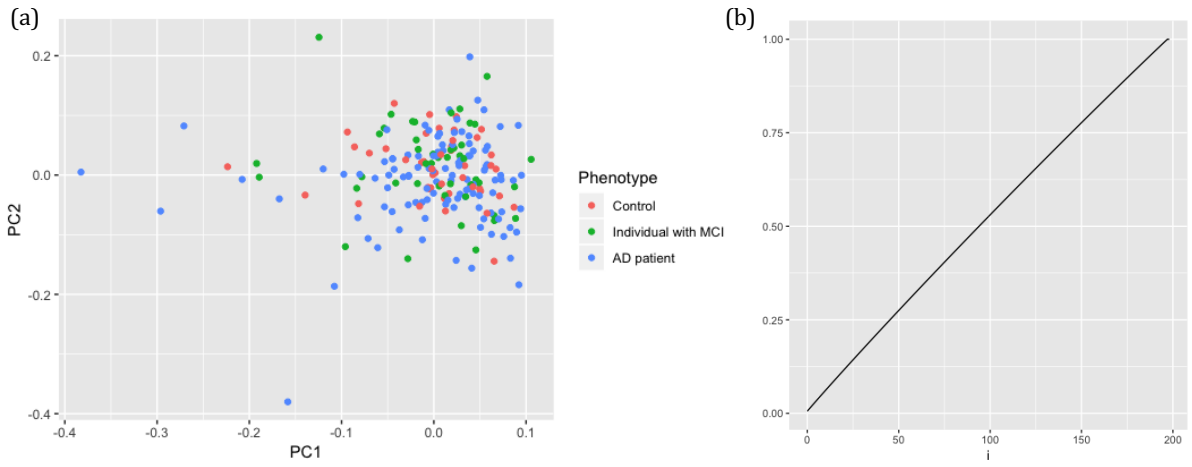
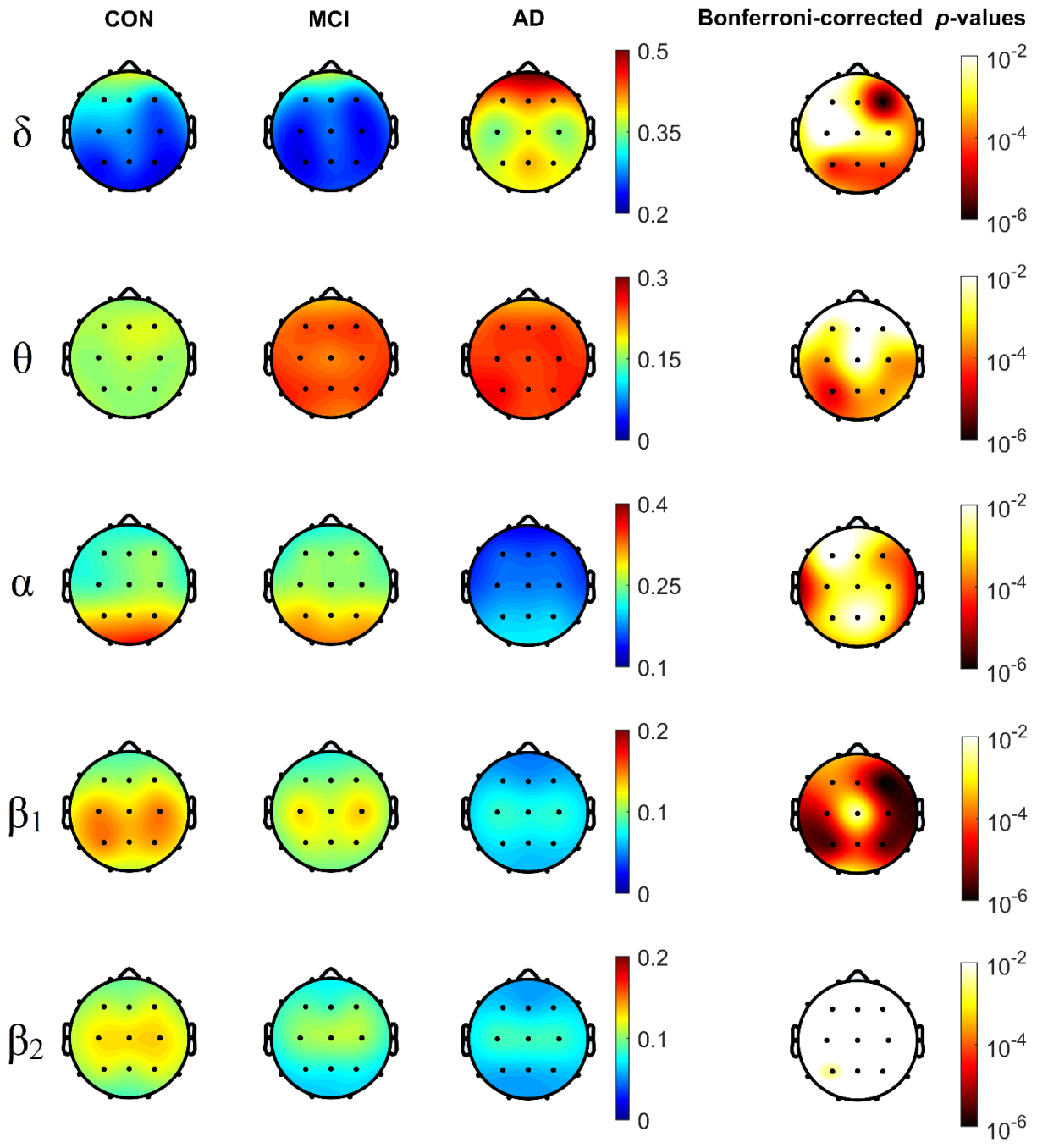
Supplementary Material

