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Risk Variants in Three Alzheimer's Disease Genes Show Association with EEG Endophenotypes

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Abstract.
Background: Dementia due to Alzheimer's disease (AD) is a complex neurodegenerative disorder, which much of heritability remains unexplained. At the clinical level, one of the most common physiological alterations is the slowing of oscillatory brain activity, measurable by electroencephalography (EEG). Relative power (RP) at the conventional frequency bands (i.e., delta, theta, alpha, beta-1, and beta-2) can be considered as AD endophenotypes.
Objective: The aim of this work is to analyze the association between sixteen genes previously related with AD: *APOE*, *PICALM*, *CLU*, *BCHE*, *CETP*, *CR1*, *SLC6A3*, *GRIN2β*, *SORL1*, *TOMM40*, *GSK3β*, *UNC5C*, *OPRD1*, *NAV2*, *HOMER2*, and *IL1RAP*, and the slowing of the brain activity, assessed by means of RP at the aforementioned frequency bands.
Methods: An Iberian cohort of 45 elderly controls, 45 individuals with mild cognitive impairment, and 109 AD patients in the three stages of the disease was considered. Genomic information and brain activity of each subject were analyzed.
Results: The slowing of brain activity was observed in carriers of risk alleles in *IL1RAP* (rs10212109, rs9823517, rs4687150), *UNC5C* (rs17024131), and *NAV2* (rs1425227, rs862785) genes, regardless of the disease status and situation towards the strongest risk factors: age, sex, and *APOE* ε4 presence.

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Conclusion: Endophenotypes reduce the complexity of the general phenotype and genetic variants with a major effect on those specific traits may be then identified. The found associations in this work are novel and may contribute to the comprehension of AD pathogenesis, each with a different biological role, and influencing multiple factors involved in brain physiology.

Keywords: Alzheimer's disease, EEG, electroencephalography, endophenotypes, genetics

INTRODUCTION

Dementia due to Alzheimer's disease (AD) is a common, age-related, neurodegenerative disorder leading to progressive memory loss and impairments in speech and behavior. The prevalence of AD is higher among females than males, even when individuals at the same age are compared [1–4]. Indeed, AD diagnosis is not straightforward in early stages, and symptoms are frequently dismissed and confused with normal aging. AD progression is often characterized in three main stages: mild (or early-stage), moderate, and severe (or late-stage) AD, depending on the level of functionality of the patient [5]. Mild cognitive impairment (MCI) is characterized by a slight but perceptible decline in cognitive abilities, including memory and thinking skills, and plays an important role in early diagnosis. Individuals with MCI do not necessarily develop AD, but are in greater risk, especially those with amnestic MCI, which is considered a prodromal stage of the disease [6, 7].

Heritability plays an important role in AD [8], *APOE* having been reported since the early 1990s as the strongest genetic risk for the disease, through allele $\varepsilon 4$ (reviewed in [9]). From the genetic point of view, two subtypes of the disease are generally considered: 1) familial early-onset AD, and 2) late-onset AD (LOAD). LOAD appears in sporadic cases after 65 years old, and is approximately 20 times more prevalent than the familial early-onset subtype [10]. Heritability of familial AD is often explained by the presence of rare variants in a few genes, which are expected to have a strong effect [11–13]. Contrarily, LOAD is generally associated with common variants, expected to have a small impact when analyzed individually, but a large effect when aggregated [14, 15]. Thus, to reliably identify the individual contribution of a single polymorphism to LOAD risk, huge genetic datasets are needed, which may carry problems of ultrahigh dimensionality when a correlation between genome-wide information and the LOAD phenotype is attempted. The analysis of endophenotypes has proven to be a useful approach to simplify the general AD phenotype, helping to dissect the role of specific genetic variants correlated with the disease [16, 17].

Electroencephalography (EEG) measures the electrical activity of the brain, acquiring voltage fluctuations (derived from synaptic potentials) by electrodes placed on the scalp. In previous works, physiological alterations caused by neurodegeneration have been studied by means of EEG analyses [18–20]. AD is known to be strongly correlated with a general slowing of the EEG, measured through relative power (RP) calculations. Specifically, a progressive increase of RP in low frequency bands (i.e., delta and theta), along with a progressive decrease at high frequency bands (i.e., alpha and beta), have been consistently associated with AD progression [21–23]. These alterations seem to be related with neurophysiological and anatomical disturbances, such as hippocampal atrophy [24], cortical disinhibition or hyper excitability [25, 26]. For comprehensive reviews on this topic see [27–30].

