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Multivariate neuroanatomical classification of cognitive subtypes in schizophrenia: A support vector machine learning approach

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ABSTRACT

Heterogeneity in the structural brain abnormalities associated with schizophrenia has made identification of reliable neuroanatomical markers of the disease difficult. The use of more homogenous clinical phenotypes may improve the accuracy of predicting psychotic disorder/s on the basis of observable brain disturbances. Here we investigate the utility of cognitive subtypes of schizophrenia – 'cognitive deficit' and 'cognitively spared' – in determining whether multivariate patterns of volumetric brain differences can accurately discriminate these clinical subtypes from healthy controls, and from each other. We applied support vector machine classification to grey- and white-matter volume data from 126 schizophrenia patients previously allocated to the cognitive spared subtype, 74 cognitive deficit schizophrenia patients, and 134 healthy controls. Using this method, cognitive subtypes were distinguished from healthy controls with up to 72% accuracy. Cross-validation analyses between subtypes achieved an accuracy of 71%, suggesting that some common neuroanatomical patterns distinguish both subtypes from healthy controls. Notably, cognitive subtypes were best distinguished from one another when the sample was stratified by sex prior to classification analysis: cognitive subtype classification accuracy was relatively low (<60%) without stratification, and increased to 83% for females with sex stratification. Distinct neuroanatomical patterns predicted cognitive subtype status in each sex: sex-specific multivariate patterns did not predict cognitive subtype status in the other sex above chance, and weight map analyses demonstrated negative correlations between the spatial patterns of weights underlying classification for each sex. These results suggest that in typical mixed-sex samples of schizophrenia patients, the volumetric brain differences between cognitive subtypes are relatively minor in contrast to the large common disease-associated changes. Volumetric differences that distinguish between cognitive subtypes on a case-by-case basis appear to occur in a sex-specific manner that is consistent with previous evidence of disrupted relationships between brain structure and cognition in male, but not female, schizophrenia patients. Consideration of sex-specific differences in brain organization is thus likely to assist future attempts to distinguish subgroups of schizophrenia patients on the basis of neuroanatomical features.

1. Introduction

Cognitive deficits are a core feature of schizophrenia and are closely linked with disability and treatment outcomes (Brekke et al., 2007; Green, 2006; Heinrichs, 2005; Jablensky, 2006; Keefe and Harvey, 2012; Ammari et al., 2010). While severe cognitive deficits are observed in many patients, the magnitude of cognitive dysfunction may vary between individuals. Attempts to reduce such phenotypic heterogeneity have seen the delineation of two subtypes of schizophrenia in large cohort studies – 'cognitive deficit' (CD) and 'cognitively spared' (CS) – based on cognitive performance across multiple domains (Green et al., 2013; Hallmayer et al., 2005; Jablensky, 2006). These subtypes of schizophrenia thus show distinct cognitive profiles, in the context of other differential illness characteristics: CD patients tend to be impaired across all cognitive domains, are more likely to be male, have earlier illness onset, and a greater severity of functional disability (Green et al., 2013); in contrast, CS cases show a cognitive profile that remains somewhat impaired relative to healthy controls (HCs), but is significantly

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better than CD cases, and is associated with greater complexity of delusional systems (Morar et al., 2011). Preliminary genetic investigation of these subtypes has revealed an association of CD case status with the MIR137 microRNA locus and negative symptoms (Green et al., 2013), and genetic linkage to chromosome 6p24 (Hallmayer et al., 2005). In contrast, CS cases show relatively stronger genetic association with Neuregulin 3 (Morar et al., 2011). These cognitive subtypes may thus represent more phenotypically homogenous patient groups with at least partially distinct neuropathological processes, about which clues may be evident in differential brain structure.

Considerable neuroanatomical evidence shows that schizophrenia is associated with substantial, diffuse brain volume loss, though the exact location of changes is not well-replicated across studies, likely reflecting the phenotypic heterogeneity among cases and samples (Shepherd et al., 2012). Recent attempts to delineate a neuroanatomical signature of schizophrenia have employed multivariate classification techniques to distinguish patients from controls on the basis of neuroanatomical feature sets (Nieuwenhuis et al., 2012; Davatzikos et al., 2005; Fan et al., 2007; Klöppel et al., 2012; Koutsouleris et al., 2009). While these studies demonstrate the capacity to successfully predict schizophrenia 'case-ness' on the basis of multivariate neuroanatomical patterns, classification accuracy in large cohort studies is typically around 70% — less than 50% above chance — leaving considerable room for improvement (Nieuwenhuis et al., 2012). Investigation of putative subtypes of schizophrenia that appear to represent more homogenous phenotypes, such as those delineated via cognitive profiling (Koutsouleris et al., 2012; Ammari et al., 2010; Green et al., 2013; Jablensky, 2006), may improve the accuracy with which schizophrenia case-ness can be predicted on the basis of brain structure.

