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Testing the expanded continuum hypothesis of schizophrenia and bipolar disorder. Neural and psychological evidence for shared and distinct mechanisms

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ABSTRACT

Despite the traditional view of Schizophrenia (SZ) and Bipolar disorder (BD) as separate diagnostic categories, the validity of such a categorical approach is challenging. In recent years, the hypothesis of a *continuum* between Schizophrenia (SZ) and Bipolar disorder (BD), postulating a common pathophysiologic mechanism, has been proposed. Although appealing, this unifying hypothesis may be too simplistic when looking at cognitive and affective differences these patients display. In this paper, we aim to test an expanded version of the continuum hypothesis according to which the continuum extends over three clusters: the psychotic, the cognitive, and the affective. We applied an innovative approach known as Source-based Morphometry (SBM) to the structural images of 46 individuals diagnosed with SZ, 46 with BD and 66 healthy controls (HC). We also analyzed the psychological profiles of the three groups using cognitive, affective, and clinical tests.

At a neural level, we found evidence for a shared psychotic core in a distributed network involving portions of the medial parietal and temporo-occipital areas, as well as parts of the cerebellum and the middle frontal gyrus. We also found evidence of a cognitive core more compromised in SZ, including alterations in a fronto-parietal circuit, and mild evidence of an affective core more compromised in BD, including portions of the temporal and occipital lobes, cerebellum, and frontal gyrus. Such differences were confirmed by the psychological profiles, with SZ patients more impaired in cognitive tests, while BD in affective ones.

On the bases of these results we put forward an expanded view of the continuum hypothesis, according to which a common psychotic core exists between SZ and BD patients complemented by two separate cognitive and affective cores that are both impaired in the two patients' groups, although to different degrees.

1. Introduction

Schizophrenia (SZ) and bipolar disorder (BD) represent two major forms of severe psychiatric conditions, frequently characterized by more or less severe alterations of reality testing. Both SZ and BD patients present with affective as well as cognitive impairments, although they do so in different ways. At the affective level, SZ is usually characterized by emotional flattening and incongruence while BD is characterized by unique, opposing emotional peaks, with manic episodes involving feelings of extreme elation, alternating with depressive episodes. At the cognitive level, individuals with SZ display large impairments in different cognitive domains, including working memory, attention, executive functions, and others (Bora, 2016; Pearlson, 2015; Hill et al., 2013; Vöhringer et al., 2013; Schretlen et al., 2007) while the milder cognitive deficits of BD may be linked to dysfunctional brain arousal regulation (Bowie et al., 2018; Wittekind et al., 2016; Clark and Goodwin, 2004; Liu et al., 2002). On the basis of the symptoms, more related to cognition for SZ and to emotion for BD, these clinical groups

Abbreviations: SZ, schizophrenia; BD, bipolar disorder; HC, healthy controls; MRI, magnetic resonance imaging; SBM, Source-based Morphometry

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were dichotomized into two distinct diagnostic categories in current diagnostic manuals, such as the Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association [APA], 2013) and the Classification of Mental and Behavioral Disorders (ICD-10; World Health Organization [WHO], 1993).

Despite the traditional consideration of SZ and BD as separate diagnostic categories, the validity of this categorical approach when differentiating these conditions is challenging. On the one hand, reality testing and thought disorder, such as hallucinations and delusional beliefs, represent the core aspect of SZ, but these symptoms are frequently observed also in BD during maniac episodes (Keck Jr et al., 2003). In addition, the differential diagnosis of SZ and BD proves difficult in the clinical setting. Indeed, patients often do not fit completely within the boundaries of a single disorder and many patients show a mixture of clinical manifestations traditionally associated with SZ and BD (Pearlson, 2015; Rosen et al., 2012; Lake, 2010; Fischer and Carpenter, 2009; Bora et al., 2008; Möller, 2003; DSM-5; APA, 2013; p.5). The problem of the differential diagnosis has been addressed in the DSM-5 with the addition in section 3 of a dimensional evaluation of transversal symptoms severity, which may help clinicians in diagnostic evaluations through the consideration of the different weight of affective and cognitive impairments in each patient (DSM-5; APA, 2013). Furthermore, genetic studies show a partial common genetic etiology for SZ and BD. Namely, family studies (Lichtenstein et al., 2009; Schürhoff et al., 2003) and twin studies (Cardno et al., 2002; Farmer, 1987) have shown that both disorders aggregate in families. These findings are consistently confirmed by molecular genetic studies that are providing increasing evidence for an overlap in genetic susceptibility across SZ and BD (Badner and Gershon, 2002; Owen et al., 2007). Finally, SZ and BD show similar response rates to atypical antipsychotic and polypharmaceutical treatments (Tamminga et al., 2014; Pearlson, 2015). The cross-domain evidence briefly mentioned raises questions about the boundaries between, and distinctiveness of, SZ and BD, suggesting the need to reappraise these disorders as distinct diagnostic categories.

Considerations of this kind have let authors to propose the hypothesis of a *psychosis continuum* between SZ and BD. According to such a hypothesis, an overlap of genetic susceptibility could lead to common symptoms (e.g., the psychotic symptoms), whereas other genetic and environmental factors may lead to a differentiation between the disorders (Crow, 1986; Benabarre et al., 2001; Walker et al., 2002; Lake and Hurwitz, 2007; Bora and Berk, 2011; Pearlson, 2015). According to this view, common vulnerability factors for psychosis could be genetically linked to both patients' groups, while a more general cognitive impairment would characterize SZ and an affective impairment would characterize BD. Some evidence is available on this issue and shows that while information processing and processing speed are impaired in both SZ's and BD's first-degree relatives, general intellectual ability, verbal learning, planning and working memory seem to be more associated with risk for SZ (Bora, 2017). On the other hand, BD are characterized by mood alterations that affect measures of emotional control such as impulsivity, which is greater than in SZ, and is linked to the course of illness only in BD (Reddy et al., 2013; Swann et al., 2009).

In line with this evidence, several authors have proposed dimensional approaches and have argued for a continuous rather than for a purely categorical distribution of pathologies and symptoms (Pearlson, 2015; Keshavan et al., 2011, 2013; Insel and Cuthbert, 2009; Boteva and Lieberman, 2003).

