

Distinct structural brain circuits indicate mood and apathy profiles in bipolar disorder

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ABSTRACT

Bipolar disorder (BD) is a severe manic-depressive illness. Patients with BD have been shown to have gray matter (GM) deficits in prefrontal, frontal, parietal, and temporal regions; however, the relationship between structural effects and clinical profiles has proved elusive when considered on a region by region or voxel by voxel basis. In this study, we applied parallel independent component analysis (pICA) to structural neuroimaging measures and the positive and negative syndrome scale (PANSS) in 110 patients (mean age 34.9 ± 11.65) with bipolar disorder, to examine networks of brain regions that relate to symptom profiles. The pICA revealed two distinct symptom profiles and associated GM concentration alteration circuits. The first PANSS pICA profile mainly involved anxiety, depression and guilty feelings, reflecting mood symptoms. Reduced GM concentration in right temporal regions predicted worse mood symptoms in this profile. The second PANSS pICA profile generally covered blunted affect, emotional withdrawal, passive/apathetic social withdrawal, depression and active social avoidance, exhibiting a withdrawal or apathy dominating component. Lower GM concentration in bilateral parietal and frontal regions showed worse symptom severity in this profile. In summary, a pICA decomposition suggested BD patients showed distinct mood and apathy profiles differing from the original PANSS subscales, relating to distinct brain structural networks.

1. Introduction

Bipolar disorder (BD) is a debilitating psychiatric disorder that causes morbidity and disability worldwide throughout the lifespan (Grande et al., 2016; Merikangas et al., 2011). Despite continuous research efforts, the neurobiological mechanism of BD remains unclear (Dunner, 2003; Lawrie et al., 2016). However, noninvasive brain imaging such as structural magnetic resonance imaging (sMRI) has successfully characterized BD with wide range brain abnormalities (Hibar et al., 2018).

In the recent large cohort meta-analysis of sMRI studies, the ENIGMA (Enhancing Neuro Imaging Genetics Through Meta-Analysis) bipolar working group identified consistent and robust subcortical volume differences including smaller hippocampus, thalamus and enlarged lateral ventricles (Hibar et al., 2016), and thinner frontal, temporal and parietal cortex (Hibar et al., 2018) in patients compared to

controls. These differences show overlap with volumetric differences also found in schizophrenia (SZ) but are not as marked (Rimol et al., 2010; Rimol et al., 2012; van Erp et al., 2018); they are also similar but not identical to differences found in major depressive disorders (MDD) (Wise et al., 2017).

BD patients can exhibit a wide range of cognitive deficits and symptoms, which overlap with other psychiatric disorders (Hozer and Houenou, 2016; Whalley et al., 2012). Various cognitive domain deficits have been related to corresponding brain regions in BD (Fears et al., 2015; Gutierrez-Galve et al., 2012; Kieseppa et al., 2014; Killgore et al., 2009; Shepherd et al., 2015). The clinically observed behaviors and symptoms are even more difficult to explore, and yield inconsistent findings (Sharma et al., 2017; Wise et al., 2017). BD are often studied together with MDD for mood symptoms or together with the schizophrenia spectrum for psychosis symptoms. Though BD along with MDD commonly show reductions in prefrontal, frontal, temporal and anterior

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cingulate cortex (Han et al., 2019), the relationship with depression severity is unclear and inconsistent (Wise et al., 2017). Mania, however, shows a close relationship with prefrontal regions, and the onset times of mania leading to reduction of GM (Abe et al., 2015). Anhedonia severity relates to some shared deficits in the reward system in BD, MDD, and SZ (Nusslock and Alloy, 2017; Redlich et al., 2015; Sharma et al., 2017). Similar to SZ, BD subjects show cortical deficits in frontal and temporal regions associated with positive symptoms, and frontal regions also with negative symptoms (Hartberg et al., 2011; Padmanabhan et al., 2015; Strauss et al., 2019). However, many of these associations are inconsistent due to the disorders' heterogeneity, both in terms of brain structural underpinnings (Wolfers et al., 2018) and clinical symptoms (Nunes et al., 2018). Considering the complexity, it is important to study the patients' symptoms from a multivariate profile point of view, and the aggregation of regional brain alterations may help to reveal the brain mechanism behind specific symptom profiles (Liu and Calhoun, 2014; Xu et al., 2009).

