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Defective involuntary attention to novelty in type 1 diabetes and impaired awareness of hypoglycaemia

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ABSTRACT

Aim: To determine if there are differences in terms of neurophysiology and neurocognitive functioning in a group of type 1 diabetes (T1D) patients regarding hypoglycaemia awareness.

Methods: 27 patients with T1D were classified according to Clarke score as having impaired awareness of hypoglycaemia (IAH; n = 11) or normal awareness to hypoglycaemia (NAH; n = 16). We measured several clinical and sociodemographic variables and cognitive performance using neuropsychological tests. Electroencephalography was assessed during an auditory oddball task. We compared the groups in terms of clinical/sociodemographic variables as well as two event-related brain potentials (ERPs): The P3a which is associated with automatic orientation of attention to novelty, and the P3b which is associated with target detection and processing.

Results: The IAH group performed significantly worse on the Trail Making Test part A (TMT-A) ($p = 0.05$). Compared to the NAH group, P3a and P3b amplitudes in the frontal-central sites were significantly lower in the IAH group ($p < 0.05$). The P3a was strongly associated with worse performance on the TMT-A in the IAH group ($r = 0.540$; $p < 0.005$)

Conclusion: IAH is accompanied by decreased neurophysiological activity in ERPs associated with information processing and with the automatic orientation of attention to novelty and environmental changes. These findings suggest a possible framework to better understand the cognitive origin of IAH in this patient population.

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1. Introduction

In type 1 diabetes (T1D), long-term insulin treatment is not only essential due to the insulinopenic state that defines this group of patients, but it is also required to control glucose levels to reduce the risk of complications derived from chronic hyperglycaemia [1,2]. However, insulin treatment is associated with an increased risk of hypoglycaemic events [2].

These events are characterized by several symptoms of varying severity including spontaneous sweating, dizziness, tremor, increased hunger, and irritability, among others that serve to warn the patient [3]. Patients able to identify these signs can act accordingly and take appropriate measures to address these episodes. Awareness of these signs is vitally important given that failure to prevent and manage hypoglycaemia may lead to hypoglycaemia unawareness and severe hypoglycaemia (SH) [4,5].

SH is defined as a hypoglycaemic event associated with severe and potentially harmful symptoms including loss of consciousness, seizure, or coma requiring the assistance of a third person [6]. It has been reported a median rate of 1.1 episodes for patient-year and a yearly prevalence of 4–36% of SH episodes in T1D [7–10]. The main risk factor for developing an SH-related episode is impaired awareness of hypoglycaemia (IAH), defined as the inability to perceive the symptoms of hypoglycaemia [11]. Compared to individuals with a normal awareness of hypoglycaemia (NAH), T1D patients with IAH have a much greater risk of presenting more SH episodes, and thus of developing complications associated with recurrent episodes of hypoglycaemia [12].

It is widely accepted that diabetes mellitus is associated with an increased risk for cognitive impairment [13]. This association has been extensively studied in patients with type 2 diabetes, in whom various mechanisms contribute to neuronal damage and concurrent cognitive deterioration [14,15]. Although several studies have evaluated the impact of T1D on cognitive function, the results are highly heterogenous [13,16,17]. The large, prospective Diabetes Control and Complications Trial (DDCT) found no significant differences between patients with T1D and healthy controls in cognitive function over a mean follow-up of 18 years [18]. By contrast, several cross-sectional studies and *meta*-analyses have found that, compared to healthy controls, patients with T1D generally perform worse on several cognitive domains [16,19–21].

While numerous factors are believed to be involved in the association between T1D and cognitive deterioration, a prior history of SH episodes appears to play a key role [22–24]. Although the exact mechanisms contributing to this association are unknown, it is reasonable to assume that SH episodes may be associated with some degree of neuronal damage, which contributes to cognitive deterioration. Given that IAH is associated with an increased recurrence of episodes of SH, it is plausible to hypothesize that IAH may also be associated with an increased neuronal damage load and thus a greater risk of cognitive deterioration [25–29].

