Emotion, self and psychopathology

Zhang, Liwen

Publication date:
2016

CHAPTER 6

Altered functional connectivity during self- and close other-reflection in patients with bipolar disorder with past psychosis and patients with schizophrenia

Liwen Zhang, Lisette van der Meer, Esther M. Opmeer , Jan-Bernard C. Marsman,
Henricus G. Ruhé, André Aleman

Minor revision in Neuropsychologia

Abstract

Background: Disturbances in implicit self-processing have been reported both in psychotic patients with bipolar disorder (BD) and schizophrenia (SZ). It remains unclear whether these two psychotic disorders show disturbed functional connectivity during explicit self-reflection, which is associated with social functioning and quality of life. Therefore, we investigated functional connectivity of brain regions during explicit self-reflection in BD with a history of psychosis and SZ.

Methods: Twenty-three BD-patients, 17 SZ-patients and 21 health controls (HC) performed a self-reflection task, including the conditions self-reflection, close other-reflection and semantic control. Functional connectivity was investigated with generalized psycho-physiological interaction.

Results: During self-reflection compared to semantic control, BD-patients had decreased connectivity between several cortical-midline structures (CMS) nodes (i.e., anterior cingulate cortex, insula, ventromedial prefrontal cortex) and the caudate head while HC showed increased connectivities. SZ-patients, during close other-reflection compared to semantic control, demonstrated reduced ventral-anterior insula-precuneus/posterior cingulate cortex (PCC) functional connectivity, whereas this was increased in HC. There were no differences between BD and SZ during self- and close other-reflection.

Conclusions: We propose that decreased functional connectivity between the CMS nodes and caudate head in BD-patients may imply a reduced involvement of the motivational system during self-reflection; and the reduced functional connectivity between the ventral-anterior insula and precuneus/PCC during close other-reflection in SZ-patients may subserve difficulties in information integration of autobiographical memory and emotional awareness in relation to close others. These distinctive impaired patterns of functional connectivity between BD- and SZ-patients deserve further investigation to determine their robustness and associations with differences in clinical presentation.

Key words: bipolar disorder, schizophrenia, generalized psycho-physiological interaction (gPPI), functional connectivity, self-reflection, close other-reflection

Introduction

Self-processing is important for psychotic disorders including bipolar disorder (BD) with a history of psychosis and schizophrenia (SZ), given a close relationship between psychotic symptoms and impaired distinction between the internal (self) and external world (Brookwell et al., 2013). The Default Mode Network (DMN) is assumed to be related to self-reflective processing during rest (implicit self-reflection). Previous neuroimaging studies have shown disturbed DMN-connectivity in both BD and SZ patients (Whitfield-Gabrieli and Ford, 2012). A direct comparison between BD with a history of psychosis and SZ patients has shown both shared and unique impairments in the DMN (Khadka et al., 2013; Meda et al., 2012; Ongur et al., 2010). However, there have been no studies to further elucidate the neural correlates during explicit self-reflection in BD with a history of psychosis and SZ, which has been associated with social cognition and quality of life (Dimaggio et al., 2008; Lysaker et al., 2005; Mitchell et al., 2005).

Explicit self-reflection (hereafter self-reflection) refers to the cognitive process of judging whether certain information (e.g., traits and attitudes) describes oneself (van der Meer et al., 2010), which has consistently shown activation in areas termed as cortical midline structures (CMS) and the insula (Modinos et al., 2009; Northoff and Bermpohl, 2004; Northoff et al., 2006; van der Meer et al., 2010). The CMS consist of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), dorsomedial prefrontal cortex (DMPFC) and ventromedial prefrontal cortex (VMPFC). It has been suggested that these self-reflection areas work closely together in a network (Northoff and Bermpohl, 2004; van der Meer et al., 2010). Functional connectivity of these self-reflection areas has been investigated in healthy individuals. Specifically, during self-reflection, compared to valence judgment, reduced functional connectivity among the CMS areas and increased functional connectivity between the CMS and areas outside the CMS have been observed (van Buuren et al., 2010; van Buuren et al., 2012). Interestingly, it has been shown that the DMPFC tends to have strong functional connectivity with cognitive control areas, while the VMPFC has shown strong functional connections to affective areas during self-reflection (Schmitz and Johnson, 2006). Although specific connectivities vary across studies, connections between nodes of the self-reflection network, as well as connections between these nodes and other brain areas, contribute to normal self-reflection.

However, to our knowledge, despite comparisons of the DMN between BD and SZ patients, functional connectivity within the explicit self-reflective network has not been investigated in BD and SZ patients. In addition, reflection on self and a close other has been shown comparable in many respects (Murray et al., 2012; van der Meer et al., 2010), but no study has shed light on functional connectivity during close other-reflection yet. Therefore, we also investigated functional connectivity during close other-reflection.

In summary, we aimed to investigate functional connectivity of self- and close other-reflection in BD with a history of psychosis and SZ patients. Considering the findings in healthy individuals, we expected BD and SZ patients to show changes in connectivity between the CMS nodes and non-CMS areas. A direct comparison between BD with a history of psychosis and SZ patients was included in order to explore whether they were comparable in functional connectivity during self- and close other-reflection.

