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ORIGINAL PAPER

Variation at NRG1 genotype related to modulation of small-world properties of the functional cortical network

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Abstract Functional brain networks possess significant small-world (SW) properties. Genetic variation relevant to both inhibitory and excitatory transmission may contribute to modulate these properties. In healthy controls, genotypic variation in Neuregulin 1 (NRG1) related to the risk of psychosis (risk alleles) would contribute to functional SW modulation of the cortical network. Electroencephalographic activity during an odd-ball task was recorded in 144 healthy controls. Then, small-worldness (SWn) was calculated in five frequency bands (i.e., theta, alpha, beta1, beta2 and gamma) for baseline (from −300 to the stimulus onset) and response (150–450 ms post-target stimulus) windows. The SWn modulation was defined as the difference in SWn between both windows. Association between SWn modulation and carrying the risk allele for three single nucleotide polymorphisms (SNP) of NRG1 (i.e., rs6468119, rs6994992 and rs7005606) was assessed. A significant association between three SNPs of NRG1 and the SWn modulation was found, specifically: NRG1 rs6468119 in alpha and beta1 bands; NRG1 rs6994992 in theta band; and NRG1 rs7005606 in theta and beta1 bands. Genetic variation at NRG1 may influence functional brain connectivity through the modulation of SWn properties of the cortical network.

Keywords Imaging genetics · Neuroimaging · NRG1 · Psychosis · Small-world

Introduction

Mental activity is likely contributed by the coordinated network of different cortical regions [1–3]. These brain networks show small-world (SW) properties, characterized by high local clustering and low average distance between nodes (low characteristic path length). SW architecture balances segregation (i.e., the ability of a network to work locally) and integration (i.e., the capacity to communicate separated brain areas) in functional brain networks. These properties can be quantified using a network parameter: the small-worldness (SWn) [4–6], whose heritability has been proposed to be large [7].

SWn of brain network properties can be studied using structural [anatomical (MR) or diffusion magnetic resonance (DTI)] and functional [electroencephalography (EEG) or functional magnetic resonance (fMRI)] methods [8]. Among the latter, temporal resolution of the EEG allows assessing the fast modulation of functional brain connectivity related to cognitive performance.

Neural networks are contributed by a large number of factors, some susceptible of a genetic regulation. Among them, the excitatory/inhibitory balance may play a relevant role [9]. On the other hand, abnormalities in SW properties of the brain networks have been found in the psychotic disorders [10–12], for which a high heritability is established [13]. Thus, to identify genetic contributions to network organization, one possible strategy is to assess the influence

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of gene-related factors: (1) contributing to neurotransmission, neurodevelopment and excitatory/inhibitory balance, and (2) implicated in the risk of psychosis.

Genetic variation for Neuregulin 1 (NRG1) seems to comply with both conditions. NRG1 gene codifies a pleiotropic growth factor protein with at least fifteen different isoforms. All of them have an epidermal growth factor domain (EGF), which preferentially activates tyrosine kinase receptor ErbB4. Those receptors were principally located in the postsynaptic density of parvalbumin-positive interneurons [14, 15]. NRG1 protein is related to central nervous system development, plasticity, myelination [16], migration [17] and inhibitory/excitatory balance [18, 19]. This protein and its interaction with ErbB4 could regulate glutamatergic transmission by modulating the activity of *N*-methyl-D-aspartate (NMDA) [18, 20, 21] and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) [19] receptors in the excitatory synapsis. In addition, NRG1 has a very relevant role in GABAergic interneurons, one of the main cells contributing to oscillatory activity [22, 23], through the regulation of the differentiation, migration and activity of this type of neurons [17]. Although genetic variation at NRG1 loci has not been consistently associated with psychotic disorders risk in genome-wide studies, other data support that it may play a role in the risk of schizophrenia [18, 24, 25].

Therefore, it seems of interest to assess the relation between NRG1 genetic variation relevant to psychosis and functional brain network organization. For this purpose, three NRG1 SNPs were selected due to its relation with major psychoses: rs6994992, whose T allele has been related to the risk of psychosis [26, 27], cognitive deficits and lower brain activity in schizophrenia [22, 27]; and rs6468119 and rs7005606, whose T alleles have been associated with the risk of bipolar disorder [28, 29]. Hence, the aim of the study was to assess the possible relation between genetic variations at NRG1 gene and SWn modulation during a cognitive task. The assessment of the association of brain network modulation with genetic variation in healthy population can be a first step to understand how genetic background influences the disconnectivity in clinical psychosis.