Event-related brain potentials (ERPs) permit the assessment, with high temporal resolution, of the time course of neural activity associated with various cognitive processes [30]. Of these, the P300 (or P3b) elicited during auditory oddball paradigms have been extensively studied in healthy individuals and in patients with several different conditions [31–34]. The P3b is a positive deflection appearing with maxim amplitude in central-parietal sites around 300–600 ms after detection of a target. The functional meaning of the P3b is quite heterogeneous, and the morphology of this component appears to be modulated by several variables (i.e.: older age, disease, etc). However, the P3b is undoubtably involved in target detection, processing speed and contextual update of information. The P3a or "novelty P3" displays maximum amplitude over frontal-central sites with a latency around 250–500 ms in response to involuntary processing and orientation of attention to novel or relevant stimulus [33,35]. These measures have proven sensitive for the early detection of neuronal damage, even in the absence of clear indicators of cognitive decline [36–38]. This suggests that evaluation of the morphology of these ERPs in T1D-IAH may be an objective and robust approach to exploring the potential presence of signs of neuronal damage in this patient population, and to understand the cognitive mechanisms involved in lack of awareness about hypoglycaemia. Thus, the presence of electrophysiological differences in the absence of a significant cognitive impairment is especially relevant, since these differences could be predictive biomarkers of cognitive decline.

In this context, the main aim of the present study was to assess and compare the morphology of the P3a and P3b components in patients with TD1-IAH and NAH. A second aim was to explore potential associations between neurophysiological findings and clinical parameters.

2. Material and Methods

2.1. *Clinical assessments*

The following clinical and sociodemographic data were obtained and recorded for all patients: age; years of education; disease duration; body mass index (BMI); type of insulin treatment (multiple insulin injections [MDI] or continuous subcutaneous insulin infusion [CSII]); basal and prandial insulin dose (UI/kg/day); mean HbA1c and number of self-reported SH episodes during last year and last five years defined as a hypoglycaemic event requiring the assistance of a third person; glucose levels during study; and LDL cholesterol.

The Clarke scale was used to assess the participants' awareness of hypoglycaemia [39]. The Clarke test is an 8-item questionnaire (validated for the Spanish population) in which the patient self-evaluates his or her awareness of hypoglycaemia. Based on the Clarke scores, participants were classified as NAH (Clarke score $\leq$ 2) or IAH (Clarke score $\geq$ 4) [39]. A scored of 3 points on the test was considered indeterminate and thus these patients were excluded from the study.

Mood and cognition were assessed by a battery of neuropsychological assessments. The Beck Depression Inventory (BDI) was used to determine the presence and severity of

depressive symptoms [40]. Global cognitive status was assessed with the Mini Mental- State Evaluation (MMSE) [41], a commonly used instrument that screens for global cognitive status. Scores < 26 points on the MMSE are suggestive of the presence of cognitive impairment of variable severity while scores > 26 suggest cognitive normality. The word learning subtest of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) was used to examine immediate learning, delayed recall, and recognition [42]. Attention and executive functions were assessed with the Trail Making test (TMT) parts A and B [43], the phonetic verbal fluency (words starting with letter P) during one minute, and the semantic verbal fluency (animals) during one minute. Finally, confrontation naming was assessed with the short version of the Boston Naming Test [44]. Raw scores were adjusted using the normative data for Spanish population [45].

2.2. *Auditory oddball task*

A standard auditory oddball task with a set of frequent, infrequent, and novel stimuli was used. Frequent stimuli (1500 Hz, duration: 60 ms) occurred with a probability of 0.8, infrequent stimuli (1620 Hz; 60 ms) occurred with a probability of 0.1, and novel sounds (e.g., a key or a door closing) occurred with a probability of 0.1 at 60 dB for 60 ms. Over a period of 15 min, participants were requested to respond as quickly as possible to infrequent (target) sounds with their right index finger and to ignore all other sounds. The percentage of correct responses to the target sound and the percentage or responses to non-target novel stimuli were registered.

2.3. *EEG recording*

An electroencephalogram (EEG) was recorded with the BrainAmp system and Brain Vision Recorder Software (Brain Products GmbH, Germany) at 19 standard scalp sites (Fp1/2, F3/4, C3/4, T3/4, T5/6, P3/4, O1/2, F7/8, Fz, Cz, Pz) referenced to the two mastoid leads. Vertical eye movements were recorded using a bipolar montage with two electrodes linked together and placed below each eye, which were referenced to a third electrode placed centrally above the eyes. To monitor horizontal eye movements, two electrodes were placed on the external canthi of each eye. Electrode impedances were kept below 5 kOhm. The electrophysiological signals were filtered with a bandpass of 0.1–35 Hz and digitized at a rate of 250 Hz.

