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Functional connectivity during affective mentalizing in criminal offenders with psychotic disorders: Associations with clinical symptoms

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ABSTRACT

Psychotic disorders are associated with neurobehavioral impairments in mental state attribution (mentalizing). These impairments are most severe in psychotic patients with elevated symptom levels, particularly negative and cognitive symptoms. There have been few studies of functional connectivity related to mentalizing in psychotic disorders and associations with symptoms. We conducted a functional MRI study of affective mentalizing in individuals with psychotic disorders and varying symptom levels (positive, negative, cognitive). Participants were drawn from an adjudicated inpatient forensic psychiatric population (criminal offenders). Functional MRI scans were acquired using a 32-channel ultra-fast multiband imaging sequence. Mentalizing task performance and functional connectivity were assessed in psychotic criminal offenders (n = 46) and nonpsychotic offenders (n = 41). Temporal coherent brain networks were estimated with group independent component analysis (ICA). Relative to nonpsychotic offenders, psychotic offenders showed impaired task performance and reduced activation in a component comprising the dorsomedial prefrontal cortex, superior temporal gyrus, and ventrolateral prefrontal cortex. Positive and cognitive symptoms were inversely correlated with component activity and task performance. The results are discussed with reference to potential mechanisms underlying impaired social cognition in psychotic disorders and across symptom types.

1. Introduction

Disturbances in social cognition and behavior are a core feature of psychotic disorders. Underlying these disturbances are impairments in processing social cues, such as facial emotion recognition (Kohler et al., 2010) and mental state attribution (Brüne, 2005; Savla et al., 2013). In schizophrenia, impairments in mentalizing (i.e., the ability to explain, predict, and interpret behavior by attributing mental states such as desires, beliefs, intentions and emotions to oneself and to other people) are persistent over time and periods of symptom exacerbation and stability, including prodromal periods (Bora et al., 2009; Green et al., 2012).

Although mentalizing deficits are present outside periods of symptom exacerbation, certain symptoms are associated with more severe mentalizing deficits. The most consistent associations have been found with negative symptoms (e.g., blunted affect) and cognitive symptoms (sometimes referred to as disorganized symptoms, e.g., conceptual disorganization) (Sprong et al., 2007; Ventura et al., 2013). However, some studies have also reported mentalizing deficits related to positive symptoms, particularly paranoid delusions (Corcoran et al., 1997; Frith and Corcoran, 1996; Koelkebeck et al., 2010; Marjoram et al., 2005).

The mechanisms that underlie mentalizing deficits may differ across symptom types. For example, deficits may occur because an individual

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does not have the inclination or ability to adopt the perspective of others, or because they adopt the incorrect perspective of others. This may be related to negative and positive symptoms, respectively (Frith, 2004). The inability to take another's perspective may also be due to difficulty sustaining attention and/or integrating contextual cues, which could explain mentalizing deficits associated with cognitive symptoms (Hardy-Bayle et al., 2003). Studies that incorporate functional neuroimaging measures with well-designed behavioral tasks can help elucidate specific deficits related to symptom types (Brunet et al., 2003). For example, a study with schizophrenia patients found a correlation between positive symptoms and medial prefrontal cortex (mPFC) activity during the control condition of a mentalizing task, which was interpreted as "hypermentalizing" or mentalizing in irrelevant contexts (Ciaramidaro et al., 2015). The mPFC, along with the posterior superior temporal sulcus (pSTS) and temporo-parietal junction (TPJ), is an established component of the mentalizing network (Amodio and Frith, 2006; Frith and Frith, 2003). Other regions, such as the inferior frontal gyrus (iFG), have been implicated more specifically in emotion-based mentalizing tasks in which emotional state is inferred from perceptual cues (Hooker et al., 2008).

There has been less work examining functional connectivity during mentalizing (Das et al., 2012; Hyatt et al., 2015; Martin et al., 2016; Mier et al., 2016), particularly associations between connectivity and symptoms (Schilbach et al., 2016). Impaired social functioning in schizophrenia is believed to result from early-onset disrupted neural connectivity (Friston and Frith, 1995). Whereas many prior studies focused on individual brain regions during mentalizing, examining functional connectivity could shed light on new patterns of neural dysfunction in psychosis, both trait and state (i.e., symptom) related. In line with theories regarding different mechanisms of mentalizing impairment associated with positive, negative, or cognitive symptoms (Frith et al., 2004; Hardy-Bayle, 2003), each symptom type may show different patterns of altered connectivity.

Here we examined functional connectivity during affective mentalizing (inferring emotional states in others) in individuals with psychotic disorders (defined here as schizophrenia, schizoaffective, bipolar I with psychotic features, and psychotic disorder not otherwise specified) and varying levels of positive, negative, and cognitive symptoms. Functional connectivity was evaluated using Independent Component Analysis (ICA), a multivariate analysis technique which uses spatial information between voxels to identify independent grouped "sources", i.e. spatially distinct sets of brain regions in which hemodynamic activity covaries between individuals across an fMRI timecourse. An advantage of ICA over general linear model univariate approaches is that ICA identifies sets of voxels that have similar variance patterns (components) and the component values can be compared across groups and examined in correlation analysis with clinical variables of interest. This greatly reduces the severity of multiple comparison correction (i.e., correcting for every voxel in the brain) while also providing meaningful information about voxel patterns as they relate to processes of interest (e.g., mentalizing). Additional advantages include not requiring a seed voxel or temporal filtering (Mckeown et al., 1998).