From a neural point of view, many brain alterations previously shown in SZ have also been found in BD, supporting the *continuum hypothesis* at the neural level (Anderson et al., 2013; Peri et al., 2012; Pol et al., 2012; Bora et al., 2008). Capitalizing on Voxel-based Morphometry (VBM) (Ashburner and Friston, 2000), several studies demonstrated that when compared to healthy controls, both SZ and BD patients show large overlaps of gray matter alterations in prefrontal, subcortical, temporal and parieto-occipital areas (Ellison-Wright and Bullmore, 2010; Yu et al., 2010; Brown et al., 2011; Cui et al., 2011; Nenadic et al., 2015; Maggioni et al., 2016). However, when bipolar and schizophrenic patients are directly compared, the latter show broader impairment. In particular, gray matter reduction in frontal gyri, in temporal gyri and in the insula is more pronounced in schizophrenic compared to bipolar patients (Maggioni et al., 2016, 2017; Nenadic et al., 2015; Rimol et al., 2012; Molina et al., 2011). Therefore, the anatomical evidence shows deficits in both patient groups with a modulation of the severity: some areas seem to be strongly impaired in SZ but only mildly so in BD. As a matter of fact, BD seems to lie in an intermediate level of impairment between SZ and healthy subjects (Bowie et al., 2018; Rheenen et al., 2017; Bora and Pantelis, 2015; Bortolato et al., 2015; Lewandowski et al., 2014; Krishnadas et al., 2014; Ancin et al., 2013; Hill et al., 2013; Keshavan et al., 2011).

Despite the notable results, the conclusions of these studies are limited because most of them have compared SZ and BD only indirectly by analyzing each group of patients with respect to healthy controls (Mcintosh et al., 2004; Farrow et al., 2005; Arnone et al., 2009; Yu et al., 2010; Ellison-Wright and Bullmore, 2010). Moreover, an important methodological limitation is due to the use of univariate methods (such as VBM) to investigate large-scale networks that are involved in psychiatric disorders (Pappaianni et al., 2017; Pappaianni and Grecucci, 2016), since such methods do not consider the relation between different voxels in a whole brain fashion (Xu et al., 2009).

Given these limitations, and given the complexity and heterogeneity of the psychopathological manifestations Source-based Morphometry (SBM) has been proposed as a more reliable approach to study psychiatric disorders from a whole brain and network perspective (Grecucci et al., 2016, 2017; Pappaianni et al., 2017; Xu et al., 2009). SBM is a data-driven multivariate alternative to the standard univariate VBM, which identifies patterns of covariation of gray matter in different separate areas, and it can be particularly suitable to compare anatomical changes associated with different psychopathological conditions (Grecucci et al., 2016; Xu et al., 2009).

Capitalizing on the advantages of a direct three-group comparison SBM, in the present study we aim to test an expanded view of the continuum hypothesis. Namely, we hypothesize that SZ and BD patients have a common “psychotic core”, referring to slight to severe loss of reality testing, but also two additional cores, a cognitive one and an affective one, which are differently compromised in SZ and BD.

To test for this hypothesis, we analyzed the neural and the psychological profiles of individuals diagnosed with SZ, BD and of age-matched healthy controls. Firstly, we predict a common morphometric alteration in both SZ and BD patients when compared with HC in brain areas involved in information processing and integration which may explain the “psychotic core”, such as the inferior parietal cortex, but also in the posterior cingulate and the precuneus, these areas being associated to internally directed cognition and cognitive insight (Leech and Sharp, 2013; Zhang et al., 2015). Secondly, we expect cognitive and affective deficits clustered into two additional cores: the higher cognitive functions core, associated to altered functioning of portions of the frontal and parietal cortices (Barch and Ceaser, 2012; Poppe et al., 2016), and the affective core associated to abnormalities in affect-related areas such as the cerebellar vermis, and other frontal and temporal regions (Strakowski et al., 2004; Kumari et al., 2003).

2. Methods

2.1. Participants

Given the need for large-scale samples of MR, the present study capitalizes on an existing freely available database known as the Preprocessed Consortium for Neuropsychiatric Phenomics dataset (https://openneuro.org/datasets/ds000030/versions/00016).
Cognitive tests, questionnaires and structural MR images of 158 participants (mean age 36, std. 9; M = 94, F = 64) with age-range of

Table 1
Demographic characteristics of the dataset.
Adapted from Gorgolewski et al., 2017.

	Schizophrenia	Bipolar disorder	Healthy subjects	Differences (p-values)	All
Number of subjects	46	46	66		158
Age	Mean = 36,7 (± 9)	Mean = 36.2(± 6)	Mean = 36.1 (± 8.4)	0,935	Mean = 36.3(± 8.6)
Gender	M = 36; F = 10	M = 26; F = 20	M = 32; F = 34	0,006	M = 94; F = 64
Education: years of school	Mean = 12,70 (± 1,71)	Mean = 14,61 (± 1,96)	Mean = 15,02 (± 1,74)	< 0,001	≥ 8 years of formal education
Screening					Neurological disease, psychoactive substance, mental illness (SCID-IV)

21–50 years were selected from UCLA Consortium for Neuropsychiatric Phenomics dataset (Bilder et al., 2018; Gorgolewski et al., 2017; Poldrack et al., 2016), from the Openneuro database (accession number ds000030). Forty-six of them were diagnosed with schizophrenia (SZ; mean age 37, SD 9, 36 male and 10 female), 46 with bipolar disorder (BD; mean age 36, SD 9, 26 male and 20 female), while 66 were healthy controls (HC) without history of psychiatric and neurological disease (mean age 36, SD 8, 32 male and 34 female). The consortium excluded patients with diagnoses in at least two different patient groups, left-handedness, pregnancy, or other contraindications to scanning (Table 1). Participants were screened for neurological disease, history of head injury with loss of consciousness, use of psychoactive medications, substance dependence within past 6 months, history of major mental illness or ADHD, and current mood or anxiety disorder. Self-reported history of psychopathology was verified with the SCID-IV (First et al., 1996). Urinalysis was used to screen for drugs of abuse (cannabis, amphetamine, opioids, cocaine, benzodiazepines) on the day of testing and participants were excluded if positive.

We excluded some participants due to artifacts or age matching. Supplementary material contains the IDs of participants we included in our analysis, and a table describing the differences between groups in sex, education and ethnicity, since we cannot match participants according to these variables, given the need of a large sample to perform our analyses.

2.2. Psychological measures

Cognitive tests and affective questionnaires scores were analyzed with a MANOVA.

Cognitive tests included the WAIS-R (Vocabulary, letter-number sequencing and matrix reasoning), the digit span and the spatial span of the Wechsler Memory Scale (WMS), the Spatial Maintenance and Manipulation Task (SMNM), the Verbal Maintenance and Manipulation Task (VMNM), the executive function measure (etotal) of the Delis-Kaplan Executive Function System (D-KEFS) and the Balloon Analog Risk Task.