To comprehensively assess and create a clinical profile on heterogeneous BD patients and clinical observations, the positive and negative syndrome scale (PANSS) (Kay et al., 1987) can be an appropriate tool. The PANSS provides a wide range assessment including positive, negative and general symptoms, and it is useful to detect psychotic symptom groups and behavioral traits. In PANSS, the positive symptoms score includes delusions, conceptual disorganization, hallucinations, excitement, grandiosity, suspiciousness, and hostility. The negative scores include blunted affect, emotional withdrawal, poor rapport, passive/aphathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation, and stereotyped thinking. Importantly, PANSS has already proved its usefulness in discovering the potential relationship between clinical dimensions and brain alterations (Koutsouleris et al., 2008; Wang et al., 2018). The PANSS positive symptom severity has been associated with GM concentrations in left perisylvian regions and thalamus, and negative symptom severity with orbitofrontal, prefrontal, temporal and limbic regions in SZ (Koutsouleris et al., 2008). However, a study using the functional connectome identified the fronto-parietal control network and sensorimotor regions to be associated with PANSS positive in SZ, while in BD it is the visual and default mode network (Wang et al., 2018). The inclusion of PANSS in previous studies, however, are often still limited to the originally designed positive, negative and general subscales (Walton et al., 2017; Walton et al., 2018).

Here, we employ parallel independent component analysis (pICA) to reveal the relationship between clinical profiles and the structural brain patterns of BD patients. pICA is a higher order statistical method which can be used to establish association between different data modalities (Calhoun et al., 2009; Chen et al., 2013; Liu et al., 2009; Meda et al., 2012; Pearson et al., 2015). Single-modality ICA identifies maximally independent components through blind source separation in one data modality. pICA performs individual ICA on two data modalities simultaneously, and it aims to maximize independence in each modality while optimizing the correlation between the components from both modalities. The output of pICA provides the correlation between two modalities, and loading coefficients of both modalities are calculated for each subject which indicate the contribution of the generated pattern to the subject's original data. This blind source separation proceeds automatically, and no prior knowledge and intervention needs to be taken into account for this analytical method (Gupta et al., 2015). Previous pICA analysis in SZ has provided a mapping of symptom profiles onto the brain structures, and a distinct PANSS profile characterized by delusions, suspiciousness, hallucinations, and anxiety was associated with GM concentration patterns including inferior temporal gyrus, fusiform gyrus and the sensorimotor cortex (Mennigen et al., 2019).

In this study, pICA was performed on GM concentration and PANSS items scores obtained from 110 BD patients. We hypothesized that pICA would identify multimodal components reflecting the joint variance between specific PANSS profiles and distinct structural brain patterns.

Specifically, based on the studies reviewed above, we hypothesized that pICA would reveal patterns implicating persistent behavioral deficits and fronto-parietal brain networks.

2. Materials and methods

2.1. Participants

This study used data from 110 patients with bipolar I ($n = 69$) or II ($n = 41$) diagnoses from the Thematically Organized Psychosis (TOP) study at the Norwegian Centre for Mental Disorders Research (NORMENT) in Oslo, Norway (Rimol et al., 2012; Ringen et al., 2008). All data were collected with approval from the local institutional review board, and all participants signed informed consent. Patients met following criteria to be included in the study: 1) aged from 18 to 65 years; 2) understood and spoke a Scandinavian language; 3) had no history of severe head trauma; 4) had IQ over 70. The diagnosis of bipolar I (DSM-IV 296.0-7) and bipolar 2 (DSM-IV 296.89) was established by the Structured Clinical Interview for DSM-IV Axis I Disorders. At the stage of enrollment, the mood status of the patients was identified as depressive ($n = 60$), manic ($n = 5$), euthymic ($n = 40$), mixed ($n = 2$) and unspecified ($n = 3$). In addition, 54 patients (approximately 50%) experienced at least one lifetime psychotic episode. PANSS scores and structural MRI data were available for all the participants, and detailed demographic and scanning information are presented in Table 1.

2.2. Positive and negative symptom scores (PANSS)

All participants provided complete PANSS item scores, which included all 30 items of PANSS with positive, negative and general symptom dimensions.

2.3. Neuroimaging acquisition and preprocessing

All patients were scanned on a 1.5T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) scanner. T1-weighted structural MRI data were collected using a MPRAGE sequence. T1-weighted images were normalized to the standard Montreal Neurological Institute (MNI) template using a 12-parameter affine model, resliced to a voxel size of $2 \times 2 \times 2$ mm and segmented into GM, white matter, and cerebro-spinal fluid using Statistical Parametric Mapping 12 (SPM12, <http://www.fil.ion.ucl.ac.uk/spm/software/spm12/>). To identify possible outliers, individual scans were correlated with group GM template, and the correlation was computed. One subject showing low correlation with the group GM template ($\rho < 0.98$) was excluded. 109 participants were included in following analysis. Voxel-wise regression of age and gender was performed to remove their possible effects. Structural MRI data were smoothed with a 10 mm full width at half maximum Gaussian kernel (Gupta et al.,

Table 1
Demographic and scanning information, $N = 110$.