Methods

Participants

The study involved 23 BD patients and 17 SZ patients, who were recruited from mental health care institutions in the North of the Netherlands. Around 20-50% BD patients report psychotic episodes, representing the most severe BD population (Keck et al., 2003; Pope and Lipinski, 1978). Moreover, given that self-reflection has been associated with illness insight (clinical and cognitive insight) (van der Meer et al., 2013), the current SZ data were used from a previous study (van der Meer et al., 2013) that included measures of insight, in order to have comparable levels of illness insight in BD and SZ patients. Clinical and cognitive insight were measured with the Schedule of Assessment of Insight-Expanded version (SAI-E, Kemp and A. S. David, 1997) and the Beck Cognitive Insight Scale (BCIS, Beck et al., 2004), respectively. Diagnosis was confirmed with the Mini International Neuropsychiatric Interview-Plus 5.0.0 (MINI-Plus, Sheehan et al., 1998). Inclusion criteria were no medication change at least one week prior to scanning, no psychiatric disorders other than BD or SZ, no neurological/somatic disorders which might affect the central nervous system, no electroconvulsive therapy in the year before scanning, free from MRI-incompatibilities (e.g. metal implant, pregnancy), and for BD patients a life-time history of psychotic symptoms was required. Five BD patients with excessive head movements (more than 3º and/or 3 mm in any direction), missing log files of the task, or a lack of imaging data had to be excluded, leaving a final sample of 18 BD patients.

The Quick Inventory of Depressive Symptomatology (QIDS, Rush et al., 2003) and Young Mania Rating Scale (YMRS, Young et al., 1978) were administered in BD and SZ patients to measure the current severity of depression and mania, respectively. The Positive and Negative Syndrome Scale (PANSS, Kay et al., 1987) was conducted to assess the severity of current psychotic symptoms. Lower scores on the QIDS, YMRS and PANSS reflected less symptom severity. Intelligence was measured with the Dutch adult reading test (DART, Schmand et al., 1991).

Twenty-one healthy controls (HC) were recruited, who had no neurological/somatic disorders that could have influenced the central nervous system. The MINI-Plus was administered in HC to exclude participants with past or current psychiatric disorders. In addition, the QIDS and DART were also conducted in HC. In summary, 18 BD patients with a history of psychotic symptoms, 17 SZ patients and 21 HC were included in our final analyses.

This study was approved by the Medical Ethics Committee of the University Medical Center Groningen and was based on the Declaration of Helsinki (2008). All participants provided written informed consent. Differences in activation patterns during self- and other-reflection of the BD patients, SZ patients and HC were published previously (Zhang et al., 2015), while the current report concerns connectivity differences.

Self-reflection task

During the self-reflection task (Zhang et al., 2015), participants were instructed to judge whether a sentence with a trait word was applicable to them (self-reflection) or a close other (close other-reflection). Notably, a close other was named by the participant before scanning. Judgments were made on a four-point continuum (1-fully disagree; 4-fully agree). Valence (positive and negative) and quality (mental and physical) were balanced within the conditions self and close other. In the control condition, participants judged whether sentences with general knowledge were true or false (semantic control), with an equal number of true and false statements.

In each trial, a sentence was presented for 4000 ms followed by a fixation cross for 500 ms. Each condition included 60 sentences. These sentences were organized in blocks (five trials per block) semi-randomly in terms of the three conditions to avoid consecutive presentation of the same condition.

Image acquisition

fMRI scanning was performed using a 3.0 Tesla whole body scanner (Philips Intera, Best, NL). The head of the participant was kept still using an elastic band and foam cushions on each side of the head. Stimuli were rear-projected on a screen, which could be seen via a mirror attached to the SENSE 8-channel head coil. For avoiding artifacts due to nasal cavities, images were tilted approximately 10º to the anterior commissure-posterior commissure (AC-PC) transverse plane. The functional images were acquired using T2*-weighted echo planar imaging sequences. Each functional image comprised 37 interleaved axial slices of 3.5 mm thickness (slice gap=0 mm; TR=2.00 s; TE=30 ms; FOV=224.0 × 129.5 × 224.0 mm; 64 × 62 matrix of 3.5 × 3.5 × 3.5 voxels). A T1-weighted 3D Fast Field Echo anatomical image was acquired parallel to the bicommissural plane, covering the whole brain (170 slices; TR = 9.0 ms; TE=3.5 ms; FOV = 232.0 × 170.0 × 256.0 mm; voxel size: 1×1×1 mm).

Data analysis

Pre-processing and main task effects

Functional magnetic resonance imaging (fMRI) data were analyzed using statistical parametric mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/) implemented in Matlab 7.13.0.564 (R2011b, Math Works Inc., Natick, MA). The functional images were adjusted manually to the anatomical image and AC-PC plane for each participant. Subsequently, functional images were pre-processed including slice-time correction, realignment, co-registration to the anatomical image, warping into standard Montreal Neurological Institute (MNI) space and smoothing with a Full Width at Half Maximum (FWHM) Gaussian kernel of 10 mm.

First, main task effects were investigated to define seed regions for subsequent gPPI analysis (next section). At first-level, the conditions self, close other and semantic were modeled as separate regressors in a general linear model. A high-pass filter was defined individually as 1.1 times the longest interval between two subsequent trials of the same condition to remove low-frequency noise. Two contrasts were defined: self>semantic and close other>semantic. These contrasts were entered into a full factorial model, with condition (self>semantic and close other>semantic) as within-subjects variable and group (HC, BD and SZ) as between-subjects variable. Age was added as covariate of no interest. Main task effects independent of group for self>semantic and close other>semantic were tested whole brain at a threshold of $p<.05$ family wise error (FWE) corrected for multiple testing on voxel-level and a cluster extent threshold of k≥10 voxels.