Affective questionnaires included the Barratt Impulsivity Scale, a Scale for traits that increase risk for Bipolar II Disorder, the Dickman Impulsivity Inventory, the Chapman Hypomanic, Anhedonia and Social Anhedonia scales, the Eysenck's Impulsivity Inventory, the Hopkins Symptom Checklist and the Temperament & Character Inventory.

The independent variable of the MANOVA was the membership of a participant (SZ-BD-HC), while the dependent variables were the scores of each participant (rows of the input matrix) in each test (columns of the input matrix). The multivariate analysis of variance allows looking for the linear combinations of the original variables that have the largest separation between groups.

To visualize our results, we plotted for each participant the values of the first two canonical variables that show more separation between groups (HC, SZ and BD) (Fig. 2A). Then, we used the Pearson correlation coefficient to test the possible associations between the significant canonical variables and the networks of the morphometric analyses.

Furthermore, in order to visualize the distribution of cognitive and affective domains in each group, we plotted a score for each participant representing the means of cognitive and affective values. These values were obtained standardizing and averaging on one side all the cognitive tests, and on the other side all the affective scores (Fig. 2B). Finally, two One-Way ANOVA were applied to the cognitive and affective values obtained, to check for differences between groups (considering only the participants whose scores were available in the dataset).

2.3. Data acquisition and preprocessing

Neuroimaging data were acquired on a 3 T Siemens Trio scanner. T1-weighted high-resolution anatomical scan (MPRAGE) were collected with the following parameter: slice thickness = 1 mm, 176 slices,

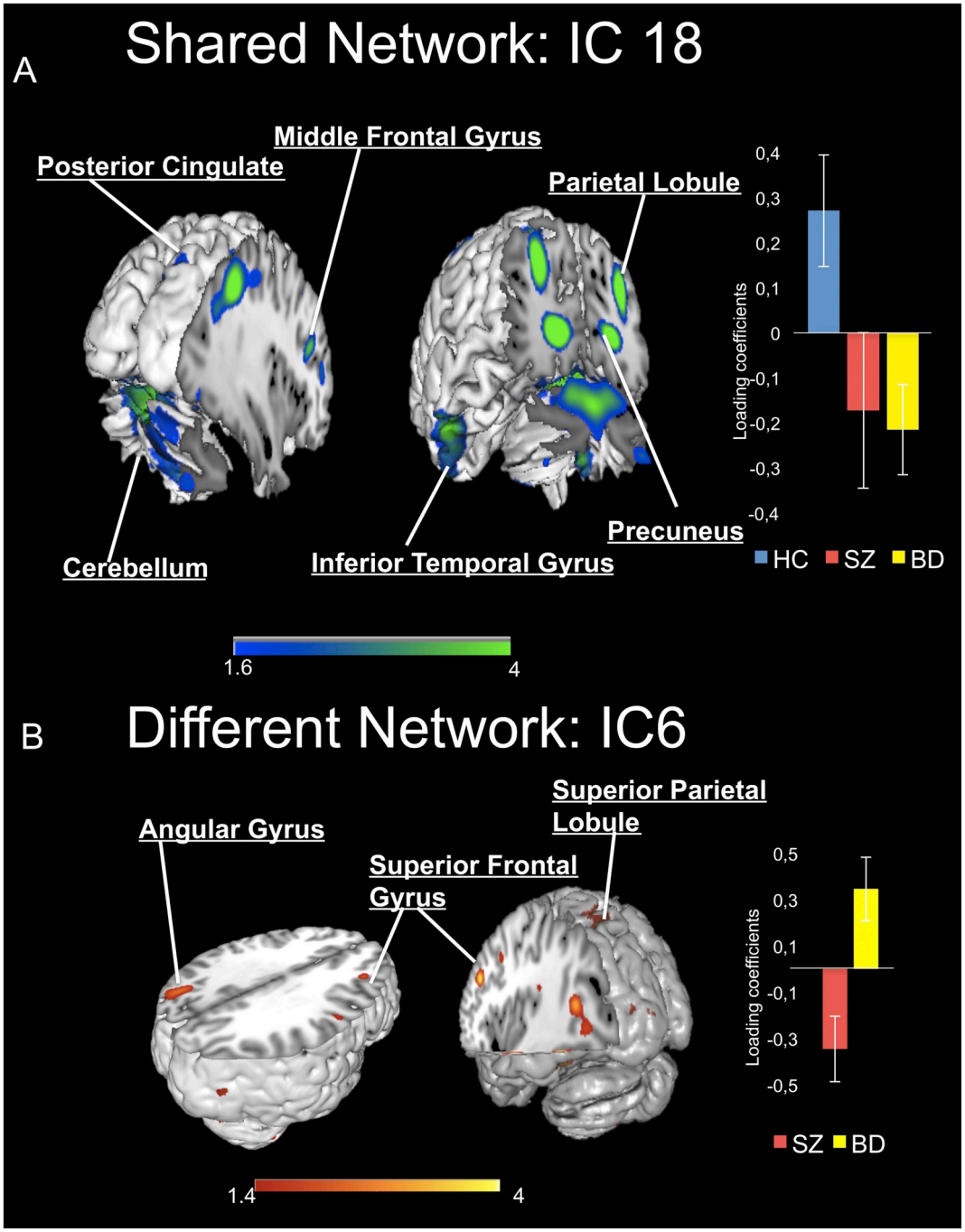

Fig. 1. Neuroanatomical profile. A) Results of the first analysis (HC-SZ-BD). IC 18 resulted significantly different between HC, SZ and BD ($p = .0145$). In particular, it showed a difference between HC and SZ ($p = .019$), between HC and BD ($p = .011$), but no difference between SZ and BD ($p = .832$), indicating a common altered network characterizing both SZ and BD patients. On the right, graphical representation of the loading coefficients' means for healthy controls (HC), schizophrenia (SZ) and bipolar (BD) patients, meaning how IC18 is expressed in each group. B) Results of the second analysis (SZ-BD). IC6 ($p < .001$) resulted significantly different between SZ and BD; On the right, the histogram shows how IC6 is expressed in each group through the loading coefficients, showing that this network is reduced in SZ.

TR = 1.9 s, TE = 2.26 ms, matrix = 256 × 256, FOV = 250 mm.

All images were preprocessed using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software) and its dedicated toolbox CAT12 (http://www.neuro.uni-jena.de/cat/) was used for the segmentation of images. After the initial check of data quality (in order to avoid critical artifacts as head-motion effect, ghosting, stripes that could potentially affect the results), each image was reoriented according to the origin and then segmented in gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) with CAT12. Since our goal was to look for gray matter abnormalities, only these images were used in our analysis.

