Brain gray matter differences among forensic psychiatric patients with psychosis and incarcerated individuals without psychosis: A source-based morphometry study

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A B S T R A C T

Background: While psychosis is a risk factor for violence, the majority of individuals who perpetrate aggression do not present psychotic symptoms. Pathological aggressive behavior is associated with brain gray matter differences, which, in turn, has shown a relationship with increased psychopathic traits. However, no study, to our knowledge, has ever investigated gray matter differences in forensic psychiatric patients with psychosis compared with incarcerated individuals without psychosis matched on levels of psychopathic traits. Here, we employed source-based morphometry (SBM) to investigate gray matter differences in these two populations.

Methods: We scanned 137 participants comprising two offender subgroups: 69, non-psychotic incarcerated offenders and 68, psychotic, forensic psychiatric patients. Groups showed no difference in age, race, ethnicity, handedness, and Hare Psychopathy Checklist-Revised scores. Source-based morphometry was utilized to identify spatially distinct sets of brain regions where gray matter volumes covaried between groups. SBM is a data-driven, multivariate technique that uses independent components analysis to categorize groups of voxels that display similar variance patterns (e.g., components) that are compared across groups.

Results: SBM identified four components that differed between groups. These findings indicated greater loading weights in the superior, transverse, and middle temporal gyrus and anterior cingulate in the non-psychotic versus psychotic group; greater loading weights in the basal ganglia in the psychotic versus non-psychotic group; greater loading weights in the frontal pole, precuneus, and visual cortex among psychotic versus non-psychotic offenders; and greater loading weights in the thalamus and parahippocampal gyrus in psychotic versus non-psychotic groups.

Conclusions: Two different offender groups that perpetrate violence and show comparable levels of psychopathic traits evidenced different gray matter volumes. We suggest that future studies of violent offenders with psychosis take psychopathic traits into account to refine neural phenotypes.

1. Introduction

Forensic psychiatric patients are some of the most unwell, diagnostically challenging, and clinically complex persons in the mental health system (Hodgins, 2002). Most of these individuals have been found not guilty by reason of insanity for their criminal actions on account of a mental disorder. Although definitions of "legal insanity" vary by jurisdiction, most forensic psychiatric patients merit this finding if symptoms of a severe and persistent mental illness – namely psychosis – prevented them from understanding the wrongfulness of their behavior during the index offense(s). Forensic patients are not incarcerated; instead, they are treated in psychiatric hospitals like civilian patients and gradually

transitioned to the community as their risk factors are mitigated (Lindqvist and Skipworth, 2000). In contrast to other groups of psychotic or psychopathic patients, there has been scant neurobiological research of forensic psychiatric patients in part due to ethical concerns and the difficulties of physically accessing this population (Coffey, 2006).

Aggression in forensic psychiatric patients is heterogeneous. Some violence is driven by delusions and hallucinations, while other aggression can be explained by maladaptive personality traits, such as high Hare Psychopathy Checklist-Revised (PCL-R) scores (Hoptman and Antonius, 2011). Additionally, poor impulse control can also contribute to aggression (Kamphuis et al., 2014). Controlling for pathological

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personality measures is one method of teasing apart the role of psychosis in the perpetration of violence among forensic psychiatric patients. Several neuroimaging studies have examined brain structure in schizophrenia (SCZ) and schizoaffective (SCZA) patients who have been violent compared to those with these diagnoses without a history of violence. Two recent systematic reviews converge in their findings of lower whole brain grey matter volume (GMV), including lower GMV in the inferior and middle temporal gyrus, fusiform, and the right insula in forensic psychiatric SCZ patients and SCZ patients with aggression (Fjellvang et al., 2018; Widmayer et al., 2018). However, these studies did not control for measures of psychopathic traits among subjects, which are also related to abnormal brain structure (Anderson and Kiehl, 2012). Moreover, few, if any, studies have compared brain correlates of subtypes of offenders (e.g., forensic psychiatric patients with psychosis versus incarcerated individuals without psychosis). This omission is noteworthy, since such investigations may serve to highlight brain volume changes key to psychotic offenders after controlling for maladaptive personality functioning. The comparison of these subtypes of offenders is a gap in the literature and the premise for this investigation.

While voxel-based morphometry (VBM) has been the traditional approach to comparing volumetric brain changes across groups, newer methodologies may offer distinct advantages. One such technique is source-based morphometry (SBM) that allows investigation of GMV within neural networks and group differences among subtypes of offenders (e.g., psychotic versus non-psychotic individuals who are both justice-involved). SBM separates GMV into maximally independent source networks. In contrast to VBM, it is a data-driven, multivariate analysis method that utilizes spatial information between voxels to pinpoint independently grouped "sources," for example, spatially distinct sets of brain regions where gray matter covaries between individuals (Xu et al., 2009). One advantage of SBM over VBM is that it uses independent components analysis (ICA) to categorize collection of voxels that display similar variance patterns (e.g., components) and the component values (e.g., loading coefficients, which represent the mean brain volume across each component after taking into account other components) that are compared across groups. This strategy decreases the problem of multiple comparison correction, for instance, correcting for every voxel in the brain, while simultaneously providing helpful information about voxel patterns. Studies in clinical populations of forensic samples have found SBM-based group differences that VBM did not detect (Harenski et al., 2020). Other SBM investigations of schizophrenia-spectrum disorders have been conducted in community populations (Kasparek et al., 2010; Wolf et al., 2014; Xu et al., 2009). To our knowledge, there has never been an SBM study of SCZ or SCZA in forensic populations.

An additional benefit of SBM is that it does not necessitate defining *a priori* regions of interest. This advantage was optimal for the reason that the brain volumes of the two offender subtypes – psychotic forensic psychiatric patients versus incarcerated controls without psychosis – have never been tested. The lack of previous neuroimaging research on forensic psychiatric patients and incarcerated individuals is hindered by the difficulties bringing imaging technologies to hospitals/jails or transporting patients/offenders outside of their confined settings, which is rarely permitted. To overcome these limitations, we used a highly innovative mobile MRI scanner that was situated on hospital and prison grounds to study participants using SBM. This procedure has been used in numerous studies of incarcerated, psychopathic populations (Anderson and Kiehl, 2012).