Neuroanatomical features associated with cognitive deficits in schizophrenia include reduced whole-brain grey matter volume and cortical thickness, localized reductions in prefrontal, temporal and parietal grey matter volume, basal ganglia and thalamic volume reductions (Cobia et al., 2011; Rais et al., 2012; Rüsch et al., 2007; Crespo-Facorro et al., 2007), and alterations in the integrity of white matter pathways (Nazeri et al., 2013; Wexler et al., 2009). Disruptions of the normal associations between cognitive performance measures and global and regional brain volumes have also been reported (Antonova et al., 2004; Ehrlich et al., 2012; Hartberg et al., 2010; Wexler et al., 2009; Nazeri et al., 2013; Cocchi et al., 2009; Killgore et al., 2009; Antonova et al., 2005; Salgado-Pineda et al., 2003; Sanfilipo et al., 2002). However, the utility of multivariate neuroanatomical profiles in discriminating between cognitive subtypes on a case-by-case basis remains unclear.

Several studies have additionally demonstrated that schizophrenia-associated disruptions to the normal relationships between cognition and brain volumes occur in a sex-related manner. For example, normal structure–cognition relationships in the cerebellum may be attenuated or absent for male patients as compared with female patients and HCs (Antonova et al., 2004; Flaum et al., 1994; Picard et al., 2008). Disruption of normal neuroanatomical sexual dimorphisms in schizophrenia patients' brains has also been reported (Abbs et al., 2011; Crow, 2013; Goldstein et al., 2002; Narr et al., 2004; Gur et al., 2004). As sexually dimorphic neuroanatomical differences arise during brain development through interaction of hormonal, genetic and epigenetic factors, their characterization in sexually asymmetric psychiatric conditions may provide insights into neurodevelopmental processes relevant to disease aetiology, and stratifying samples by sex may further assist efforts to reduce within-sample heterogeneity (Goldstein et al., 2013; Lombardo et al., 2012; Ruigrok et al., 2014; Paus et al., 2008). However, the relevance of sex-specific neuroanatomical patterns to the classification of schizophrenia and its subtypes has not yet been determined.

Here, we set out to characterize multivariate patterns of grey- and white-matter volumes that discriminate between CD patients, CS patients and HCs. We hypothesized that the cognitive and genetic differences associated with cognitive subtypes would manifest in neuroanatomical changes distinguishing each group from HCs, and from each other. We specifically predicted that CS and CD subtypes would be distinguished by changes in brain regions associated with cognition in schizophrenia, such as frontal and temporal cortices (Shepherd et al., 2012) and distributed white matter networks (Wexler et al., 2009). As schizophrenia patients show sexual asymmetries in phenotypic features including cognitive deficits, age of onset and symptom severity (Green et al., 2013; Hallmayer et al., 2005; Jablensky, 2006; Han et al., 2012), and schizophrenia is associated with disruption of sexual dimorphisms in brain structure and structure–function relationships (Antonova et al., 2004; Goldstein et al., 2002; Picard et al., 2008), we further hypothesized that neuroanatomical features distinguishing cognitive subtypes (from healthy controls, and from each other) would differ between males and females. Specifically, we predicted that classification accuracy would be higher when performed on a sex-stratified sample, as compared to when performed on a mixed-sex sample.

2. Methods

2.1. Participants

Structural MRI scans were available for 427 participants (249 cases, 179 male; 163 controls, 76 male). These comprise a subset of 629 scans obtained from the Australian Schizophrenia Research Bank (ASRB); we excluded 25 participants who met ICD-10 criteria for bipolar disorder, major depression with psychotic features, or psychosis not otherwise specified, and an additional 177 scans failing stringent exclusion criteria for excess motion or other T1 image artefacts. Scan quality control was performed by a trained investigator who was blind to participants' clinical and cognitive status. All included cases met ICD-10 criteria for schizophrenia ($N = 208$) or schizoaffective disorder ($N = 41$) with diagnoses confirmed using the OPCRIT algorithm (McGuffin and Farmer, 1991) applied to interviewer ratings on the diagnostic interview for psychosis (DIP) (Castle et al., 2006).

Detailed information regarding sampling, recruitment strategies, and consent procedures are published elsewhere (Loughland et al., 2010). Participants were aged 18–65 years and spoke fluent English. Exclusion criteria included the presence of an organic brain disorder, brain injury with post-traumatic amnesia, mental retardation, movement disorders, and recent (within 6 months) substance dependence or electroconvulsive therapy. HCs were screened for the absence of personal or family history of psychosis or bipolar-I disorder.