Instead of using SPM's traditional approaches, registration was computed with Diffeomorphic Anatomical Registration using Exponential Lie algebra (DARTEL) tools for SPM12. Finally, normalization to MNI space with spatial smoothing (full-width at half maximum of Gaussian smoothing kernel [8, 8, 8]) was then applied on modulated DARTEL images. At this point, images were ready to be analyzed, with Source-Based Morphometry.

2.4. Source-based morphometry analysis

SBM can detect dissimilarities in gray matter between participants in terms of different networks, since it takes into account the interrelationships between different voxels (Xu et al., 2009). It works entirely on the whole brain, detecting and decomposing the mixed signals coming from structural images through an Independent Component Analysis (ICA). In this way, SBM preserves spatial correlation between different brain regions while acting as a spatial filter (Gupta et al., 2018). These advantages of SBM suggest that this approach may be preferable when compared to VBM, as it shows more noise reduction in results and it takes into account the relationship among all voxels (Grecucci et al., 2016; Pappaianni et al., 2017).

Different preprocessing steps were applied in order to get smoothed and normalized gray matter images (see 2.3). Then, an Independent Component Analysis (ICA) was used to break up the mixed signal coming from all images, in order to maximally recognize spatially independent sources. This step was performed throughout Group ICA of fMRI Toolbox (GIFT, http://mialab.mrn.org/software/gift), with the sMRI modality, specifically used to perform Source-based Morphometry, applying the ICA to structural images. We chose the Infomax algorithm in order to maximize the recognition of IC from images' signal information (Bell and Sejnowski, 1995; Lee et al., 1999); the ICASSO algorithm (http://research.ics.aalto.fi/ica/icasso/) was selected to investigate the reliability of the ICA algorithm (RandInit mode), and we repeated the ICA 100 times.

Finally, GM volumes of each component were converted into a numerical vector: ICA returned a n x m matrix, composed by n subjects in rows and m Independent Components in columns (according to different comparisons, the number of participants varied), such that each value in the matrix indicated how a specific component was expressed in each participant (Pappaianni et al., 2017).

At this point, we performed statistical analyses to determine significant sources that differ between groups. We compared the three groups of participants (SZ-BD-HC) by using a One-Way ANOVA and post-hoc analysis (Fisher's least significant difference). Then, we performed a two-sample t-test in the direct SZ-BD comparison, to identify structural MRI differences between them.

To visualize the spatial coordinates and the volume of specific covariation patterns that differed between groups, we used the Mango software (http://ric.uthscsa.edu/mango/).

Finally, we checked for possible correlations between the psychological and the morphometric results.

3. Results

3.1. Brain morphometric results

In line with standard SBM methodologies (Xu et al., 2009; Canessa et al., 2013; Depping et al., 2016), we extracted 20 ICs for each comparison, considering only the ones with Iq > 0.9, that indicates a highly stable ICA decomposition. In the HC-SZ-BD, only IC18 (Iq = 0,96) was significantly different between groups (One-Way ANOVA) ($F(2,155) = 4.3539$, $p = .0145$). Post-hoc analysis showed that IC18 was equally reduced in both SZ and BD (p(SZ-BD) = 0.832) as compared to the healthy group (p(HC-SZ) = 0.019; p(HC-BD) = 0.011). This component included the Inferior and Superior Parietal Lobule, the posterior Cingulate, the Precuneus and the Cuneus, the Lingual Gyrus, the Inferior Temporal Gyrus, the Fusiform Gyrus, parts of the Cerebellum and the Middle Frontal Gyrus (Fig. 1A, Table 2).

To explore differences between SZ and BD, we extracted 20 ICs, all of them associated with an $Iq > 0.9$, indicating a highly stable ICA decomposition. Then, we computed two-sample t-test to identify which networks showed differences between schizophrenia and bipolar disorder. Three networks showed reduced gray matter in schizophrenic patients: IC 5 [$t(90) = -3.178$, $p = .002$], that included the lingual gyrus, the inferior parietal lobule, the middle and the medial frontal gyrus; IC 6 [$t(90) = -3.5175$, $p < .001$], that included the superior and the middle frontal gyrus, the superior and the inferior parietal lobule and the precuneus; and IC 7 [$t(90) = -2.068$, $p = .04$] mainly involving the middle frontal gyrus and parieto-occipital areas. Other three ICs showed stronger gray matter reduction in BD. IC 3 [$t(90) = 2.344$, $p = .02$], mainly involving portions of the cerebellum, fusiform gyrus and occipital area; IC10 [$t(90) = 2.087$, $p = .04$], mainly involving the occipital gyrus, the cuneus and the Precuneus; and IC20 [$t(90) = 1998$, $p = .049$] mainly involving the cerebellum and the inferior and middle temporal gyri. Among these 6 ICs that differ between SZ and BD, Bonferroni correction was applied in order to select the network that showed the greatest difference between groups. Indeed, only IC6 survived to Bonferroni correction, represented in Table 3 and Fig. 1B. The other ICs are in supplementary materials (Table S2-S5).

3.2. Psychological results

The MANOVA showed a significant multivariate effect for the different tasks and questionnaires taken together, in relation to the group of each participant (HC, SZ or BD). In particular, two dimensions resulted as significant ($p < .001$, Wilk's lambda = 0.19). This shows that the group means fall in a plane (characterized by two significant dimensions) but not along a line (characterized by only one significant dimension).

Furthermore, the graphical representation of our results shows that the first two canonical variables (c1 and c2) represent the two dimensions with largest separation between groups. In particular, the latent variable c1 seems to separate HC from SZ and BD, while the latent variable c2 seems to separate SZ from BD (Fig. 2A).

Then, to link our psychological results to the morphometric ones, we used the Pearson correlation coefficient to test the associations on one side between c1 and IC18 (the common network reduced in SZ and BD), and on the other side between c2 and the six ICs that differ between SZ and BD. The only significant correlation was the one between c1 and IC18 ($r = -0.257$; $p = .003$).

This significant negative correlation shows that reduced gray matter in IC18 is associated with a higher value of c1, which separates the two clinical groups from the HC group (Fig. 2A). Therefore, c1 can support the presence of a common psychological alteration between SZ and BD that is coherent with our morphometric results. A MANCOVA was used to measure the effects of sex and age (p(age) < 0.001; p(sex) = 0.001).

