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Neurobiological underpinnings of cognitive subtypes in psychoses: A cross-diagnostic cluster analysis

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ABSTRACT

Schizophrenia and bipolar disorder include patients with different characteristics, which may hamper the definition of biomarkers. One of the dimensions with greater heterogeneity among these patients is cognition. Recent studies support the identification of different patients' subgroups along the cognitive domain using cluster analysis. Our aim was to validate clusters defined on the basis of patients' cognitive status and to assess its relation with demographic, clinical and biological measurements. We hypothesized that subgroups characterized by different cognitive profiles would show differences in an array of biological data. Cognitive data from 198 patients (127 with chronic schizophrenia, 42 first episodes of schizophrenia and 29 bipolar patients) were analyzed by a K-means cluster approach and were compared on several clinical and biological variables. We also included 155 healthy controls for further comparisons. A two-cluster solution was selected, including a severely impaired group and a moderately impaired group. The severely impaired group was associated with higher illness duration and symptoms scores, lower thalamus and hippocampus volume, lower frontal connectivity and basal hypersynchrony in comparison to controls and the moderately impaired group. Moreover, both patients' groups showed lower cortical thickness and smaller functional connectivity modulation than healthy controls. This study supports the existence of different cognitive subgroups within the psychoses with different neurobiological underpinnings.

1. Introduction

Schizophrenia is likely biologically heterogeneous (Brugger and Howes, 2017; Clementz et al., 2016; Lubeiro et al., 2016), which may explain the lack of a consistent replication of cerebral findings in this disorder. Such heterogeneity may also relate to the fact that schizophrenia can be considered as a syndrome, i.e., a cluster of symptoms and signs that may have different substrates, as it is the case in other branches of Medicine. The identification of clusters within it may help in defining biomarkers and personalizing treatments.

One avenue to this aim is the study of the biological and clinical correlates of subgroups defined based on cognitive performance. According to a recent systematic review, schizophrenia spectrum disorders may include three cognitive clusters: relatively intact, intermediate and severely impaired (Carruthers et al., 2019). When attending to studies of mixed diagnostic groups (schizophrenia and mood disorders), another review revealed a 4-cluster solution, differentiating two separate groups with intermediate impairment (Green et al., 2019). However, the study with the largest sample (to our knowledge) yielded a two cognitive clusters solution (Green et al., 2013). Although cognitive

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performance has a dimensional structure in the population, the possibility supported by those results of defining groups with severely and mildly handicapped cognition within schizophrenia may help in advancing to the definition of biologically relevant subgroups in this syndrome. Very low values in general cognitive performance, such as IQ, are indeed accepted as categorically different in spite of their continuity with normal performance.

Regions harboring genes with neurodevelopmental roles and genome-wide association to schizophrenia and related to neurocognitive putative endophenotypes have been reported (Greenwood et al., 2019). Furthermore, metabolic and structural brain heterogeneity across subgroups of schizophrenia patients has been described. In particular, a recent meta-analysis revealed a widespread higher regional heterogeneity of brain structure in schizophrenia compared with healthy controls (Brugger and Howes, 2017). Such heterogeneity is coherent with the description of subgroups characterized by different structural profiles in this syndrome. Lubeiro et al. (2016) revealed the existence of a biologically distinct group within the schizophrenia syndrome characterized by increased mean cortical curvature values, low cortical thickness, reduced thalamic and cingulate metabolism and linked to persistent negative symptoms. Based on white matter abnormalities in first-episode patients, two schizophrenia subgroups were revealed, with more severe negative symptoms in the group with larger abnormalities (Sun et al., 2015). Also in this line, a recent study aimed to identify MRI-based psychosis subtypes revealed the existence of two clusters, one anatomically spared and another with significant anatomical alterations linked to decreased cortical thickness and area values, lower subcortical volumes and higher cortical curvature in some regions (Planchuelo-Gómez et al., 2020). These studies give support to the existence of diverse biologically based clusters within the schizophrenia syndrome. However, the neurobiological underpinnings of cognitive subtypes in schizophrenia have received little attention to date. Woodward and Heckers (2015) compared brain structure between neuropsychologically normal and impaired psychotic patients. The impaired group showed smaller total brain volume, less gray matter (GM) volume in frontal, temporal, and subcortical regions, and widespread white matter volume loss. Clementz et al. (2016) used cognitive, neuroanatomical and neurophysiological variables to define biotypes and reported three subgroups. The first, with a larger schizophrenia proportion, showed worse cognition and widespread GM deficits. Weinberg et al. (2016) compared brain volumes between cognitive clusters of schizophrenia patients and found widespread volumetric reductions in the cognitively more deteriorated group.

These studies suggest that cognitive subtypes may help in defining biotypes with differential biological characteristics in the psychotic syndrome. To this end, it is of interest to assess the relation of these putative subgroups with measurements known to be altered in schizophrenia and related to the global brain function, since higher cerebral functions likely involve widespread patterns of cerebral activity (Varela et al., 2001). Based on previous literature, we considered of particular interest structural connectivity based on diffusion magnetic resonance (Zhou et al., 2015) and the modulation of electroencephalogram (EEG) with cognitive activity (Molina et al., 2020). Our hypothesis was that subgroups characterized by different cognitive profiles would show differences in those biological data.

2. Materials and methods

In order to define patients' subgroups our sample included 198 patients, 127 with chronic schizophrenia, 42 with first episodes (FE) of schizophrenia and 29 with type I bipolar disorder (BD; of them 20 with psychotic features). Patients were diagnosed by one of the experienced psychiatrists in the group (OMS, JSF and VM) according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders 5th edition, taking into account current mental state, clinical records and relatives' information. We also included 155 healthy controls (HC) to compare the cognitive and biological characteristics of the resulting subgroups. Of them, EEG data were available in 114 patients and 68 controls, and magnetic resonance data (including structural and fractional anisotropy (FA) data) in 81 patients and 32 controls. Finally, social cognition data were available in 85 patients and 32 controls.

This sample overlaps in part (89 patients and 34 HC) with those in a previous report where we looked for MRI-based clusters in schizophrenia and BD (Planchuelo-Gómez et al., 2020).

Exclusion criteria were a) intelligence quotient under 70; b) present or past substance dependence (excluding caffeine and nicotine); c) head trauma with loss of consciousness; d) neurological or mental diagnosis different to schizophrenia or bipolar disorder (patients); e) any current neurological or psychiatric diagnosis (controls); f) any other treatment affecting central nervous system. All participants provided written informed consent after full written information. The local ethics committee endorsed the study. This work complies with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

2.1. Symptoms assessment

Positive and negative symptoms were scored by using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Brief Negative Symptoms Scale (BNSS) (Kirkpatrick et al., 2011).

2.2. Cognitive assessment

Cognition was assessed using the Spanish version of the Brief Assessment of Cognition in Schizophrenia (BACS) (Segarra et al., 2011), including performance in verbal memory (list learning), working memory (digit span), motor speed (token motor task), verbal fluency (categories), attention and processing speed (symbol coding) and executive function and problem solving (Tower of London), and the Wisconsin Card Sorting Test (Chelune and Baer, 1986) (WCST; percentage of perseverative errors). Global Intelligence Quotient (IQ) was evaluated with the Wechsler Adult Intelligence Scale III (Fuentes Durá et al., 2010).

2.3. Social cognition assessment

We assessed social cognition using the Mayer-Salovey-Caruso emotional intelligence test (MSCEIT) (Mayer et al., 2003) and the Spanish Group for Schizophrenia Treatment Optimization test (*Grupo Español para la Optimización del Tratamiento de la Esquizofrenia*, GEOPTE) (Sanjuan et al., 2003) tools. The MSCEIT scale is a widely used measure of four dimensions of emotional intelligence and the GEOPTE scale evaluates relational and behavioral aspects of social cognition, including scores from a relative.