RP calculations at each frequency band are objective and reliable measurements, and thus effective as AD endophenotypes [31–34]. Genetic variants with a major effect on those specific traits may be then identified, as analyzed in previous studies considering four AD risk variants in *APOE* (rs7412 and rs429358), *PICALM* (rs3851179), and *CLU* (rs11136000) genes, and cohorts composed by AD patients, MCI subjects, relatives of AD patients, or cognitively healthy young or elderly controls [35–38]. Two of these studies revealed conflicting results in what concerns the presence of *APOE* $\varepsilon 4$ allele in AD patients [35, 38]. In [38], a slowing of EEG oscillatory activity in AD patients carrying *APOE* $\varepsilon 4$ alleles (rs7412 and rs429358) was observed through a decreased power in alpha band, the same occurring for AD patients' relatives along with an increased power in delta and theta bands. Contrarily, in [35], AD $\varepsilon 4$ non-carrier patients showed a decrease in alpha frequency band and an increase in delta one. On the other hand, presence of *CLU* (rs11136000) and *PICALM* (rs3851179) risk alleles in cognitively healthy elders was associated with increased alpha and beta RP values [36, 37].

Table 1
Number of subjects that qualified for further analyses after genotyping quality control, and respective mean age and MMSE scores

Subgroups					Cases						Total
	CON		MCI		MIL		MOD		SEV		
Population	PT	ES	PT	ES	PT	ES	PT	ES	PT	ES	
Females	11	12	16	15	15	12	15	18	5	17	136
Males	10	12	7	7	6	12	2	4	1	2	63
Total	45		45		45		39		25		199
Mean age ± SD (y)	79.7 ± 7.3		84.8 ± 7.1		80.7 ± 6.5		81.3 ± 8.1		79.9 ± 6.4		81.4 ± 7.3
Mean ± SD MMSE	28.9 ± 1.1		23.3 ± 3.0		21.7 ± 3.3		13.0 ± 3.7		3.8 ± 4.2		-

CON, controls; MCI, individuals with mild cognitive impairment; MIL, patients with mild Alzheimer's disease; MOD, patients with moderate Alzheimer's disease; SEV, patients with severe Alzheimer's disease; PT, subjects residents of northern Portugal; SP, subjects residents of Castile and Leon, Spain.

The main goal of this work is to analyze the correlation between: (a) the EEG relative power in the conventional frequency bands (i.e., delta, theta, alpha, beta-1, and beta-2) measured in resting state, and (b) genetic variants in sixteen candidate genes previously associated with AD in an Iberian cohort composed by AD patients, individuals with MCI and controls. To achieve this, the correlation between EEG measurements and both (c) the strongest risk factors for AD: age, sex, and *APOE* ε4 presence, and (d) the status of the subjects regarding AD, was analyzed and RP values corrected accordingly for further analyses.

MATERIAL AND METHODS

Subjects

We studied an Iberian cohort of: 1) LOAD patients in different stages of the disease: mild (MIL), moderate (MOD), and severe (SEV) AD; 2) individuals with MCI; and 3) cognitively healthy elderly controls (CON). AD patients and MCI individuals were clinically diagnosed following the criteria of the National Institute on Aging and Alzheimer's Association (NIA-AA) [39]. AD staging was based mainly on the Mini-Mental State Examination (MMSE) [40]. The control group was composed by individuals over 68 years old, with no signs of dementia or history of neurological disease. Neither patients nor controls were diagnosed with any other neurologic and psychiatric diseases (other than AD and MCI), and were not using any drugs that might affect EEG signal.

At the time of sample collection, subjects were residents of the autonomous community of Castile and Leon, northwestern Spain, or of the northern region of Portugal. Saliva and buccal swabs were selected as sources of biological sampling to maintain the process as noninvasive as possible. Biological samples and EEG data were collected from 253 individuals, mostly equally distributed by population: Portugal (PT) and Spain (SP), and subgroup: controls (25 PT + 26 SP), individuals with MCI (26 PT + 25 SP), and patients with mild (25 PT + 26 SP), moderate (25 PT + 25 SP), and severe LOAD (25 PT + 25 SP). This project was approved by the Ethics Committee of the University of Porto (report # 38/CEUP/2018), Portugal, and written informed consent was obtained from all participants, family and/or legal representatives.