Given the aforementioned results of the systematic reviews indicating that brain volumes of violent SCZ patients were lower in the temporal gyrus, fusiform, and insular cortex compared with non-violent patients with SCZ (Fjellvang et al., 2018; Widmayer et al., 2018), we hypothesized that SBM would reveal one or more sources comprising the temporal lobe region in forensic psychiatric patients with psychosis. Temporal lobe abnormalities have previously been reported in violent SCZ patients (Wong et al., 1997). However, given that no other study of

forensic psychiatric patients controlled for psychopathic traits, we investigated but did not develop specific hypotheses regarding GMV implicated in violent populations, including the prefrontal cortex and anterior cingulate cortex (Hoptman et al., 2005; Naudts and Hodgins, 2006).

2. Method

All participants provided written informed consent after all study components were fully explained to them. All procedures were approved by the Waypoint Centre for Mental Health Care (Waypoint) Research Ethics Board in Penetanguishene, Ontario, Canada; the University of New Mexico Institutional Review Board; and Ethical and Independent Review Services. Importantly, all participants could choose to participate or not (e.g., their choice was voluntary) and the informed consent explicitly stated that study participation would not impact their legal status in any way or their status at the facility. For the incarcerated participants, their pay was yoked to the hourly wage for work assignments at the facility.

2.1. Participants

The total sample yielded 137 participants of two offender subgroups: 69, non-psychotic incarcerated offenders and 68, psychotic, forensic psychiatric patients. The incarcerated group was generated from a large database of incarcerated offenders. Offenders were recruited from medium-secure state prison facilities in New Mexico and Wisconsin. Forensic psychiatric patients were recruited from several forensic psychiatric hospitals, including Waypoint, which is the only high-secure forensic psychiatric facility in the province of Ontario. The vast majority of forensic patients in this study were found not guilty by reason of insanity (e.g., not criminally responsibility) as opposed to being adjudged unfit to stand trial. Inclusion criteria included the following: 1) age between 18 and 60 years; 2) estimated IQ of 70 or greater; 3) no history of central nervous system disorder; and 4) negative drug toxicology screening at the time of testing or negative self-report.

Waypoint participants were compensated $50 CAD for their involvement in the study procedures; for all other sites, subjects were compensated at a rate commensurate to work assignments at their respective facilities.

The presence of psychosis in the forensic psychiatric institutions was based on diagnosis (e.g., SCZ, SCZA, or bipolar disorder) and in some instances, structured screening (First et al., 1997). Conversely, incarcerated individuals were deemed not to have psychosis if they screened negative for any Axis I condition associated with psychotic symptoms.

2.2. Clinical assessments

With the exception of Waypoint, past and present DSM-IV Axis I disorders were evaluated in incarcerated offenders and hospitalized patients using the research version of the Structured Clinical Interview of DSM-IV Disorders (SCID-IV Disorders) (First et al., 1997). Diagnoses in Waypoint patients were generated by clinical reports of the treating psychiatrist and treatment team. Intelligence was estimated using the vocabulary and matrix reasoning subtests of the Wechsler Adult Intelligence Scale (WAIS) (Ryan et al., 1999) or the WASI (Wechsler Abbreviated Scale of Intelligence) (Ryan et al., 1999; Wechsler, 1999).

Participants were also administered the Hare Psychopathy Checklist-Revised (PCL-R) (Hare, 2003). The PCL-R is a semi-structured interview that indexes factors of prototypical psychopathy. The PCL-R relies on information acquired during interviews as well as collateral, file information. It includes 20 items that are scored based on the presence or absence of the trait in question (0 = definitely not present; 1 = possibly present; and 2 = definitely present). Scores between 0 and 40 are thus generated. In North America, a score of 30 or greater on the PCL-R denotes the clinical construct of psychopathy. The PCL-R can be separated

into two factors: Factor 1 captures traits relating to interpersonal and affective deficits of psychopathy, while Factor 2 indexes symptoms related to antisocial behavior. There is further evidence that the PCL-R can be decomposed into four facets, with facets 1 and 2 comprising interpersonal and affective domains, while facets 3 and 4 reflect lifestyle instability and antisocial behavior characteristic of psychopathy.

2.3. MRI acquisition and analysis

High-resolution T1-weighted structural MRI scans were collected on a Siemens 1.5 T Avanto mobile scanner, stationed at the hospital and correctional facilities, using a multi-echo MPRAGE pulse sequence (repetition time = 2530 ms; echo times = 1.64 ms, 3.50 ms, 5.36 ms, 7.22 ms; inversion time = 1100 ms; flip angle = 7°; slice thickness = 1.3 mm; matrix size = 256×256) yielding 128 sagittal slices with an in-plane resolution of 1.0 mm $\times$ 1.0 mm. Data were preprocessed and analyzed using the Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm). T1 images were manually inspected by an operator blind to subject identity and realigned to ensure proper spatial normalization. Data were then spatially normalized into the standard Montreal Neurological Institute (MNI) space, resampled to $2 \times 2 \times 2$ mm voxels and segmented into white matter, gray matter and cerebrospinal fluid. The segmented maps were modulated to preserve total cerebral volume (Ashburner and Friston, 2005) and voxels with values less than 0.15 were removed. The segmented images were then smoothed using a Gaussian kernel with a full-width at half-maximum (FWHM) of 10 mm.

The SBM analysis methods have been described in detail elsewhere (Xu et al., 2009). Briefly, SBM creates a whole brain mask based on the sample data; thus, no sample-specific template is involved. Following preprocessing, the Group ICA fMRI Toolbox (GIFT) software (http://mialab.mrn.org/software/gift) was utilized to calculate the number of maximally independent components using a modified minimum description length (MDL) method (Li et al., 2007) in all 137 subjects. Next, ICA was performed using the Infomax algorithm. Each gray matter image was converted into a one-dimensional vector and arrayed into a 137 (subjects) row by gray matter matrix. The matrix was then decomposed into a mixing matrix (subjects by components) and source matrix (components by voxels). Group differences (forensic patients with psychosis versus incarcerated offenders without psychosis) in each column of the mixing matrix were analyzed in MATLAB (Version 7.12.0, 2011; MathWorks, Natick, MA, USA) using ANOVA ($p < 0.05$, Bonferroni-corrected for multiple comparisons (e.g., number of components)) with age, IQ estimate, and total brain volume (TBV; e.g., GMV + WMV) included as covariates. Post-hoc group comparisons were analyzed in SPSS (Version 23, SPSS inc.; www.spss.com).