To maximize the information available for the subsequent ERPs, raw EEG signals were subjected to an ocular artifact minimization algorithm based on an eigenvalue decomposition of time-delayed covariance matrices. After identifying the source signals associated with eye movements, we obtained corrected EEG signals from the remaining components. The algorithm was implemented using Brain Vision Analyzer (Brain Products GmbH; Germany).

2.4. *P3a and P3b analysis*

In the auditory oddball task, the continuous EEG recording was segmented in epochs of 1000 ms starting 100 ms before the stimulus presentation and continuing until 900 ms post-stimulus. Epochs were baseline-corrected, subtracting the mean amplitude in the 100 ms before stimulus presentation. A two-step artifact rejection procedure was then applied. The first epochs were rejected if the signal in any of the 19 channels showed amplitude values > ±300 μV. Subsequently, additional epochs were excluded if amplitude values were > ±40 μV in Fz, Cz or Pz channels. After these preprocessing steps, three types of trials—epochs containing frequent, infrequent, and novel stimuli—were averaged separately. These averages were obtained for each participant and the ERP components were identified and quantified. The P3b was the most positive deflection in the ERP between 300 and 650 ms post-stimulus in the infrequent trials while the P3a was the most positive deflection in the ERP between 240 and 500 ms post-stimulus in the novel trials. The mean amplitude was calculated in the time-window defining each ERP and introduced into the statistical analysis.

2.5. *Statistical analysis*

For the clinical and sociodemographic variables, independent *t*-test comparisons between the two groups were performed for continuous variables and the $\chi 2$ test for categorical variables. ERP effects were quantified for the three midline electrodes (Fz, Cz, and Pz); these data were then evaluated by repeated-measures analysis of variance (ANOVAs), applying the Greenhouse-Geisser correction when necessary. Post-hoc comparisons were performed using paired and independent *t*-test comparisons.

3. Results

The sample was comprised of 27 adults (12 females and 15 males), with a mean ± standard deviation (SD) age of 58.5 ± 10.8 years. The mean disease duration was 30.1 ± 9.9 months. Mean basal daily insulin dose (UI/kg) was 0.28 ± 0.11 and mean prandial daily insulin dose (UI/kg) was 0.27 ± 0.17.

The mean Clarke score was 2.56 ± 2. Of the 27 patients, 16 were classified as IAH and 11 as NAH. The two groups were similar for nearly all sociodemographic and clinical variables of interest (Table 1). However, the IAH group presented significantly higher values on several parameters, as follows: mean basal daily insulin doses [t(27) 2.88; $p < 0.01$]; total number of SH episodes in the last year [t(27) = −2.1; $p < 0.05$] and last five years [t(27) = −2.57; $p < 0.05$].Table 2.

Patients in the IAH group scored significantly higher on the BDI (t(27) < 0.005), indicating worse depressive symptoms. On the cognitive measures, no significant between-group differences were observed in the MMSE and moreover, the scores obtained in this test were in the normal range (MMSE > 26). Similarly, no significant differences were observed in the total corrected scores or in the percentage of cases in each group scoring in the clinical range ($z < -1.5$) for any of the measures. However, a slight difference [t(27) = 2.03; $p = 0.05$] was found in the TMT-A regarding the percentage of cases scoring in the clinical range. This difference was found in relation to a higher proportion of patients scoring in the clinical range in the IAH group (IAH = 27.3% vs NAH = 6.3%).

Table 1 – Clinical and sociodemographic data.