After DNA quality control assessment, prior to genotyping (with a minimum quantity of 10 ng/μl in 45 μl minimum volume and integrity of 90% of gDNA greater than 10 Kb in size; see below for more details), 54 subjects were removed before microarray processing since their biological samples did not fulfill the minimum requirements. The distribution of the 199 subjects which biological samples passed the quality control procedures are presented in Table 1, along with information on sex, mean age, and MMSE scores. Situation of the cohort regarding the strongest risk factors for AD: sex, age, and *APOE* ε4 allele, was analyzed (Supplementary Tables 1 and 2). A Dunn's test of independence supported that individuals with MCI are significantly older than both AD patients ($p = 1.0e{-}03$) and controls ($p = 1.5e{-}04$), and a Chi-square test of independence showed a significant association between gender and AD status ($p = 1.4e{-}02$) with more female patients and male controls than expected (Supplementary Tables 1 and 2). Also, the distribution of *APOE* ε4 allele carriers significantly differed among sampling groups ($p = 2.8e{-}02$), with more carrier patients and non-carrier MCI individuals and controls (Supplementary Table 2).

Genotyping

A sample of saliva or three buccal swabs were collected from each of the initial 253 participants

of the study. Preference was given for collecting a saliva sample of 2 ml with the Oragene DNA 500 collection kit (DNAgenotek). Buccal swabs were only used for patients at a more advanced stage of the disease, unable to voluntarily spit. After DNA extraction and quality control assessment, samples were genotyped using the genome wide Axiom Spain Biobank Array (Thermo Fisher Scientific) at the Spanish National Center for Genotyping (CEGEN, Santiago de Compostela, Spain, CEGEN-PRB3-ISCIII; supported by grant PT17/0019, of the PE I+D+i 2013-2016, funded by ISCIII and ERDF).

Variant calling quality control (QC) was performed in accordance with the Affymetrix's best practices guide, and a widely used protocol was followed for both individual and marker analysis [41]. All the analyses were computed with Affymetrix Power Tools and PLINK [42]. In the variant calling QC, individuals with dish QC or QC call rates below the defined thresholds were not considered for further analysis, as well as those with heterozygosity rate greater than the defined acceptance threshold. Finally, the probes belonging to the recommended calling categories were selected and the corresponding variants annotated according to the Genome Reference Consortium Human Build 37 (GRCh37) single nucleotide polymorphism (SNP) assembly. In per-individual QC analysis, the sex of the individuals was confirmed through the sex chromosomes' homozygosity rate, and duplicates or related individuals were identified through the estimation of identity by descent (IBD) rates. For the pairwise cases where IBD estimates revealed to be greater than the established, one of the two individuals was removed (preference for remaining in the study was given first to patients, then to females and finally to individuals with higher call rates). Finally, individuals with divergent ancestry were disregarded. For this, principal component (PC) analyses were computed using the software EIGENSOFT [43, 44] and merging the dataset with one, publicly available, from the 1000 Genomes Project (1KGP) [45], containing 12 different populations from four ancestry groups: East Asian, African, European and Admixed American. In per-marker QC analysis, SNPs with a significant deviation ($\alpha = 1E{-}06$) from Hardy-Weinberg equilibrium in control samples were eliminated, as well as those with missingness rate greater than 5%. Significant differences in missing genotype rates between cases and controls ($\alpha = 1E{-}05$) were also considered, and SNPs with no variance in the sample were disregarded.

Gene selection

Among the plethora of markers associated with AD, sixteen candidate genes with functional relevance in the brain were selected for further analyses: *APOE*, *PICALM*, *CLU*, *BCHE*, *CETP*, *CR1*, *SLC6A3*, *GRIN2β*, *SORL1*, *TOMM40*, *GSK3β*, *UNC5C*, *OPRD1*, *NAV2*, *HOMER2*, and *IL1RAP* [14, 15, 46–69]. Some of these markers were selected among those showing strongest association with the disease in traditional case-control genome wide studies [14, 15], while others were selected among those associated with the disease via relevant quantitative endophenotypes, as measures of structural imaging or amyloid-β deposition [49, 55–57, 60–62, 64, 65, 67–69]. The second set of genes were found to be interesting to analyze as traditional case-control studies, considering general (and complex) disease phenotypes, may not uncover genetic risk associations with relevant phenotypes, through which silent signals of the disease may appear before diagnosis being possible. The inclusion of these genes in our analysis could improve the knowledge of their role in brain physiology.

The set of sixteen selected candidate genes and the QC procedures described above, resulted in the analysis of 796 common variants (minimum allele frequency $\geq$5%) in 199 subjects (Supplementary Table 3). PC analysis showed no population substructure, the gain to the understanding of data with each additional PC revealing to be approximately linear (Supplementary Figure 1). At this point is noteworthy that one of the two variants that determine the *APOE* genotype, rs7412, failed QC and was further genotyped using a standard Sanger sequencing protocol along with rs429358 SNP (this for validation purposes). The remaining three LOAD risk variants previously associated with EEG measurements in LOAD framework (i.e., *APOE* rs429358, *PICALM* rs3851179, and *CLU* rs11136000) [35–38] passed the QC procedures and their genotypes were considered for further analysis and replication purposes.