An affective mentalizing experimental task was chosen rather than a cognitive mentalizing task because affective mentalizing has been relatively less studied in psychotic disorders to date, and may have unique associations with certain symptom types (e.g., paranoid delusions may have affectively-laden manifestations such as inferring hostile emotions in others). Psychotic-disordered participants were from an adjudicated inpatient forensic psychiatric population (incarcerated criminal offenders). The use of an inpatient sample residing in a secure facility confers several benefits, including minimization of illicit substance use-related confounds, institutional files containing detailed psychosocial, clinical, and symptom evaluations, and better assurance of medication compliance. Our forensic research protocol also enabled the assessment of antisocial and psychopathic traits, which may impact neurobehavioral correlates of mentalizing (Decety et al., 2013a, 2013b) but have been relatively unexamined in prior studies of mentalizing and psychosis.

We deployed a mobile MRI scanner to state prisons, enabling us to scan psychotic-disordered offenders and a comparison group of non-psychotic-disordered offenders at each facility. We hypothesized that psychotic offenders would show impaired mentalizing performance and reduced activation within functionally connected mentalizing nodes such as mPFC, pSTS, and iFG relative to nonpsychotic offenders. Because most prior studies that examined symptom-mentalizing associations used cognitive (e.g., what is the person thinking?) rather than affective (e.g., what emotion is the person feeling?) tasks, and those studies reported associations with at least one of three symptom types (positive, negative, cognitive), we tentatively hypothesized that task performance would be inversely correlated with each symptom type. However, in accordance with theories proposing different underlying mechanisms (Frith, 2004), we expected that deficits would be related to different functional connectivity patterns. We predicted that negative and cognitive symptoms would both be associated with reduced activation in mentalizing networks, but only cognitive symptoms would be associated with increased activation in networks unrelated to mentalizing, representing distraction from task-relevant processes.

Because positive symptoms may be related to inaccurate mentalizing rather than lack of mentalizing, we considered it an open question whether they would be associated with aberrant functional connectivity in mentalizing networks. Studies have also shown associations between specific types of positive symptoms, such as delusions, and altered behavioral and neural processing of social cues that may support mental state attributions (e.g., gestures, facial expressions) (Bucci et al., 2008; Perez et al., 2015; Usnich et al., 2015; Nikolaides et al., 2016). Thus, in addition to examining total positive symptom scores we analyzed individual symptoms separately. We were particularly interested in individual positive symptoms which are also associated with antisocial tendencies, such as grandiosity (Baumeister et al., 2000; Hare, 2003). Grandiose delusions, which are typically characterized by preoccupation with ones' own status, may be associated with a reduced tendency to consider the perspective of others, resulting in impaired mental state attribution and associated functional connectivity.

2. Method

2.1. Participants

The total sample included 85 participants: a) Male criminal offenders (n = 46) who met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., DSM-IV) criteria for schizophrenia (n = 21), schizoaffective disorder (n = 12), bipolar I disorder with history of psychotic features (n = 11), or psychotic disorder not otherwise specified (n = 2); b) male criminal offenders with no history of a psychotic disorder (n = 41). Offenders were recruited from state psychiatric and prison facilities in Wisconsin and New Mexico. All participants were scanned using the same mobile MRI scanner. Inclusion criteria for the psychotic offender group were: 1) age between 18 and 60, 2) native English speaker, 3) reading level 4th grade or higher, 4) no history of epilepsy or seizures, 5) no history of mental retardation or developmental disability, 6) No history of major medical illness (e.g., HIV). These criteria were also applied to the nonpsychotic offender group, in addition to: 1) no lifetime psychotic disorder in self or first-degree relative or recurrent major mood Axis I disorder, 2) no history of paranoid, schizotypal, or schizoid Axis II disorder, 3) No history of head injury with loss of consciousness greater than 10 min. Two psychotic offenders were excluded for poor task performance: one did not respond to > 40% of trials and one had a shape matching accuracy score more than three standard deviations below the group mean. Demographic characteristics of each group are provided in Table 1. Written informed consent was obtained from all participants after a complete description of the study procedures, which were approved by the University of New

Table 1
Demographic characteristics of groups.

	Nonpsychotic Offender (n = 41)	Psychotic Offender (n = 44)		
	M(SD)	*M(SD)*	***t***	***p***
Age	30.9 (6.94)	37.6 (11.52)	3.47	0.001
IQ	101.9 (10.91)	94.6 (15.02)	2.59	0.01
	%	*%*	χ^2	***p***
Race(CA:AA:OT)	59:37:4	52:34:14	5.26	0.26
Hand (R:L:B)	80:5:15	89:9:2	4.64	0.10

CA: Caucasian, AA: African American, OT: Other. R: Right, L: Left, B: Both (i.e., no dominant hand).

