Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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SUPPLEMENTAL INFORMATION

DEFICIT OF ENTROPY MODULATION OF THE EEG: A BIOMARKER FOR THE ALTERED FUNCTION IN SCHIZOPHRENIA AND BIPOLAR DISORDER?

STRUCTURAL NETWORK PARAMETERS ASSESSMENT

MRI acquisition and processing

All the acquisitions were performed at a Philips Achieva 3 Tesla MRI unit (Philips Healthcare, Best, The Netherlands) located at the University of Valladolid. The protocol (total acquisition time was 18 minutes) included an anatomical T1-weighted image and a diffusion acquisition. For the T1-weighted images, a turbo field echo (TFE) sequence was employed, using a spatial resolution of 1x1x1 mm^3 and a matrix size of 256x256. 160 sagittal slices were acquired, covering the whole brain.

With regard to the diffusion weighted images (DWIs), an EPI acquisition was employed, obtaining 61 images with

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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different gradient directions (b-value=1000s/mm^2) and one baseline image. Matrix size was 128x128, with a voxel size of 2x2x2 mm^3. 66 axial slices were acquired.

From the raw data, a processing pipeline was applied in order to extract a connectivity matrix from each subject. The pipeline, which is explained in deeper detail elsewhere (Molina et al., 2017), makes use of freely available research-oriented software (FSL, Freesurfer and MRtrix) in order to first obtain a tissue-type segmentation, a cortical parcellation and a segmentation of subcortical gray matter structures from the T1-weighted images. This information is combined with the diffusion acquisition to obtain a whole brain, anatomically-constrained tractography (2 million streamlines were generated for each subject).

Finally, connectivity matrices were constructed from the tractography results and the (registered) cortical parcellation. Connectivity between any two cortical regions is described in terms of the averaged FA (fractional anisotropy) found along the streamlines connecting them. FA is a commonly employed diffusion metric, and quantifies how much the diffusion is predominantly oriented along one

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

DOI: 10.1503/jpn.190032

direction. FA is usually interpreted as a descriptor of white matter integrity, as several alterations (axonal destruction or demyelination, for instance) have been described to yield lower FA values.

Image processing is summarized in Figure S1.

As 84 regions were employed for cortical parcelation, 84x84 symmetric connectivity matrices were obtained. No threshold was applied to the matrices, but matrix coefficients can be equal to zero if no streamlines are found between any two cortical regions.

Graph-theory parameters

From the structural connectivity matrices, we calculated three graph parameters (Rubinov & Sporns, 2010): (i) connectivity strength (i.e. mean network node degree), (ii) network segregation using CLC, and (iii) network integration by means of PL. In addition, SW index was also computed as a useful description of the topology of the whole network. Thus, whereas connectivity strength is as a quantitative marker of global connectivity, SW gives a

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

DOI: 10.1503/jpn.190032

measure of the network efficiency, yielding complementary information of the structural network.

In order to obtain results independent of network size and network strength, SW index was computed as the ratio between normalized CLC and PL. For that purpose, an ensemble of 50 surrogate random networks was obtained by random reshuffling the connection (Stam et al., 2009). Then, CLC_n and PL_n were defined as follows (Stam et al., 2009):

$$CLC_n = \frac{\mathrm{CLC}}{\mathrm{C^{random}}}, \quad (1)$$

$$PL_n = \frac{\mathrm{PL}}{\mathrm{L^{random}}}, \quad (2)$$

where $\mathrm{C^{random}}$ and $\mathrm{L^{random}}$ represent the average of the CLC and PL values over the 50 surrogated networks. Finally, SW index is the ratio between the aforementioned CLC_n and PL_n.

It is noteworthy that the weights of the connectivity matrices represent the averaged FA along the streamlines connecting two brain regions. CLC, PL and connectivity strength parameters were computed (Rubinov & Sporns, 2010).

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

DOI: 10.1503/jpn.190032

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SUPPLEMENTARY TABLES AND FIGURES