Electroencephalographic recordings

Five minutes of resting-state EEG activity was acquired for each subject using a 19-channel Nihon Kohden Neurofax JE-921A System at the electrodes: Fp1, Fp2, Fz, F3, F4, F7, F8, Cz, C3, C4, T3, T4, T5, T6, Pz, P3, P4, O1, and O2, following the International System 10–20. Signals were recorded at a sampling frequency of 500 Hz with common

average reference. Subjects were asked to remain awake with closed eyes during acquisition. EEG data were preprocessed according to the following steps [18, 70, 71]: i) mean removal; ii) digital filtering using a Hamming window bandpass finite impulse response (FIR) filter in the band of interest (i.e., 1–30 Hz); iii) independent component analysis (ICA) to remove oculographic and cardiographic artefacts; iv) segmentation into 5 s epochs; and v) visual rejection of epochs with artefacts. In this study, conventional EEG frequency bands were considered: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta-1 (13–19 Hz), and beta-2 (19–30 Hz). Gamma band was not included in the analyses due to the possible interference of muscle artefacts in its frequency range [72, 73]. In order to quantify the relative contribution of the previous frequency bands to the global power spectrum, RP was computed. Specifically, RP was calculated from the normalized power spectral density by summing the contribution of each spectral component in a specific frequency band [74].

Statistical analysis

Power analysis

Considering the set of 796 variants and the cohort of 199 subjects, the statistical power of the study for identifying variants explaining a range of phenotypic variance was quantified in the non-centrality parameter [75], taking into account the interplay between experimental sample size, allele frequency and effect size (Supplementary Table 4). For detecting a SNP explaining 10% of trait variance, the statistical power reached 75.8%, increasing this figure to 97.3% considering a proportion of variance of 15% (Bonferroni-corrected significance level $\alpha = 6.28\text{E}-05$).

The variance in phenotype Y: *Var(Y)*, explained by genetic variant X, can be decomposed into two components: $Var\,(Y) = \beta^2 Var\,(X) + \sigma^2$, where β is the effect size of *Var (X)* and σ^2 quantifies the remaining variance that can be explained by other factors or genetic variants. The first parcel can be estimated by $2\hat{\beta}^2 MAF\,(1 - MAF)$, where $\hat{\beta}$ is the effect size estimate and *MAF* the minor allele frequency of the variant X [76]. The proportion of variance in phenotype explained by a given SNP (PVE) is computed through the ratio $PVE = \frac{\beta^2 VAR(X)}{VAR(Y)}$, which can be estimated by $PVE \approx \frac{2\hat{\beta}^2 MAF(1-MAF)}{2\hat{\beta}^2 MAF(1-MAF)+\left(se\left(\hat{\beta}\right)\right)^2 2*N\cdot MAF\cdot(1-MAF)}$, where $se\left(\hat{\beta}\right)$ is the standard error of the effect size of the genetic variant X [76].

Correlation between EEG data and covariates: age, sex, APOE ε4 presence, and AD status

The normality of the EEG data was assessed (Shapiro-Wilk test), as well as the correlation between EEG data and the strongest risk factors for AD: sex (Kruskal-Wallis' test), age (Pearson's correlation test), and *APOE* ε4 presence (Kruskal-Wallis' test). Independence analyses were also computed considering the AD status of the subjects (Dunn's test), either assuming AD patients as a unique group or considering the stage of the disease. RP spatial patterns were also explored considering subjects' status. All the computations were performed using R and PLINK [42, 77], and the significance threshold considered for rejecting the null hypothesis was $\alpha = 0.05$, corrected accordingly through Bonferroni's method. Results reaching nominal statistical significance may be presented and highlighted, but only correlations reaching the corrected statistical significance were considered for further analyses.

Before assessing correlation with the genetic data, RP values of each frequency band were corrected for the covariates significantly correlated with each one of them. This was computed by adding them as covariates in the linear model: $E\,(Y) = \beta_0 + \beta_X X + \beta_G G$ where β_0 is the intercept coefficient, β_x is the coefficient of the covariates present in matrix X, and β_{G} is the coefficient of genotype G, i.e., the parameter that quantifies the association between the genotype and the expected value of the outcome Y, which is one of the five brainwaves.

