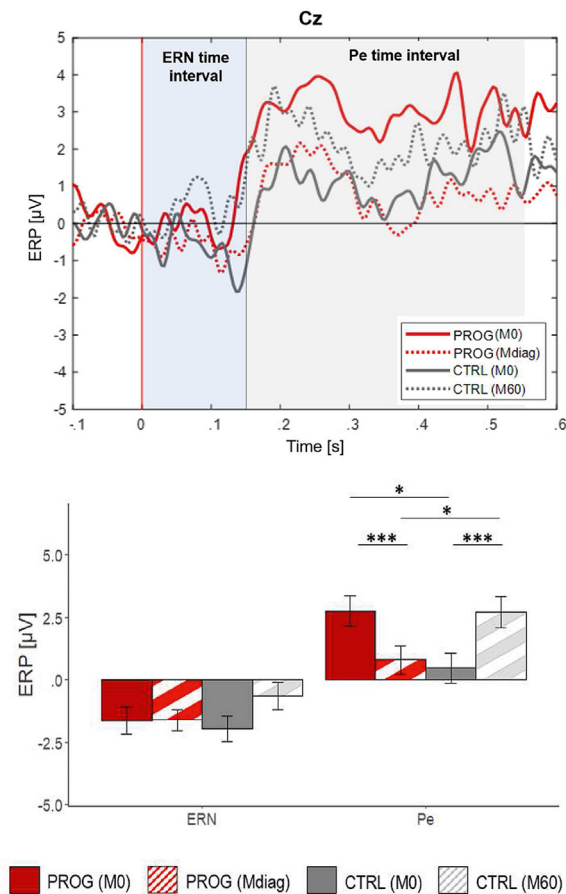


Fig. 4 – Grand average ERP (ERN and Pe) amplitudes, time-locked to the (erroneous) response occurring at time 0 sec, recorded at electrode Cz. ERN is found in the 0–150 ms time interval post-error (top panel). Pe is found within the 150–550 ms time interval. Barplots show the estimated marginal means and standard errors of the ERPs at M0 and Mdiag/M60 for both groups (bottom panel), as estimated from the linear mixed-effects modeling. Significant differences are indicated by asterisks: $***p < .001$, $**0.001 \leq p < .01$, $*0.01 \leq p < .05$.

4. Discussion

Episodic memory relies on constructive processes that are sometimes prone to error (Schacter & Addis, 2007). Learning from our previous mistakes, avoiding the repetition of errors, requires an error-monitoring system that allows for rapid detection and evaluation of errors in order to adjust our behavior and improve our performance on goal-directed tasks (Ridderinkhof et al., 2004). This ability might be necessary for subjects to identify, for example, an error when unable to recognize a word in a memory task. An amnesic episodic syndrome is typically observed in prodromal stages of AD (Dubois & Albert, 2004), with growing evidence that these patients are often unaware of their memory impairment (Bastin et al., 2021; Vannini et al., 2020). Relatedly, we have observed that the PROG group overestimated their cognitive

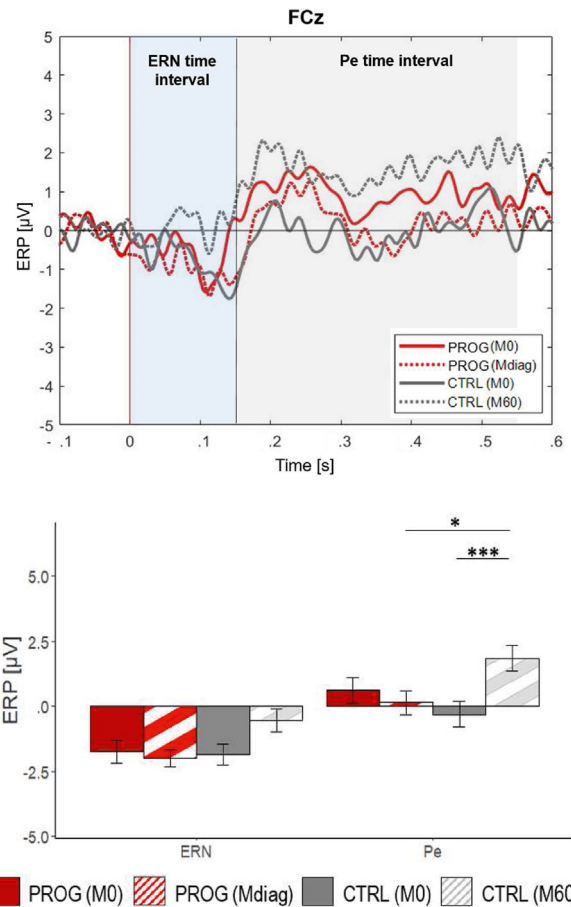


Fig. 5 – Grand average ERP (ERN and Pe) amplitudes, time-locked to the (erroneous) response occurring at time 0 sec, recorded at electrode FCz. ERN is found in the 0–150 ms time interval post-error (top panel). Pe is found within the 150–550 ms time interval post-response.