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

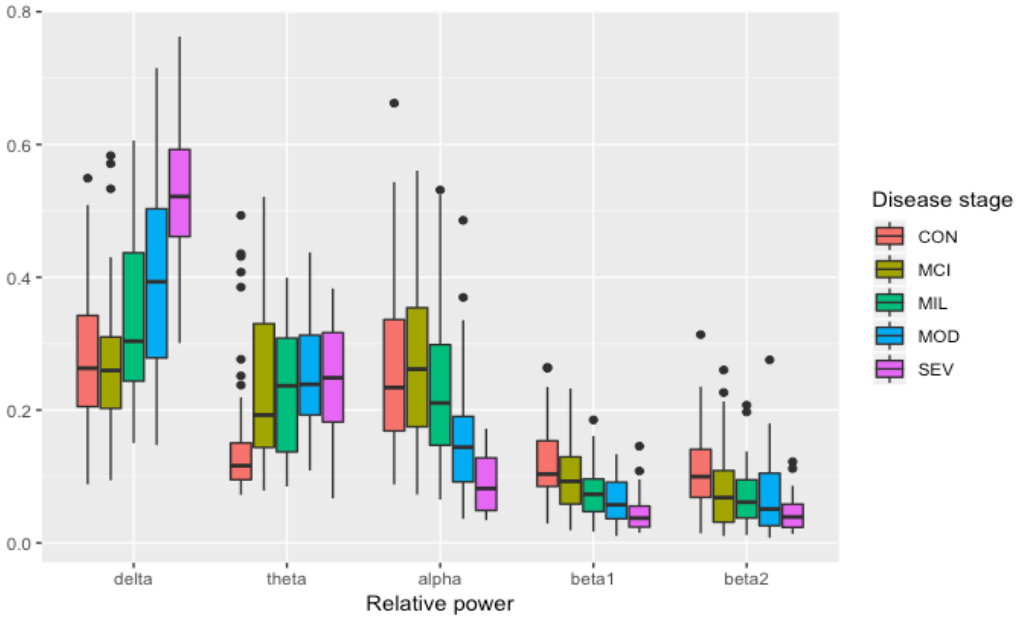
Supplementary Figure 1. Principal component (PC) analysis considering the genotypic information of the 199 subjects under study. (a) Plot of the first two PCs; (b) proportion of variability explained by the first *i*-th PCs, $i = 1, \ldots, 198$.