	PCA-F1	PCA-F2	PCA-F3	PCA-F4
SE modulation_fp1	0.794	-0.065	0.137	0.287
SE modulation_fp2	0.754	0.050	0.047	0.393
SE modulation_f7	0.794	0.277	0.007	-0.145
SE modulation_f3	0.792	-0.251	0.038	0.318
SE modulation_fz	0.816	-0.466	-0.108	0.061
SE modulation_f4	0.725	-0.218	0.019	0.334
SE modulation_f8	0.770	0.265	-0.348	0.143
SE modulation_c3	0.707	0.281	0.295	-0.016
SE modulation_c4	0.795	-0.404	-0.277	-0.105
SE modulation_p7	0.796	-0.452	-0.238	-0.158
SE modulation_p3	0.834	-0.374	-0.231	-0.065
SE modulation_pz	0.638	0.406	-0.084	0.295
SE modulation_p4	0.729	0.094	0.231	-0.249
SE modulation_p8	0.718	0.057	-0.281	0.109
SE modulation_o1	0.711	0.190	0.047	-0.192
SE modulation_o2	0.753	0.122	-0.326	0.122
SE modulation_fc5	0.689	0.344	0.190	0.023
SE modulation_fc1	0.807	0.249	-0.361	-0.135
SE modulation_fc2	0.789	0.190	-0.214	-0.264

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

DOI: 10.1503/jpn.190032

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SE modulation_fc6	0.661	0.354	-0.005	0.237
SE modulation_fcz	0.609	0.488	0.313	-0.124
SE modulation_t7	0.745	-0.087	0.354	-0.296
SE modulation_t8	0.726	0.344	-0.024	-0.215
SE modulation_cp5	0.724	0.030	0.176	0.123
SE modulation_cp2	0.747	-0.341	0.423	-0.049
SE modulation_cp6	0.659	-0.377	0.364	0.108
SE modulation_oz	0.696	-0.218	0.447	-0.114
SE modulation_cz	0.793	-0.185	-0.310	-0.347

Table S1: Factor structure resulting from the factor analysis of the Spectral Entropy modulation values (from 235 subjects). Individual factor scores were saved for further analyses in the 156 subjects included in the study.

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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	Sz	**Bip**	**Controls**
Fp1	-0,34	-0,12	-0,83 (1,46)
Fp2	-0,41	-0,07 (0,76)	-0,77 (1,28)
F7	-0,21	0,05 (0,66)	-0,73 (1,47)
F3	-0,42	-0,09 (0,84)	-1,18 (1,18)
Fz	-0,69	-0,57 (0,64)	-1,61 (1,46)
F4	-0,39	-0,11 (0,60)	-0,75 (1,13)
F8	-0,32	-0,04 (0,91)	-0,75 (1,41)
FC5	-0,12	0,32 (0,91) **	-0,21 (1,37)
FC1	-0,69	-0,66 (0,57)	-1,70 (1,59)
FCz	-0,74	-0,69 (0,52)	-1,83 (1,55)
FC2	-0,55	-0,55 (0,56)	-1,57 (1,51)
FC6	-0,11	0,21 (0,83) **	-0,17 (1,17)
T7	-0,22	0,17 (0,85)	-0,93 (1,60)
C3	-0,37	0,02 (0,75)	-0,98 (1,43)
C4	-0,29	-0,03 (0,68)	-0,71 (1,33)
T8	-0,25	0,24 (1,28)	-0,77 (1,56)
CP5	-0,01	0,17 (0,93)	-0,31 (1,13)
CP1	-0,41	-0,31 (0,63)	-1,10 (1,32)
CP2	-0,34	-0,25 (0,50)	-0,91 (1,40)
CP6	-0,14	0,22 (0,87)	-0,37 (1,15)
P7	-0,14	0,10 (0,86) **	-0,34 (1,16)
P3	-0,23	-0,15 (0,56)	-0,55 (0,96)
Pz	-0,08	0,11 (0,96)	-0,49 (1,16)
P4	-0,13	0,09 (0,52) **	-0,45 (0,89)
P8	-0,14	0,10 (0,76)	-0,65 (1,08)
O1	-0,35	-0,03 (0,68)	-0,71 (1,16)
Oz	-0,14	0,08 (0,72)	-0,64 (1,17)
O2	-0,21	0,11 (0,72) **	-0,44 (1,18)
Cz	-0,64	-0,57 (0,78)	-1,79 (1,62)

Table S2. MF modulation values in schizophrenia, bipolar and control groups. Modulation was significantly larger (i.e., more negative values) from baseline to response in

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

DOI: 10.1503/jpn.190032

controls as compared to both patient groups, implying a larger slowing in the controls (ANOVA with post-hoc comparisons, $p<0.05$; $p<0.01$; $p<0.005$)

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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	Yes	**No**	**Statistics (p)**
Lithium (bipolar only)	0.494(0.563)	0.558(0.616)	U=76, z=-0.823, p=0.430
Benzodiazepines (all patients)	0.176(0.677)	0.293(0.604)	U=659, z=-0.897, p=0.370
Benzodiazepines (bipolar only)	0.249(0.510)	0.527(0.626)	U=34, z=-1.304, p=0.192
Antidepressants	0.209(0.601)	0.255(9.654)	U=560, z=-0.622, p=0.534
Antidepressant (bipolar only)	0.212(0.361)	0.524(0.650)	U=32, z=-1.180, p=0.261

Table S3. Comparison of Spectral Entropy modulation values between patients receiving or not lithium, benzodiazepines and antidepressants. These comparisons were repeated in the bipolar group.