	Mean	SD
Age(years)	34.87	11.65
Females (N/%)	72 (65%)	
Duration of illness(years)	12.13	10.09
PANSS positive score	9.81	3.28
PANSS negative score	9.75	3.54
PANSS general score	25.42	5.82
PANSS total score	44.96	10.33
Field strength (T)	1.5	
Sequence	MPRAGE	
Voxel size (mm)	$1.33 \times 0.94 \times 1$	
Scanning orientation	Sagittal	

PANSS: Positive and Negative Syndrome Scale.

2015).

2.4. Parallel independent component analysis (pICA)

Fusion ICA Toolbox (FIT, <http://mialab.mrn.org/software/fit/>) was employed to perform pICA on the preprocessed structural images and PANSS item scores. The optimal component number of structural MRI data was estimated to be 25 by the minimum description length (MDL) algorithm (Rissanen, 1978). The components for PANSS items was set to three according to its inner structure (positive, negative and general symptom dimensions). A GM mask was applied on structural images before ICA was performed. To ensure stability of component estimation, infomax ICA was run 20 times, and the central point of 20 runs was selected as the final component using ICASSO (Himberg et al., 2004). Using the default setting of pICA, three components in each modality were constrained to be optimized (Liu et al., 2009). More specifically, the correlation between the loading coefficients of sMRI and PANSS was optimized through pICA while independence within each modality was further maximized.

2.5. Validations

After the original pICA analysis, 10-fold cross-validation was performed to ensure that the pICA estimation was not driven by a subset of participants or potential outliers. Each validation run included 90% of the individuals of the sample. Parameter settings of 10-fold validation were essentially the same as the original analysis. The results from each fold were examined for overlap with the original pICA.

2.6. Additional analysis

To control possible confounders, duration of illness (DOI) and current medication status were assessed in this study. The current medication status was included as a binary variable according to whether or not the patient was currently on antipsychotic, antiepileptic or lithium treatment (Hartberg et al., 2015; Jorgensen et al., 2016). The medication effect was tested on GM concentrations and PANSS loading coefficients.

The relations of original PANSS subscale scores (positive, negative and general symptoms), PANSS loading coefficients and sMRI loading coefficients from pICA were also assessed.

3. Results

3.1. Parallel independent component analysis

Two pairs of sMRI and PANSS components showed significant correlations, passing the Bonferroni correction threshold of 6.67×10^{-04} (determined by 25 sMRI components and 3 PANSS components). In the first pair of components, the correlation between the structural MRI and PANSS components was Pearson's $r = -0.41$ ($p = 7.67 \times 10^{-06}$) (Fig. 1). In the second pair, the correlation was Pearson's $r = -0.35$ ($p = 1.80 \times 10^{-04}$) (Fig. 3). The negative correlation indicated that greater loading coefficients of sMRI correlated with lower loadings of symptom profile represented by PANSS.

In the first pair, the sMRI component showed positively contributing GM concentration mainly in right middle/superior temporal gyrus in the more medial aspect (extended to inferior frontal gyrus, see Fig. 2a and Table 2). The corresponding PANSS component was positively weighted strongly on anxiety (G2), guilty feelings (G3) and depression (G6); the lack of spontaneity and flow of conversation (N6) was negatively associated with this component (Fig. 2b). Participants with higher preserved GM concentration in right superior/middle temporal gyrus exhibited reduced severity in these symptoms consisting of anxiety, guilty feelings and depression.

In the second pair, positively contributing GM concentration was

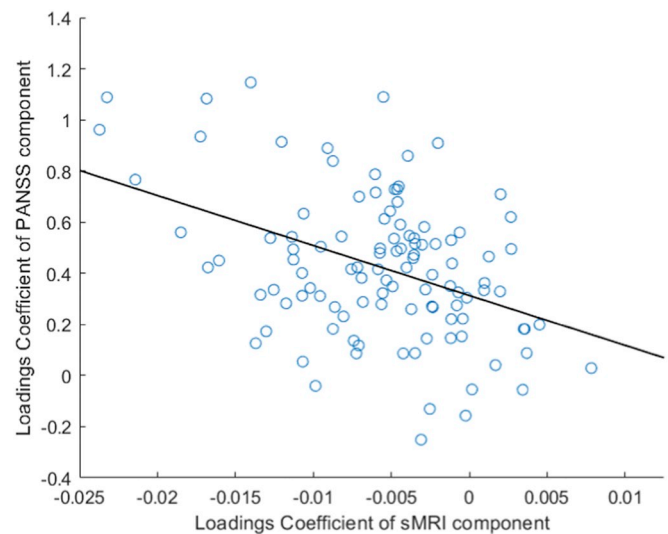


Fig. 1. Negative correlation between loading coefficients of the first PANSS component and sMRI component.