2.4. Structural data

2.4.1. MRI acquisition

High resolution 3D T1-weighted and diffusion-weighted MRI data were acquired using a Philips Achieva 3 T MRI unit (Philips Healthcare, Best, The Netherlands) with a 32-channel head. For the anatomical T1-weighted images, acquisition parameters were: Turbo Field Echo (TFE) sequence, repetition time (TR) = 8.1 ms, echo time (TE) = 3.7 ms, flip angle = 8°, 256 × 256 matrix size, 1 × 1 × 1 mm^3 of spatial resolution and 160 slices covering the whole brain. Diffusion-weighted images (DWI) were acquired using the next parameters: TR = 9000 ms, TE = 86 ms, flip angle = 90°, 61 gradient directions, one baseline volume, b-value = 1000 s/mm^2, 128 × 128 matrix size, 2 × 2 × 2 mm^3 of spatial resolution and 66 axial slices covering the whole brain. T1 and diffusion-weighted scans were acquired during the same session, starting with the T1 scan followed by the diffusion-weighted scan.

2.4.2. MRI processing

From the T1 images, automatic cortical parcellation was performed using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) version 6.0.0

(Dale et al., 1999). From the parcellation, average cortical thickness and subcortical GM volume were extracted, according to the Desikan-Killiany atlas (Desikan et al., 2006). We restricted our analysis to 14 bilateral cortical regions, thalamus, caudate, putamen and pallidum, as in our previous work (Lubeiro et al., 2016). The cortical regions were the caudal anterior cingulate gyrus, caudal middle frontal gyrus, cuneus, inferior parietal cortex, medial orbito-frontal cortex, para hippocampal gyrus, pars orbitalis, pars triangularis, precentral gyrus, rostral anterior cingulate gyrus, rostral middle frontal gyrus, superior frontal cortex, superior temporal cortex, hippocampus and insula.

2.4.3. Diffusion Tensor Imaging (DTI) data

FA in connections between pairs of regions was obtained from the diffusion MRI data. The processing pipeline is fully described elsewhere (Lubeiro et al., 2017). Briefly, an anatomically-constrained tractography was performed using the MRtrix software after obtaining five-tissue type images from each T1-weighted volume (Smith et al., 2012), a mask from the diffusion-weighted volumes, and the orientation distribution function from the diffusion data. The FA was calculated from the estimated diffusion tensor. The FA value is considered as an index of fiber myelination in the corresponding white matter tract, thus higher FA values in the tracts linking cerebral regions would imply better structural connectivity between the regions connected by those tracts. The analyzed connections were focused on regions from the prefrontal cortex (rostral middle frontal and superior frontal gyri) and the limbic system (entorhinal cortex, parahippocampal gyrus and hippocampus). Connections in which null values were found in a third (or more) of the subjects were discarded. A total of 46 homolateral connections were analyzed.

2.5. EEG data

EEG data were recorded from 32 sensors during an auditory oddball task following the international 10-10 system. In previous studies we identified a deficit of brain activity modulation with cognition in schizophrenia patients during a P300 task using the Spectral Entropy (SE) parameter (Bachiller et al., 2014; Gomez-Pilar et al., 2018a; Molina et al., 2018). The concept of entropy originally comes from the field of thermodynamics and involves the uncertainty of information in terms of disorder, diversity and discrepancy (Bachiller et al., 2014). In this particular context, SE is a measure of the entropy applied over the EEG power spectrum: it is an estimation of the flatness of the spectral content (Scheeringa et al., 2011). Thus, SE can be considered an index of signal irregularity, since it measures how its spectral components are distributed (Gomez-Pilar et al., 2018a). For example, a signal with a large range of spectral components, e.g. white noise, has a flat power spectral density and, therefore, high values of SE. On the contrary, a signal with few spectral components, e.g. a pure sinusoidal wave, yields minimum SE values. In the present study, the SE was computed from the normalized continuous wavelet transform (CWT), which is a form of time-frequency representation of a signal that is conceptually related to the short-term Fourier transform (Núñez et al., 2017). The CWT allows for better detection of dynamic ERP components due to its balance between frequency and time resolution (Núñez et al., 2017). The time-dependent wavelet-based SE can be defined as follows:

$$SE(t) = -\frac{1}{\log(M)} \cdot \sum_f WS(t,f) \cdot \log[WS(t,f)]$$

where SE is the spectral entropy (as a function of time) and WS is the normalized wavelet scalogram. The SE was computed in two windows: baseline (300 ms before stimulus to stimulus onset) and response (150 ms to 450 ms from the stimulus onset, centered around the P300 peak). Afterwards, it was averaged in each of the two windows.

Further details of the well-validated oddball task can be found in our previous studies (Gomez-Pilar et al., 2018b). In addition, in order to illustrate the behaviour of the SE, a simulation using a synthetic signal was performed (see Fig. S1 in Supplementary material).

SE modulation was computed as the SE difference between response and pre-stimulus windows (Gomez-Pilar et al., 2018b), providing a measure of the degree of the signal regularity change across time. Since a decrease on SE in the response window has been robustly observed as normal behaviour in normal controls, negative SE modulation values are expected in these subjects (Bachiller et al., 2014; Gomez-Pilar et al., 2018a; Molina et al., 2018). EEG data also allowed us to calculate three graph-theory parameters to characterize global connectivity properties of the brain network: network segregation using clustering coefficient (CLC), network integration by means of path length (PL) and connectivity strength by means of network density (D), as in previous work (Gomez-Pilar et al., 2018a). Complete details of its calculation are found in the Supplementary material.

2.6. Data analyses

For descriptive purposes, we performed a Principal Component Analysis (PCA) on the cognitive variables described above to summarize their information, excluding the global IQ. We computed the least-squares fitted linear model, using the first two PCA scores as the response variable and the patient groups as the predictor variable. The model residuals were displayed together for a descriptive analysis in Fig. S2.

For the clustering, we employed the K-means cluster algorithm using the original cognitive variables, i.e., the PCA scores were not used in this process. The silhouette method was used to obtain the optimal number of clusters (Rousseeuw, 1987), comparing the silhouette width for a number of clusters between 1 and 10 (both included). To assure the number of clusters, we employed the values from 25 additional indices available on the NbClust package (Charrad et al., 2014). For a specific number of clusters, K-means was performed using 50 initial random centroids and the centroid with the best silhouette profile was chosen. To verify the clusters obtained with the silhouette method, we also employed the hierarchical clustering technique. This clustering process was implemented in R statistical software, version 3.5.2. Clusters (using K-means results) characterization on demographic and clinical variables was determined using analysis of variance (ANOVA), or *t*-test when applicable or chi squared for categorical comparisons. Cognitive and biological variables were analyzed using analysis of covariance (ANCOVA) adjusting the results by age, considering the possible impact of age in cognition, especially in patients. Post-hoc tests with Bonferroni adjustment were conducted in order to compare Clusters of patients with HC. In the ANCOVA analyses, to consider the effect of age on two-by-two comparisons, Tukey-Kramer post-hoc tests were performed. Since cortical thickness, SE modulation and frontal connectivity included many different variables potentially colineal, these variables were reduced to principal components using PCA. The number of factors retained was determined by scree plot examination. These data analyses were performed using SPSS statistical software, version 23 for Windows (IBM). A database with the main data supporting the present results is available (Mendeley Data doi:10.17632/bmxs325v88.1).

3. Results

3.1. Cluster solutions

The analysis yielded two groups based on their neurocognitive profile, i.e. severely impaired (Cluster 1 from here on) and moderately impaired (Cluster 2), integrated of 93 and 105 patients respectively. According to the majority rule, the optimal number of clusters was also two, being this number of clusters obtained in 11 out of 26 indices, including the silhouette index. Regarding the second clustering method, the hierarchical clustering, 92.93% (184/198) of the subjects were equally classified with respect to the silhouette technique. Each

Table 1
Demographic and clinical characteristics by Clusters.