Correlation between genetics and EEG measures

Correlation between (corrected) RP values at each EEG frequency band and the genetic variants exhibited by the subjects was assessed through Kruskal-Wallis testing. Information of linkage disequilibrium (LD) between pairs of genetic variants was obtained from LDlink [78], accessed on July 15, 2020, for "Iberian Populations in Spain". For each one of the 796 variants where differences reached the significance level $\alpha = 0.005$, allele analysis were performed to assess the possibility of identifying a 'risk allele', consistently associated with the slowing of brain activity. Indeed, the results concerning the relationship between the set of 796 genetic variants and the EEG measurements were presented considering $\alpha = 0.005$ and $\alpha = 0.05/796 = 6.28\text{E}{-}05$. Aware of the modest size of the sample compared to the number

Table 2
Genetic variants showing statistically significant differences in RP values of at least one frequency band (Kruskal-Wallis' test, significance level $\alpha = 0.005$). RP values corrected for: [1]AD, MCI, and CON status, [2]MIL, MOD, and SEV stage, or [3] the age of the subjects. The risk allele is the one associated with the EEG slowing, reflected in an increase of RP in delta and theta bands, and a decrease of RP in alpha and beta bands. Proportions of variance in phenotype explained by the genetic variants (PVE) are presented in parentheses

Gene	Ref. SNP	Risk allele	Significant *p*-values (PVE)				
			Delta[1,2]	Theta[1,3]	Alpha[1,2]	Beta-1[1]	Beta-2[1]
IL1RAP	rs10212109	C		0.000265 (5.41%)			
IL1RAP	rs9823517	G		0.000965 (7.96%)			
IL1RAP	rs4687150	T	3.37E–05* (6.11%)			0.000647 (3.80%)	
UNC5C	rs17024131	T			0.000887 (1.95%)		
NAV2	rs1425227	T		0.001434 (5.57%)		0.000292 (6.69%)	
NAV2	rs862785	G		0.000280 (5.00%)			

*Significance level reached after Bonferroni's correction ($\alpha = 6.28e{-5}$).

of variants analyzed, the first significance level was considered to identify candidate variants to be further analyzed in the future.

RESULTS

Correlation between EEG data and covariates: age, sex, APOE ε4 presence, and AD status

Evidence to refute the null hypothesis regarding normality of the EEG data was found for all brainwaves (delta $p = 4.7E{-}06$, theta $p = 5.3E{-}07$, alpha $p = 2.0E{-}07$, beta-1 $p = 9.5E{-}09$, and beta-2 $p = 1.8E{-}10$).

RP values showed no association neither with the sex of the subjects nor with the presence of *APOE ε4* allele in their genotype ($\alpha = 1.0E{-}02$, Supplementary Table 5). On the other hand, age showed to be positively correlated with RP theta values ($\alpha = 1.0E{-}02$, Supplementary Table 5).

Statistically significant correlations between EEG-based measurements and sampling groups: AD patients, individuals with MCI and controls, were found for the five frequency bands ($\alpha = 3.3E{-}03$, Supplementary Table 6) and were in accordance with previous studies. Particularly, when controls were compared with AD patients, statistically significant differences were found for all frequency bands, with patients showing higher RP values for low frequency bands (i.e., delta and theta), while lower for alpha, beta-1, and beta-2. Noteworthy, theta rhythms differentiated between controls and both MCI and AD groups, at a statistically significant level, which may point to the suitability of RP in theta band as case-control biomarker. We also explored the RP spatial patterns for AD, MCI, and control groups. Supplementary Figure 2 shows the previously mentioned slowing process of brain activity associated to AD and MCI. The statistically significant differences between groups mainly appear at parietal and right frontal areas in delta band, at central and parietal areas in theta band, at temporal areas in alpha band, and across all the scalp in beta-1 band. Beta-2 band only showed statistically significant differences at the P3 channel.

When AD patients were analyzed in subgroups according to the disease stage, delta and alpha RP values showed statistically significant differences within AD subgroups ($\alpha = 1.0E{-}03$, Supplementary Table 7, Supplementary Figure 3).

For further analyses, theta RP values were then corrected for the age of the subjects, RP values of all frequency bands were corrected for the status of the subject: AD patient, individual with MCI and control, and RP values of delta and alpha were also corrected for the stage of the disease. Correlation analyses considering separately the sampling subgroups were also computed.