Pearson's $r = -0.41$, $P = 7.67 \times 10^{-06}$ (Bonferroni-corrected threshold = 6.67×10^{-04}).

mainly located in bilateral middle frontal gyrus, bilateral parietal lobe including postcentral gyrus with temporal regions on the left side (left inferior, middle and superior temporal gyrus), and negatively contributing GM concentration was located in left supramarginal gyrus for the sMRI component (see Fig. 4a and Table 2). The PANSS component was positively weighted strongly on blunted affect (N1), emotional withdrawal (N2), passive/apathetic social withdrawal (N4), depression (G6) and active social avoidance (G16), and excitement (P4) and guilty feeling (G3) was negatively associated with this component (Fig. 4b). In summary, participants with higher preserved GMC in bilateral frontal, parietal and left temporal regions show milder severity for these symptoms.

3.2. 10-Fold validation

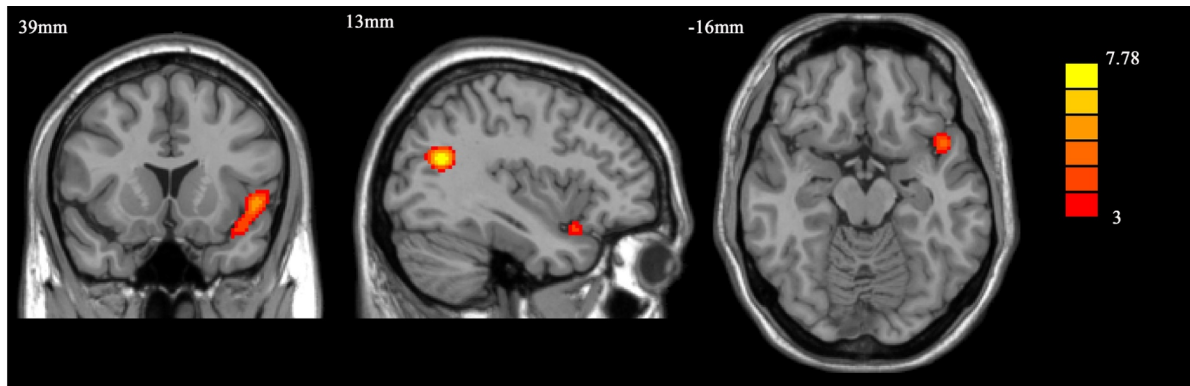
The 10-fold validation showed high correlation with the original pICA results in both of the pairs of components. For the first pair, 7 out of 10 validation runs showed similar results to the original output, with one of run showing an inverted direction of sMRI and PANSS correlation to the other runs. The first pair presented a mean correlation of Pearson's $r = 0.75$ of above replicated runs. The second pair also presented similar stability, with 7 out of 10 validation runs showing similar results to the original output and two of the runs showing inverted direction of sMRI and PANSS correlation to the other runs. The second pair presented a mean correlation of Pearson's $r = 0.67$ of its replicated runs.

3.3. Additional analysis

In the regression model including loadings coefficients of sMRI components as dependent variable and DOI values as predictors, there was no significant association between the DOI and component 1 ($\beta = -0.10$, $t = -1.06$, $p = .29$) or component 2 ($\beta = -0.004$, $t = -0.043$, $p = .97$). The regression model including loadings coefficients of PANSS components as dependent variable and DOIs as predictors also showed no significant association in component 1 ($\beta = 0.01$, $t = 0.08$, $p = .94$) or component 2 ($\beta = -0.05$, $t = -0.49$, $p = .63$).

There was no significant correlation between medication status and the sMRI loading coefficients in component 1 (Spearman's $\rho = 0.10$, $p = .33$) or component 2 (Spearman's $\rho = -0.06$, $p = .56$). In addition,