2.2. Cognitive and clinical characterization

Cognitive subtypes of patients were previously determined (Green et al., 2013) by applying multi-dimensional Grade of Membership (GoM) analysis to cognitive performance data from a broader sample of ASRB schizophrenia patients ($N = 617$). In brief, nine cognitive performance measures contributed to the GoM: the Wechler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999), Wechsler Test of Adult Reading (WTAR) (Wechsler, 2001), Letter Number Sequencing (Wechsler, 1997), Controlled Oral Word Association Test (Spreen and Strauss, 1998), and five subscales from the Repeatable Battery for Assessment of Neuropsychological Status (Randolph, 1998). The GoM analysis identified two latent subtypes (CD and CS) within the sample of schizophrenia cases (Green et al., 2013). Within the subset of patients for whom MRI scans were available, 74 patients (57 male) were classified into the CD subtype and 126 patients (74 male) were classified into the CS subtype.

The DIP (Castle et al., 2006) was used to establish a lifetime diagnosis of a psychotic disorder, according to ICD-10 criteria (McGuffin and Farmer, 1991). In addition, the DIP provides data on socio-demographic data, family and medical history, and drug and alcohol assessment. As per methods outlined by Green et al. (2013), lifetime data for 11 DIP items assessing hallucinations and delusions were summed to provide an index of positive symptom severity; a negative symptom severity

score was derived by summing the ratings on affective restriction or blunting and negative formal thought disorder, as well as responses to the ASRB Sociodemographic and Clinical History Schedule items on social withdrawal and social interests. A modified version of the Neurological Evaluation Scale (NES) (Buchanan and Heinrichs, 1989) was used to assess neurological soft signs, and general level of functioning was assessed using the Global Assessment of Functioning (GAF) scale (A.P.A., 1994).

2.3. Image processing

High-resolution T1-weighted structural MRI scans (MPRAGE) were collected on Siemens Avanto 1.5 T scanners across five Australian research sites (Loughland et al., 2010). 176 contiguous 1 mm sagittal slices were collected (field-of-view 250 × 250 mm^2, time-to-repetition 1980 ms, time-to-echo 4.3 ms, data acquisition matrix 256 × 256, voxel size 0.98 × 0.98 × 1.0 mm^3, flip angle 15°). Scans were individually reviewed for motion and other artefacts. The VBM8 toolbox for SPM8 (http://dbm.neuro.uni-jena.de/vbm/) was used for image preprocessing. Images were segmented into grey matter, white matter and cerebrospinal fluid using a unified segmentation approach combined with Hidden Markov Random Fields to improve signal-to-noise ratio. Images were subsequently normalized and modulated with the Jacobian determinants of the deformation parameters in order to preserve the absolute tissue volumes. Modulation of non-linear effects without affine normalization allows interpretation of relative volumes, negating the need to further account for total individual brain volume. No spatial smoothing was applied (Klöppel et al., 2008; Chu et al., 2012).

2.4. Whole-brain multivariate pattern analysis

Linear kernel support vector machine (SVM) classifiers were used to perform binary classification between three participant sets. Set 1 included CD cases and HCs. Set 2 included CS cases and HCs. Set 3 included CS cases and CD cases. To control for effects of covariates on classification, participants in each set were matched on sex, age (±5 years), and MRI scanning site using an automated procedure. To avoid order effects, participants were matched in a random order, and a random match was chosen when multiple potential matches were available.

To ensure classification was stable and representative of the sample set, we maximized the number of participants classified and minimized classification variability (Nieuwenhuis et al., 2012) by applying an ensemble learning approach with 200 resample iterations. In each iteration a distinct matched sample was created using the automated procedure described above, and leave-two-out cross-validation was applied. On each cross-validation fold, one matched pair of participants was set aside as testing data, and data from the remaining participants was used to train the classifier. This cross-validation procedure was repeated until all matched pairs had been used as test data once. A final class prediction was assigned to each scan based on the average prediction made for it across all 200 classifier iterations.

To investigate the specificity (vs. generalizability) of the multivariate neuroanatomical patterns that distinguished each cognitive subtype from controls, we also (1) trained classifiers on all Set 1 participants and tested on all Set 2 participants, and (2) trained classifiers on all Set 2 participants and tested on all Set 1 participants. Importantly, for these analyses we used matched samples in which unique HCs were matched with each CD and CS patient; the classifiers trained on Sets 1 and 2 were therefore independent. Final class predictions were made using the ensemble procedure described above, except that training and testing were performed once only on each iteration.