3. Results

Groups did not differ significantly on age, race, handedness, or Hare PCL-R total score. Groups differed on IQ; consequently, it was treated as a covariate in the analyses (Table 1).

3.1. Group differences in gray matter source volumes (SBM)

The ICA analysis generated 30 independent components. Three of these components were labeled as artifacts (e.g., motion related) according to previously developed criteria (Xu et al., 2009), leaving 27 components to analyze. The analysis of covariance (ANCOVA) revealed main effects for four sources, three of which survived correction for multiple comparisons: 1) Component 8, which showed greater loading weights (e.g., a combination of volume and covariation between the volumes in each voxel within the component) in the non-psychotic group versus psychotic group. This component included the superior temporal gyrus/insula as well as the anterior cingulate (red) ($F_{1,132} = 11.4$, $p = 0.001$); 2) Component 12, which showed greater loading

Table 1
Clinical and Demographic Variables.

	Psychotic[π]	Non-psychotic[§]	Statistics	p-value
Age (years)[a]	38.9 ± 12.4	37.9 ± 10.2	$t = 0.5$	0.62
Sex (M/F)	69/0	68/0	/	/
Handedness (R/L/ Ambidextrous)[b]	63/5/1	58/7/3	$\chi^2 = 5.2$	0.074
Race[b]	/	/	$\chi^2 = 7.2$	0.20
Caucasian (#)	41	34	/	/
Black (#)	17	27	/	/
Aboriginal (#)	7	2	/	/
Asian (#)	1	2	/	/
Pacific Islander (#)	1	0	/	/
Unknown	2	3	/	/
IQ[a]	93.8 ± 14.1	101.4 ± 14.1	$t = -3.1$	0.002
Antipsychotic medication (CPZ[Ω] equivalents)	600.4 ± 789.2	/	/	/
PCL-R (total score)[a,θ]	21.1 ± 5.9	22.4 ± 7.5	$t = 1.2$	0.25

a = independent samples *t*-test; b = chi-square test; π = forensic psychiatry patients with psychosis; § = non-psychotic criminal controls; Ω = chlorpromazine; θ = Hare Psychopathic Checklist-Revised.

weights in the psychotic group versus non-psychotic group. This component included the basal ganglia (putamen) ($F_{1,132} = 9.7$, $p = 0.002$). Only a trend toward significance existed for this result; 3) Component 15, which indicated greater loading weights in the psychotic group versus non-psychotic group. This component included the frontal pole along with precuneus and visual cortex ($F_{1,132} = 13.1$, $p = <0.001$); and 4) Component 18, which also included greater loading weights in the psychotic group compared with the non-psychotic offenders. This component primarily comprised portions of the basal ganglia, thalamus, and parahippocampal gyrus ($F_{1,132} = 16.5$, $p = <0.001$) (Figs. 1–4 and Tables 2–5).

3.2. Association with antipsychotic medication

None of these components were significantly correlated with antipsychotic dosages (e.g., chlorpromazine equivalents) in the psychotic group (all *p*-values > 0.05). Some patients received irregular PRN doses of antipsychotics to combat acute aggression, but these were not factored into the analysis of overall chlorpromazine equivalents.

4. Discussion

To our knowledge, this study is the first to investigate GMV between two subtypes of offenders: forensic psychiatric patients with psychosis and incarcerated offenders without psychosis. Importantly, groups were matched on PCL-R scores. We employed SBM, a novel, data-driven approach that identifies ICA with shared variance as well as component loading weights representing average brain volumes across each component. Four components (e.g., numbers 8, 12, 15, and 18) emerged, representing differences in brain regions between groups, which we discuss in turn. These findings are notable, since they describe key brain regions relevant to psychosis in forensic patients after controlling for psychopathic traits.

Results indicated that patients with psychosis demonstrated lower loading weights in the superior temporal gyrus/insula as well as the anterior cingulate cortex (ACC). These findings accord well with previous studies reporting reductions in these regions among samples of psychotic individuals. For example, VBM studies of individuals with SCZ or schizophreniform disorder showed GMV deficits in the superior temporal gyrus and insula (Hulshoff Pol et al., 2001; McDonald et al., 2005), while a sample of participants with prodromal signs of psychosis evidenced reduced cingulate cortex volumes bilaterally (Pantelis et al., 2003). It is unsurprising that the cingulate cortex emerged as a region of interest among psychotic patients with a history of violence. The
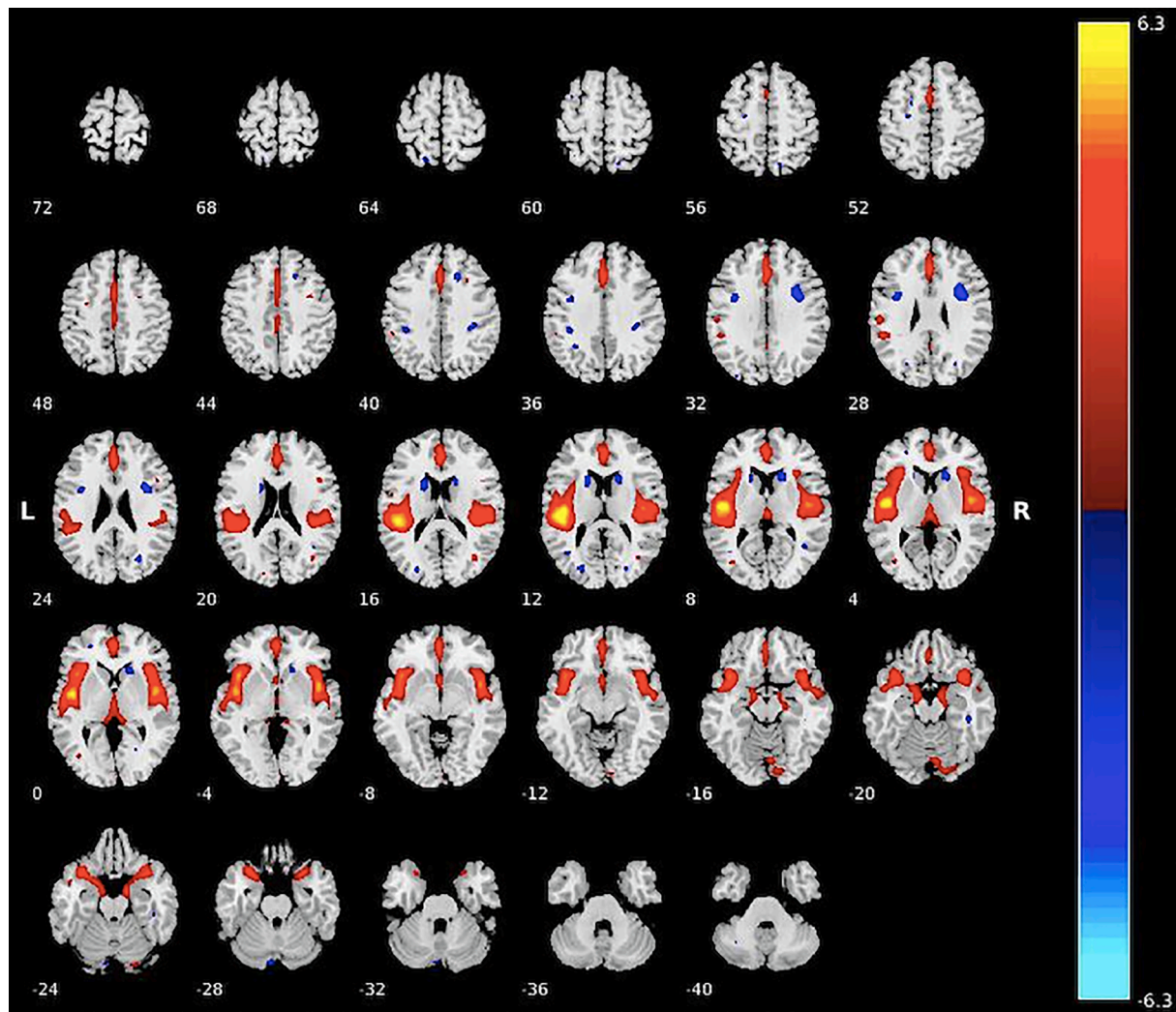
Fig. 1. Source 8 regions discovered by SBM. The regions in the figure represent a pattern of covarying gray matter, which is expressed more in the non-psychotic versus psychotic group. That is, the non-psychotic group expressed this pattern of linked increases in red regions and decreases in blue regions more and the psychotic group less.