Mexico Institutional Review Board. Participants were paid at a rate commensurate to work assignments at their facility.

2.2. Assessments

DSM-IV Axis I disorders were evaluated using the Structured Clinical Interview for DSM-IV Disorders (SCID-IV) (First et al., 1997a, 1997b). Psychotic disorder diagnoses in incarcerated offenders were confirmed with additional file reviews of previous psychiatric evaluations by trained research assistants. Discrepancies with file information, which were rare, were resolved via additional review by the authors (C.H./J.B.). Three psychotic offenders did not complete the SCID, thus diagnoses were based on file review only.[1] Current symptoms were evaluated in psychotic offenders using the Positive and Negative Symptom Scale (Kay et al., 1987). We used factor-model validated measures of positive, negative, and cognitive symptoms which pool specific PANSS items across the positive, negative, and general categories (Lindenmayer et al., 1995).[2] The positive symptom measure included delusions, hallucinations, grandiosity, suspiciousness/persecution, and unusual thought content. The negative symptom measure included blunted affect, emotional withdrawal, poor rapport, passive withdrawal, lack of spontaneity, and active social withdrawal. The cognitive symptom measure included conceptual disorganization, difficulty in abstract thinking, mannerisms/posturing, disorientation, and poor attention. Illness duration was calculated by subtracting the onset age of psychotic symptoms from current age. Data from three participants was not included due to insufficient file/interview information. IQ was estimated using the vocabulary and matrix reasoning subtests of the Wechsler Adult Intelligence Scale (WAIS) (Ryan et al., 1999; Wechsler, 1997). Other cognitive abilities including response inhibition, verbal fluency, and set shifting were assessed in psychotic offenders with the Delis-Kaplan Executive Function Scale (Delis, 2001). Nine psychotic offenders did not complete the D-KEFS.

Most psychotic offenders had either no history of head injury (n = 20) or had a prior head injury with no loss of consciousness (n = 7). All except seven psychotic offenders were taking antipsychotic medications. Medication dosages were converted to daily olanzapine equivalents (Gardner et al., 2010).[3] See Supplementary data section for further information regarding medications, head injury, and associations with clinical and neuroimaging variables.

We also evaluated traits that are relevant to forensic populations. Psychopathy, which is more prevalent among offenders (Hare, 2003) and associated with aberrant brain function during affective mentalizing (Decety et al., 2013a, 2013b), was assessed using the Psychopathy Checklist-Revised (PCL-R) (Hare, 2003). Two psychotic offenders did not complete the PCL-R. Antisocial personality disorder and other personality disorders were evaluated using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (First et al., 1997a, 1997b). Four psychotic offenders did not complete the SCID-II. See Supplementary data section for further information regarding these measures and associations with clinical and neuroimaging variables.

2.3. MRI stimuli and task

During fMRI scanning participants completed an affective mentalizing task based on the paradigm developed by Derntl et al. (2010). The task has been shown to engage brain regions implicated in mentalizing such as the superior temporal gyrus, temporo-parietal junction, inferior frontal gyrus, and medial prefrontal cortex (Derntl et al., 2010; Haas et al., 2015). Activity in mPFC during the task has also been found to correlate with empathic accuracy abilities (Haas et al., 2015). In the emotion condition, participants viewed visual stimuli depicting social interactions in which one individuals face was “blanked out”. Below the scene were two different emotional facial expressions (angry, fear, sad, neutral, or happy), and participants were instructed to choose which expression best matched the blanked out face. In the control condition, participants indicated which of two shapes matched the shape embedded within the social scene (Fig. 1). For additional task details see Haas et al. (2015). Trials were 4 s long and preceded by an instruction cue (E = emotion, S = shape). Trials were blocked into 3 or 4 consecutive emotion or shape stimuli, and a total of 70 trials (35 emotion and 35 shape, 10 blocks for each) were presented. The number of trials for each emotion category (angry, fear, sad, neutral, or happy) was the same for emotion and shape conditions, and the types of emotional expressions shown alternated within blocks. All participants practiced the task (different stimuli from the MRI task) immediately prior to the scanning session.

2.4. Behavioral data analysis

All analyses were conducted using SPSS. One-way ANOVA was conducted to compare performance between psychotic offenders and nonpsychotic offenders. Correlation analysis was used to examine associations between task performance and symptoms in psychotic offenders. Alpha was set to $p < 0.05$ (two-tailed) for all analyses.

IQ and age were significantly different across groups (Table 1) and IQ and illness duration were significantly correlated with at least one symptom type (Table 2). Additionally, cognitive symptoms were significantly correlated with positive and negative symptoms. Because group assignment and symptom distribution across participants was not random, it is not statistically possible to determine (or remove the influence of) associations with these covariates that occurred due to chance vs. being meaningfully related to group or symptom level (Miller and Chapman, 2001). We thus present all behavioral (and MRI) results with and without covariates.