Generalized psycho-physiological interaction analysis

Generalized psycho-physiological interaction (gPPI, http://brainmap.wisc.edu/PPI) is a method to investigate the functional connectivity between a seed region and the rest of the brain during modulation of psychological variables (e.g. task conditions), which allows for more flexibility in analyses (e.g. to test conditions or contrasts in one model) compared to the conventional PPI (McLaren et al., 2012). To obtain the physiological variable, blood oxygen level dependent (BOLD) signals were extracted from the seed region and deconvolved. The gPPI interaction variable was created by multiplying the neural signal of the seed with the task condition regressors (self, close other and semantic).

The gPPI analyses for self- and close other-reflection were conducted separately. The centers of the seeds were defined based on (sub-)peak coordinates of the main task effects (see Table S1), which corresponded to areas within the CMS/insula reflective network suggested by previous literature (Northoff and Bermpohl, 2004; van der Meer et al., 2010). This resulted in the following peak coordinates for self-reflection: (1) VMPFC (*x, y, z* =0, 60, 14; *t* = 14.43); (2) ACC (*x,y,z* = -6, 50, 2; *t* = 10.89); (3) PCC (*x, y, z* =-2, -46, 28; *t* = 13.34; (4) insula (*x, y, z*=-34, 18, -14, *t*=7.43). Three peak coordinates were defined for close other-reflection: (1) VMPFC (*x, y, z* =0, 60, 16; *t* = 16.15); (2) Insula (*x, y, z* = -28, 16, -14; *t* = 9.47); (3) PCC (*x, y, z* =0, -50, 30; *t* = 17.35). A sphere with a radius of 6 mm was drawn around each peak to construct the corresponding seed region, with no overlap between seeds.

New models were built to conduct the gPPI analyses. On first-level, for each participant, a separate gPPI model was estimated for each seed. The gPPI generated 7 regressors: three for the task conditions, one for the seed and three for the seed × condition interaction regressors. The obtained interaction variable was convolved with the canonical hemodynamic response function to associate it with the BOLD level. The contrast self > semantic was created for each gPPI model corresponding to a self-reflection seed, by subtracting the gPPI interaction regressor of the semantic condition from the interaction regressor of the self condition. Similarly, the contrast close other > semantic was obtained for each gPPI model of the close other-reflection seeds.

On second-level, to investigate the normal functional connectivity, the obtained contrast images of HC were entered into a one-sample *t*-test model. Both increased and decreased connectivity between the seeds and coupling areas were investigated. Furthermore, a one way ANOVA model was built, with group (BD, SZ and HC) as independent variable. Because of our specific interest in deviations in BD and SZ patients from HC, and in differences between BD and SZ, we planned *t*-tests between BD patients and HC, between SZ patients and HC, and between BD and SZ patients. Moreover, to investigate whether any potential group differences were due to a difference during the semantic control in the areas showing a group difference, a one way ANOVA was conducted on the semantic condition between BD patients, SZ patients and HC. Age was added as covariate of no interest. A threshold was set to $p<.05$ FWE corrected on cluster-level with an initial voxel-defining threshold of $p<.001$ uncorrected.

In addition, in order to explore influences of depression on functional connectivity, we repeated the analyses by adding depression severity (QIDS-score) as covariate of no interest, Of note, this was an exploratory analysis for the purpose of providing more complete information and not our main analysis because depression is an inherent feature of BD and SZ. The same threshold was applied as in the main analysis.

Results

Sample characteristics

Detailed demographical and clinical information are reported in Table 1. All groups (BD patients, SZ patients and HC) were statistically comparable on intelligence, sex and level of education. There was a main effect of group on age, which was driven by a difference between HC and BD patients (29.95 versus 40.22, $p=.006$), therefore age was included as covariate of no interest in the analyses. BD and SZ patients had on average higher QIDS-scores than HC (6.22 [BD], 7.94 [SZ] versus 2.00 [HC]), implying more depressive symptoms in patients. Furthermore, patient groups were statistically matched on severity of depression and mania, and level of insight (clinical and cognitive insight). As expected, SZ patients had higher level of severity on psychotic symptoms compared to BD patients. BD patients had on average 7.60 manic episodes and 5.33 depressive episodes (lifetime). Based on the QIDS (score range: 0-20) and YMRS (score range: 0-4), 14 BD patients were scanned during an euthymic episode (YMRS≤8 and QIDS≤10 (Mercer and Becerra, 2013; Rush et al., 2006), and four had moderate to severe depressive symptoms (QIDS>10). Four SZ patients had moderate to severe depressive symptoms at scanning. All patients were taking medication except for one BD patient and one SZ patient. Behavioral performance of this sample has been described previously (Zhang et al., 2015).

Connectivity analyses

In HC, during self-reflection compared to semantic control, we found increased connectivity between the VMPFC and caudate, and decreased connectivity between the VMPFC and inferior parietal lobule/supramarginal gyrus (IPL/SMG); decreased connectivity of the ACC with the IPL/SMG and precuneus; increased connectivity between the PCC and the middle frontal gyrus (MFG), inferior frontal gyrus (IFG) and DMPFC, and reduced connectivity between the PCC and precuneus. For close other-reflection compared to semantic control, the VMPFC showed less connectivity with the mid-cingulate cortex (MCC), and there was reduced connectivity between the PCC and the parahippocampal gyrus/fusiform gyrus, precuneus, cuneus, MCC, middle temporal gyrus, superior temporal gyrus and SMG (Table 2, see Table S2 and Table S3 for results in BD and SZ patients respectively).