	Control	Cluster 1	Cluster 2	Test statistic	p value
Age, years	37.84 (9.41)	41.31 (11.44)	36.91 (10.95)	F(2,339) = 4.622	0.010*,a,b,d
Sex, M/F	86/69	56/37	67/38	χ^2 = 1.850 (2)	0.397
Education level, years	17.31 (5.27)	11.52 (3.69)	14.23 (4.20)	F(2,237) = 32.021	<0.0001*,a,b,c,d
Illness duration, months	–	175.30 (144.114)	128.77 (124.558)	t = 2.019	0.045*,d
Diagnoses S/FE/BD	–	74/17/7	58/25/22	χ^2 = 9.543 (2)	0.008*,d
Lifetime hospitalizations	–	3.89 (5.65)	3.29 (6.68)	t = 0.501	0.617
CPZ equivalents	–	618.17	370.33	t = 1.866	0.064
PANSS positive	–	13.61 (5.44)	11.60 (4.72)	t = 2.393	0.018*,d
PANSS negative	–	19.56 (8.60)	14.04 (6.42)	t = 4.450	<0.0001*,d
PANSS total	–	64.24 (22.93)	49.21 (19.31)	t = 4.289	<0.0001*,d
BNSS total	–	31.13 (16.29)	19.07 (16.48)	t = 3.278	0.002*,d

Data are given as mean (standard deviation).
S, chronic schizophrenia.
* $p < 0.05$.
[a] Significant post hoc Bonferroni-adjusted test results.
[b] Healthy controls significantly different from Cluster 1.
[c] Healthy controls significantly different from Cluster 2.
[d] Significant differences between both patients' Clusters.

diagnosis was represented in both Clusters, although not evenly distributed (see Table 1). The comparison of the optimal number of clusters with diverse indices is shown in Fig. S3. The complete cluster classification comparing the silhouette and the hierarchical clustering techniques is shown in Table S1. The average silhouette width for diverse number of clusters and the clusters silhouette plot for two clusters can be seen in Figs. S4–5. In Fig. 1 the residuals plot with the first two PCA scores (summary of the cognitive variables employed in the analysis) and the identified Clusters are shown.

3.2. Demographic comparison by Clusters

There were no significant differences between patients and HC in sex distribution. Groups differed significantly on age. Cluster 1 patients were significantly older than Cluster 2 patients (adjusted p = 0.012) and HC (adjusted p = 0.042). Patients in Cluster 2 did not differ in terms of age with HC. Cluster 1 patients had lower educational attainment than HC and Cluster 2 patients. Cluster 2 had also lower educational attainment than HC (Table 1).

3.3. Clinical characteristics by Clusters

Cluster 1 patients showed longer illness duration. Both Clusters did not differ in number of lifetime hospitalizations nor in daily chlorpromazine equivalent dose (Table 1), neither in the use of benzodiazepines (χ^2 = 1.299, df = 1, p = 0.254), anticonvulsant drugs (χ^2 = 0.704, df = 1, p = 0.401), lithium (χ^2 = 0.417, df = 1, p = 0.471) nor antidepressants (χ^2 = 0.030, df = 1, p = 0.863). Cluster 1 showed significantly higher positive, negative and total PANSS and BNSS scores.

3.4. Cognitive characteristics by Clusters

All cognitive scores showed significant differences between patients Clusters and HC (Table 2 and Fig. 2). Cluster 1 performed significantly worse on all cognitive domains than Cluster 2 and HC (all adjusted p_s < 0.0001). Furthermore, Cluster 2 performed significantly worse on all cognitive domains than HC except motor speed and problem solving.

Correlations between antipsychotic doses with BACS scores were non-significant (−0.151 < r < 0.140, p = n.s.), and marginally significant with percent of perseverative errors (r = −0,227, p = 0.057).

3.5. Social cognition

When compared with healthy controls, both patients' subgroups showed significantly worse social cognition without differences between them (Table 2).

3.6. EEG modulation by Clusters

The first principal component for SE modulation accounted for 55% of variance (eigenvalue 15.95). All sensors positively correlated with this factor (Table S2). Thus, higher factor scores represent lesser decrease in SE from pre-stimulus to response windows, i.e., lesser modulation. Both Clusters showed significantly smaller SE modulation than HC,

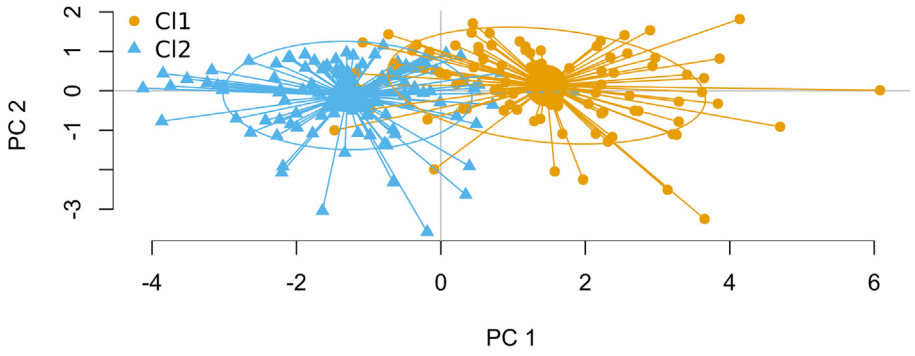

Fig. 1. Scatter plot of the distribution of the values of the two first principal components (PC) for the cognitive variables in the identified clusters. Circles represent patients from Cluster 1 (Cl1) and triangles patients from Cluster 2 (Cl2). The big circle and triangle represent the centroids for each Cluster. The ellipsoids have a radius of one standard deviation.

Table 2
Cognitive characteristics by Clusters.

	Control	Cluster 1	Cluster 2	Test statistic	p value
Verbal memory	52.25 (8.67)	30.31 (9.25)	41.51 (9.28)	F (2,338) = 173.55	<0.0001*,a,b,c,d
Working memory	22.55 (4.28)	13.95 (5.05)	18.46 (3.93)	F (2,338) = 106.432	<0.0001*,a,b,c,d
Motor speed	74.01 (14.77)	42.12 (13.14)	70.84 (12.19)	F (2,338) = 158.964	<0.0001*,a,b,d
Verbal fluency	27.29 (5.70)	16.65 (4.54)	21.99 (5.54)	F (2,338) = 109.094	<0.0001*,a,b,c,d
Processing speed	62.83 (12.15)	30.03 (10.43)	48.78 (10.56)	F (2,338) = 252.10	<0.0001*,a,b,c,d
Problem solving	17.65 (3.29)	12.66 (5.25)	17.26 (2.87)	F (2,338) = 53.23	<0.0001*,a,b,d
Executive function (WCST %pe)	10.65 (6.15)	21.02 (10.57)	15.92 (9.81)	F (2,338) = 41.15	<0.0001*,a,b,c,d
Total IQ	115.84 (11.48)	84.94 (13.38)	97.46 (13.26)	F (2,165) = 82.64	<0.0001*,a,b,c,d
MSCEIT total	122.59 (11.93)	91.86 (24.21)	101.92 (20.54)	F (2,112) = 18.37	<0.0001*,a,b,c
GEOPTE total	19.99 (2.57)	34.31 (7.89)	30.71 (10.66)	F (2,81) = 16.615	<0.0001*,a,b,c

Data are given as mean (standard deviation).
WCST % pe, percentage of perseverative errors in the Wisconsin Card Sorting Test.
* $p < 0.0001$.
[a] Significant post hoc Tukey-Kramer test results.
[b] Healthy controls significantly different from Cluster 1.
[c] Healthy controls significantly different from Cluster 2.
[d] Significant differences between both patients Clusters.

without differences between them (Fig. S6). Table 3 summarizes biological data.