a) Structural MRI component



b) PANSS component

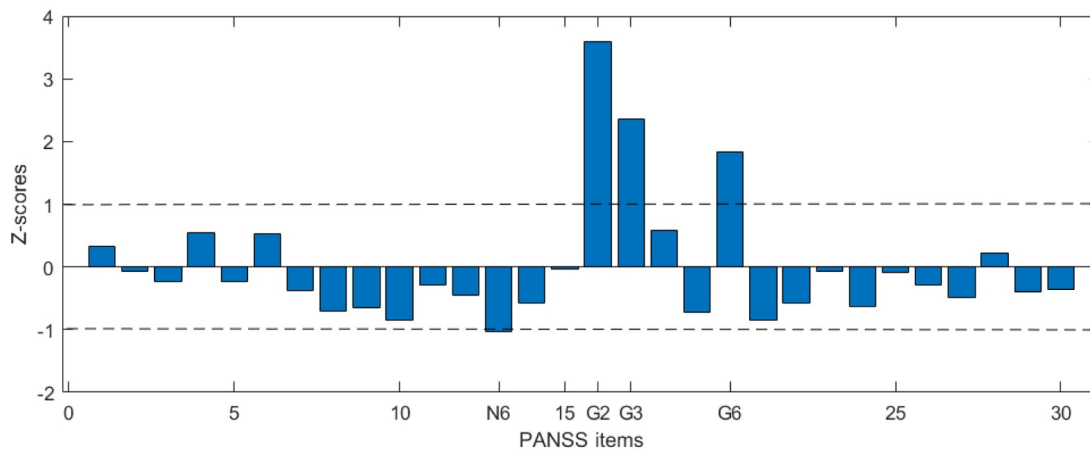


Fig. 2. Parallel ICA results - the first pair – ‘mood’ component a) structural MRI and b) PANSS components. PANSS items with $|Z| > 1$: N6 – Lack of spontaneity and flow of conversation; G2 – Anxiety; G3 – Guilty feelings; G6 – Depression.

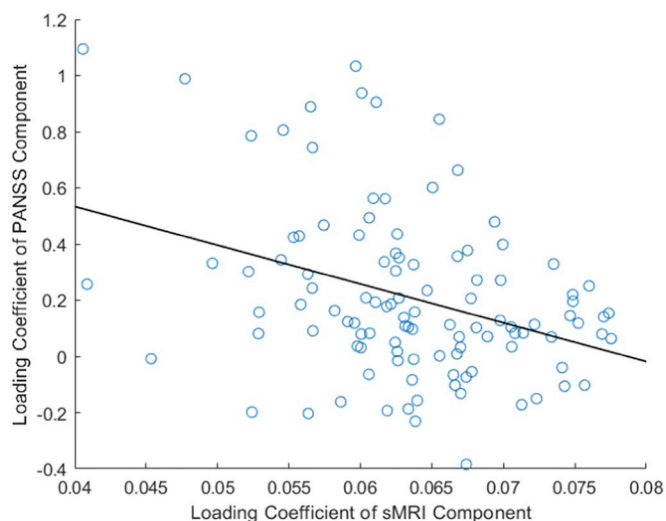


Fig. 3. Negative correlation between loading coefficients of the second pair of PANSS component and the sMRI component. Pearson's $r = -0.35$, $P = 1.80 \times 10^{-04}$ (Bonferroni-corrected threshold = 6.67×10^{-04}).

there was no significant correlation between medication status and the PANSS loading coefficients in component 1 (Spearman's $\rho = -0.06$, $p = .57$) or component 2 (Spearman's $\rho = -0.14$, $p = .88$).

In the first pair, the correlation between the original PANSS subscale scores and the pICA derived PANSS loading coefficients revealed no association with PANSS positive (Pearson's $r = 0.017$, $p = .86$), negative (Pearson's $r = 0.15$, $p = .88$), or general (Pearson's $r = 0.062$, $p = .53$) scores. In addition, sMRI component loading coefficients were not significantly correlated with PANSS positive (Pearson's $r = 0.023$, $p = .82$), negative (Pearson's $r = -0.039$, $p = .69$), and general (Pearson's $r = -0.031$, $p = .75$) scores.

In the second pair, there was also no significant correlation found between the pICA PANSS component loading and PANSS positive (Pearson's $r = 0.074$, $p = .45$), negative (Pearson's $r = 0.11$, $p = .27$), or general (Pearson's $r = 0.11$, $p = .26$) scores. In the sMRI, the loading coefficients were not significantly correlated with PANSS positive (Pearson's $r = 0.072$, $p = .45$), negative (Pearson's $r = -0.031$, $p = .75$) and general (Pearson's $r = -0.061$, $p = .53$) scores.

4. Discussion

In this study, we find two gray matter networks that relate to two different patterns of symptom severity in a large BP sample. Importantly, the PANSS profiles highlighted here were not constructed according to the typical PANSS subscales, but were driven by the

Table 2
Brain regions, peak coordinates and volumes of component 1 and 2.