2.5. MRI acquisition/preprocessing

MRI images were collected on the Mind Research Network 1.5-Tesla Siemens Avanto mobile scanner. EPI data was collected on a 32-channel head coil using a multiband EPI gradient-echo pulse sequence (TR/TE 350 ms/39 ms, flip angle 38°, FOV 248 × 248 mm, 70 × 70 matrix, 3.5 mm isotropic resolution, 48 slices, multiband factor = 12) and covered the whole brain in 350 ms. Head motion was minimized using padding and restraint.

Functional data were analyzed using the Statistical Parametric

[1] It is sometimes difficult to complete every assessment with participants due to the prison environment (e.g., unannounced unit or facility transfers, early releases). There were no discernable patterns to the distribution of missing assessments, e.g., missing data was not more common among offenders scoring higher (or lower) on any symptom dimensions.

[2] Unlike Positive, Negative, and Cognitive factors, the two other factors included in the Lindenmayer model, Excitement and Depression, have been less implicated in mentalizing and were not explicitly examined in the present study. Neither factor was significantly correlated with any of the dependent variables (mentalizing task accuracy or component loading weights).

[3] One psychotic participants’ daily olanzapine equivalent was five SD above the group mean. This participant was excluded from Table 2 results. All behavioral and imaging results reported in this study remained significant when this participant was excluded.

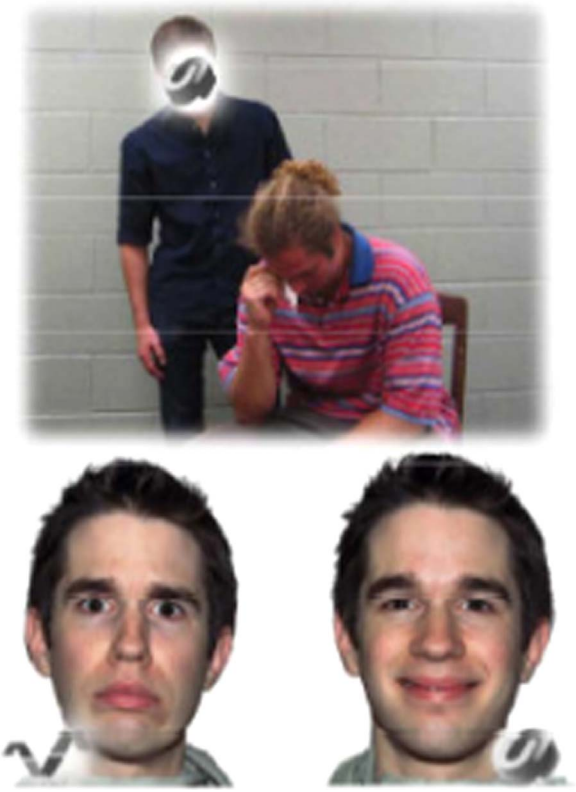

Fig. 1. Example trial stimulus from the affective mentalizing task. Participants were instructed to match either the facial expression or shape on each trial.

Table 2
Correlations between symptoms, demographic, and clinical variables in psychotic offenders.

	Mean (SD)	Positive Symptoms *r*	Negative Symptoms *r*	Cognitive Symptoms *r*
Positive Symptoms	11.39 (4.92)	–	–	–
Negative Symptoms	11.02 (5.28)	0.05	–	–
Cognitive Symptoms	8.16 (2.75)	0.52**	0.32*	–
Age	37.6 (11.52)	0.22	−0.09	0.01
IQ	94.6 (15.02)	0.03	−0.39**	−0.48**
Illness duration	14.1 (11.41)	0.34*	0.04	0.36*
Olanzapine equiv.	18.6 (14.98)	0.12	0.02	0.19
PCL-R	22.2 (6.67)	−0.11	0.04	0.04
Response Inhibition	8.21 (3.54)	−0.14	−0.12	−0.24
Verbal Fluency	8.91 (3.34)	0.07	−0.29	−0.02
Set Shifting	7.00 (3.94)	−0.07	−0.10	−0.22
	%	*F/t*	*F/t*	*F/t*
Race (CA:AA:OT)	62:12:26	2.41	1.35	2.02
Handedness (R:L:B)	73:8:19	0.32	0.51	0.59
Psychotic Disorder (SZ/SAD:BP:OT)†	70:25:5	4.78*	3.18*	4.70*

CA: Caucasian, AA: African American, OT: Other. R = Right, L = Left, B = Both (i.e., no dominant hand).

* $p < 0.05$.

** $p < 0.01$.

† Bipolar disorder patients had lower positive, negative, and cognitive symptoms compared to all other groups (i.e., Schizophrenia/Schizoaffective, Other Psychotic Disorder).

Mapping software (SPM12, http://www.fil.ion.ucl.ac.uk/spm/). The ArtRepair toolbox was used to remove images with severe artifacts and replaced by a rolling mean image (Mazaika et al., 2009). Any replaced images were regressed in the general linear model (GLM) analysis. Functional images were then realigned using INRIAlign (Freire et al., 2002), and realignment parameters were used to regress variance due to movement in the statistical model. The images were then spatially normalized to MNI space and smoothed using an 8 mm FWHM Gaussian kernel.