Initial analyses were performed on the overall sample, which included males and females. To investigate sex-specific differences in classification accuracy, a second set of analyses were performed after stratifying the sample by sex. Furthermore, we investigated the predictive value of three feature sets: grey matter only (GM), white matter only (WM), and concatenated grey and white matter (GM + WM). As the same matched sample sets were used for each analysis, we employed McNemar tests to assess whether classification accuracies for each participant differed depending on the feature set classified, and whether the sample was stratified by sex. Chi-square tests were used to compare classification accuracies of independent groups (e.g., males vs. females).

Classifier performance was assessed by calculating the accuracy, sensitivity and specificity with which test observations were classified. Sensitivity was defined as TP / (TP + FN), where TP is the number of true positives and FN is the number of false negatives. Specificity was defined as TN / (TN + FP), where TN is the number of true negatives and FP is the number of false positives. For Sets 1 and 2 (HC vs. CD, and HC vs. CS), sensitivity and specificity were defined as the ability to identify patients. For Set 3 (CD vs. CS), sensitivity and specificity were defined as the ability to identify CD cases. Classification accuracy was calculated as the average of the sensitivity and specificity. We also performed receiver operating characteristic (ROC) curve analysis for each classifier, from which area under the curve (AUC) was calculated.

The statistical significance of classifier results was assessed using permutation testing (2000 permutations). For each permutation, the class membership of participants was randomized, and ensemble learning classifier accuracy was assessed as described above. The same matched samples were used for the original and the permuted analyses. Permutation testing was applied to accuracy data as this reflects the overall predictive power of the classifier. Classification accuracies obtained with permuted data were used to form a null distribution against which we assessed the significance of classification accuracy obtained using the original dataset.

Classification was performed using custom scripts in Matlab v8.1 (Mathworks, Sherborn, Massachusetts), and the PRoNTo (Schrouff et al., 2013) and LIBSVM (Chang and Lin, 2011) toolboxes with the default cost parameter of $C = 1$.

2.5. Weight map and region of interest (ROI) analyses

SVM classifier training involves identification of a multidimensional hyperplane that maximally discriminates groups of interest. For linear SVMs, the hyperplane orientation is described by a unit weight vector that is orthogonal to the hyperplane. The weight vector may therefore be interpreted as a spatial representation of the decision boundary, with the absolute value of individual indicating each voxel's relative importance to classification decisions (Mourao-Miranda et al., 2005; Mourão-Miranda et al., 2012). Here, large negative weights at voxels may reflect that tissue volume was lower at that location in schizophrenia cases compared with HCs for Sets 1 and 2, and in CD cases compared with CS cases for Set 3; large positive weights may indicate the converse. Importantly, however, to minimize model over-fitting, each SVM hyperplane is defined relative to the subset of training set examples that are most difficult to classify, and classification weights may be affected by factors such as correlations between feature variables. While classification weights may be indicative of the direction and magnitude of volume differences between groups, individual weights can therefore be interpreted only in the context of the whole-brain weight maps they are derived from (Ecker et al., 2010; Pereira et al., 2009; Schrouff et al., 2013; Hastie et al., 2009).

Here, we investigated the spatial structure underlying classification by averaging the weight maps from the classifiers trained on each of our 200 matched samples, and then computing the average weight across voxels within ROIs covering the entire brain. For GM weight maps, average weights were calculated for ROIs from the Harvard–Oxford cortical and subcortical atlases (Desikan et al., 2006), and the probabilistic cerebellar atlas (Diedrichsen et al., 2009). For WM weight maps, average weights were calculated for ROIs from the JHU white-matter tractography atlas (Hua et al., 2008), the thalamus, putamen and pallidum ROIs from the Harvard–Oxford subcortical atlas – which overlapped with our WM mask — and left and right cerebellar ROIs

from the Talairach atlas (Lancaster et al., 2000). The relative strength with which regions made a positive or negative contribution to classification was compared across classifiers using two-tailed Pearson correlations.

3. Results

3.1. Classification accuracy

3.1.1. Sex non-specific effects

For the overall sample that included males and females, the matching procedure resulted in a total of 164 participants contributing to Set 1 (72 CD cases and 92 HCs, comprising 56 and 52 males, respectively), 252 participants contributing to Set 2 (126 CS cases and 126 HCs; 87 and 65 males, respectively), and 170 contributing to Set 3 (72 CD cases and 98 CS cases; 57 and 79 males, respectively). Note that only a subset of these participants contributed to each iteration of the analysis. For Set 1, an average of 53 ± 1.1 participants (μ ± S.D.) contributed to each of the 200 ensemble learner iterations. For Sets 2 and 3 respectively, 90 ± 1.2 and 66 ± 1.3 participants contributed to each iteration of the ensemble learner. Demographic, clinical and cognitive data for participants contributing to analyses are provided in Table S1.