Supplementary Figure 2. Topography of RP values at each frequency band for control, MCI, and AD groups, as well as the corresponding Bonferroni-corrected p-values (Kruskal-Wallis test).



Supplementary Figure 3. Distribution of RP values for each EEG frequency band according to sampling subgroups, including disease stage: controls (CON), individuals with MCI (MCI), patients with mild (MIL), moderate (MOD), and severe AD (SEV).



Supplementary Table 1. Dunn's test p-values obtained when comparing age of sampling groups: controls, individuals with MCI, and AD patients. The trend of the analysis is indicated whenever the significance level was reached.

Sampling group	Individuals with MCI	AD patients
Controls	*p*=1.5e-04** (Controls < MCI)	*p*=1.1e-01
Individuals with MCI	-	*p*=1.0e-03** (MCI > AD patients)
**** Statistical significance level reached at Bonferroni corrected α=1.7e-02.**		

Supplementary Table 2. Chi-squared test differences between observed and expected frequencies of female/male subjects (p-value = 1.4e-02) and *APOE* ε4 carriers/non carriers (*p* = 2.8e-02) by sampling group.

Sampling group	Sex		*APOE* ε4	
	Female	Male	Non carrier	Carrier
Control	-7.8	7.8	7.6	-7.6
Individuals with MCI	0.2	-0.2	5.2	-5.2
AD patients	7.5	-7.5	-12.8	12.8

Supplementary Table 3. Number of common variants (minimum allele frequency ≥ 5%) analyzed for each candidate gene.

Gene	Number of analyzed variants
OPRD1	13
GSK3B	12
BCHE	55
IL1RAP	55
UNC5C	89
SLC6A3	21
CLU	30
PICALM	24
SORL1	81
NAV2	219
GRIN2B	116
CETP	17
HOMER2	10
TOMM40	24
APOE	8
CR1	22
Total	796

Supplementary Table 4. Statistical power for detecting variants explaining a range of proportions of variance, considering the analysis of 796 variants in a cohort of 199 subjects, conditioned by the Bonferroni-corrected significance level α=6.28E-05.

Proportion of Variance (%)	Statistical Power
1	0.004880264
2	0.02347594
3	0.06411392
4	0.1308342
5	0.2219349
6	0.3307013
7	0.4475807
8	0.5627194
9	0.6679942
10	0.7581186
11	0.8308182
12	0.886337
13	0.926618
14	0.9544582
15	0.9728247

Supplementary Table 5. *p*-values regarding the analysis of independence between RP values for each EEG frequency band and sex (male/female), *APOE* ε4 presence (carriers C and non-carriers NC), and age. The trend of the analysis is indicated whenever the significance level (either nominal or after Bonferroni correction) was reached.

Covariates	EEG relative power				
	Delta	**Theta**	**Alpha**	**Beta-1**	**Beta-2**
Sex[1]	p=7.1E-01	p=7.6E-01	p=1.7E-01	p=8.9E-01	p=5.7E-01
***APOE* ε4 presence**[1]	p=2.4E-01	p=1.2E-01	p=5.5E-02	p=2.5E-02* (C < NC)	p=2.0E-01
Age[2]	p=2.4E-01	p=1.7E-04** (ρ=0.26)	p=9.5E-01	p=6.3E-01	p=4.6E-02* (ρ=-0.14)

[1] Kruskal-Wallis' test, [2] Pearson's correlation test
* Nominal significance level reached (α=5.0E-02)
** Significance level reached after Bonferroni's correction (α=1.0E-02).

