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Deficits of entropy modulation in schizophrenia are predicted by functional connectivity strength in the theta band and structural clustering

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ABSTRACT

Spectral entropy (SE) allows comparing task-related modulation of electroencephalogram (EEG) between patients and controls, i.e. spectral changes of the EEG associated to task performance. A SE modulation deficit has been replicated in different schizophrenia samples. To investigate the underpinnings of SE modulation deficits in schizophrenia, we applied graph-theory to EEG recordings during a P300 task and fractional anisotropy (FA) data from diffusion tensor imaging in 48 patients (23 first episodes) and 87 healthy controls. Functional connectivity was assessed from phase-locking values among sensors in the theta band, and structural connectivity was based on FA values for the tracts connecting pairs of regions. From those data, averaged clustering coefficient (CLC), characteristic path-length (PL) and connectivity strength (CS, also known as density) were calculated for both functional and structural networks. The corresponding functional modulation values were calculated as the difference in SE and CLC, PL and CS between the pre-stimulus and response windows during the task. The results revealed a higher functional CS in the pre-stimulus window in patients, predictive of smaller modulation of SE in this group. The amount of increase in theta CS from pre-stimulus to response related to SE modulation in patients and controls. Structural CLC was associated with SE modulation in the patients. SE modulation was predictive of negative symptoms, whereas CLC and PL modulation was associated with cognitive performance in the patients. These results support that a hyperactive functional connectivity and/or structural connective deficits in the patients hamper the dynamical modulation of connectivity underlying cognition.

1. Introduction

Mental functions are partially based on the dynamic coordination of cerebral networks (Dehaene and Changeux, 2011; Tanaka, 1996; Varela et al., 2001) whose interactions evolve in hundreds of milliseconds (Bressler and Tognoli, 2006; Sporns, 2011). The temporal resolution of electroencephalography (EEG) allows the assessment of this dynamic coordination, which can be applied to the study of functional underpinnings of mental disorders. Measurements summarizing the EEG properties and their modulation with cognition can be useful for that purpose. One of these measurements is Spectral Entropy (SE), a parameter derived from information theory that estimates regularity by quantifying the degree of uncertainty in a signal (Duff et al., 2013). Larger SE values correspond to more uniform spectra whose frequency content is broader (i.e., more random), and low SE values to spectra with only a few frequency components (i.e., more regular).

In schizophrenia, we have described a SE modulation deficit during a P300 task in response to relevant tones (Bachiller et al., 2014). SE decreased in healthy controls secondarily to task-related increased theta power, and both SE decrease and theta power increase were of smaller magnitude in patients (Bachiller et al., 2014), which seems coherent with the expected increase in theta band power during P300 (Mazaheri and Picton, 2005). Later, we replicated the same SE modulation deficit in schizophrenia in a larger and completely different

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sample (Molina et al., 2017a), showing its relation to cognition and symptoms. In these reports we defined modulation as the difference in SE values between the pre-stimulus and the response windows of the P300 task being performed by the subjects. Neither treatment dose nor illness duration were associated to the SE deficit, also found in first episode patients.

Given the apparent robustness of the SE modulation deficit, we considered it worthy to attempt to characterize it. This could help describing a reliable functional alteration in schizophrenia. Since cognition during P300 involves a global network rather than focal engagement (Bledowski et al., 2004), we hypothesized that the analysis of global properties of the functional network would help to identify underpinnings of the SE modulation deficit in schizophrenia. Global network properties can be assessed at system level using graph theory. Thus, parameters derived from graph-theory can help assessing both basal network properties predictive of SE modulation and properties of global network dynamics associated to SE modulation deficits.

Among the graph parameters of interest to this purpose, local clustering coefficient (*CLC)* is related to the degree of local connectivity. Specifically, clustering coefficient is the ratio between the number of triangles in which a node is included and the total number of possible triangles that include the node. This measure, when averaged across the network, indicates the segregation and local efficiency for information transfer. In turn, characteristic path length (*PL*) is the average of shortest distances for all possible pairs of nodes. Thus, *PL* is related to information integration across areas. Mean connectivity strength (*CS*, sometimes also known as density) in a weighted graph can be interpreted as the average of connections among nodes in a network. The application of these parameters to functional connectivity analyses is based on the degree of similarity of signals, based in turn on phase-locking values (PLV) of the signals between regions or (for the EEG) sensors. These parameters can be also applied to structural connectivity measurements derived from diffusion magnetic resonance imaging (dMRI), such as fractional anisotropy (FA), which may allow a description of the dependence of functional connectivity modulation on structural connectivity. Although a direct relation between both connectivity dimensions could seem intuitive, functional connections are found between regions without direct anatomical connections (Honey et al., 2009).