	IAH (n = 11)	NAH (n = 16)	*p*
Age (years)	57 ± 12.8	59.5 ± 9.4	0.570
Gender (% female)	58.3	41.7	0.096
Education (years)	13.2 ± 6.3	14.7 ± 4.5	0.478
BMI (kg/m^2)	25.7 ± 6.8	27.5 ± 3.7	0.407
Disease duration (years)	29.6 ± 12.6	30.5 ± 8.1	0.818
MDI/CSII (%)	61.1/38.9	73.7/26.3	0.315
Clarke score	4.8 ± 0.8	1 ± 0.7	<0.001
Basal insulin dose (UI/kg/day)	0.21 ± 0.4	0.32 ± 0.1	0.020
Prandial insulin dose (UI/kg/day)	0.22 ± 0.1	0.31 ± 0.21	0.129
HbA1c (%)	7.7 ± 1	6.8 ± 3.2	0.364
Last year	7.5 ± 0.9	7.5 ± 0.7	0.949
Last 5 years	7.5 ± 0.8	7.5 ± 0.5	0.811
SH episodes in previous year	0.6 ± 1	0.06 ± 0.2	0.097
SH episodes in last 5 years	2.1 ± 3	0.1 ± 0.3	0.059
DKA episodes in previous year	0.1 ± 0.5	0.07 ± 0.2	0.829
DKA episodes in last 5 years	0.3 ± 0.6	0.1 ± 0.3	0.262
Retinopathy (% prevalence)	23.1	35.3	0.377
Glycaemia at study (mg/dL)	134.5 ± 85.1	154.5 ± 80.1	0.546
LDL cholesterol (mg/dL)	186.3 ± 29.9	159.7 ± 51.7	0.138
MMSE (score)	29.5 ± 0.6	29.3 ± 1.2	0.676
BDI (score)	10 ± 5.5	4.3 ± 3.7	0.004

Abbreviations: IAH, impaired awareness of hypoglycaemia; NAH, normal awareness to hypoglycaemia Body mass index; [2]Multiple daily insulin injections/continuous subcutaneous insulin infusion; SH, severe hypoglycaemia; DKA, diabetic ketoacidosis; MMSE, Mini-mental State Examination; BDI, Beck Depression inventory.

Table 2 – Neuropsychological assessment data.

	IAH (n = 11)	NAH (n = 16)	*p*
CERAD word list memory	8.18 ± 1.6	7.8 ± 1.8	0.660
Corrected standardized score	-	-	
% cases scoring z < -1.5	18.2	12.5	0.545
CERAD word list recall	6.2 ± 1.8	5.5 ± 2.3	0.408
Corrected standardized score	–	–	
% cases scoring z < -1.5	9.1	12.5	0.643
CERAD word list recognition	19.4 ± 1	19.4 ± 1.2	0.864
Corrected standardized score	–	–	
% cases scoring z < -1.5	0	6.3	0.398
TMT-A[2]	52.9 ± 20.3	42.4 ± 15.9	0.144
Corrected standardized score	6.73 ± 2.5	9.2 ± 3.4	0.053
% cases scoring z < -1.5	27.3	6.3	0.131
TMT-B[2]	125.8 ± 81.3	95.1 ± 60.8	0.271
Corrected standardized score	7.5 ± 2.1	9 ± 2.5	0.119
% cases scoring z < -1.5	9.1	12.9	0.643
Phonetic verbal fluency	15.3 ± 4.5	15.1 ± 4.9	0.899
Corrected standardized score	10 ± 1.6	9.5 ± 2.7	0.569
% cases scoring z < -1.5	0	12.5	0.342
Semantic verbal fluency	19.8 ± 4.9	19.6 ± 5.7	0.929
Corrected standardized score	9.1 ± 2.8	8.5 ± 2.7	0.537
% cases scoring z < -1.5	9.1	18.8	0.488
Boston naming test	12.3 ± 1.2	13 ± 1.6	0.282
Corrected standardized score	9.9 ± 1.8	10.8 ± 3.1	0.368
% cases scoring z < -1.5	0	6.3	0.398

Abbreviations: IAH, impaired awareness of hypoglycaemia; NAH, normal awareness to hypoglycaemia; BMI, body mass index; CERAD. Consortium to Establish a Registry for Alzheimer's Disease; TMT, Trail Making Test parts A and B.