2.6. Independent component analysis

Functional connectivity during the mentalizing task was assessed using group independent component analysis (ICA) (Calhoun et al., 2001; Calhoun and Adali, 2012). ICA is an application of blind source separation that decomposes an fMRI dataset into maximally spatially independent components and their associated timecourses. ICA was performed using the GIFT toolbox (version 4.0a, http://mialab.mrn.org/software/gift). Principal component analysis was first used to reduce the dimensionality of the data to 120 components. Then group ICA (all 111 subjects) was performed using entropy-bound minimization (EBM) (Li et al., 2011), a flexible ICA algorithm which does not make specific assumptions about the source distributions. This reduced the data to 100 maximally independent components. The EBM algorithm was repeated five times in ICASSO (http://www.cis.hut.fi/projects/ica/icasso) to estimate the reliability of the decomposition (Himberg et al., 2004). Subject specific component maps and timecourses were then computing using back-reconstruction (Erhardt et al., 2011).

The 100 components were evaluated to identify and remove components determined to be motion or physiology-related or otherwise artifactual. Such components were identified based on the ratio of low to high frequency power as well as peak activations outside gray matter, or spatial overlap with known vascular, ventricular, motion, and susceptibility artifacts (Allen et al., 2012). This yielded 54 remaining components. Next, a multiple regression was performed with the ICA component timecourses and GLM design matrix from SPM12. The regression produced beta values representing the correlation between each component timecourse and the experimental regressors (emotion and shape conditions) for each subject, which were then entered into a one-sample *t*-test. To select components related to mentalizing, we first identified components whose beta weights were significantly correlated (positively or negatively) with emotion trials ($p < 0.05$, corrected for multiple comparisons, i.e., number of components – $p < 0.00009$). Betas for those components ($n = 26$) were entered into a one-way ANOVA contrasting the emotion and shape regressors, and components showing significantly greater emotion vs. shape correlations were retained. In other words, the timecourses of the remaining components were significantly modulated (positively or negatively) by emotion trials relative to shape trials. This resulted in 11 remaining components.

The beta values (i.e., correlation between component timecourse and emotion condition regressor) for the 11 components were compared across the psychotic and nonpsychotic offenders using ANOVA. Components that showed a significant group difference and contained at least one of the hypothesized mentalizing regions (e.g., mPFC, pSTS, iFG) were then entered into a regression analysis in the psychotic offender group with positive, negative, and cognitive symptoms as independent variables.

3. Results

3.1. Group differences in task performance

Psychotic offenders had lower emotion accuracy scores ($M = 0.66$) compared to nonpsychotic offenders ($M = 0.75$) ($F_{(1,85)} = 22.61$, $p < 0.001$). They also had lower shape accuracy scores ($M = 0.82$)

compared to nonpsychotic offenders ($M = 0.92$) $F_{(1,85)} = 10.95$, $p = 0.001$). The group difference in emotion accuracy remained significant when age and IQ were included as covariates ($p = 0.004$) but the difference in shape accuracy did not ($p = 0.10$).

3.2. Correlations with PANSS symptoms

Prior to all correlation and partial correlation analyses including PANSS cognitive symptoms reported below, one patient whose cognitive symptom score was 3.1 SD above the group mean was removed. Emotion accuracy was inversely correlated with positive symptoms ($r(44) = -0.42$, $p = 0.004$; partial correlation with illness duration, cognitive symptoms, and IQ estimate: $r(35) = -0.31$, $p = 0.058$). The correlation with shape accuracy was not significant ($r(44) = -0.11$, $p = 0.48$; partial correlation with illness duration, cognitive symptoms, and IQ estimate: $r(35) = 0.14$, $p = 0.41$). There were no significant associations between emotion or shape accuracy and negative symptoms ($r(44) = -0.23$, $p = 0.14$; $r(44) = 0.06$, $p = 0.67$, respectively), apart from a marginally significant correlation with shape accuracy when including covariates (partial correlation with illness duration, cognitive symptoms, and IQ estimate: $r(35) = -0.03$, $p = 0.86$ (emotion accuracy); $r(35) = 0.32$, $p = 0.058$ (shape accuracy).

Emotion and shape accuracy were inversely correlated with cognitive symptoms ($r(44) = -0.63$, $p < 0.001$, $r(44) = -0.51$, $p < 0.001$, respectively). The correlation with emotion accuracy was reduced when including covariates (partial correlation with illness duration, positive symptoms, negative symptoms, and IQ estimate: $r(34) = -0.32$, $p = 0.06$) and the correlation with shape accuracy was no longer significant ($r(34) = 0.11$, $p = 0.53$).

3.3. Group differences in functional connectivity

One component (C99; Fig. 2) passed selection criteria for identifying mentalizing-related networks (i.e., significant correlation with emotion condition time course, significantly greater activity during emotion vs. shape trials, included at least one of the hypothesized mentalizing regions) and showed group differences in component loadings. See Table 3 for a summary of the regions that comprised C99. Nonpsychotic offenders had higher C99 component loadings compared to psychotic offenders ($F_{(1,85)} = 9.83$, $p = 0.002$; with age and IQ included as covariates: $F_{(3,85)} = 5.23$, $p = 0.025$; Fig. 2).