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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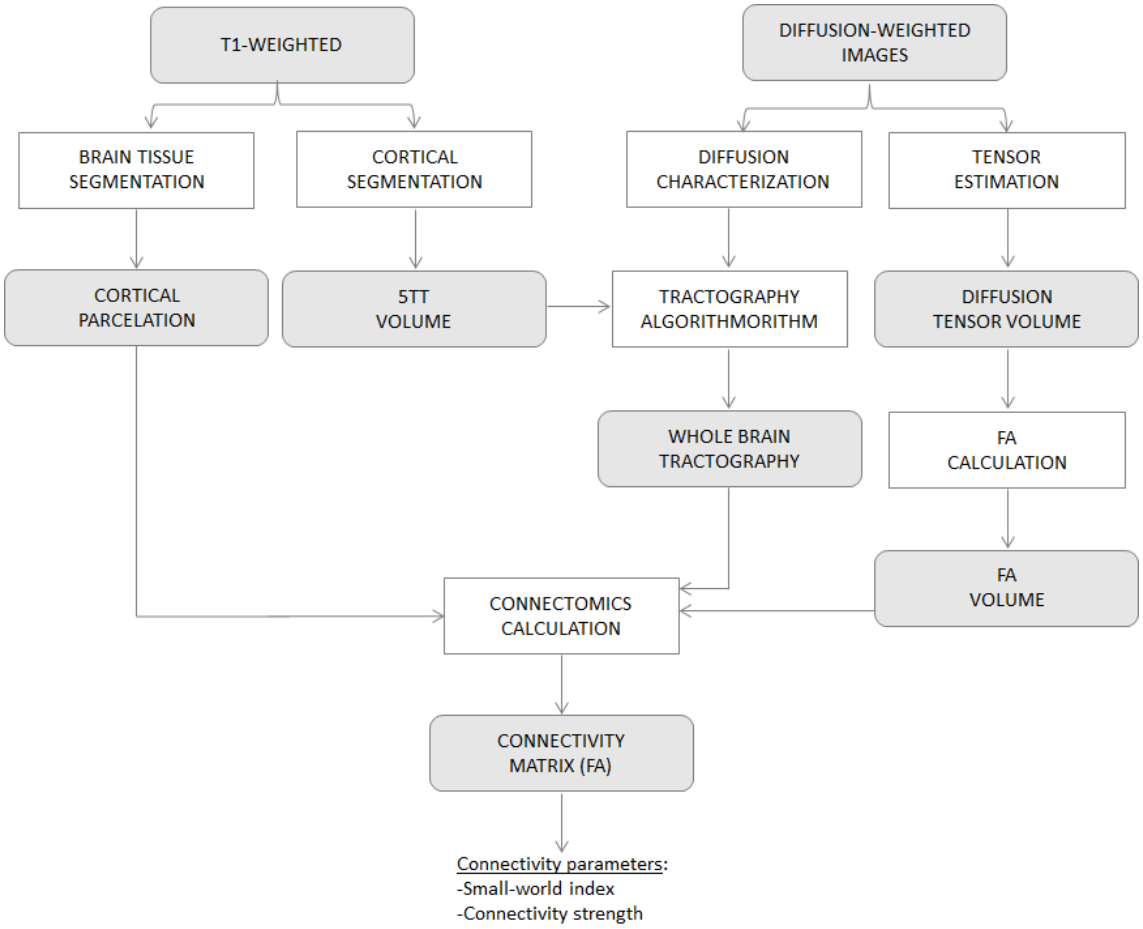

Figure S1: Processing pipeline yielding fractional anisotropy values to be used in graph-theory calculations of structural connectivity. Gray matter, white matter and CSF were separated, and subcortical gray matter structures were obtained. These structures were combined to form a "five-tissue-type" image (5tt). From the diffusion weighted images (DWIs), brain was then extracted. Afterwards, orientation distribution functions were estimated from the

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

DOI: 10.1503/jpn.190032

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diffusion data. and anatomically-constrained tractography was carried out (using the diffusion data and the 5tt obtained from the T1-weighted anatomical images).