With respect to group comparisons, during self-reflection, the ACC, insula and VMPFC had decreased functional connectivity with the caudate head in BD patients compared to HC (Table 3, all $p<.05$, FWE corrected on cluster-level). Specifically, during self-reflection compared to semantic control, there was reduced functional connectivity between these seed regions and the head of the caudate in BD patients, while these functional connectivities were increased in HC (Figure 1). Moreover, we also observed decreased functional connectivity between these self-reflection seed regions and corpus callosum in BD patients compared to HC (Figure 1). No differences in functional connectivity were observed between SZ patients and HC during self-reflection. During close other-reflection, there was decreased connectivity

Table 1 Demographic and clinical information

Variables	BD[a]	SZ[b]	HC[c]	*p*
Age, *M (SD)*	40.22	35.53	29.95	.02*
Male/Female, N	8/10	11/6	12/9	.47
Education level[d], *M (SD)*	5.94 (.87)	5.65 (.86)	5.76 (.83)	.58
BD type I/II[e], N	15/2			
Intelligence (DART)				
Total correct, *M (SD)*	42.76 (3.63)	38.50	41.15	.14
Manic episodes, *N, M (SD)*	7.60 (10.73)			
Depressive episodes, *N, M (SD)*	5.33 (4.35)			
QIDS, *M (SD)*	6.22 (6.02)	7.94 (3.88)	2.00 (1.18)	.002*
YMRS, *M (SD)*	1.29 (1.45)	1.71 (1.86)		.49
PANSS, *M (SD)*				
Total	40.53 (6.19)	52.59		.003*
Positive	9.35 (2.62)	12.71		.015*
Negative	10.00 (3.37)	13.47		.021*
General psychopathology	21.76 (3.46)	26.41		.019*
Insight				
SAI-E	22.36 (1.99)	21.64		.29
BCIS				
Composite score	8.00 (5.36)	7.29 (4.27)		.67
Self-reflectiveness	15.29 (4.36)	16.41		.51
Self-certainty	7.29 (2.52)	9.12 (4.41)		.15
Psychopharmacological drug (N)				
Haloperidol		1		
Pimozide	1			
Aripiprazole		9		
Clozapine		2		
Olanzapine	2	5		
Quetiapine	6	4		
Risperidone		1		
Clomipramine		1		
Lithium	7			
Sertraline	1			
Trazodone	1			
Valproic acid	4			
Bupropion	1			
Oxazepam	1			
None	1	1		

Abbreviations: BCIS=Beck Cognitive Insight Scale; BD=bipolar disorder; DART=Dutch Reading Test for Adults; HC=healthy controls; M=mean; N=number; PANSS=Positive and Negative Syndrome Scale; QIDS=Quick Inventory of Depressive Symptoms-Self Report; SAI-E=Schedule of Assessment of Insight-Expanded version; SD=standard deviation; YMRS=Young Mania Rating Scale. *p<.05. [a]One BD withdrew from the study after scanning, with no clinical interview data. The number of depressive/manic episodes was unavailable for another two BD patients. [b]We recruited three SZ patients from another study whose information on DART and YMRS are not available. [c]Clinical interview data were unavailable for seven HC. Another HC did not have data for DART. [d]Education level was based on Verhage (1964). [e]Diagnosis of one BD was confirmed by a psychiatrist, without the BD type information.

Table 2 gPPI results for healthy controls

Seed	Brain region (grey matter)	BA	voxels	MNI coordinates			Z score
				x	y	z	
self > semantic							
ACC_dec	IPL/SMG	40	594	48	-50	42	4.65
				56	-46	44	4.51
				44	-54	58	3.42
	Precuneus	7	266	10	-58	36	4.52
				14	-60	28	3.26
PCC_inc	DMPFC	8	341	-2	30	58	3.85
				-6	38	56	3.75
				0	38	46	3.31
	MFG/IFG	9/45	323	-46	26	30	3.81
		/46		-42	16	34	3.31
PCC_dec	Precuneus	7	217	-8	-70	42	4.73
VMPFC_inc	Caudate[a]		244	-2	10	-2	4.10
				0	-6	12	3.53
				-4	-2	6	3.50
VMPFC_dec	IPL/SMG	40	247	58	-44	46	4.25
close other > semantic							
PCC_dec	Parahippocampal gyrus	37	324	34	-50	-6	5.07
	/fusiform gyrus			28	-40	-6	4.23
	Precuneus	7	447	-12	-74	36	4.91

Table 2 Continued

Seed	Brain region (grey matter)	BA	voxels	MNI coordinates			Z score
				x	y	z	
	Precuneus /cuneus	7	641	14	-66	32	4.47
				24	-60	16	3.57
				14	-60	20	3.43
	MCC	31	717	-4	-22	44	4.05
				0	-40	50	3.69
				4	-46	34	3.66
	MTG/STG/SMG	22/40	924	56	-46	24	4.03
				54	-58	12	3.93
				46	-56	8	3.79
VMPFC_dec	MCC	31	383	-10	-24	42	4.11
				4	-18	42	3.49
				-4	-18	38	3.49

Abbreviations: ACC=anterior cingulate cortex; dec=decreased coupling; DMPFC=dorsomedial prefrontal cortex; IFG=inferior frontal gyrus; inc=increased coupling; IPL=inferior parietal lobule; MCC=mid-cingulate cortex; MFG=middle frontal gyrus; MTG=middle temporal gyrus; PCC=posterior cingulate cortex; SMG=supramarginal gyrus; STG=superior temporal gyrus; VMPFC=ventromedial prefrontal cortex. [a]Caudate nucleus extends into neighboring tissue.

between the ventral-anterior insula and precuneus/PCC in SZ patients compared to HC (Table 3, p=.016, FWE corrected on cluster-level). To be more exact, during close other-reflection compared to semantic control, SZ patients showed reduced functional connectivity between the ventral-anterior insula and precuneus/PCC whereas enhanced connectivity was seen in HC (Figure 1). In contrast, there was no difference in functional connectivity between BD patients and HC during close other-reflection. Comparing BD to SZ patients did not reveal differences in functional connectivity during self- and close other-reflection. Notably, there was no group difference of functional connectivity in the observed areas during the semantic condition from the corresponding seed regions.