3.4. Correlations with PANSS symptoms

Cognitive symptoms were inversely correlated with C99 loading parameters ($r(43) = -0.35$, $p = 0.02$; partial correlation with illness duration, positive symptoms, negative symptoms, and IQ estimate: $r(34) = -0.35$, $p = 0.03$). Neither positive nor negative symptoms were significantly correlated with C99 loading parameters ($r(43) = -0.23$, $p = 0.14$; $r(43) = -0.06$, $p = 0.72$; respectively).

Table 3
List of MNI coordinates and regions corresponding to the functional map for Component 99.

Region	BA	MNI (x,y,z)
C99		
Inferior Frontal Gyrus	9, 10, 11, 13, 44, 45, 46, 47	(−51, 17, −4)/(51, 20, −7)
Superior Temporal Gyrus	22, 38	(−54, 14, −4)/(54, 17, −7)
Insula	13, 22, 47	(−48, 11, −1)/(42, 17, −1)
Precentral Gyrus	9, 44	(−54, 17, 8)/(60, 14, 8)
Middle Frontal Gyrus	9, 10, 11, 46, 47	(−54, 20, 29)/(54, 23, 26)
Middle Temporal Gyrus	21, 38	(−42, 8, −40)/(45, 14, −40)
Inferior Temporal Gyrus	20	(−39, −1, −43)/(39, 2, −43)
Medial Frontal Gyrus	8, 9	(0, 20, 53)/(3, 23, 53)
Insula	13	(−30, 17, 2)
Medial Frontal Gyrus	6, 8, 9, 10	(−3, 56, 26)/(3, 29, 44)
Temporal Pole	38	(−27, 2, −43)
Medial Frontal Gyrus	8	(−3, 23, 44)

3.5. Correlations with individual positive symptoms

Behavioral and imaging results related to individual positive symptoms are presented in Table 4. Correlations with individual negative and cognitive symptoms are included in the Supplementary data section. None of the positive symptoms were significantly correlated with Table 2 variables, except for negative correlations between P6 (Suspiciousness) and age ($r(44) = 0.36$, $p = 0.015$) and illness duration ($r(44) = 0.42$, $p = 0.007$). The partial correlation between P6 and emotion accuracy including (age-adjusted) illness duration was marginally significant ($r(41) = 0.27$, $p = 0.08$). Negative correlations were also observed between Delusions, Grandiosity, and emotion accuracy, and between Grandiosity, Unusual Thought Content, and C99 loading weights (all p's < 0.05). However, only the correlation with Delusions survived correction for multiple comparisons ($p = 0.002$).

3.6. Results by psychotic disorder type

Bipolar disorder patients had lower positive, negative, and cognitive

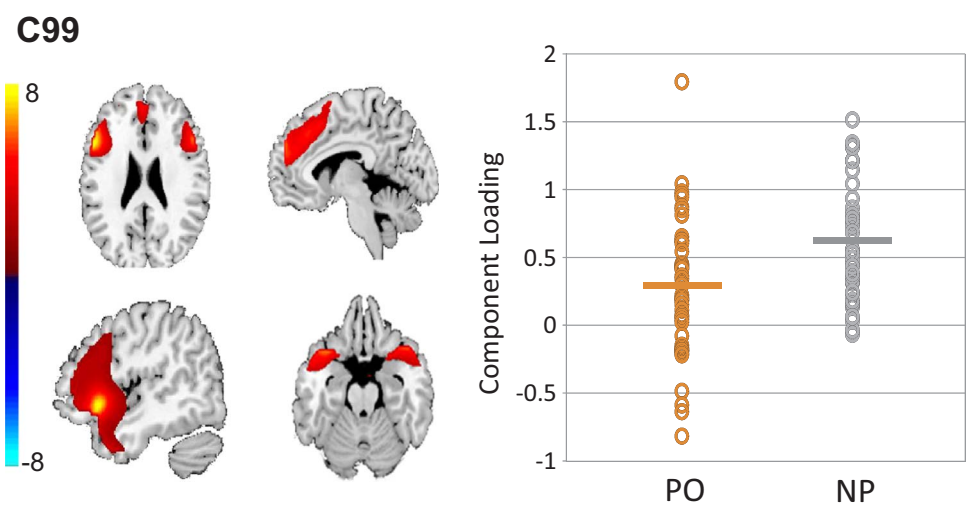

Fig. 2. Component 99 map and loading weights across groups. *PO:* Psychotic offender, *NP:* Nonpsychotic offender.

Table 4
Correlations with individual positive symptoms.