Table 2
List of MNI coordinates and regions comprising component 8.

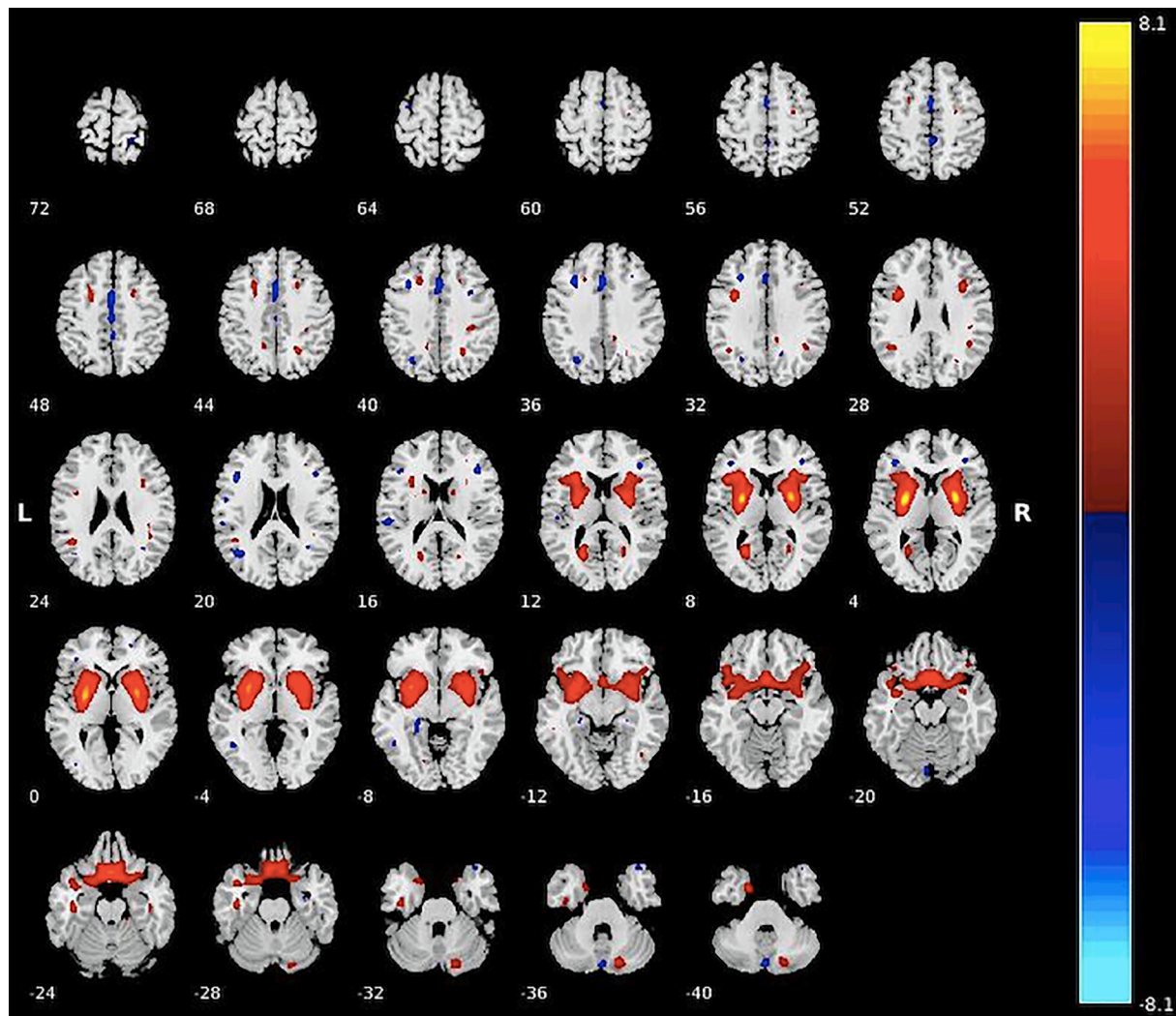| Area	Brodmann Area	Left (max Z)	Right (max Z)	Left (voxels)	Right (voxels)	MNI Left (x,y,z)	MNI Right (x,y,z)
Superior Temporal Gyrus	13, 22, 38, 41, 42	6.4	5.6	2015	1244	−48, −12, 7.5	46.5, 3, −3
Insula	13, 22, 40	6.3	5.5	1985	1304	−45, −15, 9	46.5, −1.5, 0
Transverse Temporal Gyrus	41, 42	6.2	4.4	296	207	−46.5, −22.5, 12	52.5, −16.5, 10.5
Postcentral Gyrus	40, 43	6.1	4.1	237	119	−51, −25.5, 13.5	52.5, −24, 15
Precentral Gyrus	6, 13, 43	6.1	4.9	207	178	−51, −9, 6	49.5, −12, 7.5
Inferior Frontal Gyrus	13, 45, 47	5.4	4.6	741	593	−42, 18, −3	37.5, 15, −19.5
Extra-Nuclear	13, 47	4.5	4.2	89	89	−36, 21, 0	48, 0, 4.5
Inferior Parietal Lobule	40	3.6		89		−49.5, −39, 24	
Medial Frontal Gyrus	9	3.5	3.8	30	89	0, 30, 37.5	1.5, 40.5, 16.5
Sub-Gyral	21	3.5	3.5	89	30	−42, −4.5, −9	45, 0, −12
Parahippocampal Gyrus	34	3.5	3.2	59	30	−13.5, −6, −19.5	13.5, −7.5, −21
Medial Frontal Gyrus	9, 10	3.4	3.3	178	59	−1.5, 51, 10.5	3, 51, 4.5
Anterior Cingulate	32	3.4	3.3	89	89	0, 34.5, 22.5	1.5, 39, 12
Cingulate Gyrus	32	3.3		30		−1.5, 27, 31.5	
Sub-Gyral	44	3.1	4.2	30	178	−36, 4.5, 27	34.5, 10.5, 28.5
Uncus	38	3		30		−28.5, 9, −25.5	
Middle Temporal Gyrus	19		3.4		30		39, −70.5, 16.5
Inferior Frontal Gyrus	44		4.4		89		36, 6, 28.5
Precentral Gyrus	6		3.8		30		36, 3, 31.5
Caudate	N/A		3.3		30		18, 21, 6

