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

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ABSTRACT

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...
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 mal-adaptive 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 grey 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 (Kasperek 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, psychopathological 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 1.00 mm × 1.00 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 × 2 × 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 IMRI 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) (F1,132 = 11.4, p = 0.001); 2) Component 12, which showed greater loading weights in the psychotic group versus non-psychotic group. This component included the basal ganglia (putamen) (F1,132 = 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 (F1,132 = 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 (F1,132 = 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 schizoparenform 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          | 3.0           | 30            | 178            | –36, 4.5, 27     | 34.5, 10.5, 28.5  |
| Uncus                       | 44            | 3.1          | 4.2           | 30            | 178            | –28.5, 9, –25.5  |                   |
| Middle Temporal Gyrus       | 19            | 3.4          | 3.4           | 30            |                | 39, –70.5, 16.5  |                   |
| Inferior Frontal Gyrus      | 44            | 4.4          | 4.4           | 89            |                | 36, 6, 28.5      |                   |
| Precentral Gyrus            | 6             | 3.8          | 3.8           | 30            |                | 36, 3, 31.5      |                   |
| Caudate                     | N/A           | 3.3          | 3.3           | 30            |                | 18, 21, 6        |                   |
The 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. 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
been implicated in the pathophysiology of temporal lobe epilepsy, a neurologic condition often characterized by intractable violence (Wernhahn 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.

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, 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  | 27, -81, 18       |
| Middle Occipital Gyrus      | 19            | 3.1          | 5.2           | -             | -              | -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 | -     |
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         |
| Nuc-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   | 16.5, 7.5, –12    |
| Putamen                     | N/A           | 3.9          | 3.9           | 386           | 237            | –15, 7.5, –10.5  | 13.5, 10.5, –13.5 |
| Precuneus                   | 7             | 3.8          | 59            |               |                | –12, –6.3, 36    | 3, –1.5, –4.5     |
| 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  | 46, –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
SZC or SCZA (Hopmam et al., 2006). Several reasons may explain the
current findings. A recent meta-analysis confirmed that higher anti-
psychotic 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 vol-
ume is more strongly related to exposure of first-generation (e.g.,
haloperidol) versus second-generation (e.g., risperidone) antipsychotics
(Öhddrup 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 compo-
tents 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 psy-
copathic traits have been shown to exhibit less GMV in the left putamen
and amygdala (Veira et al., 2015). Increased GMV in the basal ganglia
of psychotic patients could, therefore, represent an artifact of reduced
cerebral structures in patients with 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 psy-
chotic disorders, antisocial personality disorder (ASPD) and psychopa-
thy present similar findings (Narayen 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 vol-
ume 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 struc-
tures, this finding was not observed in violent SCZ, suggesting that ef-
fects may have been due to antisocial/psychopathic traits. Instead, the
SCZ group with a violent history exhibited reduced whole brain vol-
umes, reduced hippocampal volumes, and increased putamen size. Left
orbitofrontal cortex gray matter volumes have also shown to correlate
with aggression in SCZ and SCZA (Hopmam 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 encom-
passes a large region, SBF 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
functionally independent component of the default mode network that plays a role
in source memory retrieval and self-consciousness (Cavanaugh 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 abnormal-
ities of the parahippocampal gyrus in psychopathy have also been
extensively described (Kiehl et al., 2001; Muller et al., 2003). The par-
ahippocampal 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 psychopa-
thy. Smaller volume loss of the parahippocampal gyrus among in-
dividuals with high psychopathic traits relative to offenders with
psychosis could result in greater loading weights among the latter group.

Although SBF 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
take the two factors into account when determining the loading weights for both components to ascertain
whether the greater voxel value is due to a single component or a
combination of components. This approach represents one of the strengths of SBF, 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 hos-
pital 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 expo-
res from forensic patients. We only had their current medications.
This omission is important, as anamnestic data about prior anti-
psychotic 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

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**Competing interests**

None.

**Role of the funding source**

NIMH had no role in the design of the study, collection, analysis, and interpretation of data, in writing the manuscript, or in the decision
to submit the manuscript for publication.

**Supplementary information**

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**Data availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Abbreviations**

ASPD = antisocial personality disorder

ICA = independent component analysis

PCL-R = Psychopathy Checklist-Revised

SCZ = schizophrenia

SCZA = schizophrenia and bipolar affective disorder

SBS = structural brain scan

VBM = voxel-based morphometry

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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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