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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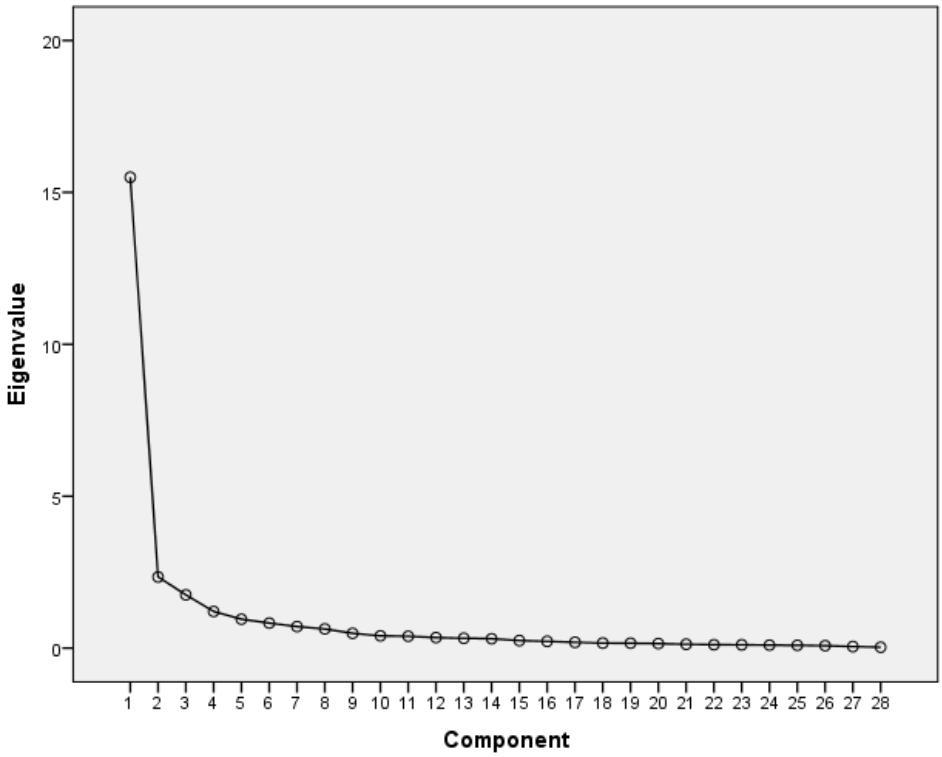

Figure S2. Scree plot for the factor analysis of Spectral Entropy modulation.

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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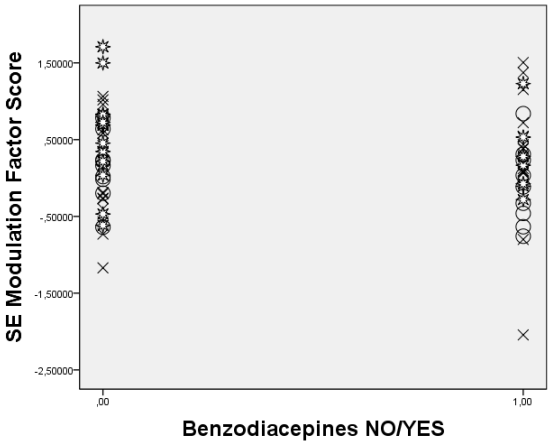

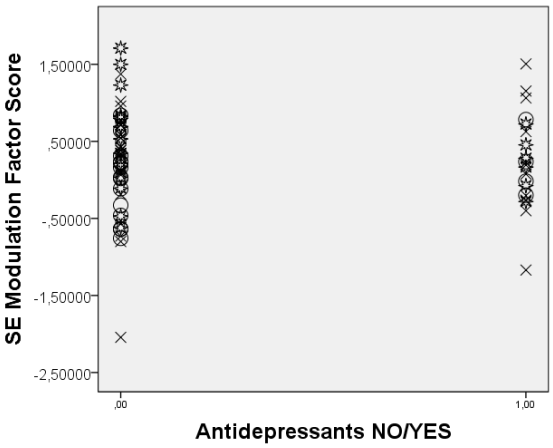

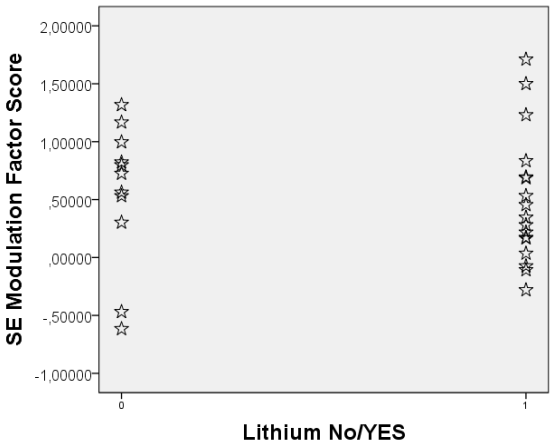

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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Figure S3: Spectral entropy modulation values in bipolar patients receiving or not lithium, and between patients receiving or not antidepressants and benzodiazepines. There were no significant differences between all patients considered together or bipolar patients alone depending on their treatment.