Correlation between genetics and EEG measures

Some of the analyzed 796 common variants showed to be correlated with the (corrected) EEG-based measures. Considering a significance level $\alpha = 0.005$, six variants within *NAV2* (rs1425227 and rs862785), *IL1RAP* (rs10212109, rs9823517 and rs4687150), and *UNC5C* (rs17024131) genes showed to be correlated with RP values (Table 2). One variant, rs4687150, in *IL1RAP*, reached a significant correlation after Bonferroni correction, with RP in delta ($p = 3.37E{-}05$). The variants within *NAV2*, rs1425227 and rs862785, showed to be in low LD ($R^2 = 0.006$), as well as the pair of variants rs4687150 and rs10212109 ($R^2 = 0.002$) in *IL1RAP*. On the other hand, variants rs10212109 and rs9823517 in *IL1RAP* are in non-negligible LD ($R^2 = 0.143$). The smallest *p*-

Table 3
p-values regarding pairwise correlation (Kruskal-Wallis' test, significance level $\alpha = 0.005$) between the genetic variants presented in Table 2 and the RP values for each EEG frequency band, considering the sampling groups: AD patients, individuals with MCI, and controls. Theta RP values were corrected for the age of the subjects

Gene		*IL1RAP*			*UNC5C*	*NAV2*	
Ref. SNP		rs10212109	rs9823517	rs4687150	rs17024131	rs1425227	rs862785
Delta	Controls					4.53e–02	
	MCI Individuals						
	AD patients			5.62e–05*			
Theta[1]	Controls	4.01e–05*	1.72e–06*				3.98e–04
	MCI Individuals						1.38e–02
	AD patients	5.21e–03	6.70e–03			2.21e–03	
Alpha	Controls				2.82e–02		
	MCI Individuals				9.78e–03		
	AD patients			5.12e–03			
Beta-1	Controls		4.21e–02			1.97e–02	
	MCI Individuals					4.55e–03	
	AD patients			1.26e–03			
Beta-2	Controls		1.42e–02				
	MCI Individuals					2.19e–02	
	AD patients			8.25e–04			

[1]RP values corrected for the age of the individuals; *Significance level reached after Bonferroni's correction ($\alpha = 6.28e–05$).

values were observed for the variants in *IL1RAP* with the lowest level of LD: rs4687150 and rs10212109 ($R^2 = 0.002$), regarding delta ($p = 3.37E–05$) and theta ($p = 2.65E–04$) frequency bands, respectively. Proportions of variance in phenotype explained by a given variant (PVE) were computed for each of the found significant correlations (Table 2). Despite PVEs not being routinely computed, the range of obtained estimates (from 1.95% to 7.96%) are acceptable in the framework of a complex human trait, although admittedly high. Indeed, polygenic combinations, which may include dozens of variants, can explain a great amount of the variance. This is the case, for example, of the total variance in each lipid trait [79]. The power of our study to detect an association like the one of rs4687150 and delta frequency band (PVE = 6.11%) is ∼34% (see the Statistical Analysis section and Supplementary Table 4). Generically, the larger the effect size of a variant, the larger is expected to be the proportion of variance of the phenotype explained by it, and so the more likely is to detect such association.

When the sampling groups: AD patients, individuals with MCI, and controls were analyzed separately, statistically Bonferroni corrected significant differences were found for the three *IL1RAP* variants in some subgroups and frequency bands (Table 3). Indeed, rs4687150 showed to be correlated with delta RP values in AD patients group ($p = 5.62e–05$), while rs10212109 and rs9823517, showed to be correlated with theta RP values in the subgroup of controls ($p = 4.01e–05$ and $p = 1.72e–06$, respectively).

For all the six variants where the significance level $\alpha = 0.005$ was reached, allele correlation was analyzed and in all the cases a risk allele was associated with the slowing of brain activity (higher delta and theta, and lower alpha and beta mean RP values). It is noteworthy that no evidence of differentiation were found between the frequency of the risk allele among AD patients and controls (Supplementary Table 8). The distribution of genotypes according with AD status is presented in Supplementary Table 9.

Concerning the four variants previously associated with RP values in the context of AD [35–38], only *APOE* variants rs7412 and rs429358, showed evidence of correlation with RP values in beta-1 frequency band (Supplementary Table 10).

DISCUSSION

Correlation between EEG data and covariates: age, sex, APOE ε4 presence, and AD status

When analyzed independently, EEG data provided results in accordance with the literature [80]. As expected, AD patients showed a significant slowing of brain oscillatory activity compared with controls, and within AD subgroup a progressive slowing of EEG was observed along with an increasing of the severity of the disease. Also, theta RP values showed to be correlated with the age of the subjects. From the obtained results is noteworthy that theta rhythms can differentiate between controls and both MCI and AD groups, at a statistically signif-

icant level. The suitability of theta band to reflect dementia conditions was already reported in previous studies [81–83]. This agrees with our results, appointing EEG theta band alterations as a potential biomarker to detect hints of neural deterioration, even in pre-clinical states. Indeed, our results supports a likely association between EEG power in theta band and cognitive impairment. Previous studies reported correlation between healthy cognition and reduced tonic theta power [84–86], indicating higher values during resting state as a potential consequence of cognitive impairment. In addition, negative correlation between theta power and hippocampal volume was obtained by means of magnetic resonance imaging [87, 88], which could be related with loss of CA1 hippocampal pyramidal neurons [89]. Another well-known negative correlation in AD is delta and theta power with MMSE [90], which may provide diagnostic value to EEG.