3.1. *Auditory oddball task*

No between-group differences in the number of averaged epochs or correct responses (response to target signal) were observed. Repeated measures ANOVA in the overall sample using the factors "electrode" (Fz, Cz, Pz) and "condition" (frequent/infrequent) showed significant effects at Pz [$F(1,26) = 15.9$; $p < 0.001$] driven by significant increased positivity at Pz [$t = -3.99$; $p < 0.001$] around 400 ms after delivery of an infrequent stimulus (P3b). When novel stimuli were added to

the factor "condition", significant effects were found at Fz [F (1,26) = 27.1; p < 0.001], Cz [F (1,26) = 11.2; p < 0.005], and Pz [F (1,26) = 21.08; p < 0.001], driven by a significantly increased positivity at Fz [t = −5.2; p < 0.001], Cz [t = −3.3; p < 0.005] and Pz [t = −4.5; p < 0.001] around 250 ms–400 ms following the novel stimulus (P3a) (Fig. 1) (see Fig. 2.).

Repeated measures ANOVA using the factors "group" (IAH; NAH) and "condition" (frequent; novel) showed a significant group × condition interaction for the P3a at Fz [F (1,26) = 5.02; p < 0.05], and Cz [F (1,26) = 4.59; p < 0.05]. Post-hoc *t*-test comparisons showed that this effect was driven by a significant reduction in P3a in the IAH group at Fz [t