SVM classification results and ROC curves for the combined sample including males and females are presented in Table 1 and Fig. S1. Classification of CD cases versus HCs (Set 1) achieved a significant accuracy of 72% (permutation $p < 0.001$) using the concatenated grey matter and white matter (GM + WM) feature set. Significant classification accuracies were also obtained using the GM-only or WM-only feature sets (70% and 64%, respectively; all permutation $p < 0.001$), although accuracy was higher for the GM + WM than WM feature set (McNemar test: $p < 0.05$). All CS versus HC (Set 2) classifier accuracies were also significantly above chance (WM + GM accuracy 67%, all permutation $p < 0.001$), and classification accuracy was again significantly higher for the GM + WM than WM feature set (McNemar test: $p < 0.01$). SVM classification significantly differentiated CD cases from CS cases, though with relatively low accuracy, for the GM and GM + WM feature sets (59% accuracy, $p < 0.01$; and 56% accuracy, $p < 0.05$, respectively).

To directly test whether common neuroanatomical patterns provided the basis for classification of both CD and CS cases versus HCs, classifiers were trained on HCs versus CD cases and tested on HCs versus CS cases, and vice versa. Significant classification accuracy was achieved in both cases. The classifier trained on CD case versus HC status using the GM + WM feature set distinguished CS versus HC status with an accuracy of 71% (permutation $p < 0.001$), sensitivity of 71% and specificity of 71%. The classifier trained on Set 2 using the GM + WM feature set distinguished CD case versus HC status with an accuracy of 71% (permutation test, $p < 0.001$), sensitivity of 68% and specificity of 74%.

3.1.2. Sex-specific effects

To investigate whether sex-specific neuroanatomical patterns distinguished participant sets, classification analyses were repeated after stratifying the sample by sex (see Tables 2 and 3; ROC curves are presented in Fig. S1). Sex-specific sample details and demographic, clinical and cognitive data are provided in Table S2.

When stratified by sex, CD versus HC and CS versus HC classification accuracies were significantly above chance (for all permutation tests $p < 0.01$) except for when the WM feature set was used for male CD versus HC (marginal $p < 0.06$) or female CS versus HC classification ($p > 0.1$). CD versus HC and CS versus HC classification accuracies were not significantly different compared to when participants were not stratified by sex, with the exception of male CS versus HC classification using GM data, which was higher after stratification (66% vs. 61%; McNemar test: $p < 0.05$).

When stratified by sex, CD versus CS classification accuracy was significantly above chance for females, for all three feature sets (GM + WM accuracy 83%, permutation test $p < 0.001$), and for males when using the GM + WM or GM-only feature sets (accuracy 60% and 58%, respectively; permutation $p < 0.01$ and $p < 0.05$, respectively). When stratified by sex, classification accuracy for females was significantly greater than when participants were not stratified for the GM + WM feature set (McNemar test: $p < 0.05$). Chi-square tests revealed that CD versus CS classification accuracy was significantly higher for females than males when using the GM + WM or WM-only feature sets (both $p < 0.01$).

To test whether distinct neuroanatomical patterns distinguished CD versus CS cases for males and females, we trained classifiers on male scans and tested them on female scans, and vice versa. Surprisingly, this revealed that classification accuracy was significantly below chance for the GM classifier trained on females and tested on males (accuracy 41%, two-tailed permutation test $p < 0.05$). All other cross-validation accuracies were not significant (all accuracies between 43% and 54%).

3.1.3. Effect of cognitive subtype segregation on classifier accuracy

To determine whether classifier accuracy was improved when patients were stratified according to cognitive subtypes, classification analyses were repeated to determine the accuracy with which HCs could be distinguished from a sample of SZ cases that included both cognitive subtypes. The resulting classification accuracies were similar to those obtained for each cognitive subtype (see Table 4), and McNemar tests revealed no significant differences in HC versus CD or HC versus

Table 1
SVM classification accuracy (and sensitivity/specificity) for the overall sample (males and females).

	Tissue type		
	GM + WM	GM-only	WM-only
HC versus CD	**.72** (.64/.79)***	**.70** (.65/.74)***	**.64** (.61/.66)***
HC versus CS	**.67** (.64/.70)***	**.63** (.62/.64)**	**.59** (.61/.56)*
CD versus CS	**.56** (.57/.55)*	**.59** (.61/.57)**	.54 (.57/.51)

Significant ($p < 0.05$) accuracies are highlighted in bold.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 2
SVM classification accuracy (and sensitivity/specificity) for male participants.