Correlation between genetics and EEG measures

After correlating the genetic information of 796 variants from 16 genes previously associated with LOAD and the RP at each EEG frequency (corrected accordingly for the different covariates), three genes harbored the highest number of variants correlated with EEG-related measures: *IL1RAP*, *UNC5C*, and *NAV2*. Among the genotyped variants are those from *APOE* (rs7412 and rs429358), *PICALM* (rs3851179), and *CLU* (rs11136000) genes previously associated with RP values [35–38]. Our analysis only showed evidence of correlation between *APOE* variants and RP values in beta-1 frequency band. Theories considering that hyperactivity and hyperconnectivity in preclinical stages of AD may drive to profound disconnection and hypoactivity in AD patients have been supported [91], which may be the cause of these discrepancies.

Overall, theta RP values showed the highest correlation with the genetic variants tested. Previous studies considered alterations in theta-related EEG activity to be associated with amyloid plaque deposition, which is strongly correlated with AD [92]. Also, correlations between theta band disturbances and known AD biomarkers, such as total-tau (*T*-tau) and phosphorylated tau (*P*-tau) presence in cerebrospinal fluid, have been reported [93]. At the physiological level, cerebellar-evoked prefrontal synchronization in theta frequency band showed to be modulated by GABA, and positively associated with working memory performance [94]. This may indicate that a GABAergic dependent set of interneurons have a key role on the cortex, modulating theta-burst stimulation the cortical excitability of distant interconnected cortical areas [95]. Evidence suggests that the cerebellum likely exerts its control on the cortex by a GABAergic dependent set of interneurons and cerebellar theta-burst stimulation modulates cortical excitability of distant interconnected cortical areas [96]. The hippocampal theta oscillations are also functionally relevant in humans since they appear to explain how the hippocampus organizes information from a broad range of neocortical networks, being correlated with behaviors such as memory and spatial navigation [97]. All in all, these observations suggest that theta rhythms are intimately related with complex brain processes that become hindered with neurodegeneration.

Relationship between IL1RAP and RP in delta and theta frequency

A genome-wide association study of longitudinal amyloid accumulation in AD patients implicated the microglial activation of *IL1RAP* [69], presenting the rs12053868-G allele association with raised amyloid accumulation and greater declines in temporal cortex thickness (over 2 years). Moreover, MCI carriers of this allele showed to be more likely to progress into dementia due to AD, having a faster 2-year decline in episodic memory performance. Indeed, this gene presents itself as a molecular link between the immune system and synapse formation. In this work, three variants from *IL1RAP* gene were found to be correlated with RP in at least one frequency band. Variants rs4687150 and rs10212109 are in low LD ($R^2 = 0.002$) and the smallest *p*-values were found for delta ($p = 3.37\text{E}{-}05$) and theta ($p = 2.65\text{E}{-}04$) frequency bands. *IL1RAP* (Interleukin-1 receptor accessory protein) is a constituent of the IL-1 (interleukin-1), a potent pro-inflammatory cytokine that promotes microglial activation, receptor complex and its downstream signaling pathway, essential components for mediating the immune responses of the IL-1 family of cytokines [98]. Besides neuroinflammation and cell death in neurodegenerative conditions (such as stroke and head injuries), IL-1 signaling is also involved in sleep regulation, learning, memory, and the lipid metabolism in the brain [99–102]. In the brain, *IL1RAP* exists in two isoforms, IL1RAP and IL1RAPb, with differences only in the C-terminal region [103]. Although this gene is not highly expressed in the brain

(https://www.gtexportal.org/), synaptogenic activities of this receptor were found in cultured cortical neurons. Knockdown of both isoforms suppressed synapse formation and knock-out mice showed a decreased of the spine densities of cortical and hippocampal pyramidal neurons, suggesting that these receptors function as cell adhesion molecules and organize synapse formation in the brain [104]. IL-1 is chronically upregulated in dementia due to AD and it is believed to be part of an inflammatory cycle that drives AD pathology. Sustained IL-1β overexpression has been shown to increase tau phosphorylation, despite a substantial reduction in amyloid load [105]. Previous evidence indicates that higher rates of phosphorylation of tau protein is related with neuronal and axonal loss [106]. Also, greater amounts of phosphorylated tau have been found to be associated with alterations in theta rhythms due to lower neuronal excitability [107], probably due to axonal degradation. In addition, higher power in delta band has been attributed to neuronal injury [108], which could be a side effect of the previous point.