Results of the group comparisons after adding depression severity as covariate of no interest are described in Table S4. Briefly, during close other-reflection, similar results were seen. However, during self-reflection, we did not find group differences in functional connectivity between the CMS areas and the head of the caudate as observed in our main analysis, but there was reduced functional connectivity in BD patients between the ventral-anterior insula and the superior parietal lobule (SPL), precuneus, supplementary motor area (SMA), middle occipital gyrus, and lingual gyrus compared to HC, Moreover, SZ patients showed decreased functional connectivity between the ventral-anterior insula and the SMA, precuneus and SPL.

Table 3 gPPI results for group comparisons

Seed	Brain region (grey matter)	BA	voxels	Z score	MNI coordinates		
					x	y	z
self > semantic							
ACC _HC>BD	caudate[a]		381	4.27	16	28	2
				3.94	-2	24	12
				3.68	6	24	2
Insula_HC>BD	caudate[a]		705	3.90	-2	26	12
				3.85	14	26	4
				3.81	22	46	6
VMPFC_HC>BD	caudate[a]		491	5.23	-6	24	14
				3.88	-20	32	0
				3.64	-10	30	0
	caudate[a]		392	4.25	20	30	0
				3.97	14	24	6
				3.88	26	36	6
close other>semantic							
Insula_HC>SZ	Precuneus	7	319	3.86	14	-60	30
	/PCC	/31		3.82	14	-52	28
				3.34	-4	-64	30

Abbreviations: ACC=anterior cingulate cortex; BD=bipolar disorder; HC=healthy controls; PCC=posterior cingulate cortex; SZ=schizophrenia; VMPFC=ventromedial prefrontal cortex.
[a]Caudate nucleus extends into neighboring tissue.

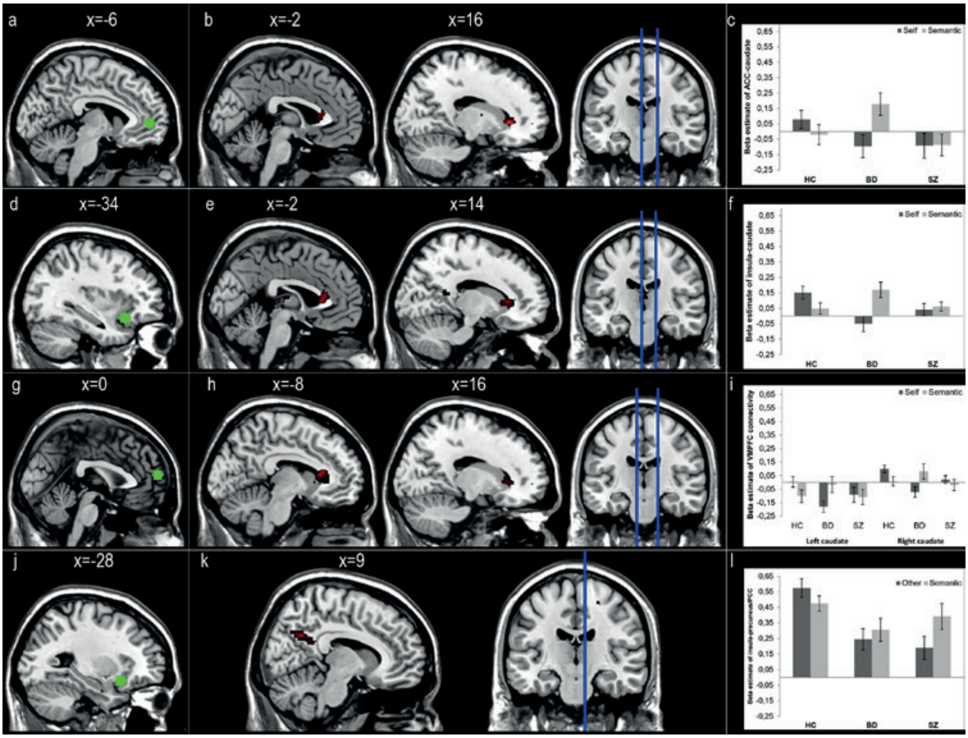

Figure 1 Group comparison of functional connectivity. During self-reflection, there are decreased functional connectivities between the seed regions (a) ACC, (d) insula, and (g) VMPFC and the caudate head/corpus callosum (b, e, h, respectively) in BD patients, whereas increased connectivities between these areas were found in HC compared to semantic control (c, f, i, respectively). During close other-reflection, SZ patients show reduced functional connectivity between the seed region ventral-anterior insula (j) and the precuneus/PCC (k) while HC showed increased ventral-anterior insula-precuneus/PCC functional connectivity compared to semantic control (l). Error bar means one standard error in each direction. Abbreviations: ACC=anterior cingulate cortex; BD=bipolar disorder; HC=healthy controls; PCC=posterior cingulate cortex; SZ=schizophrenia; VMPFC=ventromedial prefrontal cortex.