Fig. 2. Source 12 regions discovered by SBM. The regions in the figure represent a pattern of covarying gray matter, which is expressed more in the psychotic versus non-psychotic group. That is, the psychotic group expressed this pattern of linked increases in red regions and decreases in blue regions more and the non-psychotic group less.

Table 3
List of MNI coordinates and regions comprising component 12.

Area	Brodmann Area	Left (max Z)	Right (max Z)	Left (voxels)	Right (voxels)	MNI Left (x,y,z)	MNI Right (x,y,z)
Putamen	N/A	8.1	7.9	3111	2696	−27, −3, 4.5	28.5, −1.5, 4.5
Rectal Gyrus	11	5.9	6.1	296	296	−4.5, 16.5, −22.5	4.5, 16.5, −22.5
insula	13	5.2	5.6	741	682	−34.5, 1.5, −6	31.5, 9, −4.5
Medial Frontal Gyrus	25	5	5.3	119	119	−4.5, 13.5, −19.5	4.5, 13.5, −19.5
Inferior Frontal Gyrus	13, 45, 47	4.5	3.6	770	326	−34.5, 6, 30	31.5, 10.5, −13.5
Posterior Cingulate	30	4.4		89		−22.5, −61.5, 9	
Precentral Gyrus	45	4		30		−42, 18, 9	
Subcallosal Gyrus	25, 34	3.9	4.4	89	59	−24, 6, −13.5	1.5, 12, −16.5
Amygdala	N/A	3.4		60		−24, 9, −25.5	
Supramarginal Gyrus	39	3.3		30		−43.5, −51, 25.5	
Precentral Gyrus	BA8	3.2		30		−31.5, 19.5, 37.5	
Cuneus	18	3.1		30		−21, −69, 12	
Middle Frontal Gyrus	BA9	3.1		30		−30, 24, 34.5	
Orbital Gyrus	47	3		30		−12, 27, −25.5	
Caudate	N/A		3.2		30		16.5, 15, 1.5
Cerebellum	N/A		3.1		30		18, −84, −34.5