The cognitive and affective profiles of SZ and BD, which emerged from the tasks and the questionnaires scores, are reported in Fig. 2B and in Table S6. It is evident that the cognitive domain shows differences between groups ($F(2,132) = 26.73$; $p < .001$). Post-hoc comparisons show that it is largely compromised in SZ as expected by our hypothesis of a cognitive core, and only mildly compromised in BD (p(SZ-BD) < 0.001). No significant effect was found when controlling for age and sex as covariates (p(age) = 0.25; p(sex) = 0.31). The opposite is true of the affect component ($F(2,148) = 34.42$; $p < .001$), for which BD is more compromised than SZ in the affective core (p(SZ-BD) < 0.001). No significant effect was found when controlling for age and sex as covariates (p(age) = 0.45; p(sex) = 0.74). In Fig. 2B, all three groups show the continuum across the cognitive and affective dimensions.

4. Discussion

In the present paper, we tested the expanded continuum hypothesis between schizophrenia (SZ) and bipolar disorder (BD). Although the emerging hypothesis of a continuum between these two syndromes is appealing, we believe its original formulation is too simplistic when considering these disorders in a wider perspective. To better characterize this continuum, we analyzed profiles of SZ and BD both at the neural and at the psychological level. First, a whole brain multivariate

Table 2
Independent component 18. Talairach labels of regions of interest, Brodmann area, volume (expressed in cc) and max values coordinates are shown.

Area	BA	volume (cc)	Max value (x, y, z) L/R
Culmen	*	1.5/1.6	4.9 (−3, −59, −6)/5.1 (1, −59, −6)
Posterior cingulate	23,29, 30	1.2/1.1	10.3 (−22, −59, 8)/7.3 (22, −62, 10)
Precuneus	7, 19	1.1/0.5	8.3 (−25, −61, 35)/6.9 (33, −64, 35)
Inferior parietal lobule	39	1.0/1.3	7.2 (−27, −64, 32)/9.2 (30, −61, 33)
Declive	*	0.8/0.8	4.8 (0, −63, −14)/4.5 (4, −63, −13)
Cuneus	17, 30	0.8/0.4	9.1 (−19, −68, 9)/5.5 (19, −68, 13)
Posterior cingulate	23	0.6/0.5	9.7 (−22, −55, 8)/8.2 (25, −53, 8)
Lingual gyrus	18, 19	0.6/0.1	6.1 (−21, −55, 4)/4.2 (21, −48, 2)
Inferior temporal gyrus	20	0.4/0.0	4.3 (−56, −27, −21)/ -
Parahippocampal gyrus	30	0.3/0.2	5.9 (−16, −49, 5)/4.9 (25, −49, 4)
Lateral ventricle	*	0.1/0.3	7.1 (−27, −58, 8)/6.3 (27, −49, 8)
Intraparietal sulcus	39	0.1/0.1	4.2 (−31, −61, 36)/3.8 (33, −55, 36)
Superior parietal lobule	7	0.1/0.0	4.0 (−25, −60, 43)/−
Fusiform gyrus	20	0.1/0.0	3.7 (−50, −23, −24)/−
Middle frontal gyrus	9	0.0/0.1	− /4.1 (37, 16, 31)
Fourth ventricle	*	0.0/0.1	− /3.7 (1, −52, −29)

Table 3
Independent component 6. Talairach labels of regions of interest, Brodmann area, volume (expressed in cc) and max values coordinates are shown.

Area	BA	Volume (cc)	Max value (x, y, z) L/R
Angular gyrus	39,9	0.3/0.0	3.8 (−27, −67, 31)/ −
Middle frontal gyrus		0.0/0.2	− /4.5 (28, 31, 27)
Precuneus	39,7	0.2/0.1	4.4 (−25, −64, 34)/4.3 (25, −59, 40)
Middle frontal gyrus	9,6	0.1/0.1	5.0 (−33, 26, 28)/3.6 (27, 2, 45)
Inferior parietal lobule	39	0.1/0.0	4.6 (−42, −62, 13)/ −
Superior frontal gyrus	10	0.1/0.0	4.0 (−25, 52, −5)/ −
superior parietal lobule	7	0.0/0.1	− /3.6 (25, −62, 43)

morphometric method was applied to test for differences and similarities in a three-group (SZ, BD, HC) analysis. Source-based Morphometry (SBM) - a multivariate procedure based on independent component analysis - was used to analyze structural image data of patients suffering from SZ or BD, and of matched controls. Notably, this is the first application of SBM for the comparative investigation of the neural bases of SZ and BD patients. Unlike previous approaches, such as Voxel-based Morphometry (VBM) or ROI-based analyses between groups, SBM is a multivariate data-driven approach to analyze the interrelationships among voxels in order to identify naturally grouped circuits. This approach allowed us to detect different levels of expression in maximally independent networks in gray-matter concentrations (Xu et al., 2009).

The hypothesis of a psychotic continuum is partially supported as we found clear evidence in SZ and BD of an altered network of brain areas, when compared to HC, which could represent the neural underpinnings of an altered interpretation of reality connected with psychosis that affects both disorders. As predicted, some differences emerged when directly comparing the two clinical conditions. These differences allow us to formulate an expanded version of the continuum hypothesis that could explain cognitive and affective differences between the two clinical populations considered. In the following sections, we discuss the hypothesis and the supporting evidence in more detail.