	Brain regions	Brodmann area	Volumes (cc ³)	Peak coordinates (Z and coordinates)
Component 1				
Cluster 1	R superior temporal gyrus (extended to inferior frontal gyrus & insula)	48	3.6	6.0 (48, 14, -6)
Cluster 2	R middle temporal gyrus	39	2.7	7.8 (38, -62, 22)
Component 2				
Cluster 1/2	L/R parietal lobe (postcentral gyrus)	3,3	5.7/5.5	3.3(-40,-26,40)/5.5(46, -26, 36)
Cluster 3/4	L/R frontal lobe (middle frontal gyrus)	9,8	5.4/3.0	5.4(-26,32,32)/6.4(22, 12, 46)
Cluster 5	L inferior middle temporal gyrus, posterior	37	3.4	7.6(-46,-58,-6)
Cluster 6	L inferior parietal lobule	41	2.9	7.6(-46,-46,22)
Cluster 7	L parietal lobe (L angular gyrus)	7	2.7	7.3(-30,-60,38)
Cluster 8	L supramarginal gyrus	40	4.6	-7.3(-42,-46,38)

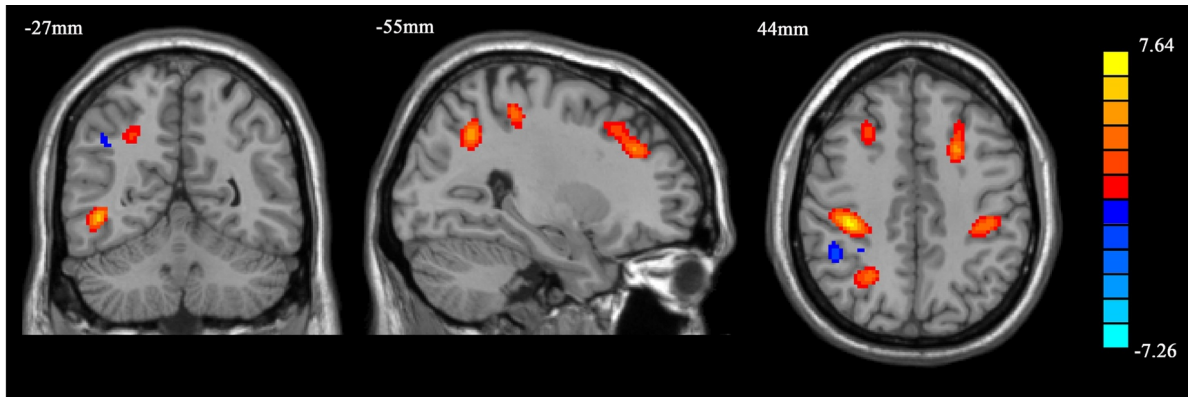
Note: For both components, Z score was set > 3, and cluster volumes were set > 2 cc³ to retain their most significant results. Brodmann areas are listed for the peak coordinates. The directions of peak Z scores indicate whether the brain region contributed positively or negatively to the component as red for positive and blue for negative in brain maps.

underlying relationships with gray matter patterns. The mood profile was correlated with reductions in the right temporal gyrus, while the apathy/asocial profile correlated with a more widespread network including frontal, temporal and parietal regions. It implicated the GM deficits in regional temporal lobe and frontal-temporal-parietal circuits that were separately related to clinical profiles as mood and apathy.

The PANSS component for the first pair mainly included anxiety,

guilty feelings and depression (all Z-scores > 1.5), with the lack of spontaneity and flow of conversation contrasting with those symptoms but less strongly (Z-score = -1.08). This represents a generally negative mood component, differing from the original design of the PANSS of positive, negative and general symptom dimensions. This mood component showed similar affective items emphasized in affective temperaments (Rihmer et al., 2010). In addition, affective