Positive	Emotion accuracy *r*	Shape accuracy *r*	Component 99 *r*
P_1 (Delusions)	-0.51	−0.20	−0.07
P_3 (Hallucinations)	−0.05	0.04	−0.23
P_5 (Grandiosity)	−0.31	−0.13	−0.29
P_6 (Suspiciousness)	−0.36	−0.02	−0.08
G_9 (Unusual Thought Content)	−0.21	−0.06	−0.32

symptom scores (Table 2), lower individual positive symptom scores for all positive symptoms (all p's < 0.05) except grandiosity ($p = 0.11$), and higher emotion accuracy scores ($F_{(2,41)} = 3.99$, $p = 0.03$) compared to patients with schizophrenia or schizoaffective disorder. There were no significant differences related to disorder type in shape accuracy or C99 loading weights. Thus, lower symptom scores in bipolar patients may partly account for the inverse correlations between emotion task accuracy and symptoms (i.e., total positive symptoms, total cognitive symptoms, delusions). To examine results without this potential confound, and also to enable comparisons with prior studies which have mostly focused on schizophrenia and schizoaffective disorder, we present results for all analyses with SZ/SAD participants only in the Supplementary data section. The results of this analysis indicated that the correlations between emotion accuracy and total positive and cognitive symptom scores were no longer significant (p's = 0.16, 0.10, respectively). The correlation with delusions remained significant ($p = 0.01$). The group difference between SZ/SAD and BP patients in emotion accuracy was also no longer significant when including delusions ($p = 0.09$) as a covariate.

4. Discussion

The current study examined functional connectivity during affective mentalizing in individuals with psychotic disorders and associations with clinical symptoms. Consistent with hypotheses, psychotic offenders showed impaired mentalizing performance, and reduced activation in the mentalizing network that included dmPFC and superior temporal gyrus, relative to nonpsychotic offenders. Mentalizing task performance was inversely correlated with delusion severity but not with total positive symptom scores. Mentalizing network activity was inversely correlated with total cognitive symptoms and two types of positive symptoms: grandiosity and unusual thought content. Overall, the results shed new light on the specific dimensions of psychosis symptomatology that are related to affective mentalizing and associated brain networks.

Psychotic offenders showed significantly lower mentalizing performance compared to nonpsychotic offenders. These results add to the literature demonstrating impaired mentalizing in psychotic disorders (Green et al., 2015) and extend it to psychotic individuals with comorbid antisocial tendencies. Psychotic offenders also performed worse on the shape matching task than the comparison groups. Because we predicted deficits specific to mentalizing, this finding was unexpected. One possibility concerns the subtle presentation of the shape embedded in the picture (unlike the facial expressions, which were more clearly visible). Deficits in visual perception, which have been demonstrated in schizophrenia (Donnell et al., 1996; Doniger et al., 2001; Tek et al., 2002), in combination with the time constraint, may have explained the reduction in shape matching performance.

Mentalizing performance was significantly lower in psychotic offenders with higher delusion severity, but not higher total positive symptoms (after excluding bipolar patients – see below). Factor analysis studies of the PANSS and related symptom scales have consistently yielded a positive symptom dimension, and the symptom types included within that dimension are generally similar across studies (Emsley et al., 2003; Lancon et al., 2000; Liddle et al., 2002; Lindenmayer et al., 1995; Lykouras et al., 2000; Van den Oord et al., 2006; van der Gaag et al., 2006). However, our findings suggest that associations with social cognition may differ across positive symptom types. It might be expected that symptoms related to mentalizing impairment include those involving misunderstandings of others' communication and/or intentions (e.g., delusions). As opposed to, for example, for example, hallucinations, which tend to be internally generated rather than deriving from impressions of other individuals. It may be fruitful in future work to consider individual symptoms based on the theoretical expectation that they would be related to mentalizing.

The results are also consistent with prior findings that patients with bipolar disorder perform better on social cognition tasks than those with schizophrenia (Bora and Pantelis, 2016; Lee et al., 2014). In this study, bipolar patients outperformed schizophrenia and schizoaffective disorder patients on the emotion matching task. Bipolar patients also had lower levels of positive symptoms compared to schizophrenia patients. Thus, when bipolar patients were excluded from the analysis, the correlation between emotion accuracy and positive symptoms was not significant. Importantly, however, the correlation between emotion accuracy and delusions remained significant. This further underscores the importance of examining individual positive symptoms and their relation to social cognition.

Interestingly, cognitive symptoms were not significantly correlated with emotion accuracy, contrary to some prior studies (Sprong et al., 2007; Ventura et al., 2013). This is likely related to how relevant covariates are accounted for in data analysis across studies. Our results showed that the significant cognitive symptoms – emotion accuracy correlation was rendered nonsignificant after the inclusion of covariates including illness duration and IQ, as well as the inclusion of positive and negative symptoms which both correlated with cognitive symptoms. We also did not find significant correlations between emotion accuracy and negative symptoms (with or without covariates). This may be related to our use of an affective rather than cognitive mentalizing task, the latter of which was used in most prior studies that reported associations with negative symptoms. One study found a negative correlation between affective mentalizing and negative symptoms (Shamay-Tsoory et al., 2007), but the stimuli were different from those used here (matching line drawn facial expressions based on explanatory text) and the correlations were found with a different measure of negative symptoms than the PANSS.