Table 1 Socio-demographic data and SWn_C^b values for the cohort of subjects enrolled in the study

	Non-risk allele carriers Mean (SD)	Risk allele carriers Mean (SD)
rs6468119		
N	28	85
Age (years)	26.64 (8.57)	27.24 (8.59)
Gender (M:F)	12:16	35:50
Education (years)	15.89 (1.57)	16.89 (1.85)
SWn_C-theta	0.25 (0.57)	0.42 (0.5)
SWn_C-alpha	−0.14 (0.36)*	0.05 (0.43)
SWn_C-beta1	−0.12 (0.28)*	0.03 (0.29)
SWn_C-beta2	−0.04 (0.13)	0.01 (0.17)
SWn_C-gamma	−0.01 (0.08)	0.01 (0.06)
rs6994992		
N	24	120
Age (years)	28.29 (10.9)	27.41 (8.87)
Gender (M:F)	14:10	48:72
Education (years)	16.69 (1.89)	16.07 (2.32)
SWn_C-theta	0.14 (0.56)*	0.36 (0.48)
SWn_C-alpha	−0.13 (0.39)	−0.02 (0.41)
SWn_C-beta1	−0.06 (0.33)	−0.03 (0.31)
SWn_C-beta2	−0.03 (0.14)	−0.02 (0.16)
SWn_C-gamma	−0.003 (0.07)	−0.003 (0.06)
rs7005606		
N	27	111
Age (years)	26.44 (10.16)	27.96 (9.11)
Gender (M:F)	12:15	43:68
Education (years)	16.16 (1.64)	16.27 (2.44)
SWn_C-theta	0.15 (0.48)*	0.36 (0.48)
SWn_C-alpha	−0.18 (0.34)	−0.02 (0.41)
SWn_C-beta1	−0.14 (0.31)*	−0.01 (0.3)
SWn_C-beta2	−0.06 (0.14)	−0.01 (0.16)
SWn_C-gamma	−0.02 (0.07)	0.002 (0.06)

Data were divided into two groups, which were defined depending on the presence of NRG1 risk polymorphisms for psychoses. SWn_C values were calculated as the difference between SWn at response and baseline windows ($SWn_R^b - SWn_{BL}^b$). Positive values represent a SW increase at response. Statistically significant differences between risk and no-risk allele carriers are marked with an asterisk: * $p < 0.05$. *M* male, *F* female

Methods

Participants: demographic and clinical assessment

We recruited 144 healthy controls through newspaper announcements, all of them from Caucasian race. A semi-structured interview prior to the study was used to discard current or past psychiatric diagnoses or treatments. Exclusion criteria were: (1) comorbid axis-1 diagnosis; (2) family antecedents of psychosis; (3) psychoactive treatment; (4) substance abuse; (5) history of head trauma or any disease affecting the central nervous system; and (6) intelligence quotient (IQ) below 70. Socio-demographic data are given in Table 1.

Electrophysiological recordings

EEG recordings were acquired during the performance of an auditory odd-ball task. The task consisted of random

series of 600 stimulus (duration 50 ms, rise and fall time 5 ms, intensity 90 dB) composed by three different tones with different probabilities: (1) S1, 2000 Hz standard tone, probability 0.60; (2) S2, 1000 Hz distractor tone, probability 0.20; and (3) S3, 500 Hz target tone, probability 0.20. The subjects were asked to press a bottom when they listened the target tone. During the recording, they remained seated, relaxed and with their eyes closed. Only attended target tones were considered for further analysis.

EEG activity was recorded using a Brain Vision electroencephalographic system (Brain Products, Germany), with 17 electrodes (Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T5, T6, Fz, Pz and Cz) placed following the specifications of the 10–20 international system (Electro-Cap International, Inc.; Eaton, OH, USA). Electrooculogram (EOG) was also recorded to detect eye movements. Impedance was kept under 5 kΩ during EEG acquisition. The sampling rate was 500 Hz.

Signal processing

EEG preprocessing

Each EEG recording was initially re-referenced over Cz electrode to minimize the effect of microsaccadic artifacts [30]. Then, EEG signals were bandpass-filtered between 1 and 70 Hz. In addition, a 50-Hz notch filter was used to remove the power line artifact. Independent component analysis (ICA) was applied to visually discard components related to ocular and muscular artifacts. A segmentation into 1-s-length trials, ranging from −300 ms before stimulus onset to 700 ms after stimulus onset, was performed. Finally, an adaptive thresholding method was used to discard those epochs whose amplitude exceeded the threshold [31].