Males only	Tissue type		
	GM + WM	GM-only	WM-only
HC versus CD	**.70** (.63/.77)**	**.67** (.63/.71)***	.60 (.63/.58)$^{p < .06}$
HC versus CS	**.71** (.69/.74)***	**.66** (.67/.65)**	**.65** (.64/.66)**
CD versus CS	**.60** (.65/.54)**	**.58** (.61/.54)*	.52 (.51/.53)

Significant ($p < 0.05$) accuracies are highlighted in bold.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 3
SVM classification accuracy (and sensitivity/specificity) for female participants.

Females only	Tissue type		
	GM + WM	GM-only	WM-only
HC versus CD	**.68** (.56/.80)***	**.70** (.63/.78)***	**.68** (.63/.73)***
HC versus CS	**.72** (.69/.74)***	**.70** (.64/.75)***	.54 (.56/.51)
CD versus CS	**.83** (.87/.79)***	**.65** (.67/.63)*	**.77** (.80/.74)***

Significant ($p < 0.05$) accuracies are highlighted in bold.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 4
SVM classification accuracy (and sensitivity/specificity) for HCs vs SZ.

	Tissue type		
	GM + WM	GM-only	WM-only
Males + females	**.68** (.67/.70)***	**.65** (.66/.65)***	**.59** (.62/.57)**
Males only	**.67** (.66/.68)***	**.63** (.66/.59)***	**.63** (.64/.62)***
Females only	**.71** (.73/.70)***	**.75** (.73/.77)***	**.58** (.62/.55)

Significant ($p < 0.05$) accuracies are highlighted in bold.

* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

CS classification accuracy compared to when patients were stratified by cognitive subtype.

3.1.4. Effects of cannabis and alcohol abuse history

Although the ASRB excluded participants with current (within 6 months) substance dependence, male patients in our sample had higher frequencies of lifetime history of cannabis and alcohol abuse (see Table S2). If drug abuse effects modulate brain heterogeneity, then classification accuracy may vary systematically with these variables; for example, neuroanatomical heterogeneity may be higher in participants with a lifetime history of drug use compared to those without, leading to reduced classification accuracy when this heterogeneity is present in the sample. We therefore investigated whether the greater (CD vs. CS) classification accuracies that were observed for females versus males could be attributed to the effects of sex-specific differences in these variables.

We directly addressed this question by repeating our CD versus CS classification after excluding all samples with a lifetime diagnosis of either cannabis or alcohol abuse. Significant classification accuracies (all > 70%) were obtained for females using all three feature sets. Classification accuracy was significant for males using the GM + WM feature set, but was relatively low (55%, $p < 0.05$). Importantly, as in our original analysis, classification accuracy was significantly higher for females than for males when using the GM + WM (chi-square test: $p < 0.05$) and WM-only feature sets (chi-square test: $p < 0.01$). Classification accuracies did not significantly differ compared to the original classification analysis that included individuals with and without a history of abuse (McNemar's tests, all $p > 0.1$). Furthermore, no significant differences were revealed by chi-square tests assessing whether CD versus CS classification accuracies from the original classification analysis differed with diagnosis of a lifetime history of abuse (all $p > 0.1$).

3.2. Weight map analysis

To investigate the spatial structure underlying classification, we averaged the weight map values from classifiers that successfully distinguished cognitive subtypes from healthy controls, and from each other. Consistent with the whole-brain classification results, ROI analyses identified similar patterns of GM and WM weights for the HC versus CD and HC versus CS analyses using the combined male and female sample (Supplementary Tables S3 and S4), with high negative weights for subcortical regions including the hippocampus and amygdala, and for several cerebellar ROIs (e.g., left X GM, left cerebellar WM). High positive weights were identified for the putamen, caudate and a distinct set of cerebellar ROIs. Given that our cross-validation analyses had revealed that HC versus CD and HC versus CS classification may be achieved using similar classifier weight maps, we directly compared the weight map values for each classifier. The similarity of the weight map patterns was reflected in a strong positive correlation between the GM and WM weights (GM: $r = 0.66$, $p < 0.001$; WM: $r = 0.67$, $p < 0.001$) for the HC versus CD and HC versus CS classifiers.

For all CD versus CS classifiers, weight map analysis highlighted a distributed network of cerebellar, subcortical and cortical regions (Supplementary Tables S5 and S6). Consistent with the fact that approximately two-thirds of our patient sample were males, average GM weights for the combined male/female classifier were highly similar to those obtained for the male-only classifier ($r = 0.92$, $p < 0.001$) but not to those for the female-only classifier ($r = 0.04$, $p > 0.10$), and both sex-specific classifiers showed significant correlations with the combined male/female WM weights (male-only: $r = 0.80$, $p < 0.001$; female-only: $r = 0.56$, $p < 0.01$). We therefore focussed our analyses on the male- and female-specific weight maps.