The ICA results revealed one network that was modulated by the mentalizing task and showed significant psychotic vs. nonpsychotic group differences. Component 99 included established mentalizing regions such as the dorsomedial PFC and superior temporal gyrus and was positively modulated by the emotion relative to shape condition. Consistent with our hypothesis, psychotic offenders showed reduced C99 loadings, meaning this network was less engaged during the mentalizing task in the psychotic relative to nonpsychotic offenders. As further evidence that deficits in this network were related to psychosis, component loadings were inversely correlated with cognitive symptoms. They were also inversely correlated with two types of positive symptoms: grandiosity and unusual thought content. The latter correlations were not as robust as the correlation between emotion accuracy and delusions and were not corrected for multiple comparisons. Thus, they should be viewed as tentative and replicated in future studies. Overall, the results provide new evidence that cognitive symptoms are associated with aberrant functional connectivity related to affective mentalizing, and further preliminary evidence of associations between specific types of positives symptoms and neurobehavioral mechanisms underlying affective mentalizing.

Psychotic symptoms may vary in severity across different time points. While we examined the association between active symptom levels and mentalizing, it may also be worthwhile to examine an

individual's history of symptoms relative to their mentalizing abilities. Although the participants in our study had a reasonable range of low to high symptom levels, the overall means were generally low, which is unsurprising given that the patients were being managed in a secure treatment setting. It is possible that lower mean symptom levels may have minimized correlations between task accuracy, brain activity, and symptoms.

The mentalizing task used in this study was dependent on accurate recognition of facial expressions, which raises the question of whether impaired performance was related to facial expression recognition deficits. While studies have found that schizophrenia and bipolar patients are unimpaired in implicit facial expression processing (Chen et al., 2006; Linden et al., 2010), recent work suggests that such impairments may exist, particularly as they relate to inferring social trait information (Trémeau et al., 2015). A deficit in facial expression processing seems more likely to impact task accuracy rather than functional connectivity within mentalizing brain regions (i.e., participants can still engage in mentalizing even if the facial expression determination is inaccurate). However, prior work using a highly similar task to ours evaluated facial expression recognition and reported significant mentalizing deficits in schizophrenia patients even after accounting for facial expression recognition abilities (Derntl et al., 2009). The same study found that schizophrenia deficits on the mentalizing task were more severe than deficits in age discrimination, despite the two tasks having equivalent levels of difficulty. Thus, the mentalizing deficits we observed in psychotic offenders are likely not explained by facial expression recognition deficits or general task difficulty. Nevertheless, the task we used included other emotional and social cues besides facial expressions such as body language and gestures, and it is certainly possible that deficits related to psychosis are attributable to impaired processing of such cues. It has also been argued that emotion recognition and mental state inference are distinct processes and caution should be exercised in generalizing emotion perception/understanding deficits to mentalizing or theory of mind deficits (Oakley et al., 2006). In this context, it is notable that brain regions which have been implicated in mentalizing tasks focused on identifying emotional states from observable cues, such as the inferior frontal gyrus (Hooker et al., 2008), comprised a substantial part of C99. Future studies that tease apart the contributions of socio-emotional cue perception and emotion understanding to metalizing can shed greater light on these issues.

A final note regarding the task is that the shape condition involved perceptual matching rather than inferential judgement. This, the current results do not demonstrate that the psychotic disorder or symptom-related deficits are exclusive to affective mentalizing vs. other types of inferential judgments.

The current study was conducted in psychotic individuals with comorbid antisocial tendencies. Whether our results are generalizable to non-forensic psychotic patients remains to be determined. However, we did demonstrate that none of the reported results were attributable to or otherwise explained by antisocial or psychopathic traits (see Supplementary data section). The use of a forensic sample will also enable future investigations on the associations between psychotic symptoms, mentalizing, and forensically-relevant outcomes (e.g., aggressive behavior). Also, while the implicit assumption of the present research is that the hypothesized symptom-neurobiology-mentalizing associations would be observed across additional psychosis syndromes (beyond schizophrenia, which represented the majority of our sample), and that such syndromes have a sufficient distribution of psychotic symptoms to examine such questions, we could not test this directly due to the small sample sizes and this is an important question for future research. Whether the current findings extend to females with psychotic disorders is also a question for future research.

In summary, we conducted the first (to our knowledge) ICA study of functional connectivity during mentalizing in psychotic-disordered criminal offenders. Psychotic offenders showed reduced activity in mentalizing-related networks along with impaired task performance, which were related to specific psychotic symptoms. Future work investigating individual symptoms, symptom history, as well as multiple imaging modalities (e.g., joint functional-structural ICA) may shed even more light on the neurobiological underpinnings of impaired social cognitive processes in schizophrenia and other psychotic disorders.

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Author contributions

C.L. Harenski, K.A. Kiehl, B.W. Haas, and J. Decety designed the study. C.L. Harenski and J.R. Bustillo supervised clinical assessments and resolved any conflicts in psychotic disorder diagnoses or PANSS scores. C.L. Harenski, V.D. Calhoun, and K.A. Harenski devised and implemented the analytical approach. M. Koenigs, M.F. Caldwell, G.J. VanRybroek and D.M. Thornton coordinated data collection in Wisconsin prisons. All authors provided critical manuscript revisions and approved the final version.

Conflict of interest

The authors have no competing interests to disclose.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pscychresns.2017.11.003.

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