Continuous wavelet transform

Continuous wavelet transform (CWT) was used to estimate time–frequency maps, since it is a suitable technique to analyze non-stationary recordings [32]. In this study, we used two different time windows: (1) the baseline window, [−300, 0] ms previous to the stimulus onset; and (2) the response window, [150, 450] ms post-stimulus [31]. In order to avoid CWT edge effects in short-time recordings, a cone of influence (COI) was defined for the two windows under study [33]. It is noteworthy that evoked response is included in the response window.

Five frequency bands were considered for subsequent analyses. They were defined according to the conventional EEG frequency bands: theta (θ, 4–8 Hz), alpha (α, 8–13 Hz), beta1 ($\beta 1$, 13–19 Hz), beta2 ($\beta 2$, 19–30 Hz) and gamma (γ, 30–70 Hz). Delta frequency band was not analyzed, since it is associated with a wavelet duration of hundreds of milliseconds [31].

Mean squared coherence

Coherence measure assesses the functional interaction between couple of signals from a specific brain region [34]. In this study, mean squared coherence (MSC) was used to quantify the spectral content between couples of EEG channels. Therefore, MSC between two signals is the cross-function of the normalized power spectral density divided by the normalized power spectral density of the two signals separately [34]:

$$\mathrm{MSC}_{\mathrm{XY}}(t,f) = \frac{\left|\mathrm{WS}_{\mathrm{XY}}(t,f)^2\right|}{\mathrm{WS}_{\mathrm{XX}}(t,f)\cdot \mathrm{WS}_{\mathrm{YY}}(t,f)} \tag{1}$$

where $\mathrm{WS}_{\mathrm{XY}}$ is the cross-spectral density of two signals (X and Y) from the wavelet scalogram (which summarizes the distribution of the signal energy in the time–frequency plane), and $\mathrm{WS}_{\mathrm{XX}}$ and $\mathrm{WS}_{\mathrm{YY}}$ are the auto-spectral density functions from the wavelet scalogram. Finally, MSC values were averaged in each of the spectral bands under study.

Complex network theory

To model a system as a graph, nodes may represent the dynamical units and their links stand for the interactions between them [35]. We have used the SWn parameter, since it summarizes two different properties of a network: integration and segregation. First, cluster coefficient (ClC, a segregation measure) is computed for each node of the network and each frequency band:

$$\mathrm{ClC}_i^b = \frac{\sum_{k=i}\sum_{\substack{l\neq i\\ l\neq k}} w_{ik}^b w_{il}^b w_{il}^b}{\sum_{k=i}\sum_{\substack{l\neq i\\ l\neq k}} w_{ik}^b w_{il}^b}, \quad b\in\{\theta,\ \alpha,\ \beta 1,\ \beta 2,\ \gamma\} \tag{2}$$

where b represents the frequency band under study and w_{ij}^b the weight between two nodes provided by the MSC measure. Second, averaged path length (PL, an integration measure) was computed for each node following the following equation:

$$\mathrm{PL}_i^b = \frac{\sum_{j\neq i} d_{ij}^b}{N-1}, \quad b\in\{\theta,\ \alpha,\ \beta 1,\ \beta 2,\ \gamma\} \tag{3}$$

where N is the total number of nodes of the network (17 in this case) and d_{ij}^b is the minimum distance between nodes i and j. Then, ClC and PL values were averaged over all nodes in order to obtain global parameters of the network. Finally, in order to obtain measures that are independent of

the network size, CLC and PL were normalized dividing by <$CLC_{surrogate}$> and <$PL_{surrogate}$>:

$$PL_n^b = \frac{PL}{\langle PL_{surrogate} \rangle} \quad (4)$$

$$ClC_n^b = \frac{ClC}{\langle PL_{surrogate} \rangle} \quad (5)$$

where <$CLC_{surrogate}$> and <$PL_{surrogate}$> denote weighted clustering coefficient and path length averaged over an ensemble of 50 surrogate random networks that were derived from the original [36]. Therefore, SW was independent of the network size [37]:

$$SWn^b = \frac{ClC_n^b}{PL_n^b} \quad (6)$$

Parameter baseline correction

The baseline correction process is used to achieve a stimulus-independent characterization [31]. Once the spectral parameters were computed for each temporal 1 s-length trial, they were decomposed into the baseline and the response window [38]. Firstly, the spectral analysis provides a value for each temporal window. Secondly, the values of the previous parameters in the [−300, 0] ms interval were averaged to obtain a baseline parameter mean. Then, the baseline correction was carried out using a simple subtraction. For that purpose, the SW during the baseline window for each frequency band under study (SWn_{BL}^b) is subtracted from the response value (SWn_R^b) for each participant (mean of the values in the [150, 450] ms interval) obtaining the corrected SWn (SWn_C^b). It should be noted that negative values indicate a parameter decrease in the response window, while positive values represent an increase from baseline to response window.

$$SWn_C^b = \left\langle SWn_R^b - SWn_{BL}^b \right\rangle \quad (7)$$

where $\langle . \rangle$ denotes the average across trials.

Genetic analyses

We obtained from each individual approximately 10 ml of venous blood using a K3-EDTA (ethylenediaminetetraacetic acid) tubes. The samples were centrifuged with Ficoll-Paque following the Trizol protocol (Invitrogen, Carlsbad, CA, USA) to obtain genomic DNA from white cells. The genotyping was carried out via TaqMan assays through real-time polymerase chain reaction (PCR) with custom-made probes and primers (Applied Biosystems, Foster City, CA). The final volume of reaction was 10 µl, and the amplification program protocol used the following temperatures for 40 cycles: 94 °C (denaturing), 60 °C (annealing) and 72 °C (extension).

The polymorphism distribution results were evaluated with χ^2 tests to analyze Hardy–Weinberg equilibrium. SNPs rs6994992 and rs7005606 showed Hardy–Weinberg equilibrium ($p = 0.8248$ and $p = 0.1312$). In contrast, SNP rs6468119 does not fit to Hardy–Weinberg proportions ($p = 0.0387$), which could be contributed by the smaller genotyping success rate in this polymorphism (75.94 %).

Statistics

For each SNP, cases were dichotomized into non-risk allele carriers and risk alleles carriers. The distribution of SWn values was evaluated with one-sample Kolmogorov–Smirnov tests.

Demographic data were compared with Chi-square test or Student's t test when appropriate.

The significance of SWn modulation on each frequency band (or SWn_C^b) between carriers and non-carriers was assessed in each band of the EEG (except for delta) using Student's t tests. Moreover, to assess whether possible differences in SWn modulation were contributed by the baseline window, SWn_{BL}^b, values were compared between risk and non-risk allele carriers.

Results

Socio-demographic data

There were no significant differences between risk and non-risk allele carriers for any SNP in age, sex distribution and school years (Table 1).

NRG1 SNPs and SW

SWn values for each subgroup of risk allele carriers and non-risk allele carriers were normally distributed according to results of Kolmogorov–Smirnov tests (range of values: Z values from 0.309 to 1.075 and p values from 0.198 to 1).

There were significant differences in SWn modulation between rs6468119 carriers and non-carriers in alpha and beta1 frequency bands (SWn_C^{α}: $t = -2.06$, $df = 106$, $p = 0.042$; $SWn_C^{\beta 1}$: $t = -2.390$, $df = 106$; $p = 0.019$) (Table 1). Non-risk allele carriers (CC; $n = 28$) showed a significant decrease in SWn_C^{α} and $SWn_C^{\beta 1}$, while risk allele carriers (CT/TT; $n = 85$) showed a slight SWn increase in these bands (Table 1; Fig. 1). SWn_{BL}^b did not show significant differences between groups in any frequency band (Table 2).

We also found a significant difference in theta SWn (SWn_C^{θ}) between rs6994992 risk and non-risk allele