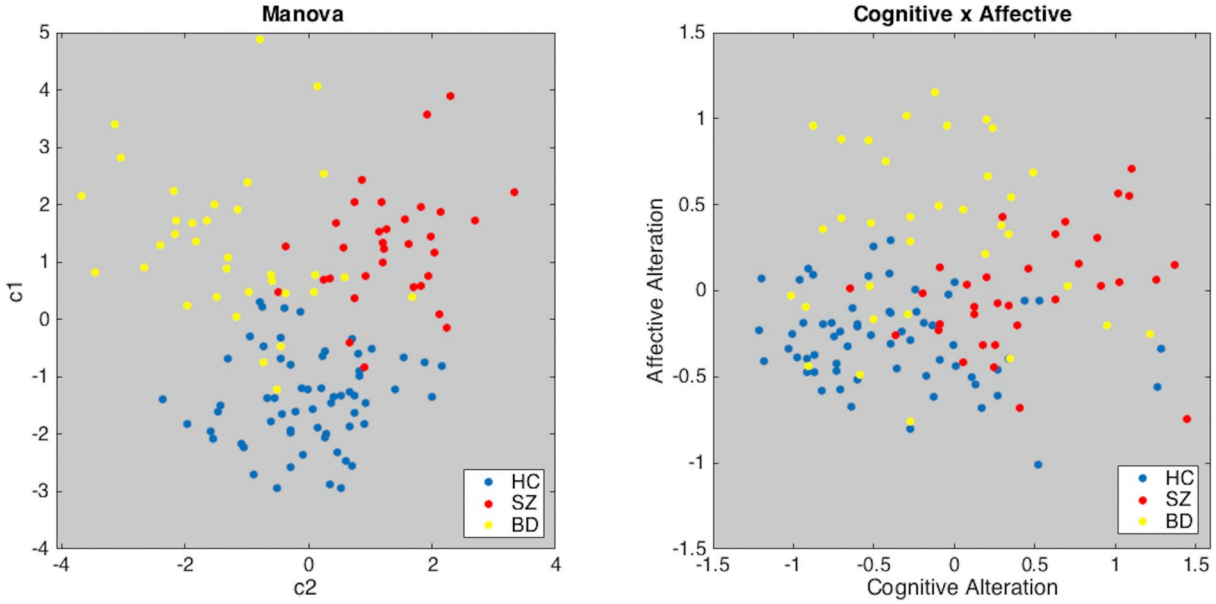

Fig. 2. Psychological profile. A) Manova results. Each point represents the values of the first two canonical variables (c1 and c2) of each participant (HC in blue, SZ in red and BD in yellow). It is evident that c1 separates the HC group from SZ and BD, while c2 separates the two clinical groups. B) Cognitive and Affective Scores. Each point represents the mean values for each participant (HC in blue, SZ in red and BD in yellow) of the standardized scores of some cognitive and affective scores. It is evident that both dimensions rely on a continuum: HC < BD < SZ when considering the cognitive alteration, and HC < SZ < BD when considering the affective alteration.

4.1. Neural evidence of the psychotic core

In the present study, we found an overlap of abnormal cortical regions for schizophrenia and bipolar disorder, when compared to controls. These results are in line with the hypothesis of a *continuum of psychosis*, (Pearlson, 2015; Cheniaux et al., 2008; Möller, 2003; Benabarre et al., 2001; Crow, 1986), according to which bipolar disorder and schizophrenia occur across a continuum rather than existing as discrete, non-overlapping entities (Crow, 1990; Rosen et al., 2012; Martinez-Aran and Vieta, 2015; Bora and Pantelis, 2015; Goodkind et al., 2015); and, along this continuum, prototypic individuals fall at the extremes (SZ vs. BD) while a large group of patients rely between them, showing a mixture of symptoms. (Keshavan et al., 2013).

The present study extends such results by providing evidence concerning the neural substrates of these similarities. We found a network (Fig. 1A, Table 2) including ventrotemporal, medial parieto-occipital areas, as well as portions of the cerebellum and the middle frontal gyrus, similarly impaired in both clinical groups (no difference between SZ and BD in this circuit) with respect to controls. In previous studies, these areas have been found to exhibit structural abnormalities in both schizophrenic (Kaspárek et al., 2010; Gupta et al., 2015; Laidi et al., 2015) and bipolar patients (Lochhead et al., 2004; Ha et al., 2009; Rimol et al., 2010). One possibility is that this network could reflect the psychotic functioning common in SZ and BD involving altered information processing of these areas that affects the evaluation and interpretation of reality at different perceptual stages. On a finer grained level the “psychotic functioning” of our hypothesis could be explained by an altered neuronal activity due to genetic predisposition. For example, altered information processing can emerge due to neurotransmission alterations (e.g. such as shifts in the balance of excitation and inhibition) (Tatti et al., 2016; Yizhar et al., 2011) characteristic of both disorders (Perova et al., 2007; Anticevic and Lisman, 2017). Regarding our morphometric results, this altered functioning could influence information processing, ranging from basic representation of visual inputs in the ventro-temporal areas to more complex integration and interpretation of sensory stimuli, thoughts and experiences, probably involving parietal, frontal and cerebellar areas.

Indeed, neuropsychological evidence shows that brain damage in these regions, such as the cerebellum, posterior temporo-parietal areas, and fronto-temporo-parietal areas, particularly in the right hemisphere may produce psychotic symptoms (Rabins et al., 1991; Kumral and Ozturk, 2004; Bielawski and Bondurant, 2015; Stangeland et al., 2018), such as multimodality hallucinations (Ffytche and Wible, 2014). More specifically, the abnormality of the ventro-temporo occipital area of SZ and BD (Lochhead et al., 2004; Mcdonald et al., 2000) may underlie visual processing impairments characteristic of both disorders (Doniger et al., 2002; Butler et al., 2008; O'Bryan et al., 2014; Fernandes et al., 2017), altering the information needed for real-world perception (Ffytche and Wible, 2014; Logothetis et al., 1995).

The parietal impairments of this network, instead, could result in abnormalities in higher cognitive processes that can create abnormal perceptions of reality, such as multimodal integration in heteromodal cortices (Andreasen, 1997; Arzy et al., 2006), aberrant saliency of stimuli in the intraparietal cortex (Wolter et al., 2016), and dysfunctional representation and consciousness of self-related concepts (Torrey, 2007). Indeed, inferior parietal and nearby areas also mediate one's intentions together with the feeling of being the agent of the movement (Ffytche and Wible, 2014; Desmurget et al., 2009). Abnormal activity or damage in these areas may cause alterations in self-other discrimination (Uddin et al., 2006), altered experience of the self (e.g., out-of-body experience) and the perception of a “presence” (Blanke and Arzy, 2005; Brugger et al., 2006; Wible, 2012). Also, the precuneus and the posterior cingulate cortex, impaired in this network, are related to self-reflection in SZ (Meer et al., 2012), internal cognition, and cognitive insight (Leech and Sharp, 2013; Zhang et al., 2015). Finally, altered functioning of associative thinking relying on the inferior parietal lobule has been found in both SZ and BD (Jamadar et al., 2013), probably affecting aberrant thinking.

Therefore, we can hypothesize that the information coming from different senses would be altered due to deficits in the temporo-occipital area. This information would be further distorted in its integration and interpretation due to the parietal impairment together with other heteromodal association areas such as the dorsolateral prefrontal cortex. As a result, the patient would be flooded by sensory stimulation, unable to integrate sensory data in a coherent pattern, from early sensations to the creation of intentions and self-related concepts. To conclude, these areas may underlie a psychotic core that alters the perception of reality and the feeling of agency that, in turn, lead to delusional episodes (Wible, 2012; Torrey, 2007).

4.2. Neural evidence of the cognitive and affective cores

Our analysis showed not only common abnormalities between these disorders but also differences. In particular, the direct comparison between the two clinical groups showed that SZ are characterized by broader gray matter deficits in a network (IC6) including fronto-parietal areas (Fig. 1B, Table 4), such as the superior and middle frontal gyrus (SFG, MFG), the angular gyrus and the medial superior parietal lobule (SPL).