Our hypotheses are that functional (prior to cognitive activity) and structural graph-derived network measurements would predict task-related SE modulation and that the dynamics of functional network parameters would be associated to SE modulation. As in previous reports (Bachiller et al., 2014; Mazaheri and Picton, 2005) modulation will be defined and the corresponding EEG change (for SE and functional network parameters) associated to task performance. These ideas could reveal relevant insights on the functional deficits in schizophrenia. Based on previous findings supporting a smaller increase of theta power in patients in the response to target (Bachiller et al., 2014) and the relevance of theta power for the task used, the P300 (Mazaheri and Picton, 2005), we focused our analyses on the theta EEG band.

2. Subjects and methods

We included 48 schizophrenia subjects (of them, 23 first episodes (FE) and 87 healthy subjects with normal hearing. Patients were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. They were receiving stable doses of antipsychotic monotherapy. Of them, MRI data were also collected in 33 patients (20 males) and 24 controls (15 males). Out of the sample, 42 patients and 65 controls were included in a previous report on SE modulation deficit in schizophrenia (Molina et al., 2017a).

First episode patients were treated with antipsychotics for less than 72 h. prior to MRI and EEG data acquisition, with a wash-out period of 24 h prior to the acquisitions to avoid possible bias due to the selection of patients able to cooperate during EEG acquisition without prior treatment.

Table 1
Demographic, clinical and cognitive characteristics of patients and controls, as well as latency and amplitude of the P300 (P3b) potential. Between-group statistically significant differences were marked with asterisks: $^{***}p < 0.001$.

	Controls	*Patients*
Age (years)	30.51 (10.77)	33.58 (9.27)
Antipsychotic dose (CPZ equivalents)	N/A	377.92 (196.94)
Duration (months)	N/A	97.84 (116.94)
Sex	44/43	25/23
Positive symptoms	N/A	11.63 (3.39)
Negative symptoms	N/A	18.03 (7.52)
Total PANSS score	N/A	54.35 (18.56)
Verbal memory***	51.65 (8.26)	33.92 (12.74)
Working memory***	21.46 (3.90)	15.81 (5.01)
Motor speed***	68.59 (17.84)	58.14 (14.41)
Verbal fluency***	27.13 (5.33)	17.99 (5.70)
Performance speed***	68.79 (13.25)	42.83 (15.78)
Problem solving***	17.54 (2.72)	15.40 (4.64)
Total IQ***	111.83 (11.87)	91.22 (14.19)
WCST (perseverative errors)***	10.17 (5.81)	27.31 (47.43)
WCST (completed categories)***	5.79 (0.72)	4.39 (1.87)
P3b amplitude (microvolts)***	3.20 (1.76)	1.92 (1.21)
P3b latency (miliseconds)	472.28 (67.54)	461.53 (87.57)

Exclusion criteria were: (i) any neurological illness; (ii) history of cranial trauma with loss of consciousness; (iii) past or present substance abuse, except nicotine or caffeine (iv) intelligence quotient (IQ) smaller than 70; and (iv) for patients, any other psychiatric process, and (v) for controls, any psychiatric or neurological diagnosis or treatment.

Schizophrenia symptoms were scored using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Healthy controls were recruited through advertisements. Demographic and clinical data are shown in Table 1.

Cognitive data for both groups were collected using: the Wechsler Adult Intelligence Scale, WAIS-III (IQ), the Wisconsin Card Sorting Test (WCST; completed categories and percentage of perseverative errors), and the Spanish version of the Brief Assessment in Cognition in Schizophrenia Scale (BACS)(Segarra et al., 2011).

After receiving full printed information, subjects gave their written informed consent. The ethical committees of the Hospital Clínico de Valladolid endorsed the study.

2.1. EEG processing

2.1.1. EEG acquisition and preprocessing

EEG recordings were obtained following MRI scans, after a resting period of 30 minutes. Data were recorded using a 17-channel EEG system (BrainVision®, Brain Products GmbH). Active electrodes were placed in an elastic cap at Fp1, Fp2, F3, F4, F7, F8, C3, C4, P3, P4, O1, O2, T5, T6, Fz, Pz and Cz (international 10–20 system). Impedance was kept under 5 kΩ. Sampling frequency was 500 Hz. During EEG acquisition, each channel was referenced over Cz electrode and re-referenced to the average activity of all active sensors (Bledowski et al., 2004; Gomez-Pilar et al., 2018). Thirteen minutes of eyes-closed EEG was obtained during an auditory odd-ball 3-stimulus paradigm, which consisted of 600 random sequences of target (500 Hz-tone, probability 0.2), distractor (1000 Hz-tone, probability 0.2), and standard (2000 Hz-tone, probability 0.6) tones. The tone duration was 50 ms, rise and fall time being 5 ms and intensity being 90 dB. Inter-stimulus interval between tones randomly jittered between 1.16 and 1.44 s. The participants were asked to press a button whenever they detected the target tones. Target tones were considered ‘attended tones’ when they were followed by a button press. Only ‘attended’ target tones were taken into account for further analysis (Gomez-Pilar et al., 2015). Alertness differences across groups were controlled by comparing accuracy of target responses.

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