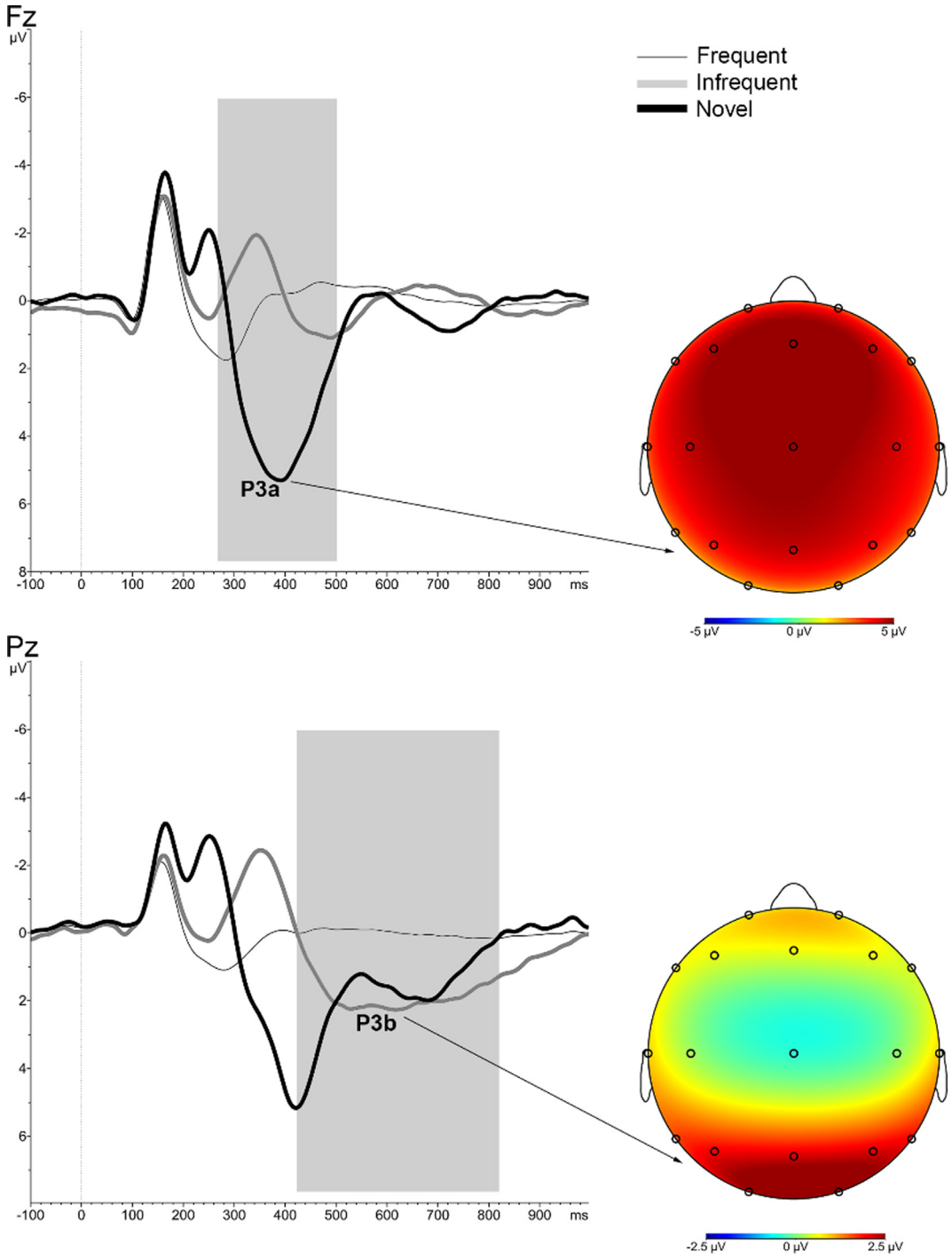

Fig. 1 – Stimulus-locked grand average ERPs for the whole sample. Grand average at Fz and Pz electrodes depicting the ERPs for frequent (thin line), infrequent (grey line) and novel (black line) stimuli. The P3a was identified as the most positive ongoing deflection between 240 and 500 ms (grey area) post-stimulus in the novel trials. The P3b was identified as the most positive deflection in the ERP between 400 and 8000 ms (grey area) post-stimulus in the infrequent trials. The topographical map shows the frontal-central distribution of the P3a, and the central-parietal distribution of the P3b.