3.7. MRI parameters by Clusters

The first principal component of cortical thickness accounted for 49.25% of variance (eigenvalue 13.79), with all regions directly related to this factor except for caudal anterior cingulate cortex and parahippocampal cortex (Table S3). Thus, higher values in this factor represent larger global cortical thickness. Both Clusters showed significantly lower thickness than HC, without differences between them (Table 3 and Fig. S7). Regarding to frontal structural connectivity, the PCA yielded two principal components which accounted for 36.08% and 8.12% of variance (eigenvalues 10.82 and 2.44), respectively. The first component reflected the FA of white matter tracts connecting medial frontal cortex with caudate, insula and anterior cingulate cortex. The second was contributed by FA of tracts connecting superior frontal cortex with hippocampus, thalamus, caudate and insula (Table S4). Cluster 1 showed significant lower values of the first component than Cluster 2 and HC (i.e., lower FA values in the corresponding tracts). This was also found in Cluster 2 patients when compared with HC (Table 3 and Fig. S8).

3.8. Functional connectivity

We found significantly higher pre-stimulus connectivity strength (CS) in Cluster 1 compared to both Cluster 2 and HC, thus a hypersynchronic state. We also found a higher increase from pre-stimulus (i.e., a higher CS task-related increase) in HC compared to both patients' subgroups (Table 3 and Fig. S9A and B).

3.9. Subcortical volumes

Cluster 1 patients showed bilaterally lower thalamus volumes compared to Cluster 2 patients and HC. There were no significant differences between the latter. Additionally, Cluster 2 showed higher left caudate volume than Cluster 1 and HC, and higher right caudate volume than Cluster 1. Finally, Cluster 2 showed higher bilateral putamen volume than Cluster 1 (Table 3 and Fig. S10).

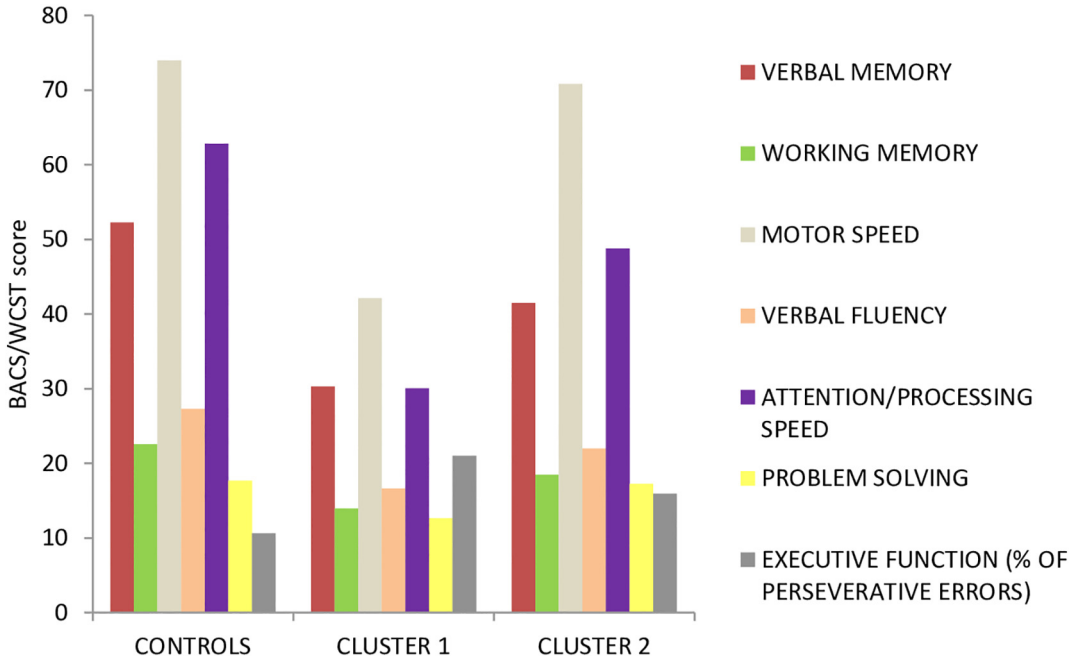

Fig. 2. Cognitive profiles for HC, Cluster 1 and Cluster 2 patients.

Table 3
Biological characteristics by Clusters.

	Control	Cluster 1	Cluster 2	Test statistic	p value
EEG modulation	−0.39 (1.35)	0.26 (0.59)	0.22 (0.63)	F (2,177) = 8.682	0.0002*,a,b,c
Cortical thickness	0.55 (0.83)	−0.40 (0.97)	−0.10 (0.98)	F (2,109) = 11.76	<0.0001*,a,b,c
Fractional anisotropy					
PC1	0.603 (0.859)	−0.631 (0.983)	0.041 (0.861)	F (2,106) = 16.51	<0.0001*,a,b,c,d
PC2	0.035 (1.033)	−0.169 (1.034)	0.085 (0.966)	F (2,106) = 0.691	0.503
PC3	0.133 (1.173)	−0.069 (0.850)	−0.034 (0.990)	F (2,106) = 0.360	0.699
Pre-stimulus					
Clustering coefficient	1.0071 (0.0042)	1.0095 (0.0077)	1.0072 (0.0045)	F (2,177) = 2.755	0.066
Path length	1.1017 (0.0262)	1.1084 (0.0453)	1.1002 (0.0223)	F (2,177) = 0.781	0.460
Density	0.3524 (0.0357)	0.3772 (0.0486)	0.3571 (0.0363)	F (2,177) = 5.157	0.007*,a,b,d
Modulation					
Clustering coefficient	0.0050 (0.0060)	0.0015 (0.0043)	0.0012 (0.0039)	F (2,177) = 12.114	<0.0001*,a,b,c
Path length	0.0178 (0.0315)	0.0034 (0.0243)	0.0070 (0.0190)	F (2,177) = 5.049	0.007*,a,b,c
Density	0.0639 (0.0451)	0.0119 (0.0273)	0.0187 (0.0236)	F (2,177) = 41.637	<0.0001*,a,b,c
Subcortical volumes					
L thalamus	7702.72 (820.55)	6741.42 (813.75)	7398.57 (879.59)	F (2,109) = 13.16	<0.0001*,a,b,d
R thalamus	7233.56 (730.39)	6472.23 (662.94)	7027.81 (832.49)	F (2,109) = 10.14	<0.0001*,a,b,d
L hippocampus	4110.22 (477.01)	3692.98 (404.71)	4109.92 (432.67)	F (2,109) = 11.29	<0.0001*,a,b,d
R hippocampus	4240.73 (436.51)	3831.05 (463.05)	4216.48 (405.86)	F (2,109) = 10.30	<0.0001*,a,b,d
L caudate	3309.05 (443.34)	3303.95 (522.95)	3575.12 (635.35)	F (2,109) = 4.57	0.012*,a,c,d
R caudate	3423.02 (454.94)	3413.16 (463.53)	3673.26 (643.71)	F (2,109) = 4.156	0.018*,a,d
L putamen	4823.74 (631.94)	4625.43 (617.29)	5059.27 (703.50)	F (2,109) = 5.928	0.004*,a,d
R putamen	4806.52 (648.56)	4609.96 (609.79)	5002.35 (695.47)	F (2,109) = 4.821	0.010*,a,d

Data are given as mean (standard deviation).
EEG Modulation and Cortical Thickness are expressed as first principal component values. Volumes are expressed in mm^3.
PC1, PC2, PC3, first, second and third principal components respectively; L/R, left, right, respectively.
* $p < 0.05$.
[a] Significant post hoc Tukey-Kramer test results.
[b] Healthy controls significantly different from Cluster 1.
[c] Healthy controls significantly different from Cluster 2.
[d] Significant differences between both patients Clusters.

Cluster 1 patients also showed bilaterally lower hippocampal volumes that HC and Cluster 2 patients. This mentioned here because the FreeSurfer tool groups it with subcortical structure despite being allocortical.

For a summary of post-hoc comparison results in all variables see Table S5.

4. Discussion

Our cluster analysis of cognitive data revealed a severely impaired and a moderately impaired patients group, supporting the possibility of defining subgroups within the psychotic syndrome (including schizophrenia and bipolar disorder, at least) which might have some biological validity. The existence of these groups could help explaining the co-occurrence of functional and anatomical cerebral abnormalities in schizophrenia and BD and its lack of sensitivity and specificity to characterize these diagnoses. The higher heterogeneity of many structural findings in schizophrenia as compared to HC (Brugger and Howes, 2017) is coherent with the coexistence of several biotypes within this syndrome, as suggested by our findings.