cingulate cortex is implicated in the regulation of behavior to social cues and predicting expectancies of reward and punishment (Blair, 2004). When compromised, it comprises a neural circuit that elicits aggressive behavior mediated by bottom-up limbic structures such as the insula (Blair, 2004). This regulatory system likely operates similarly in both psychotic and non-psychotic individuals. There is less evidence for the involvement of the superior temporal gyrus in the aggression of psychosis; however, dopaminergic dysregulation observed in SCZ has also
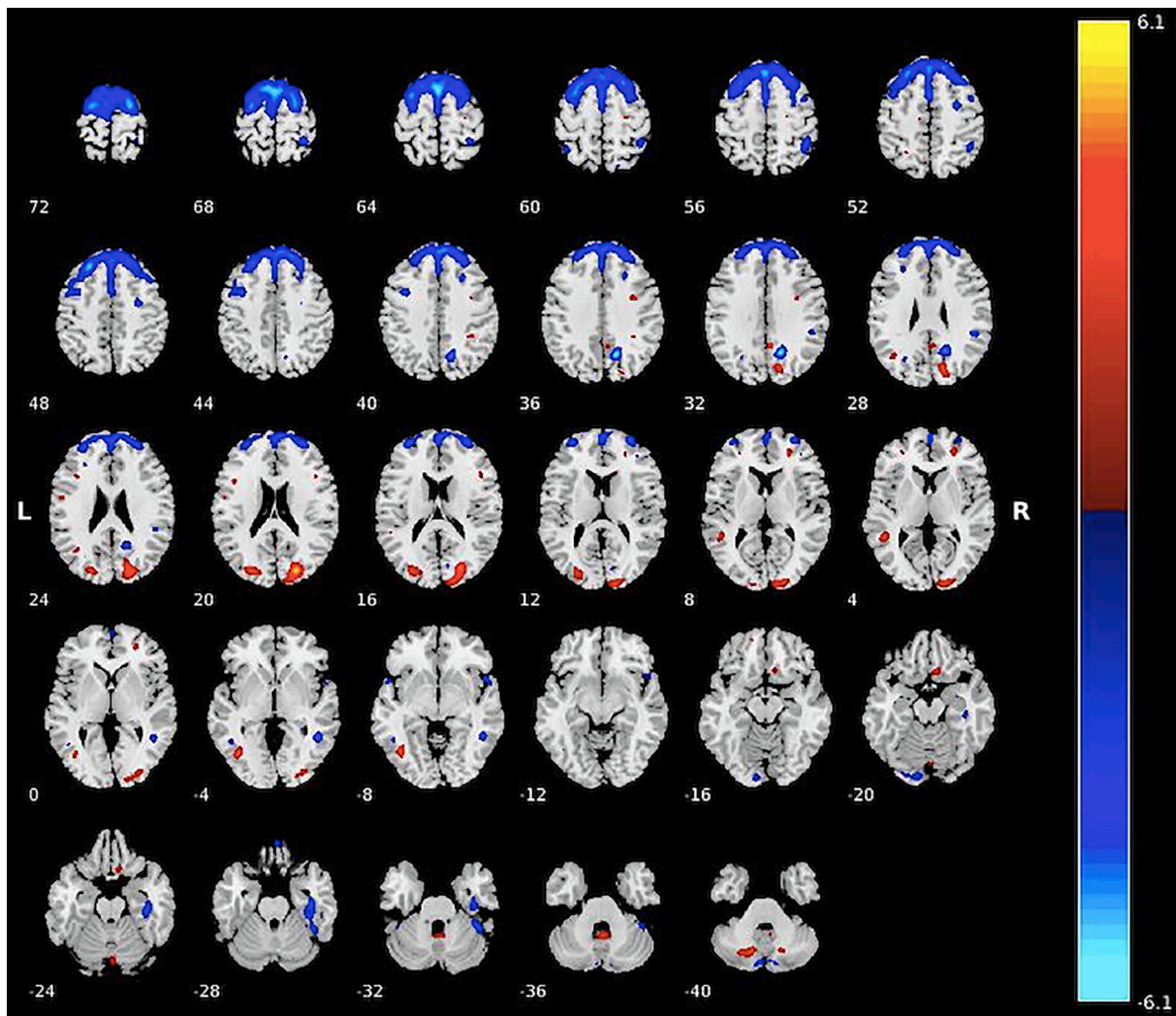
Fig. 3. Source 15 regions discovered by SBM. The regions in the figure represent a pattern of covarying gray matter, which is expressed more in the psychotic versus non-psychotic group. That is, the psychotic group expressed this pattern of linked increases in red regions and decreases in blue regions more and the non-psychotic group less.

Table 4
List of MNI coordinates and regions comprising component 15.

Area	Brodmann Area	Left (max Z)	Right (max Z)	Left (voxels)	Right (voxels)	MNI Left (x,y,z)	MNI Right (x,y,z)
Superior Frontal Gyrus	6, 8, 9, 10	5.6	5.5	2815	2933	−4.5, 16.5, 66	22.5, −1.5, 70.5
Middle Frontal Gyrus	6, 8, 9, 10	5.1	4.7	1185	859	−28.5, 9, 63	24, 1.5, 67.5
Medial Frontal Gyrus	6, 8, 9, 10	4.2	4.9	119	296	−3, 46.5, 46.5	6, 54, 40.5
Cerebellum	N/A	3.2		30		−30, −70.5, −48	
Middle Occipital Gyrus	19	3.1	5.2	89	89	−27, −84, 16.5	27, −81, 18
Cuneus	7, 18		5.6		356		24, −84, 19.5
Precuneus	31		3.5		30		27, −78, 15
Precuneus	31		6.1		356		18, −60, 34.5
Precentral/Central	6		4.6		59		1.5, 9, 61.5
Posterior Cingulate	23		4.2		119		19.5, −55.5, 27
Fusiform	37		4		59		49.5, −51, −4.5
Cingulate Gyrus	23		3.6		30		15, −57, 27
Postcentral Gyrus	3		3.3		30		33, −42, 67.5
Inferior Parietal Lobule	40		3.2		30		51, −39, 27
Parahippocampal Gyrus	20		3.1		30		40.5, −25.5, −25.5