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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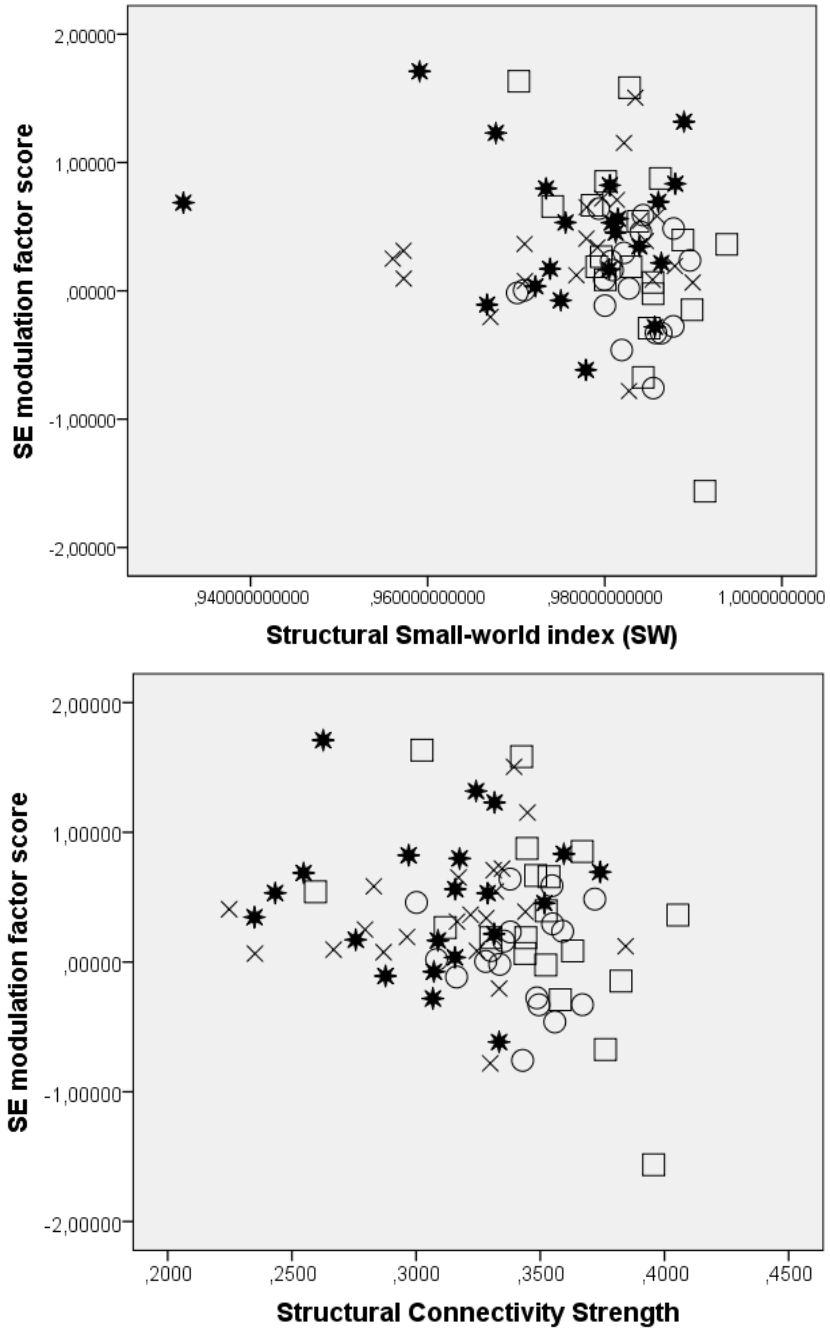

Figure S4. Relations between structural network parameters (derived from DTI) and SE modulation. These relations were

Appendix 1 to Molina V, Lubeiro A, de Luis Garcia R, et al. Deficit of entropy modulation of the EEG: A biomarker for altered function in schizophrenia and bipolar disorder? *J Psychiatry Neurosci* 2020.

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not statistically significant in either group. Crosses: chronic SZ; circles: FE SZ; stars: bipolar; squares: HC.