Our results are coherent with previous studies. Woodward and Heckers (2015) classified 101 schizophrenia or schizoaffective and 30 BD patients according to predefined criteria into neuropsychologically normal or impaired (divided into compromised and deteriorated according to premorbid IQ estimations), and assessed its structural differences. Interestingly, impaired patients showed GM decreases in hippocampus, thalamus and frontal and temporal lobes, similarly to our Cluster 1. In this line, Weinberg et al. (2016) carried out a study in order to identify cognitive subtypes of schizophrenia and subsequently compared brain volumes among subtypes, also finding reduced hippocampal and gray matter volumes in the patients who made up the cognitive severely deteriorated cluster.

Our data are also in line with the inverse relation between Brodmann's area 9 GM volume and performance on the WCST and part B of the Trail Making Test (Bonilha et al., 2008), as well as with the relations in FE of schizophrenia between deficits in hippocampal volume and working memory and orbitofrontal volume and executive functions (Guo et al., 2014). Verbal memory was associated in schizophrenia but not in healthy controls to hippocampal volume, according to a recent meta-analysis (Antoniades et al., 2018). In the context of our data and others (Woodward and Heckers, 2015), these results might be coherent with the coexistence of groups within the schizophrenia syndrome with high and low cognitive deficits respectively associated to large and small anatomical alterations. Moreover, our findings suggest these alterations could already be present in some FE patients, since the severely impaired group included a proportion of them. This is in line with other studies revealing similar impaired cognitive profiles in FE and multiple-episode patients (Sauvé et al., 2018).

One potential limitation of data-driven methods to classify cognitive subgroups in psychosis is the use of different neurocognitive measures between studies. For example, using the MATRICS Consensus Cognitive Battery (Kern et al., 2008) a 3-cluster solution was reported in a large sample (Van Rheenen et al., 2017). The difference with our 2-cluster solution may relate to the inclusion of social cognition and visual learning in the MATRICS but not in the BACS. However, other authors have used a partially similar approach to ours by including BACS scores and other cognitive and neurophysiological measurements in cluster definition on a large sample of affective and non-affective psychoses (Clementz et al., 2016). They reported three biotypes, two with a significant cognitive impairment and one cognitively spared. Remarkably, the two first biotypes showed a higher proportion of non-affective psychoses and prominent gray matter reductions in cortex, basal ganglia and thalamus, similar to our findings.

While most groups aiming to identify neuropsychological subgroups reported a 3-groups solution, including a cognitively preserved cluster, our solution only reveals one moderately and one severely impaired Cluster. Data inspection suggests that a proportion of our patients have a cognitive performance like that of HC. Therefore, a 3-cluster solution might arise with a higher sample size. This however does not invalidate the identification of a Cluster with large cognitive deficit and

associated biological characteristics. According to our data some of these traits reported in schizophrenia, such as hippocampal or thalamic volume deficits (Haukvik et al., 2018; Okada et al., 2016; Penadés et al., 2019; Van Erp et al., 2016) or increased global functional connectivity (Cea-Cañas et al., 2020) may instead be found only in cognitively impaired patients.

Higher functional connectivity strength in Cluster 1 is coherent with an increased cortical excitation, which would translate in an increased average synchrony of EEG signal. This may be in turn consistent with a deficit of inhibitory activity as described for schizophrenia in the cortex and proposed to underlie cognitive deficits in this syndrome (Gonzalez-Burgos and Lewis, 2012; Lewis et al., 2012). Again, our data may suggest that this deficit might be characteristic of a patient's subpopulation. The higher synchrony during task performance (i.e., higher CS) in Cluster 1 patients is coherent with the finding of an increased hippocampal activity during successful encoding in a memory task in schizophrenia patients (Pirnia et al., 2015). Both Clusters showed a similar deficit in EEG activity modulation during a cognitive task. This is a replicated trait in different schizophrenia populations (Bachiller et al., 2014; Molina et al., 2020, 2018), and its presence in both Clusters suggests that different cerebral mechanisms may contribute.

Our data may also be coherent with the genetic evidence supporting an association between cognitive phenotypes and genetic variants. Genetic risk factors in schizophrenia and BD are multiple (Horwitz et al., 2019). Considering our data in the context of the association described between cognitive phenotypes and genetic variation in risk genes (Greenwood et al., 2019), genetic variation might underpin patients' Clusters.

In a previous study in a completely different population, we used neuroanatomical data to generate patients' clusters in schizophrenia and BD (Lubeiro et al., 2016). Although cognitive data were not available there, some similarities with the present results could be mentioned. A group with higher cortical curvature and lower cortical thickness, as well as with smaller thalamic volume and activity was identified. Since cortical curvature seems associated to cortico-cortical FA (Lubeiro et al., 2017), this subgroup may overlap with the cognitively impaired cluster in the present study. Similarly, in a completely different sample overlapping in part with the present one, we described that a cluster could be found in schizophrenia and BD primary characterized by global cortical thinning associated to cognitive deficit (Planchuelo-Gómez et al., 2020).

Although not statistically significant, Cluster 1 patients received higher antipsychotic doses than Cluster 2 patients, likely an effect of the higher positive symptoms scores in the former. However, this is not likely to be the cause driving patients' classification, since correlations between cognitive performance and antipsychotic dose were non-significant. Moreover, antipsychotics, at least in this range, are unlikely to affect cognitive performance (MacKenzie et al., 2018).

The present study has several limitations. First, a larger sample would be of great interest in order to reveal further valid clusters. In addition to a larger sample size, we did not replicate our findings in an independent sample to assure the generalization of the two clusters that we identified. Anyway, we obtained similar classification results employing two different clustering methods, which supports our results. Additionally, MRI and EEG data were available only for a subset of cases. Although it would have been desirable to have these data available in all subjects, the consistency of our results with previous studies examining cerebral differences in cognitive subtypes of psychotic patients (Weinberg et al., 2016; Woodward and Heckers, 2015) suggests that a larger sample would not have lead into different results.

5. Conclusions

In conclusion, our study supports segregating at least two groups within the schizophrenia syndrome based on cognitive performance and with different biological underpinnings. This would mean that not all schizophrenia patients but some cases within them may be characterized by biological substrates previously ascribed to this syndrome, such as hippocampal volume reductions or, perhaps, inhibitory dysfunction. It would be important to better clarify cognitive subgroups in terms of disease outcome profiles, response to treatment and stability over the time, purposes for which longitudinal studies would be appropriate. Further studies are necessary to replicate and refine these findings.

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CRediT authorship contribution statement

V. Molina and I. Fernández-Linsenbarth were responsible for the study design, statistical analysis and drafting, editing and final approving of the manuscript. I. Fernández-Linsenbarth, A. Arjona-Valladares, A. Díez, J. Benito-Sánchez, A. Pérez-Laureano, D. González-Parra, C. Montes-Gonzalo, R. Melero-Lerma and S. Fernández-Morante were responsible for data acquisition. A. Planchuelo-Gómez and R. de Luis conducted cluster and DTI analysis. A. Planchuelo-Gómez was also responsible for drafting and revising some parts of the manuscript. J. Gómez-Pilar and P. Núñez-Novo were responsible for the spectral entropy analysis of EEG Data. V. Molina, O. Martín-Santiago and J. Sanz-Fuentenebro were responsible for accessing the patients sample.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2020.11.013.

References

Antoniades, M., Schoeler, T., Radua, J., Valli, I., Allen, P., Kempton, M.J., McGuire, P., 2018. Verbal learning and hippocampal dysfunction in schizophrenia: a meta-analysis. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2017.12.001.

Bachiller, A., Díez, A., Suazo, V., Domínguez, C., Ayuso, M., Hornero, R., Poza, J., Molina, V., 2014. Decreased spectral entropy modulation in patients with schizophrenia during a P300 task. Eur. Arch. Psychiatry Clin. Neurosci. 264, 533–543. https://doi.org/10.1007/s00406-014-0488-6.