Relationship between UNC5C and RP in alpha frequency band

UNC5C has been identified as related to AD in various association studies, suggesting a notable role in the disease [53, 60, 109, 110]. Evidence from cell models show that UNC5C polymorphisms could lead to AD pathogenesis by activating death-associated protein kinase 1 (DAPK1). Meanwhile, DAPK1 itself was shown to be involved in modulating tau protein accumulation, amyloid-β toxicity and neuronal apoptosis/autophagy [53, 111, 112]. This gene belongs to the *UNC5H* receptor family, including *UNC5A*, *UNC5B*, *UNC5C*, and *UNC5D*, which are highly expressed in the nervous system (https://www.gtexportal.org/), and seems to be enriched in the hippocampus of AD brain [113]. It is a transmembrane receptor for netrin-1 and can trigger apoptosis under the absence of the netrin-1 ligand. As the receptor of neurin-1, *UNC5C* plays a crucial role in mediating axon repulsion of neuronal growth cones and cell migration in the developing nervous system [114, 115]. Being *UNC5C* involved in mechanism during axon development, alterations in this gene could trigger alterations in connections between neuronal groups equivalent to lesions in the cerebral white matter. In this line, a positive correlation between white matter vascular injury and sources of alpha EEG, were found in MCI individuals [116]. Additional evidence showed correlations between alpha power and white matter volume [117]. These findings suggest that alpha activity may be affected by aberrant neuronal pathways caused by altered development mechanisms of the nervous system.

Relationship between NAV2 and RP in theta and beta frequency bands

NAV2 (neuron navigator-2), expressed in the brain, is essential for nervous system development [118]. *NAV2* is highly expressed in the hippocampus, cortex, cerebellum, and thalamus [119] and, more specifically, in postmitotic neurons involved in cell migration and neurite outgrowth. There is some evidence that the variant rs1425227 can alter the binding motive of a transcription factor active in bipolar neurons, and thus may have a regulatory effect in *NAV2*. Indeed, this variant lies within a promoter region, with enhancer histone marks, and within open chromatin in the brain, which suggests active transcription. *NAV2* mutant mice embryos have been shown to display a reduction in nerve fiber density, as well as specific defects in cranial nerves, being required for normal cranial nerve development and blood pressure regulation [120]. In this study, *NAV2* SNPs are associated mostly with theta and beta band alterations. This gene was previously mentioned to be involved in episodic memory tasks [121]. It turns out that processes of this type are closely related to theta band activity [122–124], which seem reasonable to occur during an EEG recording. Hence, we suggest a greater impact of *NAV2* expression in certain cognitive functions under neurodegeneration conditions.

Limitations and future research lines

Some limitations were faced in this work and should be examined in future research. Since this study aimed to ascertain relations between RP values and a reasonable quantity of genetic features, the reliability of the results may be sensitive to database size. This was particularly noticeable when the analyses were computed considering separately the sampling subgroups: AD patients, MCI individuals, and controls. The genetic associations found in this work are novel and future research is important to ensure the correlation with the disease. In order to improve statistical power, enlarging the sample of study should be taken into account. It is also note-

worthy that RP was the only feature considered in this study to characterize neurodynamic alterations. Although RP is reliable describing the deterioration process of dementia, connectivity measures (amplitude envelope correlation, weighted phase lag index, etc.) or network parameters (clustering coefficient, characteristic path length and betweenness centrality, among others), could provide additional insights in this regard. In future research, we aim to apply alternative metrics that allow to obtain further information on physiological deterioration associated to the progression of AD. In addition, whole scalp EEG activity was considered, losing spatial-relative data. Several studies pointed particular brain areas to be associated with more marked EEG alterations in AD [125–128], and hence the average activity from all electrodes may diminish the statistical significance of the associations, which in fact may be stronger.

CONCLUSIONS

RP values at the conventional EEG frequency bands (i.e., delta, theta, alpha, beta-1, and beta-2) showed to be correlated with some genetic variants in genes previously associated with AD. Globally, theta frequency band showed the greatest correlation with the analyzed genetic variants and is noteworthy its potential as case-control biomarker.

Novel associations between variants in *IL1RAP*, *UNC5C*, and *NAV2* genes, and the RP values of some frequency bands (delta and theta, alpha, and theta and beta, respectively) were identified. In all the cases a risk allele was associated with the slowing of brain activity, specifically with the increase of RP values in low frequency bands (i.e., delta and theta), and with a decrease at high frequency bands (i.e., alpha and beta).

These associations may contribute to the comprehension of AD pathogenesis, each with a different biological role, and influencing multiple factors that contribute to brain physiology.

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SUPPLEMENTARY MATERIAL

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