been implicated in the pathophysiology of temporal lobe epilepsy, a neurologic condition often characterized by intractable violence (Werhahn et al., 2006). Interestingly, the component we identified here via the SBM analysis and the difference across groups (e.g., lower in psychosis) was nearly identical to a component identified in an SBM study in a community sample that also showed lower loading weights in those with a psychotic disorder (Xu et al., 2009). These brain regions included the bilateral temporal lobes, thalamus, basal ganglia, parietal lobe, and frontotemporal regions, suggesting that these areas could be central to the pathophysiology of psychosis independent of violent behavior.
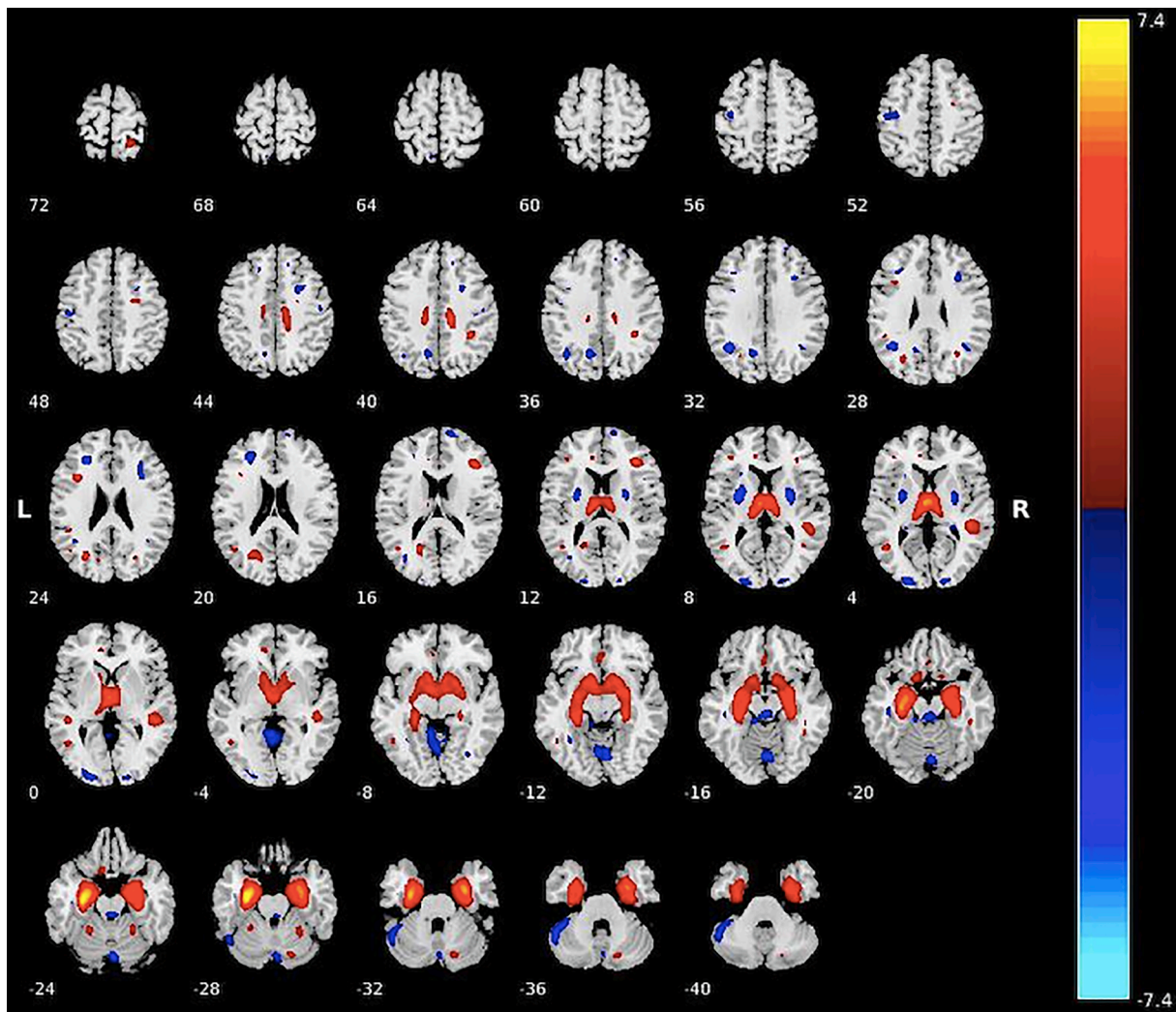
Fig. 4. Source 18 regions discovered by SBM. The regions in the figure represent a pattern of covarying gray matter, which is expressed more in the psychotic versus non-psychotic group. That is, the psychotic group expressed this pattern of linked increases in red regions and decreases in blue regions more and the non-psychotic group less.

Table 5
List of MNI coordinates and regions comprising component 18.

Area	Brodmann Area	Left (max Z)	Right (max Z)	Left (voxels)	Right (voxels)	MNI Left (x,y,z)	MNI Right (x,y,z)
Parahippocampal Gyrus	28, 34, 35, 36	7.6	6	2608	2193	−31.5, −15, −27	31.5, −9, −30
Hippocampus	54	6.7	5.3	178	119	−31.5, −12, −24	24, −7.5, −25.5
Uncus	20, 28, 34, 36	6.3	6.1	681	859	−25.5, −4.5, −27	30, −1.5, −34.5
Thalamus	N/A	6.3	5.9	1214	474	−1.5, −10.5, 3	3, −9, 3
Nucc-Accumbens	52	4.2	4	148	89	−10.5, 6, −10.5	12, 7.5, −10.5
Supramarginal Gyrus	39	4		89		−39, −55.5, 30	
Putamen	N/A	3.9	3.9	386	237	−15, 7.5, −10.5	16.5, 7.5, −12
Precuneus	7	3.8		59		−12, −63, 36	
Subcallosal Gyrus	34	3.6	3.7	89	178	−13.5, 4.5, −13.5	13.5, 10.5, −13.5
Hypothalamus	25	3.6	3.1	30	30	−3, 1.5, −7.5	3, 1.5, −4.5
Cerebellum	N/A	3.4		148		−51, −54, −36	
Middle Occipital Gyrus	18	3.3		30		−21, −97.5, 3	
Cingulate Gyrus	24, 31	3.2	3.9	30	119	−13.5, −22.5, 40.5	15, −24, 40.5
Middle Temporal Gyrus	21	3.2	3.7	30	59	−46.5, −60, 4.5	48, −33, 0
Inferior Temporal Gyrus	20	3.2	3.2	30	30	−31.5, −3, −42	33, −1.5, −43.5
Angular Gyrus	39	3.2		30		−37.5, −58.5, 33	
Cerebellum	N/A	3.1	3.5	30	60	0, −70.5, −12	3, −79.5, −24
Inferior Frontal Gyrus	46		4		89		39, 34.5, 13.5
Inferior Parietal Lobule	40		3.6		30		37.5, −42, 39
Superior Temporal Gyrus	21		3.5		59		51, −39, 4.5
Premotor Cortex	6		3		30		27, 9, 43.5

Forensic psychiatric patients exhibited greater loading weights in the basal ganglia (e.g., putamen) compared with non-psychotic incarcerated offenders. Technically, the significance level for this component fell just outside the corrected threshold of $p = 0.00185$ and is not significant. Yet, we still report these results given the exploratory nature of the study. A previous investigation has reported that caudate volumes positively correlate with aggressive behavior in patients with chronic SCZ or SCZA (Hoptman et al., 2006). Several reasons may explain the current findings. A recent meta-analysis confirmed that higher antipsychotic exposure is associated with increased basal ganglia volume ($r = 0.10$) (Huhtaniska et al., 2017). Indeed, antipsychotics are known to affect regional blood flow in the basal ganglia (Goozee et al., 2014). Previous research has suggested that the increase in basal ganglia volume is more strongly related to exposure of first-generation (e.g., haloperidol) versus second-generation (e.g., risperidone) antipsychotics (Ebdrup et al., 2013), although this distinction lacks clarity. Since most of the psychotic patients in our sample were prescribed second-generation antipsychotics and, more importantly, none of the components correlated with antipsychotic dosages, this explanation is less likely. However, we only had current antipsychotic dosages. Forensic patients have often been institutionalized for years and may have varied types and dosages of antipsychotics, which could potentially have longer lasting effects on brain volumes. Moreover, even though the correlation between current dosage and loading weights was not significant, there was still more overall antipsychotic exposure in the psychosis group. Finally, healthy individuals without psychosis who endorse high psychopathic traits have been shown to exhibit less GMV in the left putamen and amygdala (Vieira et al., 2015). Increased GMV in the basal ganglia of psychotic patients could, therefore, represent an artifact of reduced basal ganglia volumes in high psychopathy scorers without psychosis.