Supplementary Table 6. Dunn's test *p*-values regarding pairwise differences of RP values for each EEG frequency band between sampling groups: AD patients (AD), individuals with MCI (MCI), and controls (CON). The trend of the analysis is indicated whenever the significance level (after Bonferroni correction) was reached. In all the cases, the observed trend of RP values is concordant with the expected, given the subjects' status.

Relative power	CON versus MCI	CON versus AD	MCI versus AD
Delta	*p*=3.4E-01	*p*<5.0E-05 * (CON < AD)	*p*<5.0E-05 * (MCI < AD)
Theta	*p*<1.5E-04 * (CON < MCI)	*p*<5.0E-05 * (CON < AD)	*p*=1.8E-01
Alpha	*p*=4.2E-01	*p*<5.0E-05 * (CON > AD)	*p*<5.0E-05 * (MCI > AD)
Beta-1	*p*=6.8E-02	*p*<5.0E-05 * (CON > AD)	*p*<5.0E-05 * (MCI > AD)
Beta-2	*p*=3.2E-03 * (CON > MCI)	*p*<5.0E-05 * (CON > AD)	*p*=1.1E-01
* Significance level reached after Bonferroni's correction (α=3.3e-03).			

Supplementary Table 7. Dunn's test *p*-values from pairwise comparisons of RP values for each EEG frequency band considering the sampling subgroups, including disease stage: controls (CON), individuals with MCI (MCI), patients with mild (MIL), moderate (MOD), and severe AD (SEV). The trend of the analysis is indicated whenever the significance level (either nominal or after Bonferroni correction) was reached. In all the cases, the observed trend of RP values is concordant with the expected, given the subjects' status.

Relative power	Sampling subgroups	Sampling subgroups			
		MCI	**MIL**	**MOD**	**SEV**
Delta	CON	*p*=3.4E-01	*p*=3.2E-02 * (CON < MIL)	*p*<2.5E-04 ** (CON < MOD)	*p*<5.0E-05 ** (CON < SEV)
	MCI		*p*=1.2E-02 * (MCI < MIL)	*p*<5.0E-05 ** (MCI < MOD)	*p*<5.0E-05 ** (MCI < SEV)
	MIL			*p*=4.0E-02 * (MIL < MOD)	*p*<5.0E-05 ** (MIL < SEV)
	MOD				*p*=2.7E-03 * (MOD < SEV)
Theta	CON	*p*<1.5E-04 ** (CON < MCI)	*p*<5.0E-05 ** (CON < MIL)	*p*<5.0E-05 ** (CON < MOD)	*p*<5.0E-05 ** (CON < SEV)
	MCI		*p*=4.3E-01	*p*=9.7E-02	*p*=2.0E-01
	MIL			*p*=1.3E-01	*p*=2.4E-01
	MOD				*p*=3.9E-01
Alpha	CON	*p*=4.2E-01	*p*=1.0E-01	*p*<5.0E-05 ** (CON > MOD)	*p*<5.0E-05 ** (CON > SEV)
	MCI		*p*=7.0E-02	*p*<5.0E-05 ** (MCI > MOD)	*p*<5.0E-05 ** (MCI > SEV)
	MIL			*p*=2.4E-03 * (MIL > MOD)	*p*<5.0E-05 ** (MIL > SEV)
	MOD				*p*=2.9E-03 * (MOD > SEV)
Beta-1	CON	*p*=6.8E-02	*p*<1.5E-04 ** (CON > MIL)	*p*<5.0E-05 ** (CON > MOD)	*p*<5.0E-05 ** (CON > SEV)
	MCI		*p*=1.4E-02 * (MCI > MIL)	*p*<5.5E-04 ** (MCI > MOD)	*p*<5.0E-05 ** (MCI > SEV)
	MIL			*p*=1.2E-01	*p*=1.7E-03 * (MIL > SEV)
	MOD				*p*=3.3E-02 * (MOD > SEV)
Beta-2	CON	*p*=3.2E-03 * (CON > MCI)	*p*=2.2E-03 * (CON > MIL)	*p*<1.5E-04 ** (CON > MOD)	*p*<5.0E-05 ** (CON > SEV)
	MCI		*p*=4.5E-01	*p*=1.6E-01	*p*=1.3E-02 * (MCI > SEV)
	MIL			*p*=1.9E-01	*p*=1.7E-02 * (MIL > SEV)
	MOD				*p*=9.6E-02