Given that our cross-validation analysis indicated below-chance or non-significant performance when a CD/CS classifier trained on GM data females was applied to males, we investigated the consistency of weight map values across male- and female-specific classifiers. This revealed a significant negative correlation between the average GM weights for males and females ($r = -0.32$, $p < 0.01$), and a non-significant correlation for WM weights ($r = 0.05$, $p > 0.1$). Given that a large number of cerebellar ROIs had high average weights, and previous schizophrenia results demonstrating sex-specific volumetric and structure–cognition relationships in the cerebellum (Antonova et al., 2004; Flaum et al., 1994; Szeszko et al., 2003a; Szeszko et al., 2003b), we examined whether our negative GM weight correlations were consistent across the brain. The GM weight correlation for male and female CD versus CS classifiers was negative and significant when restricted to cerebellar ROIs ($r = -0.74$, $p < 0.001$), and non-significant when performed on all other ROIs ($r = 0.11$, $p > 0.1$).

We emphasize that individual weights reflect the weight applied to volumetric data at a given voxel in the context of the weights at all other voxels. Individual voxel weights can therefore be interpreted only in the context of the whole-brain maps they are derived from. In the present study, for example, the Spearman correlation coefficient between voxel-wise mean classifier weights and t-statistics and was between 0.93 and 0.95 for CD versus CS classifiers using the GM + WM feature set, and up to 12.2% of voxels had negative univariate difference and positive weight map values, or positive univariate differences and negative weight map values (see Fig. S2).

4. Discussion

The present study investigated the utility of multivariate patterns of grey- and white-matter volumes in discriminating CD and CS schizophrenia subtypes from healthy controls, and from each other. Application of support vector machine classifiers allowed mixed-sex samples of CD and CS cases to be discriminated from HCs with an accuracy of up to 72%. Similar classification accuracies for the prediction of schizophrenia case-ness were obtained regardless of whether patients were stratified by cognitive subtype. These findings accord with previous schizophrenia classification studies involving large case-control cohorts, which have typically discriminated cases from controls with an accuracy of ~70% (Nieuwenhuis et al., 2012). Cross-validation analyses showed that the neuroanatomical pattern distinguishing HCs from CD cases also discriminated HC versus CS case status, and vice versa, with an accuracy of 71%, and strong positive correlations were found between the multivariate weight map patterns underlying HC versus CD and HC versus CS classification.

These results thus demonstrate considerable overlap in the neuroanatomical patterns that distinguish both cognitive subtypes from controls in a mixed sex sample, and indicate that the use of putatively homogenous cognitive subtypes does not significantly improve classification accuracy above that demonstrated in previous studies. The ability to successfully differentiate either the cognitive deficit, or cognitively spared, subtype from HCs using a combined GM and WM feature set was not dependent on stratification of the sample by sex. The core neuroanatomical differences between cases and controls thus appear to be common across cognitive subtypes and sex.

The ability to distinguish CD from CS cases within the schizophrenia sample appears to be highly dependent on sex stratification. For

example, in the context of a mixed-sex or male-only sample, the accuracy with which CD cases could be distinguished from CS cases was low (≤60%). In contrast, for female-only samples, CD cases could be distinguished from CS cases with an accuracy of up to 83%. Consistent with the greater number of males than females in our sample and recent data indicating that male dominated samples bias detection of psychosis-associated grey matter abnormalities towards male-specific patterns (Bora et al., 2012), classification accuracy for males was not significantly improved by sex stratification. Furthermore, GM weight map patterns from mixed-sex classification analysis showed strong positive associations with male-specific weight map patterns and no correlation with the female-specific weight map pattern. These results thus highlight the importance of sexual dimorphism in structural brain changes in schizophrenia, consistent with previous evidence for sex-specific disruptions to volumetric and structure–function relationships in schizophrenia (Antonova et al., 2004; Crow, 2013; Abbs et al., 2011; Goldstein et al., 2002; Dean and McCarthy, 2008; Szeszko et al., 2003b; Szeszko et al., 2003a). In further support of this notion, CD/CS classifiers trained on a female-only sample predicted cognitive status within a male-only sample (and vice versa) at, or significantly below, chance rates, indicating sex-specificity to the associated neuroanatomical patterns. ROI weight map analyses highlighted opposing multivariate changes in the cerebellum for males versus females, consistent with previous reports that cerebellar volume is correlated with IQ in female schizophrenia patients and HCs, and that this structure–function relationship may be specifically disrupted in male schizophrenia patients (Antonova et al., 2004; Flaum et al., 1994; Picard et al., 2008). Together, these results suggest that future attempts to delimit homogenous subtypes of schizophrenia patients and associated intermediate phenotypes should consider the relevance of interactions with sex. Investigation of the factors underlying sexually dimorphic relationships in schizophrenia – such as the effects of genetic and sex hormone differences on foetal and early postnatal development – may provide insights into the neurodevelopmental origins of disease-associated brain abnormalities (Abbs et al., 2011; Abel et al., 2010; Giedd et al., 2012; Goldstein et al., 2013; Jazin and Cahill, 2010; Goldstein et al., 2002; Dean and McCarthy, 2008).