abilities at Mdiag, as revealed by both intra-group (Mdiag vs M0) and inter-group (PROG vs CTRL at Mdiag/M60) analyses on the HABC-M cognitive subscale discrepancy scores, thus corroborating the emergence of anosognosia at that critical time point.

Also, at Mdiag, the Pe amplitudes of the PROG group were significantly smaller, the reaction times longer, and the error rates larger, than they were at M0 (intra-group analysis), and than those of the CTRL group at M60 (inter-group analysis). Consistent with the ERP results on errors, EEG potentials evoked by correct responses followed a similar pattern of evolution over time within and between groups. Together with the behavioral results on the cognitive HABC-M, as well as the results on accuracy and RT observed in the memory task during the EEG session, these ERP findings seem to reflect a lack of awareness for memory deficits, but also a learning disability of the subjects of the PROG group at the moment of their AD diagnoses. Notably, the Pe (but not the ERN) is a robust neural index of error awareness (Kirschner et al., 2021), with additional evidence of post-error behavioral modulation by consciously perceived errors. Moreover, in addition to error detection and awareness, the amplitude of the Pe has also

been associated with the confidence in error judgment (Boldt & Yeung, 2015). Accordingly, it has been proposed that an increased Pe amplitude could also reflect a learning strategy allowing subjects to avoid future errors (Orr & Carrasco, 2011), with further assumptions that both CRN and Pc could be associated with brain processes identical to those implicated in the emergence of ERN and Pe, respectively.

Overall, these behavioral and ERP results strongly support our mechanistic hypothesis, thereby suggesting that a synaptic failure in the error-monitoring system is probably the underlying neural mechanism explaining why AD patients are often unaware of their memory deficits since the very early stages of the disorder.

On the other hand, the higher amplitude of the Pe observed in the PROG group at M0 relative to Mdiag suggests that a neural mechanism of “less-wiring-more-firing” type might be at work (Daselaar et al., 2015), probably activated in these subjects in order to perform the memory task at M0 with success. In fact, despite some difficulties observed already at study entry, as reflected by a lower, although normal total recall score on the FGSRT when compared to the subjects of the CTRL group at the same time point (Supplementary Table 3), the PROG group performed accurately the memory task during the EEG session at M0. Supporting this view, evidence from monkey studies has shown an increase in the PGC firing rate early in conditions of poor learning related, for example, to the lack of focus during an experiment (Heilbronner & Platt, 2013). Considering its origin (O’Connell et al., 2007), it seems very plausible that the higher Pe amplitude observed at M0 in the PROG group reflects a similar neural mechanism, allowing these subjects to still compensate for subclinical difficulties in learning.

Lastly, whether the ERN and the Pe represent two independent error-monitoring processes is still an open question (Di Gregorio et al., 2018). According to our results, the amplitude of the ERN does not necessarily co-vary with the amplitude of the Pe. In fact, while the Pe amplitude – particularly related to error awareness – decreased over time for the PROG group (and increased for the CTRL group), the ERN amplitude did not change significantly between the two studied time points for both groups.

The ERN has been associated with preconscious error-monitoring processes and may vary with stimulus novelty (Wessel et al., 2012) or expectedness (Nieuwenhuis et al., 2003), with evidence of higher ERN magnitudes (i.e., more negative) occurring after unexpected stimuli than after expected ones (O’Connell et al., 2007). Due to their memory deficits, it is possible that the “surprise effect” or novelty of the presented words (that is, the task stimuli) remained relatively intact for the PROG group at Mdiag and, therefore, without impact on the ERN amplitude. For the CTRL group, it is possible that the practice effect resulting from the task repetition over time had contributed to the reduction of the ERN magnitude at M60 (Nieuwenhuis et al., 2003), probably reflecting a habituation to the task stimuli, although this finding remained only a trend. Interestingly, however, despite being globally different, both groups took more time in erroneous than correct responses at the two studied time points (M0 and Mdiag/M60), as illustrated in Fig. 3. This behavior suggests that, even at Mdiag, the subjects of the PROG group