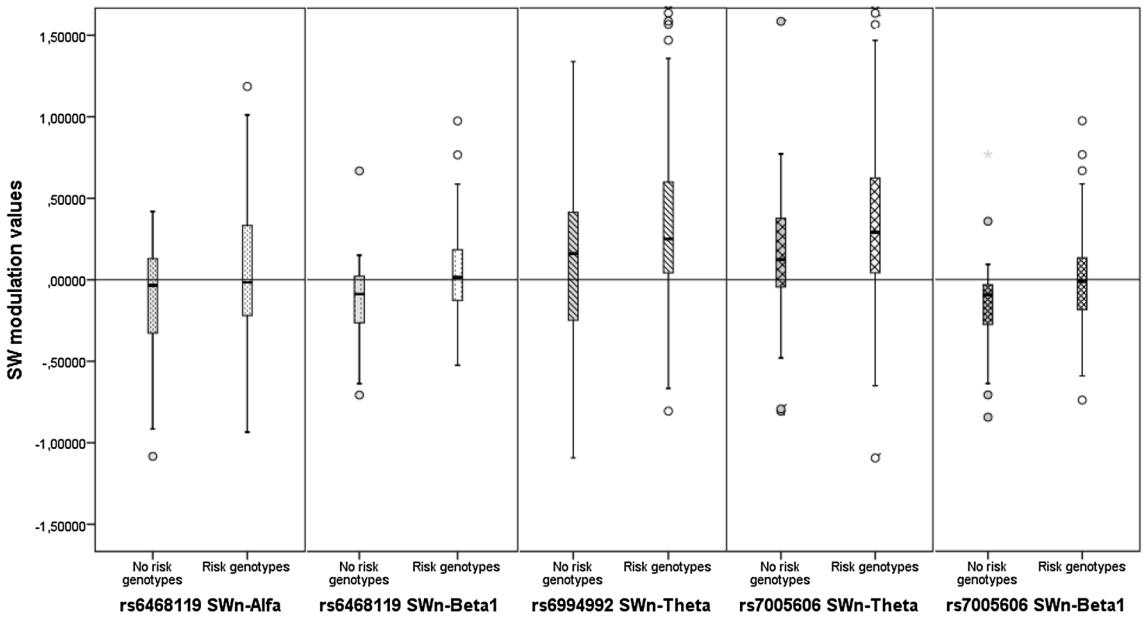

Fig. 1 Distribution of significant SWn^{b}_{C} modulation values ($SWn^{b}_{R} - SWn^{b}_{BL}$) in non-risk allele carriers and risk allele carriers

Table 2 SWn^{b}_{BL} values in baseline window for NRG1 SNPs

	Non-risk allele carriers Mean (SD)	Risk allele carriers Mean (SD)
rs6468119		
Theta	1.92 (0.40)	1.91 (0.57)
Alpha	2.68 (0.99)	2.73 (0.97)
Beta1	2.03 (0.52)	2.02 (0.53)
Beta2	1.49 (0.33)	1.46 (0.31)
Gamma	1.09 (0.07)	1.09 (0.08)
rs6994992		
Theta	2.26 (0.70)**	1.84 (0.49)
Alpha	3.35 (1.16)***	2.58 (1.01)
Beta1	2.29 (0.62)*	1.98 (0.54)
Beta2	1.53 (0.32)	1.44 (0.30)
Gamma	1.10 (0.08)	1.09 (0.08)
rs7005606		
Theta	1.92 (0.48)	1.90 (0.54)
Alpha	2.66 (1.15)	2.70 (1.06)
Beta1	1.99 (0.58)	2.03 (0.56)
Beta2	1.43 (0.32)	1.45 (0.31)
Gamma	1.12 (0.07)	1.09 (0.08)

The statistically significant differences between risk alleles carriers and non-risk allele carriers are marked with asterisks: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

carriers. Both risk allele carriers (CT/TT; $n = 120$) and non-carriers (CC; $n = 24$) showed a positive modulation of SWn in this band, significantly larger in risk allele carriers ($t = -2.02$, $df = 142$, $p = 0.046$) (Table 1; Fig. 1). For this allele and band, SWn values were significantly different at baseline in theta band (SWn^{θ}_{BL}) between risk allele carriers and non-carriers. SWn^{θ}_{BL} was significantly smaller in risk allele carriers (Table 2).

Finally, a significant difference in SWn modulation was observed between rs7005606 risk and non-risk allele carriers in theta (SWn^{θ}_{C}) and beta1 ($SWn^{\beta 1}_{C}$) bands. Risk allele carriers (GT/TT; $n = 111$) showed a significantly larger positive modulation SWn^{θ}_{C} (i.e., a larger increase from baseline to window) than non-carriers (GG; $n = 27$) ($t = -1.99$, $df = 136$, $p = 0.048$) (Table 1; Fig. 1). Moreover, risk allele carriers showed a significantly lower negative modulation in beta1 band (less decrease in $SWn^{\beta 1}_{C}$ from baseline to response) ($t = -2.06$; $df = 136$, $p = 0.042$) (Table 1; Fig. 1). There were no significant differences at SWn^{b}_{BL} for this allele.