Discussion

This study is the first investigation of task-related functional brain connectivity during self/other reflection in patients with bipolar disorder (BD) and a history of psychosis and patients with schizophrenia (SZ), as compared to healthy controls.

Most importantly, during self-reflection compared to semantic control, BD patients showed decreased connectivity between the anterior cingulate cortex (ACC), insula and ventromedial prefrontal cortex (VMPFC) and the head of the caudate, while HC showed increased connectivity for these regions. Moreover, during close other-reflection, reduced connectivity between the ventral-anterior insula and precuneus/posterior cingulate cortex (PCC) was seen in SZ patients while this connectivity was increased in HC. Of note, these group differences were not related to connectivity differences during the semantic control condition, suggesting that the group differences were specific for self- and close other-reflection.

Group difference during self-reflection in BD patients

During self-reflection, BD patients showed decreased connectivity of the ACC, VMPFC, and insula with the head of the caudate compared to HC, which could not be explained by activation differences in these two areas (Zhang et al., 2015). Structural abnormalities in these areas have been reported in BD patients (Canales-Rodríguez et al., 2014; Phillips and Swartz, 2014). The caudate has been associated with multiple functions, especially action-related processing, including motor planning and execution (Gerardin et al., 2004), and reward processing (Delgado et al., 2000; Delgado et al., 2004; Farr et al., 2012). Although the caudate is not generally regarded as a self-reflection area, it was activated during self-reflection (Table S1), corroborating previous studies that identified caudate activation during self-reflection and in relation to self-relevance (Denny et al., 2012; Grigg and Grady, 2010; Moran et al., 2006). Notably, Enzi *et al*. (2009) have reported activation of the head of the caudate during both reward and self-reflective processing. These authors therefore suggested that the head of the caudate might be involved in linking reward to self-relevance. This is also suggested by the close connections between the head of the caudate and self-reflection areas (e.g. the ACC and medial prefrontal cortex) (Postuma and Dagher, 2006). In line with this suggestion, activation in the head of the caudate has been seen during imagining future (especially positive) self-related events (D'Argembeau et al., 2008). Shany-Ur *et al.* (2014) have found increased involvement of the head of the caudate during overestimation of self-functioning, which may be associated with the attribution of more rewarding information to oneself. Taken together, these studies show that the head of the caudate is important for reward-related and self-reflective processing.

The ACC, VMPFC and insula have been shown to be important nodes in the cortical midline structures (CMS) network during self-reflection. Previous models and meta-analysis of self-reflection have suggested functionally distinctive parts of the CMS, in which the ACC and VMPFC (ventral CMS) are assumed to be involved in directing attention and labeling external stimuli as self-relevant, respectively (Northoff and Bermpohl, 2004; Northoff et al., 2006; van der Meer et al., 2010). Moreover, activation in the insula has been observed during physical self-reflection (e.g., self-face) (Hu et al., 2016), and also psychological self-reflection (e.g., reflection on traits) (Modinos et al., 2009; van der Meer et al., 2010). Our seed-region in the insula was located anterior and the anterior insula has been involved in self-awareness, representing an integrated sentient self (Craig, 2009). In addition, specifically the ventral part of the anterior insula has been found to be associated with social-emotional functions (e.g., recall of one's emotions, feeling other's emotional feelings) (Kurth et al., 2010). Taken together, it might be suggested that the ventral-anterior insula is involved in emotional awareness during reflective processing. Notably, all the three seed-regions appear to be activated during self-reflection in the emotional domains (Northoff et al., 2006), and also during reward related processing (De Greck et al., 2008; Rogers et al., 2004; Tanaka et al., 2004). Given that self-reflection might be emotional and rewarding, and in line with the finding that healthy individuals often show a positive self-serving bias (more positive and less negative self-attributions (Mezulis et al., 2004), our finding of reduced functional connectivity with the head of the caudate during self-reflection in BD patients may imply that BD patients have less capacity to self-reflect and have difficulties in experiencing reward during reflecting on themselves. Indeed, evidence on the behavioral level has shown less positive self-serving bias (less positive and more negative self-attributions) in BD patients (Zhang et al., 2015). Furthermore, considering the mainly stable BD sample in the current study, we speculate that such a functional connectivity pattern during self-reflection in BD with a history of psychosis might represent a vulnerability factor for future presence of psychotic symptoms and/or emotional episodes (e.g., depression and mania).

Moreover, in addition to our observed alterations in functional connectivity in grey matter, we also found reduced functional connectivity between these CMS nodes (i.e., ACC, VMPFC, and insula) and the corpus callosum in BD patients. There have been studies showing involvement of the corpus callosum during task activation

(Mazerolle et al., 2008; Mazerolle et al., 2010), suggesting a role of the corpus callosum in connecting brain areas activated during tasks (Mazerolle et al., 2010). It might be speculated that the disturbed functional connectivity with the corpus callosum in BD patients indicates less efficient connections between hemispheres for areas involved during self-reflection, which might contribute to self-reflection disturbances, requiring further research.