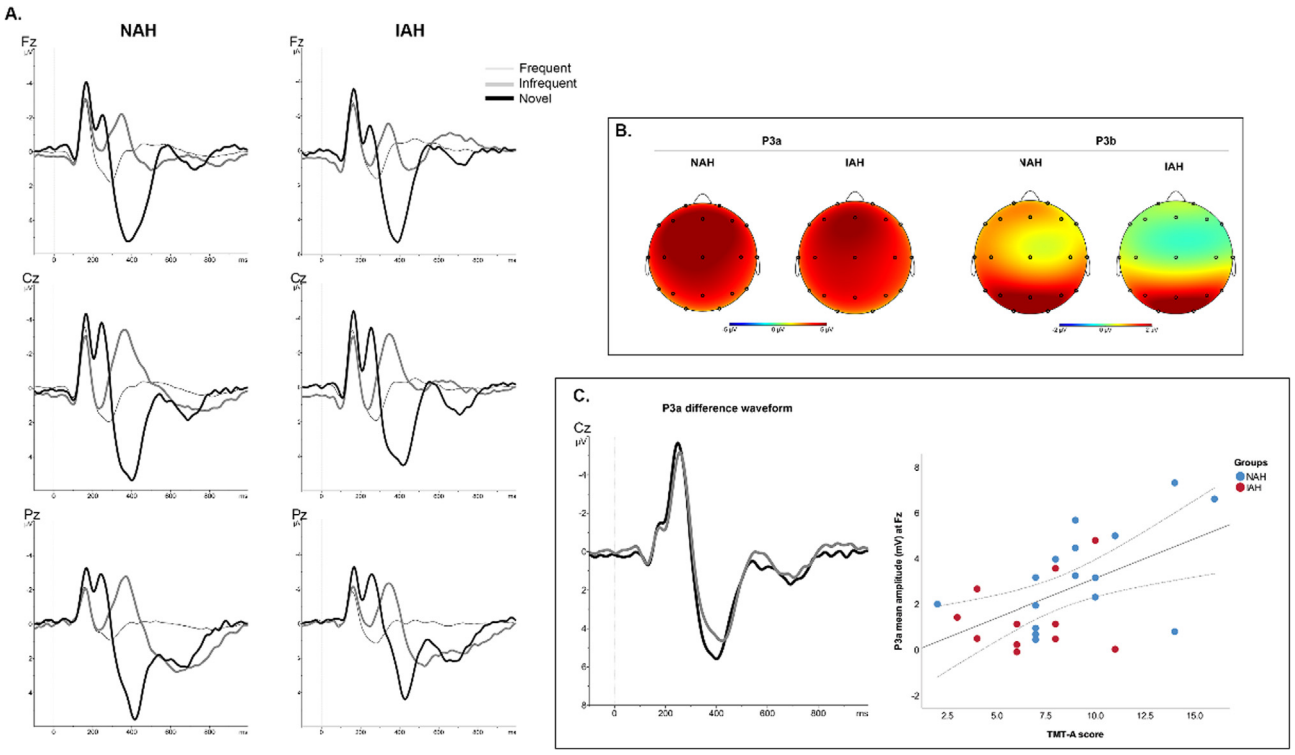

Fig. 2 – A) Stimulus-locked (grand average) ERPs in each group. B) Topographical maps showing the scalp distribution of the mean voltage of the ERPs in each group. A decreased voltage is seen in the IAH group both for the P3a and P3b. C) Difference wave-form for the novelty P3a and scatter-plot showing the association between the amplitude of the difference wave-form and performance in the TMT-A.

(27) = 2.63; $p < 0.05$] and Cz [t(27) = 2.39; $p < 0.05$]. In parallel, the comparisons made with the difference waveform (novel - frequent) also corroborated a lower amplitude of P3a in the IAH group at Fz [t(27) = 2.61; $p < 0.05$] and Cz [t(27) = 2.36; $p < 0.05$]. Repeated measures ANOVA using the factors "group" (IAH; NAH) and "condition" (frequent; infrequent) showed a significant group × condition interaction for the P3b at Fz [F (1,26) = 4.3; $p < 0.05$]. Post-hoc *t*-test comparisons showed that this effect was driven by a significant reduction in the P3b in the IAH group at Fz [t(27) = 2.1; $p < 0.05$], also seen at Fz [t(27) = 2.1; $p < 0.05$] using the difference waveform (infrequent – frequent).

In terms of ERP latency, a trend towards significance was found for the P3a [t(27) = −1.8; $p = 0.076$], resulting from an increased latency in the IAH group (IAH = 424 ± 34 ms vs. NAH = 391 ± 53 ms). A bivariate correlation analysis showed that the P3a amplitude was significantly associated with the normalized score on the TMT-A ($r = 0.540$; $p < 0.005$), with a non-significant trend with the Clarke score ($r = -0.344$; $p = 0.085$).

4. Discussion

The aim of the present study was to characterize the effects of impaired awareness of hypoglycaemia in patients with T1D using specific neurophysiological parameters associated with attention and cognitive processing. We also sought to determine the association between the presence of IAH and other measures of neuropsychological functioning. We found that T1D patients with IAH presented significant neurophysiological differences in both the P3a and P3b signals compared to patients with NAH. Importantly, both groups were comparable in terms of almost all sociodemographic and clinical variables, but the IAH group had higher scores for depressive mood and worse performance in the TMT-A, a processing speed and attention task.

T1D patients with IAH exhibited significantly decreased amplitudes in both the P3a and P3b components in frontal-central locations, and a tendency to elicit the P3a with a delayed latency. Although no between-group differences were observed in cognitive parameters assessed through neuropsychological assessment, performance in the TMT-A was worse in the IAH group. Interestingly, the amplitude of the P3a was strongly associated with performance of these tasks, suggesting the involvement of disrupted neurophysiological mechanism in the IAH group.

Our findings suggest that IAH is associated with disrupted neuronal processes that have minimal effects on cognitive functioning, at least at the point in time that the study was performed. Nevertheless, as our findings show, dysfunctional neuronal processes can be detected through the measurement of neurophysiological differences. Although the functional meaning of these findings cannot be determined from the data obtained in the present study, these results suggest several interesting possible interpretations. First, given the association between IAH and more frequent recurrence of severe hypoglycaemia, it is reasonable to suppose that there may be a causal relationship between these recurrent epi-

sodes and the concurrent presence of subtle neuronal damage [22,29,46]. Depending on the individual's clinical stage, these patterns may not accumulate sufficient neuronal damage load to produce evident cognitive deficits, even though may be detectable through neurophysiological measures. Thus, it is also reasonable to assume that, in the long term, continued and recurrent SH episodes will cause progressive, cumulative neural damage, eventually leading to significant cognitive impairment with important implications for the patient's quality of life [13,17,26].