Bonilha, L., Molnar, C., Horner, M.D., Anderson, B., Forster, L., George, M.S., Nahas, Z., 2008. Neurocognitive deficits and prefrontal cortical atrophy in patients with schizophrenia. Schizophr. Res. 101, 142–151. https://doi.org/10.1016/j.schres.2007.11.023.

Brugger, S.P., Howes, O.D., 2017. Heterogeneity and homogeneity of regional brain structure in schizophrenia: a meta-analysis. JAMA psychiatry 74, 1104–1111. https://doi.org/10.1001/jamapsychiatry.2017.2663.

Carruthers, S.P., Van Rheenen, T.E., Gurvich, C., Sumner, P.J., Rossell, S.L., 2019. Characterising the structure of cognitive hetereogenity in schizophrenia spectrum disorder: a systematic review and narrative synthesis. Neurosci. Biobehav. Rev. https://doi.org/10.1016/j.neubiorev.2019.09.006.

Cea-Cañas, B., Gomez-Pilar, J., Núñez, P., Rodríguez-Vázquez, E., de Uribe, N., Díez, Á., Pérez-Escudero, A., Molina, V., 2020. Connectivity strength of the EEG functional

network in schizophrenia and bipolar disorder. Prog. Neuro-Psychopharmacology Biol. Psychiatry 98, 109801. https://doi.org/10.1016/j.pnpbp.2019.109801.
Charrad, M., Ghazzali, N., Laval, U., Niknafs, A., 2014. NbClust: an R package for determining the relevant number of clusters in a data set. JSS Journal of Statistical 61, 1–36.
Chelune, G.J., Baer, R.A., 1986. Developmental norms for the Wisconsin Card Sorting Test. J. Clin. Exp. Neuropsychol. 8, 219–228. https://doi.org/10.1080/01688638608401314.
Clementz, B.A., Sweeney, J.A., Hamm, J.P., Ivleva, E.I., Ethridge, L.E., Pearlson, G.D., Keshavan, M.S., Tamminga, C.A., 2016. Identification of distinct psychosis biotypes using brain-based biomarkers. Am. J. Psychiatry 173, 373–384. https://doi.org/10.1176/appi.ajp.2015.14091200.
Dale, A.M., Fischl, B., Sereno, M.I., 1999. Cortical surface-based analysis: I. Segmentation and surface reconstruction. Neuroimage 9, 179–194. https://doi.org/10.1006/nimg.1998.0395.
Desikan, R.S., Ségonne, F., Fischl, B., Quinn, B.T., Dickerson, B.C., Blacker, D., Buckner, R.L., Dale, A.M., Maguire, R.P., Hyman, B.T., Albert, M.S., Killiany, R.J., 2006. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. Neuroimage 31, 968–980. https://doi.org/10.1016/j.neuroimage.2006.01.021.
Fuentes Durá, I., Peris, M.R., Vivó, C.D., Ruiz, J.C.R., 2010. Versión abreviada del WAIS-III para su uso en la evaluación de pacientes con diagnóstico de esquizofrenia. Psicothema 22, 202–207.
Gomez-Pilar, J., de Luis-García, R., Lubeiro, A., de la Red, H., Poza, J., Núñez, P., Hornero, R., Molina, V., 2018a. Relations between structural and EEG-based graph metrics in healthy controls and schizophrenia patients. Hum. Brain Mapp. 39, 3152–3165. https://doi.org/10.1002/hbm.24066.
Gomez-Pilar, J., de Luis-García, R., Lubeiro, A., de Uribe, N., Poza, J., Núñez, P., Ayuso, M., Hornero, R., Molina, V., 2018b. Deficits of entropy modulation in schizophrenia are predicted by functional connectivity strength in the theta band and structural clustering. NeuroImage Clin 18, 382–389. https://doi.org/10.1016/j.nicl.2018.02.005.
Gonzalez-Burgos, G., Lewis, D.A., 2012. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. Schizophr. Bull. 38, 950–957. https://doi.org/10.1093/schbul/sbs010.
Green, M.J., Cairns, M.J., Wu, J., Dragovic, M., Jablensky, A., Tooney, P.A., Scott, R.J., Carr, V.J., 2013. Genome-wide supported variant MIR137 and severe negative symptoms predict membership of an impaired cognitive subtype of schizophrenia. Mol. Psychiatry 18, 774–780. https://doi.org/10.1038/mp.2012.84.
Green, M.J., Girshkin, L., Kremerskothen, K., Watkeys, O., Quidé, Y., 2019. A systematic review of studies reporting data-driven cognitive subtypes across the psychosis spectrum. Neuropsychol. Rev. https://doi.org/10.1007/s11065-019-09422-7.
Greenwood, T.A., Lazzeroni, L.C., Maihofer, A.X., Swerdlow, N.R., Calkins, M.E., Freedman, R., Green, M.F., Light, G.A., Nievergelt, C.M., Nuechterlein, K.H., Radant, A.D., Siever, L.J., Silverman, J.M., Stone, W.S., Sugar, C.A., Tsuang, D.W., Tsuang, M.T., Turetsky, B.I., Gur, R.C., Gur, R.E., Braff, D.L., 2019. Genome-wide association of endophenotypes for schizophrenia from the Consortium on the Genetics of Schizophrenia (COGS) study. JAMA Psychiatry 76, 1274–1284. https://doi.org/10.1001/jamapsychiatry.2019.2850.
Guo, X., Li, J., Wang, J., Fan, X., Hu, M., Shen, Y., Chen, H., Zhao, J., 2014. Hippocampal and orbital inferior frontal gray matter volume abnormalities and cognitive deficit in treatment-naive, first-episode patients with schizophrenia. Schizophr. Res. 152, 339–343. https://doi.org/10.1016/j.schres.2013.12.015.
Haukvik, U.K., Tamnes, C.K., Söderman, E., Agartz, I., 2018. Neuroimaging hippocampal subfields in schizophrenia and bipolar disorder: a systematic review and meta-analysis. J. Psychiatr. Res. https://doi.org/10.1016/j.jpsychires.2018.08.012.
Horwitz, T., Lam, K., Chen, Y., Xia, Y., Liu, C., 2019. A decade in psychiatric GWAS research. Mol. Psychiatry https://doi.org/10.1038/s41380-018-0055-z.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276. https://doi.org/10.1093/schbul/13.2.261.
Kern, R.S., Nuechterlein, K.H., Green, M.F., Baade, L.E., Fenton, W.S., Gold, J.M., Keefe, R.S.E., Mesholam-Gately, R., Mintz, J., Seidman, L.J., Stover, E., Marder, S.R., 2008. The MATRICS Consensus Cognitive Battery, part 2: co-norming and standardization. Am. J. Psychiatry 165, 214–220. https://doi.org/10.1176/appi.ajp.2007.07010043.
Kirkpatrick, B., Strauss, G.P., Nguyen, L., Fischer, B.A., Daniel, D.G., Cienfuegos, A., Marder, S.R., 2011. The brief negative symptom scale: psychometric properties. Schizophr. Bull. 37, 300–305. https://doi.org/10.1093/schbul/sbq059.
Lewis, D.A., Curley, A.A., Glausier, J.R., Volk, D.W., 2012. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci. https://doi.org/10.1016/j.tins.2011.10.004.
Lubeiro, A., Rueda, C., Hernández, J.A., Sanz, J., Sarramea, F., Molina, V., 2016. Identification of two clusters within schizophrenia with different structural, functional and clinical characteristics. Prog. Neuro-Psychopharmacology Biol. Psychiatry 64, 79–86. https://doi.org/10.1016/j.pnpbp.2015.06.015.
Lubeiro, A., de Luis-García, R., Rodríguez, M., Álvarez, A., de la Red, H., Molina, V., 2017. Biological and cognitive correlates of cortical curvature in schizophrenia. Psychiatry Res. - Neuroimaging 270, 68–75. https://doi.org/10.1016/j.pscychresns.2017.10.011.
MacKenzie, N.E., Kowalchuk, C., Agarwal, S.M., Costa-Dookhan, K.A., Caravaggio, F., Gerretsen, P., Chintoh, A., Remington, G.J., Taylor, V.H., Müeller, D.J., Graff-Guerrero, A., Hahn, M.K., 2018. Antipsychotics, metabolic adverse effects, and cognitive function in schizophrenia. Front. Psychiatry 9. https://doi.org/10.3389/fpsyt.2018.00622.