Group difference during close other-reflection in SZ patients

SZ patients showed disturbed ventral-anterior insula-precuneus/PCC connectivity during close other-reflection, which could not be explained by any group differences in activation during close other-reflection in these areas (Zhang et al., 2015). Although structural abnormalities have been observed in these brain regions in SZ patients (Salgado-Pineda et al., 2011; Shepherd et al., 2012), there is a lack of exploration on the function of this ventral-anterior insula-precuneus/PCC connectivity. The precuneus/PCC is important for reflective processing by its role in retrieving past autobiographical memory, and to use this information to evaluate current stimuli (Northoff and Bermpohl, 2004; van der Meer et al., 2010). This consultation of the precuneus/PCC has been suggested to be of importance not only for self-reflection, but also for reflection on close others (van der Meer et al., 2010). Interaction between the insula and precuneus/PCC has been proposed in a model of self-evaluation (van der Meer et al., 2010). Given the respective roles of the ventral-anterior insula (emotional awareness) and precuneus/PCC (autobiographical memory processing), we propose that the reduced ventral-anterior insula-precuneus/PCC functional connectivity during close other-reflection in SZ patients may correspond to a disturbance in integrating autobiographical memory and emotional awareness in relation to close others. Such a disturbance may hamper social interaction, a commonly observed problem in SZ patients (Penn et al., 2008). Clearly, more research into connectivity alterations of these regions is needed, e.g., in relationship to clinical symptoms of SZ such as apathy.

Group difference between BD and SZ patients

First, the comparable functional connectivity during self- and close other-reflection between BD patients with past psychotic symptoms and SZ patients might suggest that there are some shared functional connectivity mechanisms underlying psychotic symptoms irrespective of disorder. On the other hand, in comparison to HC, disturbed functional connectivity during self-reflection was only observed in BD patients, and visual inspection (Figure 1) demonstrated that the difference of functional connectivity between self-reflection and semantic control was intermediate in SZ patients between BD patients and HC. Similarly, disturbance in functional connectivity during close other-reflection was only seen in SZ patients, with the difference between close other-reflection and semantic control of BD patients being in between SZ patients and HC. However, these differences were not sufficiently large enough to reach statistical significance given the power of the present study. Nevertheless, our selection of patients may have influenced these results. The BD patients had life-time psychotic symptoms, representing a sub-group of the BD population with more illness severity; whereas the SZ patients included in this study had preserved illness insight to match with BD patients, and thus might represent SZ patients with a relatively mild clinical presentation. SZ patients have demonstrated more severe disturbances in cognitive functioning compared to BD patients (Krabbendam et al., 2005). This implicates that the selection bias might have blurred the differences between BD and SZ patients. It would be interesting to elucidate the generalizability of the present results further by investigating psychotic disorders with more variable level of illness severity.

Limitations

Some limitations must be mentioned. First, most patients were taking psychotropic medication, which varied across patients, leading to potential confounding effects by medication. Nevertheless, this medication is aimed to achieve euthymia (Hafeman et al., 2012; Phillips et al., 2008a), which most likely reduces rather than exaggerates differences between patients and HC. Second, BD patients were older than HC. Although we statistically controlled for this by adding age as covariate of no interest, future studies might recruit more age-matched and drug-free or even drug-naïve participants. Third, due to small samples of BD and SZ patients who were mainly stable, we could not test the association of the observed functional connectivity patterns with clinical variables (i.e., bipolar type, emotional symptomatology, psychotic symptoms and level of illness insight) in patients. Future investigation on these factors would be interesting to contribute to the understanding of BD and SZ.

Conclusions

To conclude, BD patients showed decreased connectivity between regions of the CMS network (i.e., ACC, insula and VMPFC) and the head of the caudate during self-reflection, which may imply a reduced influence of motivational processing on self-reflection. SZ patients, however, demonstrated reduced ventral-anterior insula-precuneus/PCC connectivity during close other-reflection, which might be associated with difficulties in the integration of emotional awareness and autobiographical information. Future investigation should link these disturbed functional connectivities to emotional and psychotic symptomatology in BD and SZ.

Acknowledgements

This study was supported by a grant from the European Science Foundation EURYI (NWO grant number 044.035.001 to A.A.). H.G.R. was supported by a VENI grant (NWO/ZonMW grant number 016.126.059). L.Z. obtained support from the China Scholarship Council during the PhD study at University of Groningen. We thank Drs. B. Haarman and Prof. Dr. W.A. Nolen for their help with patient inclusion. We thank Dr. R. Renken for his help with the study design. Moreover, we thank A. Sibeijn-Kuiper and J. Streurman for scanning the participants. All these people are employees of the University Medical Center Groningen.

Supplementary information

Table S1 Peak activations for the main task effects during the self-reflection task

	Region	L/R	BA	voxels	*T*-value	MNI coordinates		
						x	*y*	*z*
self>semantic								
	DMPFC/VMPFC /ACC		9/10 /32	7511	14.43	0	60	14
					10.98	-18	58	30
					10.89	-6	50	2
	Precuneus/PCC		7/31	7474	13.34	-2	-46	28
					13.10	-8	-62	32
					9.13	0	-18	36
	Angular gyrus/SMG	L	39/40	1208	8.70	-52	-66	38
					8.55	-46	-58	26
	SMG/angular gyrus	R	39/40	378	6.36	54	-64	34
	Cerebellum	R		155	7.54	28	-82	-34
	IFG/insula	L	13/45	522	7.43	-34	18	-14
					6.26	-46	22	2
	Postcentral gyrus /SMG	R	2/40	1217	7.37	56	-22	40
					6.93	38	-40	42
					6.43	56	-26	50
	MTG	L	21	193	7.12	-48	2	-26
					6.65	-52	-18	-12
	MTG	R		34	5.45	56	-14	-14
	MTG	R	21	61	6.75	52	6	-30
	MFG	L	9	236	6.89	-42	22	44
	MFG	R	6	28	5.12	30	8	50
	Caudate	L		37	5.77	-2	8	-6