The findings of this study underscore the need to avoid, or at least minimize, recurrent episodes of SH in order to prevent potentially clinically meaningful deleterious consequences for cognitive functioning. However, longitudinal studies are needed to confirm whether the observed neural damage is cause or consequence of IAH and cognitive alterations. It is also important to consider that we examined only a limited number of ERPs and neuropsychological tasks in this study. Thus, the apparent absence of clinically relevant neuropsychological deficits and/or differences between groups may be attributable to two factors: a) the selected tests may not be sufficiently sensitive to detect existing deficits and/or b) the patients could have symptoms in other domains or processes that have not been explored. A second possible interpretation of our findings is related to the frontal P3a, or novelty P3, which has been extensively associated with the engagement of attention resources, especially those involved in the orientation of attention to relevant environmental changes or novelty [32,33]. The P3b neurophysiological component has been extensively studied in recent decades and shown to be closely associated with information processing, cognitive workload, and context update. Even though the neural source of both components is only partially understood, it is accepted that the P3a is more closely related to neuronal populations in the prefrontal cortex as well as temporal-parietal regions while the P3b involves a complex circuitry of parietal and temporal regions, including hippocampal formation [35,47,48].

IAH is phenomenologically characterized by a lack of awareness or conscious detection of a set of symptoms. However, the extent to which IAH is due to the failure of endogenous mechanisms of detection of inner relevant information is not clear [49]. Unfortunately, is not possible to determine the kind of causal relationship between IAH and the differences observed in the P3a and P3b components. Therefore, new studies are needed to explore in greater depth the extent to which the observed differences in P3a and P3b morphology are a consequence of the accumulation of neuronal damage caused by recurrent SH episodes. It is not clear whether the origin of IAH is due to a failure of the involuntary and automatic mechanisms of orientation of attention to relevant and novel inner information, or a combination of both factors. In this regard, the lack of correlation between the differences in the ERPs and the number of SH episodes during the last year and five years seems to suggest that the accumulation of SH episodes may not be wholly responsible for the pattern of neural damage, which may or may not promote these differences. In turn, this suggests that the mechanisms that give rise to these differences in neurophysiological signals may already exist in patients with IAH prior to onset of these episodes. Given the between-group differences in depressive symptom severity, it would be interesting to explore the possible relationship between depression, attention, and awareness of hypoglycaemia. In fact, it is widely recognized that the amplitudes of p3a and p3b are reduced in patients with depressive symptoms, with a negative impact on attention and processing speed [50,51]. Thus, our findings may reflect mechanisms associated with the etiology of difficulties in detecting hypoglycaemic symptoms in patients with IAH.

Clearly, an in-depth study will be required to explore the mechanisms involved and the implications. Assuming that there is an association between IAH, SH, and concurrent neuronal damage, more research is needed to accurately elucidate and characterize the mechanisms that promote neuronal damage in patients with T1D-IAH. Similarly, if we assume that there is a causal association between defective attention and the development of IAH, it will be necessary to determine why some T1D patients present alterations in brain processes related to the orientation of attention that make them unable to detect hypoglycaemia symptoms.

The present study has several important limitations, particularly the small sample size, which precludes the generalization of these findings. In addition, the neuropsychological examination performed in this study does not cover all of the potential cognitive domains of interest. Consequently, future studies should use a larger battery of neuropsychological assessments. By contrast, the main strength of this study is the description of a novel, potentially explanatory and theoretical framework to understand the cognitive origin and implications of IAH in patients with T1D.

In conclusion, the findings of the present study suggest that the presence of neural damage associated with IAH in T1D patients, as evidenced by neurophysiological alterations, could act as novel biomarkers in this group of patients.

CRediT authorship contribution statement

Nicole Stantonyonge: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing-original draft, Writing-review and editing. **Saul Martinez-Horta:** Conceptualization, Data curation, Investigation, Methodology, Writing-original draft, Writing-review and editing. **Frederic Sampedro:** Investigation, Writing-review and editing. **María Belén Sánchez-Saudinós:** Investigation, Methodology, Writing-review and editing. **Ana Chico:** Conceptualization, Investigation, Supervision, Writing-review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Compliance with ethical standards

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Statement of informed consent: Informed consent was obtained from all individual participants included in the study.

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