Discussion

We found a significant association between genetic variation at NRG1 and the modulation of SW properties of the functional cortical network during the performance of an odd-ball task in healthy subjects. As far as we know, no previous studies investigated the effect of NRG1 polymorphisms on functional brain network modulation.

SW modulation in the theta band, SWn^{θ}_{C} was associated with two NRG1 SNPs: rs6994992 and rs7005606. In both cases, risk allele carriers presented larger SWn^{θ}_{C} (more positive SW changes) than non-risk allele carriers. Theta oscillations are related to long-range synchronization in brain

networks [39, 40]. According to our data, the risk allele may be associated with a larger modulation of long-range connectivity in response to a task. Such a larger modulation was associated with lower SWn^{θ}_{BL} values in risk allele carriers. Therefore, risk allele carriers with smaller SWn values in the baseline window might have to increase the SWn in this band to a larger extent than non-carriers during task performance.

NRG1 rs6994992 is located at the promotor region of the gene, inside the HAPice haplotype [21], being the only functional HAPice polymorphism and related to cognitive alterations [25]. Rs6994992 has also been related to white matter integrity in healthy subjects [24]. Thus, variation at this locus might contribute to the structural substrate of long-range connectivity [41]. However, previous studies showed a reduced fractional anisotropy in anterior limb of internal capsule and anterior thalamic radiation in risk allele carriers [24, 42]. Therefore, the role of NRG1 variation on white matter integrity may not justify the association observed in the present study with fast regulation of cortical network in the theta band.

Our findings also support an association between rs6468119 and rs7005606 and SW modulation in beta1 band, risk allele carriers showing smaller SW modulation. The same result was observed regarding SW modulation in alpha band with respect to rs6468119. Alpha and beta band may also play a role in long-range synchronization [43, 44]. Both SNPs are non-coding polymorphisms [28, 29]. Their effect is unknown, but they could be related to the regulation of NRG1 transcription [18, 45]. Either increase or decrease in the NRG1 is related to changes in the inhibitory/excitatory balance, supporting its possible contribution to connectivity supported by cerebral oscillations: An increase in NRG1–ErbB4 signaling is related to a decrease in NMDAr activation and currents [46, 47], mainly through the inhibition of Src kinases pathway [48]. Also, hypofunction of NRG1–ErbB4 might cause abnormal glutamatergic transmission through increasing NR2B phosphorylation [49]. Furthermore, the NRG1 increase is associated with an impairment of GABA release [50], and NRG1 increase or decrease is, respectively, related to promotion or reduction in miniature excitatory postsynaptic currents in GABAergic interneurons [51] that impair pyramidal neurons synchronization [52].

We a priori selected SNPs on the basis of the likely risk conferred by one of their respective alleles for major psychosis, in which a decreased SWn has been reported. However, contrary to our expectations, risk alleles in healthy subjects were rather associated with a larger SW modulation during a cognitive task. As previously stated, this may be in part justified by smaller SW values at rest, but it also seems compatible with the possibility that other genetic and non-genetic factors may have a larger and complex influence in the network organization in schizophrenia patients.

Among the study limitations, larger samples are needed to adequately detect influences of genotype on brain networks modulation. Improved genotyping success is needed before our rs6468119 genotyping results could be extrapolated to the general population. Moreover, we measured individually the effect of every SNP, but the effect of genes in brain networks is more probably epistatic or additive [41].

As a conclusion, our data are consistent with an effect of NRG1 on functional connectivity [53], perhaps through variation in expression of NRG1–ErbB4 pathway, which could contribute to GABAergic and glutamatergic imbalance. Since our results are significant in theta, alpha and beta1 frequency bands, which may support transitory, task-related coupling between distant areas of the brain [54], we could infer that genetic variation at NRG1 may influence on brain networks mostly in the modulation of long-distance connectivity in the brain.

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Compliance with ethical standards

Ethical standards All participants provided written informed consent to participate in the study. It was approved by the ethical committee of the three hospitals involved in the study (University Hospitals of Alava, Salamanca and Valladolid) according to the Code of Ethics of the World Medical Association (Helsinki Declaration of 1975, as revised in 2008).

Conflict of interest The authors declare that they have no conflict of interest.

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