a) Structural MRI component



b) PANSS component

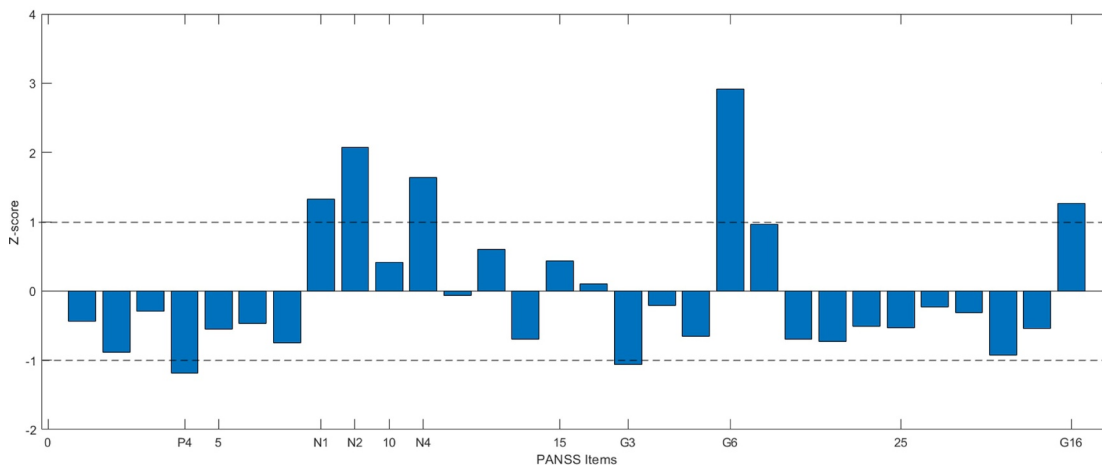


Fig. 4. Parallel ICA results - the second pair - ‘apathy’ component a) structural MRI and b) PANSS components.

PANSS items with $|Z| > 1$: P4 – Excitement; N1 – Blunted affect; N2 – Emotional withdrawal; N4 – Passive/apathetic social withdrawal; G3 – Guilty feelings; G6 – Depression; G16 – Active social avoidance.

temperaments patterns (the relative balance of hyperthymic vs cyclothymic-irritable-anxious-dysthymic) has been significantly associated with hopelessness, negative outcomes, and potential psychopathology (Pompili et al., 2012). The structural brain component for this profile was mainly located in right temporal regions (including middle and superior temporal gyrus extended to inferior frontal gyrus). The negative correlation between components indicated that higher GM concentrations in right temporal regions exhibited milder mood symptoms, or lower concentrations exhibited worse mood.

The temporal regions' deficits are common in BD and other psychiatric disorder (Abe et al., 2016; Hanford et al., 2016; Whalley et al., 2012), though its relationship with mood symptoms can be elusive, and few studies have formed a direct association between the mood symptoms and brain structure alterations (Busatto, 2013; Hozer and Houenou, 2016; Padmanabhan et al., 2015; Palaniyappan and Cousins, 2010; Selvaraj et al., 2012). Among psychiatric symptoms, temporal regions (mostly in superior temporal gyrus) are believed to be important in thought disorders, auditory verbal hallucinations and across the positive symptom domains in psychosis (Cavelti et al., 2018; Morch-Johnsen et al., 2018; Morch-Johnsen et al., 2017; Padmanabhan et al., 2015; Strik et al., 2017), while mood symptoms are usually believed to be centered in the large regions including frontal, temporal and limbic regions (Garety and Freeman, 2013; Lebow and Chen, 2016; Ramirez et al., 2015). The structural brain studies emphasize the important role of multiple involvement of temporal regions especially superior temporal gyrus (Hanford et al., 2016). Cortical thickness in right superior frontal and superior temporal has been negatively correlated with Hamilton Depression Rating Scale (Maller et al., 2014). In addition, cortical thickness reduction in middle temporal gyrus has been negatively correlated with the global assessment of functioning, which indicated worse overall symptoms. However, it must be pointed out that, despite these significant structure/mood symptom studies, there has been even more structural imaging research in BD which reported no correlation between structural alterations and mood symptom severity (Doan et al., 2017; Elvsashagen et al., 2013; Hanford et al., 2016; Lan et al., 2014; Ratnanather et al., 2014). Functional studies have provided some evidence to support the role of superior/middle temporal gyrus in mood regulations (Whalley et al., 2012). An emotional prosody task indicated BD patients exhibited stronger activation in bilateral superior temporal gyrus and right inferior frontal gyrus compared to controls (Mitchell et al., 2004). Also, in an emotional memory task, the role of left superior temporal gyrus was highlighted (Whalley et al., 2009). The exact role of the discovered middle/superior temporal gyrus in modulating such mood components clearly needs to be further investigated.

The PANSS component for the second pair was strongly weighted on blunted affect, emotional withdrawal, passive/apathetic social withdrawal, depression and active social avoidance, while excitement along with guilty feeling was contributing negatively. In addition to negative symptoms, this PANSS component also included all the withdrawal/avoidance items along with depression. The PANSS component here was a combination of negative and general symptoms highlighting behavioral deficits involving asociality. From SZ research, a two-factor model of the PANSS has identified anhedonia-asociality-avolition as a general motivation and pleasure (MAP) factor while alogia/blunted affect as an expressive (EXP) factor. However, asociality was not included in this model (Jang et al., 2016). In addition, when negative symptoms were observed across different psychiatric disorders, *apathy* was another common term to describe such motivational deficits. Moreover, previous studies using subsets of the TOP sample investigated apathy comparing Apathy Evaluation Scale (AES) and PANSS (Faerden et al., 2009; Faerden et al., 2008; Morch-Johnsen et al., 2015). In these studies, emotional withdrawal (N2), passive/apathetic social withdrawal (N4), and lack of spontaneity and flow of conversation (N6) were chosen to form the apathy score from PANSS to compare with AES, while N2 and N4 were chosen according to Marin's definition of apathy (Marin et al., 1991). They found the apathy items from PANSS

significantly correlated with AES.