The low discrimination accuracy of CD versus CS cases in a mixed-sex sample contrasts with several recent univariate analyses of schizophrenia cohorts, in which regionally-specific associations between brain volumetry and cognitive function have been demonstrated (Cobia et al., 2011; Nazeri et al., 2013; Rais et al., 2012; Wexler et al., 2009). The present results thus suggest that the small but consistent neuroanatomical differences between cognitive subtypes do not have substantial predictive validity at the level of individual cases. This is concordant with the suggestion that cognitive deficits in schizophrenia are associated with neuroanatomical changes that are largely qualitatively similar, but differ in magnitude (Cobia et al., 2011). However, it is possible that greater accuracy would be obtained using other feature sets such as cortical thickness, curvature or area (Ecker et al., 2013; Oliveira et al., 2010; Panizzon et al., 2009; Rimol et al., 2012), or alternative classification approaches such as those that incorporate feature automatic feature selection methods and non-linear kernel methods; notably, our initial investigation here focussed on WM/GM volumetric differences as well established features of schizophrenia (Shepherd et al., 2012). While a priori selection of regions of interest may also improve classification, future whole-brain classification studies appear likely to yield similar results to the present study; non-linear kernel methods offer little advantage in the context of the large number of features in whole-brain datasets, and automatic feature selection methods do not appear to increase classification accuracy when applied to brain volume data (Chu et al., 2012). Furthermore, several differences exist between current univariate VBM and multivariate classification approaches. For example, classification studies often control for effects of covariate variables using a matched sample design, as in the present study. It is possible, however, that greater classification accuracy could be obtained if the effects of covariate demographic variables such as age are appropriately estimated (and regressed out) prior to classification analysis (Barnes et al., 2010; Cobia et al., 2012; Dukart et al., 2011). While possible, such approaches are not yet commonly implemented (e.g., Schrouff et al., 2013), and this remains an important consideration for future studies. However, our results suggest that covariate removal should not be performed without careful consideration: the sex differences in the neuroanatomical patterns that differentiate cognitive subtypes of schizophrenia reported here suggest that interactions with demographic variables may be of biological significance.

One potential concern for the interpretation of the current results is that MRI data used in this study was collected from multiple scanners, which may lead to site-specific confounds in gradient non-linearities, physiological noise and subject positioning (Jovicich et al., 2006). However, the comparability of scans collected within the ASRB was maximized by using identical acquisition parameters on the same scanner type at all MRI sites, and in this study the effects of this potential confound were controlled by ensuring that all participant sets comprised cases matched for scanner site in each analysis. A second limitation of the present study relates to the lack of availability of medication dosages for this sample, owing to constraints of the original data collection (in which patient self-reports of medication dosage were deemed insufficiently reliable for research purposes). We were therefore unable to control for effects of medication dose on brain structure. However, our patient subgroups showed no difference in the proportions of patients receiving typical or atypical antipsychotics, antidepressants, or mood stabilizers. Medication-independent relationships between cognition and structural neuroanatomy are further suggested by the neuroanatomical changes seen in univariate studies of medication-naïve first episode psychosis cases, and HCs carrying rare schizophrenia-associated copy number variants (Rais et al., 2012; Stefansson et al., 2014). However, as several studies have observed negative relationships between cognitive performance and medication dosage (Knowles et al., 2010; Hori et al., 2006), it will be important for future studies to clarify the relationship between cognitive performance, structural brain changes and medication effects.

In summary, our results suggest that in mixed-sex samples of schizophrenia patients, cognitive deficit and cognitively spared subtypes can be successfully distinguished from healthy controls by patterns of neuroanatomical features that appear to comprise common regions of grey- and white-matter, including several subcortical, cortical and cerebellar regions. Volumetric patterns that distinguish between the cognitive subtypes vary in a sex-specific manner, with sex stratification improving classification accuracy for female patient groups; this is consistent with previous reports of disrupted structure–cognition relationships in the brains of male, but not female, schizophrenia patients. Further characterization of sex-specific neuroanatomical and other pathological differences among subgroups of schizophrenia patients may provide important insights into the etiological processes underlying the phenotypic heterogeneity within schizophrenia.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2014.09.009.

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