Mayer, J.D., Salovey, P., Caruso, D.R., Sitarenios, G., 2003. Measuring emotional intelligence with the MSCEIT V2.0 work-life strategies. Emotion 3, 97–105. https://doi.org/10.1037/1528-3542.3.1.97.
Molina, V., Bachiller, A., Gomez-Pilar, J., Lubeiro, A., Hornero, R., Cea-Cañas, B., Valcárcel, C., Haidar, M.K., Poza, J., 2018. Deficit of entropy modulation of the EEG in schizophrenia associated to cognitive performance and symptoms. A replication study. Schizophr. Res. 195, 334–342. https://doi.org/10.1016/j.schres.2017.08.057.
Molina, V., Lubeiro, A., de Luis-García, R., Gómez-Pilar, J., 2020. Deficit of entropy modulation of the EEG: a biomarker for the altered function in schizophrenia and bipolar disorder? J. Psychiatry Neurosci. 45 (5), 322–333. https://doi.org/10.1503/jpn.190032.
Núñez, P., Poza, J., Bachiller, A., Gómez-Pilar, J., Lubeiro, A., Molina, V., Hornero, R., 2017. Exploring non-stationarity patterns in schizophrenia: neural reorganization abnormalities in the alpha band - PubMed. J. Neural Eng. 14.
Okada, N., Fukunaga, M., Yamashita, F., Koshiyama, D., Yamamori, H., Ohi, K., Yasuda, Y., Fujimoto, M., Watanabe, Y., Yahata, N., Nemoto, K., Hibar, D.P., Van Erp, T.G.M., Fujino, H., Isobe, M., Isomura, S., Natsubori, T., Narita, H., Hashimoto, N., Miyata, J., Koike, S., Takahashi, T., Yamasue, H., Matsuo, K., Onitsuka, T., Iidaka, T., Kawasaki, Y., Yoshimura, R., Watanabe, Y., Suzuki, M., Turner, J.A., Takeda, M., Thompson, P.M., Ozaki, N., Kasai, K., Hashimoto, R., 2016. Abnormal asymmetries in subcortical brain volume in schizophrenia. Mol. Psychiatry 21, 1460–1466. https://doi.org/10.1038/mp.2015.209.
Penadés, R., Franck, N., González-Vallespí, L., Dekerle, M., 2019. Neuroimaging studies of cognitive function in schizophrenia. Advances in Experimental Medicine and Biology. Springer New York LLC, pp. 117–134 https://doi.org/10.1007/978-3-030-05542-4_6.
Pirnia, T., Woods, R.P., Hamilton, L.S., Lyden, H., Joshi, S.H., Asarnow, R.F., Nuechterlein, K.H., Narr, K.L., 2015. Hippocampal dysfunction during declarative memory encoding in schizophrenia and effects of genetic liability. Schizophr. Res. 161, 357–366. https://doi.org/10.1016/j.schres.2014.11.030.
Planchuelo-Gómez, Á., Lubeiro, A., Núñez, P., Gómez-Pilar, J., de Luis-García, R., del Valle, P., Martín-Santiago, Ó., Pérez-Escudero, A., Molina, V., 2020. Identification of MRI-based psychoses subtypes: replication and refinement. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 100, 109907. https://doi.org/10.1016/j.pnpbp.2020 Epub 2020 Feb 27.
Rousseeuw, P.J., 1987. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. J. Comput. Appl. Math. 20, 53–65. https://doi.org/10.1016/0377-0427(87)90125-7.
Sanjuan, J., Prieto, L., Olivares, J.M., Ros, S., Montejo, A., Ferrer, F., Mayoral, F., González-Torres, M.A., Bousoño, M., 2003. GEOPTE Scale of social cognition for psychosis. Actas Esp. Psiquiatr. 31, 120–128.
Sauvé, G., Malla, A., Joober, R., Brodeur, M.B., Lepage, M., 2018. Comparing cognitive clusters across first- and multiple-episode of psychosis. Psychiatry Res. 269, 707–718. https://doi.org/10.1016/j.psychres.2018.08.119.
Scheeringa, R., Fries, P., Petersson, K.M., Oostenveld, R., Grothe, I., Norris, D.G., Hagoort, P., Bastiaansen, M.C.M., 2011. Neuronal dynamics underlying high- and low-frequency EEG oscillations contribute independently to the human BOLD signal. Neuron 69, 572–583. https://doi.org/10.1016/j.neuron.2010.11.044.
Segarra, N., Bernardo, M., Gutierrez, F., Justicia, A., Fernadez-Egea, E., Allas, M., Safont, G., Contreras, F., Gascon, J., Soler-Insa, P.A., Menchon, J.M., Junque, C., Keefe, R.S.E., 2011. Spanish validation of the Brief Assessment in Cognition in Schizophrenia (BACS) in patients with schizophrenia and healthy controls. Eur. Psychiatry 26, 69–73. https://doi.org/10.1016/j.eurpsy.2009.11.001.
Smith, R.E., Tournier, J.-D., Calamante, F., Connelly, A., 2012. Anatomically-constrained tractography: improved diffusion MRI streamlines tractography through effective use of anatomical information. Neuroimage 62, 1924–1938. https://doi.org/10.1016/j.neuroimage.2012.06.005.
Sun, H., Lui, S., Yao, L., Deng, W., Xiao, Y., Zhang, W., Huang, X., Hu, J., Bi, F., Li, T., Sweeney, J.A., Gong, Q., 2015. Two patterns of white matter abnormalities in medication-naive patients with first-episode schizophrenia revealed by diffusion tensor imaging and cluster analysis. JAMA Psychiatry 72, 678–686. https://doi.org/10.1001/jamapsychiatry.2015.0505.
Van Erp, T.G.M., Hibar, D.P., Rasmussen, J.M., Glahn, D.C., Pearlson, G.D., Andreassen, O.A., Agartz, I., Westlye, L.T., Haukvik, U.K., Dale, A.M., Melle, I., Hartberg, C.B., Gruber, O., Kraemer, B., Zilles, D., Donohoe, G., Kelly, S., McDonald, C., Morris, D.W., Cannon, D.M., Corvin, A., Machielsen, M.W.J., Koenders, L., De Haan, L., Veltman, D.J., Satterthwaite, T.D., Wolf, D.H., Gur, R.C., Gur, R.E., Potkin, S.G., Mathalon, D.H., Mueller, B.A., Preda, A., Macciardi, F., Ehrlich, S., Walton, E., Hass, J., Calhoun, V.D., Bockholt, H.J., Sponheim, S.R., Shoemaker, J.M., Van Haren, N.E.M., Pol, H.E.H., Ophoff, R.A., Kahn, R.S., Roiz-Santiaez, R., Crespo-Facorro, B., Wang, L., Alpert, K.I., Jönsson, E.G., Dimitrova, R., Bois, C., Whalley, H.C., McIntosh, A.M., Lawrie, S.M., Hashimoto, R., Thompson, P.M., Turner, J.A., 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. Mol. Psychiatry 21, 547–553. https://doi.org/10.1038/mp.2015.63.
Van Rheenen, T.E., Lewandowski, K.E., Tan, E.J., Ospina, L.H., Ongur, D., Neill, E., Gurvich, C., Pantelis, C., Malhotra, A.K., Rossell, S.L., Burdick, K.E., 2017. Characterizing cognitive heterogeneity on the schizophrenia-bipolar disorder spectrum. Psychol. Med. 47, 1848–1864. https://doi.org/10.1017/S0033291717000307.
Varela, F., Lachaux, J.P., Rodriguez, E., Martinerie, J., 2001. The brainweb: phase synchronization and large-scale integration. Nat. Rev. Neurosci. 2, 229–239. https://doi.org/10.1038/35067550.
Weinberg, D., Lenroot, R., Jacomb, I., Allen, K., Bruggemann, J., Wells, R., Balzan, R., Liu, D., Galletly, C., Catts, S.V., Weickert, C.S., Weickert, T.W., 2016. Cognitive subtypes of schizophrenia characterized by differential brain volumetric reductions and cognitive decline. JAMA Psychiatry 73, 1251–1259. https://doi.org/10.1001/jamapsychiatry.2016.2925.
Woodward, N.D., Heckers, S., 2015. Brain structure in neuropsychologically defined subgroups of schizophrenia and psychotic bipolar disorder. Schizophr. Bull. 41, 1349–1359. https://doi.org/10.1093/schbul/sbv048.
Zhou, Y., Fan, L., Qiu, C., Jiang, T., 2015. Prefrontal cortex and the dysconnectivity hypothesis of schizophrenia. Neurosci. Bull. https://doi.org/10.1007/s12264-014-1502-8.