In this pICA approach we find emotional withdrawal (N2) and passive/apathetic social withdrawal (N4) along with blunted affect (N1) and depression (G6, considering depression's relationship with anhedonia) included in the 'apathy' or withdrawal profile. The role of active social avoidance is more complicated. Active social avoidance refers to the social avoidance caused by unwarranted fear, hostility, or distrust (Hansen et al., 2009). Some studies argue it is weighted on positive symptoms (van der Gaag et al., 2006), while others that it is weighted on depression or anxiety (Bell et al., 1994) or not related to the preset factors of PANSS items (White et al., 1997). We suggest active social avoidance, regardless of its cause, should be seen as part of asociality while grouped into this 'apathy' component. In addition, similar to the mood component, this 'apathy' component was also constructed beyond the original PANSS structure. In this automatic data reduction process, active social avoidance survived and weighted heavily in this component. All the PANSS items are relating to withdrawal and avoidance at the clinical observation level. This withdrawal component describes another unique clinical aspect of BD patients in TOP research. The sMRI component associated with this 'apathy' component was largely located in frontal-parietal-temporal regions with an isolated region in left supramarginal gyrus (contributing negatively).

Apathy is commonly observed in mood and psychotic disorders (Grande et al., 2016). This frontal-parietal-temporal circuit is also the important deficits in BD brain abnormalities (Dusi et al., 2019; Han et al., 2019; Shahab et al., 2018). Regarding its connection to symptoms, one recent connectome study suggested the frontal-parietal circuit was able to track the positive and negative symptoms assess by PANSS, though structural connectivity was not able to predict symptom dimensions (Wang et al., 2018). Another interesting comparison was suggested by the BSNIP research (Clementz et al., 2016; Ivleva et al., 2016; Meda et al., 2015). GM concentration was checked in these three biotypes of BSNIP study, and the concentration loss followed the same order as cognitive decline: biotype 1 showed whole brain gray matter density loss, while type 2 showed largely overlapping results with type 1, and the largest effects were found in fronto-temporal circuits, parietal cortex and cerebellum. Type 3 only showed small reductions in frontal, cingulate, and temporal regions despite their similar DSM diagnoses (Ivleva et al., 2016). Our findings show similar brain circuits as type 2, and in addition we find this pattern potentially connected with apathy symptoms in a BD sample.

Excitement, mania or aggressive are the typical positive symptoms expected in BD patients with potential behavioral effects (Dell'Osso et al., 2009). These positive profiles did not emerge through PANSS in this analysis. However, this result does not weaken the importance of such positive symptoms; it reflects that these symptoms might not show the strongest relationships with brain structure components as seen for negative mood or apathy. Similarly, we did not find any medication or DOI effects on PANSS or brain structures in the highlighted sMRI components. Previous studies exhibited commonly prescribed medications positively affecting brain structure through various pathways (Dell'Osso et al., 2016; Di Sero et al., 2019; Hartberg et al., 2015; Jorgensen et al., 2016), and large scale studies found medication effects on both cortical and subcortical regions (Hibar et al., 2018; Hibar et al., 2016). The situation was similar for DOI though the strongest effect was found in cortical thickness (Hibar et al., 2018). The pICA method prioritized the correlation of the PANSS and sMRI during the data reduction process of both modalities, so the components do not necessarily reflect brain regions most significantly affected by medication or DOI.

These findings have some limitations. This study employed participants with the diagnosis of bipolar spectrum disorders including bipolar I and II, and around half of patients experienced at least one lifetime psychotic episode. We made the effort to enhance the stability of the results. 10-fold validations were applied to pICA to avoid results

being driven by outliers, and pICA itself was running with ICASSO to ensure stability. A final limitation is that by introducing 10 mm smoothing kernel (Gupta et al., 2015; Segall et al., 2009; Silver et al., 2011), and using a relatively strict Z score, and cluster size to filter the structural brain, the main findings were restricted to the cortical regions.

In summary, our finding suggested BD patients showed negative mood symptom and apathy profile differing from the original PANSS subscales. Importantly, localized temporal deficits and fronto-parietal circuits were found associated with these profiles.

Author contributions

J.T. and W.J. contributed to idea generation, experiment design and writing; W.J. conducted the analyses and wrote the manuscript. The remaining authors contributed to the participant recruitment and data collection and ideas. All authors critically reviewed the content and approved the final version for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2019.101989>.

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