Table S1 Continued

	Region	L/R	BA	voxels	*T*-value	MNI coordinates		
						x	*y*	*z*
	Caudate	L		23	5.26	-12	16	6
	Caudate	L		24	4.95	-14	-2	16
	Brain stem			18	5.44	0	-18	-12
	Cerebellum	R		40	5.34	14	-54	-26
other>semantic								
	Precuneus/PCC		7/31	7292	17.35	0	-50	30
					8.24	0	-20	32
	DMPFC/VMPFC/ACC		9/10/32	7346	16.15	0	60	16
					13.08	-14	60	30
					11.89	0	64	-2
	Angular gyrus/SMG	L	39/40	1592	11.91	-46	-58	26
					11.36	-50	-64	36
	Angular gyrus/SMG	R		1199	9.79	48	-58	28
	IFG/MTG/STG/insula	L	13/21/22/47	1488	10.80	-48	2	-26
					9.62	-56	-16	-10
					9.47	-28	16	-14
	MTG	R	21	538	9.72	50	8	-30
					9.04	60	-6	-18
	Cerebellum	R		78	7.52	28	-82	-34
	Subgenual cingulate cortex		25	41	6.15	0	8	-6

Abbreviations: ACC=anterior cingulate cortex; DMPFC=dorsomedial prefrontal cortex; IFG=inferior frontal gyrus; MFG=middle frontal gyrus; MTG=middle temporal gyrus; PCC=posterior cingulate cortex; SMG=supramarginal gyrus; STG=superior temporal gyrus; VMPFC=ventromedial prefrontal cortex.

Table S2 gPPI results for patients with bipolar disorder

Seed	Brain region	BA	voxels	Z score	MNI coordinates		
					x	y	z
self > semantic							
ACC_dec	Thalamus /caudate		825	4.25	-2	-12	16
				4.17	4	8	4
				3.93	8	14	10
Insula_dec	Thalamus		321	4.04	8	-14	16
				3.63	-24	-12	18
				3.61	-16	-14	18
	Caudate		374	3.83	26	24	2
				3.68	12	20	4
				3.46	8	12	2
other>semantic							
Insula_dec	thalamus		1174	4.99	6	-22	6
				4.93	0	-8	18
				4.69	-6	-10	12
	STG/MTG	22/41/42	770	4.28	44	-42	-2
				4.23	46	-34	-2
				4.09	48	-32	8
PCC_dec	MCC	31	353	3.99	10	-36	36
				3.60	14	-26	38
				3.19	8	-26	44

Abbreviations: ACC=anterior cingulate cortex; dec=decreased coupling; MCC=mid-cingulate cortex; MTG=middle temporal gyrus; PCC=posterior cingulate cortex; STG=superior temporal gyrus.

Table S3 gPPI results for patients with schizophrenia

Seed	Brain region	BA	voxels	Z score	MNI coordinates		
					x	y	z
other>semantic							
PCC_dec	MCC/precuneus	7/31	1118	4.67	-10	-32	42
				4.61	6	-26	40
				4.56	0	-20	38
	IPL/SMG/STG	22	365	4.07	62	-34	28
		/40		3.75	62	-38	18
				3.57	60	-32	38
	Precuneus	7	414	4.02	10	-72	40
				3.74	-6	-74	40
				3.32	-10	-82	46
VMPFC_dec	MCC	31	1294	5.01	10	-40	36
				4.68	10	-24	34
				4.16	-8	-22	46
	IPL/SMG	40	248	4.33	-62	-34	26
				4.10	-58	-32	36
				3.83	-54	-30	20
	SMG/STG/IPL	22	691	4.15	66	-24	16
		/40		4.04	66	-32	14
		/42		3.99	64	-46	22

Abbreviations: dec=decreased coupling; IPL=inferior parietal lobule; MCC=mid-cingulate cortex; PCC=posterior cingulate cortex; SMG=supramarginal gyrus; STG=superior temporal gyrus; VMPFC=ventromedial prefrontal cortex.

Table S4 gPPI results for group comparisons (with age and depression severity as covariate of no interest)

Seed	Brain region	BA	voxels	Z score	MNI coordinates		
					x	y	z
self > semantic							
Insula_HC>BD	SPL	7	674	4.84	-30	-56	52
				3.66	-20	-68	56
				3.65	-14	-62	52
	SPL/precuneus	7	417	3.87	12	-70	60
				3.84	24	-72	52
				3.69	18	-52	54
	SMA	6	646	4.30	20	10	52
				4.29	-10	10	52
				3.93	-2	10	58
	Middle occipital gyrus		285	3.91	-28	-70	36
				3.77	-22	-64	38
				3.34	-28	-68	24
	Lingual gyrus	18	573	3.85	4	-80	0
				3.71	8	-88	-2
				3.59	26	-84	-2
Insula_HC>SZ	SMA	6	691	4.15	8	8	50
				3.87	-8	12	48
				3.86	-2	10	64
	Precuneus/SPL	7	220	3.80	12	-66	64
	(*p=.052*)			3.39	12	-60	56

Table S4 Continued

Seed	Brain region	BA	voxels	Z score	MNI coordinates		
					x	y	z
other>semantic							
Insula_HC>SZ	MFG	9	468	4.44	40	14	50
				3.70	46	20	34
				3.67	50	10	36
	Superior occipital gyrus		254	4.27	-24	-76	28
	/middle occipital gyrus			3.51	-24	-72	38
	Precuneus	7	499	4.07	8	-60	32
				3.91	0	-62	34
				3.45	-10	-60	32

Abbreviations*:* HC=healthy controls; MFG=middle frontal gyrus; SPL=superior parietal lobule; SMA=supplementary motor area; SZ=schizophrenia.