Forensic psychiatric patients showed greater loading weights in frontal regions compared with non-psychotic incarcerated offenders. Although deficits in frontal lobe volumes (Gur et al., 2000) and cortical thickness (Rimol et al., 2010) have been commonly reported in psychotic disorders, antisocial personality disorder (ASPD) and psychopathy present similar findings (Narayan et al., 2007; Raine et al., 2000; Yang et al., 2010a). Since groups had similar PCL-R scores, the greater frontal loading weights of psychotic patients may relate to frontal volume loss driven primarily by increased psychopathic traits. One study examined volumetric structural brain abnormalities in males with SCZ without violence, violent SCZ, and violent ASPD (Barkataki et al., 2006). While the ASPD group manifested reductions in anterior brain structures, this finding was not observed in violent SCZ, suggesting that effects may have been due to antisocial/psychopathic traits. Instead, the SCZ group with a violent history exhibited reduced whole brain volumes, reduced hippocampal volumes, and increased putamen size. Left orbitofrontal cortex gray matter volumes have also shown to correlate with aggression in SCZ and SCZA (Hoptman et al., 2005). These findings suggest that when controlling for PCL-R score, psychotic offenders may show larger frontal structures. However, as the frontal cortex encompasses a large region, SBM may be identifying specific subregions of the frontal cortex that differ from those that have shown reduced volumes in prior studies. Regarding the precuneus and visual cortex, most data have pointed to smaller volumes in patients with psychotic illness (Hulshoff Pol et al., 2001; Lappin et al., 2006). However, like virtually all imaging studies of psychosis and violence, these investigations did not take into account the effect of probable psychopathic traits. The precuneus is a functional component of the default mode network that plays a role in source memory retrieval and self-consciousness (Cavanna and Trimble, 2006; Utevsky et al., 2014). Deficits in processing of self-referential material have been featured prominently in the phenomenology of psychopathy (Philippi and Koenigs, 2014) and may be associated with smaller precuneus volumes (Bertsch et al., 2013). Therefore, controlling for psychopathic traits may have produced the finding of increased precuneus loading weights in forensic patients with psychosis.

Greater loading weights were also observed in the thalamus and parahippocampal gyrus of forensic patients with psychosis. Smaller thalamic (McDonald et al., 2005) and parahippocampal gyrus (Razi et al., 1999; Yang et al., 2010b) volumes have been reported in SCZ, while structural reduction of the parahippocampal gyrus is one of the most widely replicated findings in psychopathic populations that is seen in incarcerated adult males (Ermer et al., 2012) and adolescents with callous-unemotional traits (Ermer et al., 2013). Functional abnormalities of the parahippocampal gyrus in psychopathy have also been extensively described (Kiehl et al., 2001; Muller et al., 2003). The parahippocampal gyrus comprises a corticolimbic control circuit that modulates impulsivity (Brown et al., 2006) and is also implicated in moral reasoning (Sommer et al., 2014). Dysfunctional impulsivity and deficits in moral judgment are key to the phenomenology of psychopathy. Smaller volume loss of the parahippocampal gyrus among individuals with high psychopathic traits relative to offenders with psychosis could result in greater loading weights among the latter group.

Although SBM is not as widely utilized as VBM, it can be considered complementary in many ways and is arguably a strength of the current study. For example, the ICA identifies components with shared variance, whereas the component loading weights represent the average brain volume across each component (akin to a weighted seed map) after accounting for the alternative component maps. In other words, if a component has a large value in a single voxel, it is typically the most robust contributor to that voxel; similarly, a lower loading parameter represents reduced grey matter volume in that voxel. If, however, two components have equal weight in a given voxel, it is necessary to examine the loading parameters for both components to ascertain whether the grey matter volume in that voxel went up or down. This approach represents one of the strengths of SBM, as it can separate mixed information that is typically imperceptible to a VBM analysis.

Several limitations of the present manuscript must be noted. First, not all forensic psychiatric patients received structured diagnostic testing, making diagnostic precision less likely among those who did not undergo screening with structured instruments. However, it is unlikely that forensic psychiatric patients were misclassified as psychotic when, in fact, they were not given the lengthy periods of observation in hospital by numerous clinicians and the types of medication that they had been regularly prescribed (e.g., antipsychotics). Second, although all offenders had PCL-R scores generated, we do not have data on inter-rater reliability between the different sites. On the other hand, many of the sites had leaders in the field of PCL-R pedagogy instruct clinicians on how to administer the PCL-R. As a result, we can be confident in the integrity of the data arising from these sites. Similarly, we did not have factor or facet subscale scores for the PCL-R. A final limitation is that we did not have available all information about prior antipsychotic exposures for the forensic patients. We only had their current medications. This omission is important, as anamnestic data about previous antipsychotic exposures may have affected results pertaining to the basal ganglia.

In summary, we found that two subtypes of offenders – forensic psychiatric patients with psychosis and incarcerated individuals without psychosis – featured different brain GMV after controlling for PCL-R symptoms. We attribute many of these findings to the fact that we controlled for PCL-R traits. These analyses highlight the importance of taking into account psychopathic traits in neuroimaging studies of aggressive forensic psychiatric populations with psychotic illness to obtain a clearer picture of any structural brain changes relevant to the phenotype under investigation.

CRediT authorship contribution statement

NJK, CLH, and KAK conceptualized, designed, and supervised the study. KAH, MD, and JJC contributed to the design of the study and carried out the investigation. They collected the Waypoint data. CLH and KAH analyzed the combined data set and provided a detailed summary of the findings. NJK, CLH, KAK, and KAH interpreted the

findings. NJK drafted the manuscript. All authors provided critical revisions of the manuscript for important intellectual content.

Declaration of Competing Interest

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

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