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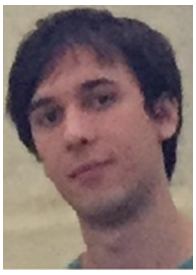

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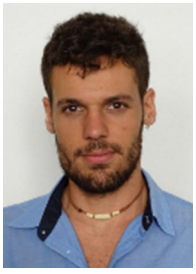
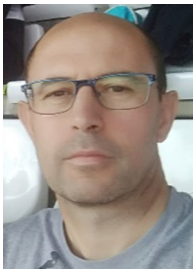
Álvaro Díez-Revuelta. Assistant professor in the Department of Psychiatry at the University of Valladolid, Spain. He has a degree in Psychology from the Complutense University of Madrid and a PhD in Neuropsychology from the University of Salamanca, in both cases with an extraordinary prize. He has enjoyed two post-doctoral scholarships at University College London and at the Complutense University of Madrid.



Antonio Arjona-Valladares. Post-doctoral researcher in the area of Psychiatry at the University of Valladolid, Spain, with more than 10 years of experience. His research interests are focused on cognitive neuroscience, neuropsychology and cognitive electrophysiology (EEG, qEEG, ERPs, NIRs). He has a degree in Psychology, a MSc in advanced studies in brain and behaviour and a PhD in Psychology from the University of Seville, Spain.

Rodrigo de Luis. He received his PhD degree from the University of Valladolid, Spain, in 2007. He is an Associate Professor with the E.T.S.I. Telecommunication at the University of Valladolid, where he also works with the Image Processing Laboratory (LPI). His research interests include medical image analysis and processing, with a special focus on magnetic resonance imaging (MRI) and diffusion MRI. In 2008, he was awarded with a Fulbright Scholarship for a two-year stay as a Research Fellow with the Laboratory of Mathematics in Imaging at Brigham and Women's Hospital, Harvard Medical School, Boston.

Óscar Martín-Santiago. He studied Medicine in Valladolid, and the Psychiatry specialty in Madrid, Spain. He has worked as psychiatrist in several hospitals in Spain. Between 2013 and 2016 he obtained a PhD in Medicine from the University of Valladolid, Spain. Since 2019 he works as assistant professor of Psychiatry at the same University. He has authored 2 original articles and co-authored several papers. He also has collaborated in research projects focused on schizophrenia, psychotic-like experiences, cognition and brain networks.



José Antonio Benito-Sánchez. He received his degree in Psychology from the University of Salamanca, Spain, in 1995. He is clinical Psychologist (Ministerio de Educación y Ciencia, Burgos, Spain, 2000) and received his PhD in Psychology from the University of Salamanca in 2009. He currently works as clinical psychologist in the University Clinical Hospital of Salamanca and as associate professor in the Medical Department of the University of Salamanca. He is also clinical psychology training coordinator tutor.

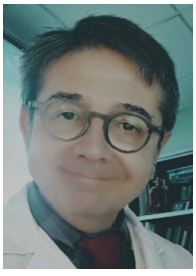
Ángela Pérez-Laureano. She has a degree in Psychology from the University of Salamanca. She is currently in her four-year residence in Clinical Psychology at the University Clinical Hospital of Salamanca.

David González-Parra. He has a degree in Medicine and Surgery with Psychiatry specialty and a PhD from the University of Salamanca, Spain. He currently works as psychiatrist and professor of the Psychiatry Department at the University Hospital of Salamanca, Spain. His research is fundamentally focused on eating disorders and metabolic syndromes associated with antipsychotic based treatments.

Carmen Montes-Gonzalo. She has a degree in Medicine and Surgery with Clinical Neurophysiological specialization from the University of Salamanca, Spain. She received her PhD from the University of Málaga, being her thesis focused on the brain bioelectrical activity in aging and dementia. He worked as associate professor in the Physiology Department of the Medical Faculty from the University of Málaga between 1998 and 2004. She was post-doctoral researcher in the Neurological and Neurosurgical Pierre-Wertheimer Hospital in Lyon, France, focusing her research on cognitive evoked potentials and pain. Since 2004 she works as clinical neurophysiologist in the Hospital Complex from Toledo and Salamanca.

Raquel Melero-Lerma. She received the degree in Medicine from the University of Valladolid, Spain, in 2017. She is currently in her second-year residence specialization in Psychiatry at the University Care Complex of Palencia, Spain. Her research interests are mainly focused on psychotic pathology.

Sonia Fernández Morante. She received the degree in Medicine in 1997 from the University of Alcalá de Henares, Madrid, Spain, and obtained the Psychiatry specialty in the University Hospital of Móstoles, Madrid, in 2002. She also has a MSc in Bioethics from the Complutense University of Madrid. Since 2002 she has worked as psychiatrist in several healthcare centers from Madrid and she is currently working at the mental health unit from Doce de Octubre University Hospital of Madrid. Her research is primarily focused on the psychotic patients' therapeutic approaches and on understanding the functionality consequences of psychoses.



Javier Sanz-Fuentenebro. PhD in Medicine with Psychiatry specialty. Associate professor of Medicine at the Complutense University from Madrid, Spain and head of Department in the 12 de Octubre Hospital in Madrid, Spain. His research is primarily focused on the biological substrates of schizophrenia, its treatment and the electro-convulsive therapy technical aspects.

Javier Gómez-Pilar. He received the degree in Telecommunication Engineering in 2012 from the University of Valladolid, Spain, where he also obtained the Master of Advanced Studies on Biomedical Engineering in 2013 and his PhD in 2018. He is currently a researcher on the Biomedical Engineering Group, associated with the Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine. His research is primarily focused on biomedical signal processing of electroencephalograms using time-frequency analysis and complex network theory to help in the diagnosis of several pathologies. Currently, he is involved in different studies applying correlation networks to integrate large sets of heterogeneous data.

Pablo Núñez-Novo. He received the B.S. degree in Telecommunication Engineering in 2014 and the M.S. degree in Telecommunications Engineering in 2015, both from the University of Valladolid, Spain. He is currently working towards a PhD degree at the Biomedical Engineering Group in Valladolid, Spain, which is associated with the Biomedical Research Networking Center in Bioengineering, Biomaterials and Nanomedicine. His main research interest is searching for potential biomarkers for different pathologies by means of electroencephalographic signal processing. He is currently focused on applying Dynamic functional connectivity techniques to study brain state switching.

Vicente Molina. Full Professor of the Department of Psychiatry at the University of Valladolid, Spain, and head of the Adult Hospitalization Unit of the Psychiatry Service of the University Clinical Hospital of Valladolid. He received his Medicine degree from the Complutense University of Madrid, Spain, where he simultaneously obtained his PhD and the Psychiatry specialty, performing his residence period at the Gregorio Marañón University Hospital from Madrid, Spain.