could, at least at some point, implicitly distinguish erroneous from correct responses, which might be consistent with the absence of changes in the amplitude of the (pre-conscious) ERN observed in this group between M0 and Mdiag. Nevertheless, their performance accuracy at Mdiag was lower when compared with the CTRL group at M60 (Fig. 2), with evidence that the CTRL group had significantly higher Pe amplitudes in both inter-group analysis (vs PROG group) at Mdiag/M60 and intra-group analysis (M0 vs M60). Such finding is pertinent because it suggests that, unlike the PROG group, the CTRL group was able to explicitly distinguish between correct and erroneous responses at M60 in line with a learning strategy probably developed from repeated practice of the task each year. In fact, the CTRL group’s faster responses and the maintenance (or even slight improvement) of their accuracy on the last visit may reflect such learning effect. Also, these findings reinforce the view that the ERN and the Pe are at least partly independent and may indeed reflect distinct brain functions implicated in performance monitoring and error awareness.

In sum, the ERP data generated on both erroneous and correct responses during the EEG memory task are consistent within and between groups at distinct time points (M0; Mdiag/M60) in two fronto-central sites (FCz; Cz), thereby strengthening their robustness despite the relatively reduced sample size that constitutes the main limitation of this study. Yet, it is worth noting that the literature examining cognitive ERPs in either AD patients or subjects at risk for AD is quite small, and most frequently focused on post-stimulus, sensory ERP components (Paitel et al., 2021), which makes this study particularly original.

5. Conclusion

The present work was based on an innovative approach focused on the study of the error-monitoring system by combining behavior and ERP data analysis in a longitudinal cohort of elderly subjects at risk for AD. Our findings provided direct evidence for the emergence of a synaptic failure in the error-monitoring system from the very early stages of AD. Such evidence was particularly corroborated by a significant decrease in the Pe amplitude during a memory task in the subjects of the PROG group between M0 and Mdiag (intra-group analysis), but also when compared with the CTRL group at Mdiag/M60 (inter-group analysis). Importantly, the Pe is known to be specifically elicited by errors that have been consciously perceived (Murphy et al., 2012). Thus, the lower Pe amplitude observed in the PROG group at Mdiag suggests a lack of awareness for erroneous responses in the memory task at that critical time point. In support of this view, the cognitive HABC-M subscale revealed a longitudinal decline of awareness for the PROG group, which is consistent with robust research evidence showing that AD patients tend to overestimate their cognitive abilities since the earliest stages of the disorder (Bastin et al., 2021; Munro et al., 2018; Theriault et al., 2018; Vannini et al., 2020). Finally, although this study focused on a memory task (during the EEG session), our rationale implies that such a failure in the error-monitoring system might be at the origin of patient’s unawareness for

any type of deficits, possibly constituting the critical neural mechanism for the emergence of anosognosia not only in AD, but also in other neurological disorders in which anosognosia frequently occurs. Future research exploring this rationale is necessary to validate our hypothesis.

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Author contributions

KA conceived the hypothesis, designed and conducted the study; participated in the acquisition of clinical data as medical investigator of the INSIGHT-preAD cohort; interpreted and discussed the results; wrote the original draft and the final manuscript.

SR and TG performed the EEG (SR) and behavioral (TG) analyses; interpreted and discussed the results; made contributions to the text, tables, and artwork in the final manuscript.

FXL and MH conducted the statistical analysis and contributed to the writing of the final manuscript. FXL also contributed to the tables included in Supplementary information.

TM co-supervised EEG preprocessing and contributed to the discussion of the results and to the writing of the final manuscript.

GD and AK contributed to the analysis, interpretation and discussion of the results, and to the writing of the final manuscript. GD further contributed to the preliminary statistical analysis.

FRP, NV, VLC and NG contributed to the discussion of the results and to the proofreading of the final manuscript.

DP supervised EEG preprocessing and analysis, contributed to the interpretation and discussion of the results, the artwork and the writing of the final manuscript.

Data availability

The current study was based on the INSIGHT-preAD cohort, whose principal investigator is Prof. Bruno Dubois.

The study data are available at <https://www.gaaindata.org/partner/INSIGHT-preAD>.

Access rights to raw data, research materials and analysis code are subject to the approval of the Scientific Committee of the INSIGHT study. Requests should be sent to bruno.dubois@aphp.fr.

Declaration of competing interest

The authors report no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.cortex.2023.05.014>.

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