* Nominal significance level reached (α=5.0e-01)
** Significance level reached after Bonferroni's correction (α=1.0e-03).

Supplementary Table 8. Genetic variants for which statistically significant differences (significance level α=0.005) were found in RP values of at least one EEG frequency band, risk allele associated and respective frequency in AD patients and controls sampling groups.

Gene	Ref. SNP	Risk allele	Frequency of risk allele		
			AD patients	Controls	p
IL1RAP	rs10212109	C	0.3211	0.2556	2.77E-01
IL1RAP	rs9823517	G	0.0872	0.0333	1.42E-01
IL1RAP	rs4687150	T	0.3073	0.3667	3.50E-01
UNC5C	rs17024131	T	0.9128	0.9333	6.51E-01
NAV2	rs1425227	T	0.7064	0.6512	4.09E-01
NAV2	rs862785	G	0.0551	0.1222	4.18E-01

Supplementary Table 9. Distribution of subjects' sex, age, and genotypes considering the genetic variants for which statistically significant differences (significance level α=0.005; see Supplementary Table 8) were found in RP values of at least one EEG frequency band (hom risk - homozygous individuals with 2 risk alleles, het - heterozygous individuals, hom alt - homozygous individuals with 2 alternative alleles).

Sampling subgroup			AD patients			MCI individuals			Controls		
Sex distribution			F	M		F	M		F	M	
			82	27		31	14		23	22	
Mean age ± SD (y)			80.7 ± 7.0			84.8 ± 7.1			79.7 ± 7.3		
Gene	Ref. SNP	Risk allele	Frequency of genotypes								
			Hom risk	Het	Hom alt	Hom risk	Het	Hom alt	Hom risk	Het	Hom alt
IL1RAP	**rs10212109**	**C**	16	38	55	5	20	20	2	19	24
IL1RAP	**rs9823517**	**G**	0	19	90	0	11	34	0	3	42
IL1RAP	**rs4687150**	**T**	11	45	53	1	21	23	6	21	18
UNC5C	**rs17024131**	**T**	91	17	1	39	5	0	39	6	0
NAV2	**rs1425227**	**T**	51	52	6	24	18	3	16	24	3
NAV2	**rs862785**	**G**	0	12	97	0	6	39	1	9	35

Supplementary Table 10. Kruskal-Wallis' p-values associated with the differences RP values for each frequency band, and the presence of risk alleles in rs7412 and rs429358 *APOE*, and *rs11136000* CLU variants.

Gene (variant)	EEG relative power				
	Delta[1.2]	Theta[1.3]	Alpha[1.2]	Beta-1[1]	Beta-2[1]
APOE (rs7412 & rs429358)	*p*=2.4e-01	*p*=1.2e-01	*p*=5.5e-02	*p*=2.5e-02* (C<NC)	*p*=2.0e-01
PICALM (rs3851179)	*p*=6.0e-02	*p*=2.9e-01	*p*=2.2e-01	*p*=4.3e-01	*p*=9.0e-01
CLU (rs11136000)	*p*=4.5e-01	*p*=4.9e-01	*p*=9.1e-01	*p*=1.9e-01	*p*=8.1e-02

RP values for each frequency band corrected for: [1]AD, MCI, and CON groups, [2] MIL, MOD, and SEV subgroups, or [3] the age of the participants.
*Nominal significance level reached (α=5.0e-02).