The widespread fronto-parietal gray matter loss characterizing schizophrenic patients is widely reported in literature (Minzenberg et al., 2009; Repovš and Barch, 2012), possibly reflecting the greater severity of cognitive impairment in domains such as executive function, verbal memory, fluency and working memory of this group of patients (Krabbendam et al., 2005; Selva et al., 2007; Bora and Pantelis, 2015; Bortolato et al., 2015). These abnormalities in cognitive areas are also confirmed by the cognitive performance in several higher functions of SZ (see 4.3). Interestingly, cognitive impairment has been proposed as a possible discriminant factor for the categorical diagnoses of SZ and BD conditions, particularly involving greater memory deficits in the former (Rheenen et al., 2016). Interestingly, cognitive and metacognitive deficits predict the presence of clinical symptoms, regardless of the diagnosis -SZ vs. BD- (Varga et al., 2007; Popolo et al., 2017). Since these deficits seem more related to SZ diagnosis (Tas et al., 2014), they could explain the more severe emergence of psychotic symptoms in this clinical group (Hugdahl et al., 2013; Jenkins et al., 2017).

Our morphometric results are in line with this hypothesis. The fronto-parietal network is reduced in SZ when compared to BD and could be associated to cognitive impairment, in particular of working memory. Indeed, training of this cognitive function has been found to increase gray matter in these areas (Klingberg, 2010; Olesen et al., 2003). Furthermore, a reduction in the activation of similar areas has been found in schizophrenia patients during working memory (Schneider et al., 2007; Barch and Csernansky, 2007) and goal maintenance tasks (Poppe et al., 2016). Notably, it has been proposed that a common mechanism underlying the different cognitive impairments across a range of domains characterizing schizophrenia, such as working memory, episodic memory and context processing, could be the inability to actively represent goal information in working memory. Our results support the fact that this ability seems to rely on the dorsolateral prefrontal cortex interacting with other brain regions, in particular the parietal cortex (Barch and Ceaser, 2012; Jamadar et al., 2013).

In the morphometric analyses, partial evidence of greater gray matter reductions in BD when compared to SZ emerged too (see supplementary materials). Using a more liberal threshold, three ICs were found, including portions of the temporal lobe, cerebellar and occipital areas. These areas may be connected with stronger affective disturbances (mood lability, lack of self-control, depressive symptoms and others), displayed by BD and less so by SZ. Indeed, the cerebellum, whose alteration is displayed in different psychiatric conditions including bipolar disorder, is not only associated with control of balance

and intentional voluntary movement, but also with other functions such as emotional processing (Phillips et al., 2015; Minichino et al., 2014). Further, temporal aberrant activity and connectivity has been associated with depressive symptoms and depression (Kumari et al., 2003; Garcia, 2012; Ma et al., 2012). Finally, bipolar disorder seems to be associated with a diminished prefrontal modulation of subcortical and temporal structures that result in mood dysregulation (Strakowski et al., 2004).

In sum, the presence of a continuum characterized by three separate dimensions (the psychotic, cognitive and affective cores) is supported by our results at a neural level.

4.3. Psychological evidence of the psychotic, cognitive and affective cores

The correlation between the first canonical variable of the MANOVA and the common network (IC18) of the SBM analysis confirmed the presence of psychotic disturbances in both groups. In our model, this psychotic core represents a common altered mechanism underlying SZ and BD, whose evidence is found not only at a neuroanatomical level, but also at a psychological one, as a latent variable emerged from all tasks and questionnaires we took into account.

Besides similarities, the cognitive impairment in SZ is more marked when compared to BD and HC, possibly worsening the psychotic functioning shared by SZ and BD. Indeed, a deficit in working memory, more associated with SZ diagnosis and probably related to genetic predisposition (Hill et al., 2013), may affect the emergence of marked psychotic symptoms, probably due to the decreased top-down cognitive control needed to suppress attention to the "voices" and other perceptual alterations (Hugdahl et al., 2013). Consistent with our hypothesis, cognitive alterations (Fig. 2A) seem to be arranged on a continuum where BD lies between HC and SZ, (Brandt et al., 2014; Sheffield et al., 2018), predicting the presence of auditory hallucinations in both clinical groups regardless of the diagnosis (Jenkins et al., 2017).

On the other hand, the affective profile (Fig. 2B) emerging from the questionnaires shows a greater alteration of individuals diagnosed with BD, when compared to SZ and HC. This is especially true for mood and impulsivity measures. Indeed, BD patients are characterized by high impulsivity scores, which are strongly related to manic symptom severity, especially in relation to the experience of strong positive emotions (Muhtadie et al., 2013). It has been suggested that impulsivity represents a trait component of BD, and therefore, a core feature of the illness (Najt et al., 2007). Interestingly, impulsivity in BD is greater than in SZ (Reddy et al., 2013), and self-reported impulsivity is related to a more severe course of BD illness (Swann et al., 2009) and emotion dysregulation (Schreiber et al., 2012). The affective profile too shows a continuum where, in this case, SZ lies in between BD and HC. In sum, the presence of a continuum characterized by three separate dimensions (what we call the psychotic, cognitive and affective cores) is confirmed by our analyses at a psychological level.

5. The expanded continuum hypothesis

Building on our results, we would like to stress the importance of adopting an expanded view of the continuum hypothesis (Derosse and Karlsgodt, 2015; Craddock and Owen, 2010). In particular, in this paper we aimed to better define the hypothesis of a continuum between SZ and BD. Our model confirms and posits that a common *Psychotic core* is shared by SZ and BD (the "P" in the model, Fig. 3). This core may be responsible for the altered reality perception and interpretation, together with the resulting lack of self and behavioral control that can lead to the common symptoms of SZ and BD. The altered network shared by SZ and BD (Fig. 1A) would represent the neural basis for their psychotic functioning, involving portions of the medial parietal and temporo-occipital areas, the cerebellum, and the middle frontal gyrus. When strongly altered, this network may be responsible for the psychotic symptoms. Noteworthy, this common network could differentially affect, and be affected by, more prototypical deficits, influencing the content and the extent of psychotic symptoms.

Besides the *Psychotic core*, two additional cores should be included for the model to fit with the empirical data: the *cognitive core* (The "C" in the model), and *the affective core* ("A"). The cognitive core refers to general cognitive dysfunction involving domains such as working memory (WMS), verbal and reasoning abilities (WAIS) and executive functioning (DKEFS). Psychological evidence for this core is given by the cognitive tasks (Fig. 2B) while neural evidence can be represented by IC6, which emerged in the SZ-BD direct morphometric analysis (Fig. 1B, Table 3). The C is largely compromised in SZ and less so in BD (Fig. 2B, Table S6). The *affective core* refers to an affective alteration involving domains such as mood, emotions and impulsivity. Psychological evidence for this core is found in testing scores on self- control (BIS), Mood Liability (BIP), dysfunctional impulsivity (Dickman), depression and anxiety (Hopkins). Considering a more liberal threshold, neural evidence for this core can be represented by the morphometric results involving reduced brain areas in BD (see Supplementary Materials, Tables S3, S4, S5). The A is largely compromised in BD and less so in SZ (Fig. 2B, Table S6).

To sum up, the expanded continuum model we are suggesting contains three cores: psychotic, cognitive, and affective. Each core represents a continuum where different individuals regardless of diagnosis can show different levels of impairment, even if the C alteration is more prototypical for SZ and the A alteration is more prototypical for BD (Fig. 2B).

Even though further data and analyses are needed to test for the functional implications of our results, they provide morphometric evidence for a continuum between SZ and BD that we interpret as underlying a psychotic core of altered perception and interpretation of reality. Further analyses are also required to test whether this network could apply to other mental illness conditions besides SZ and BD. This would be in line with Caspi et al. (2013) that one factor may underlie psychopathology involving difficulties in regulation and control. And, that this factor might explain why severe disorders tend to be comorbid, concurrently and sequentially.

To conclude, we recommend that clinical morphometric studies should rely on both direct comparisons between different patient groups and healthy controls. This will improve our diagnostic systems with morphometric evidence, and it will allow us to discern the underlying common factors across mental disorders that can emerge through extended comparisons.

6. Limitations

Some limitations of the study regards the brain evidence of the expanded continuum we provided, as we found only partial confirmation of an affective core at a brain level, since significant brain reduction in BD when compared to SZ was evident only when considering a more liberal threshold. Nonetheless, from a neural point of view, BD rarely shows gray matter reductions when compared to SZ (Maggioni et al., 2016). Future studies may want to find clearer evidence of the affective core at the neural level to match the results found at the psychological level.

Another point that needs to be further explored is the psychotic aspect of the continuum at a psychological level. Unfortunately, the dataset we used did not contain psychosis-related measures for our analysis, since results from healthy populations on this topic were not considered. So, further data and analyses are required to better characterize the psychosis continuum from a normal to a pathological population.

Finally, our analyses did not show significant subcortical differences between groups as one may expect. This may be due to alteration of the gray matter linked to the pharmacological treatments patients are subjected to (Krause and Pogarell, 2017). Unfortunately, the database we considered does not allow clarifying this point.

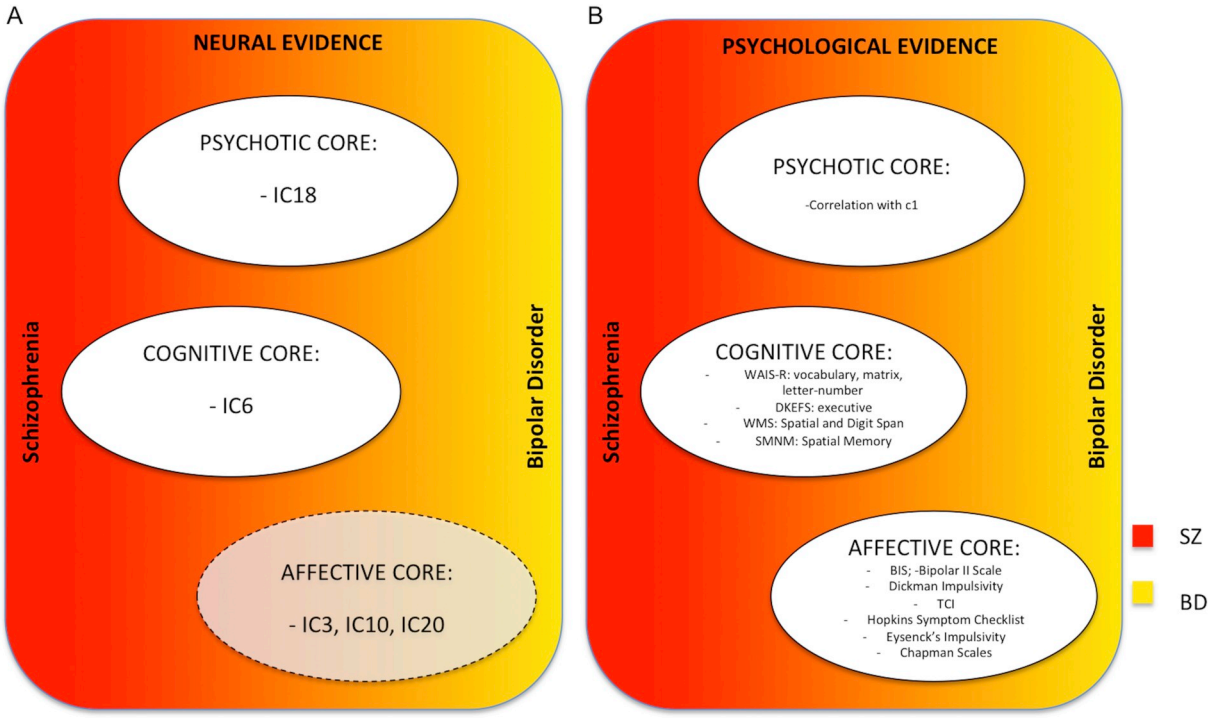

Fig. 3. The expanded continuum model. A) *Neuronatomical evidence*. The "P" (Psychotic Core) represented by IC18, the common altered network between SZ and BD when compared to HC. We suggest that this network could be responsible of a common shared psychotic functioning, probably involving an altered information processing and elaboration (Fig. 1A). The "C" (Cognitive Core) could be represented by IC6, the reduced network characterizing SZ when compared to BD (Fig. 1B). The "A" (Affective Core) could be represented by IC3, IC10, IC20 (Supplementary Materials). B) *Psychological evidence*. The "P" represents a common latent variable that emerged in the MANOVA analysis (c1), which seems to separate HC on the one side and SZ and BD on the other side (see Fig. 2A). The "C" is more impaired in SZ (Fig. 2B), and includes working memory, executive, reasoning, and vocabulary tasks. The "A" Core is more impaired in BD (Fig. 2B), and includes different impulsivity, temperament and character measures and bipolar symptoms.

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Appendix A. Supplementary data

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