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Sex chromosomes and the brain: a study of neuroanatomy in XYY syndrome

Daniel M Bryant[1], **Fumiko Hoeft**[1], **Song Lai**[2], **John Lackey**[2], **David Roeltgen**[3], **Judith Ross**[4], and **Allan L Reiss**[1]

[1]Center for Interdisciplinary Brain Sciences Research, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA

[2]Department of Radiology, Thomas Jefferson University, Philadelphia, PA

[3]Department of Neurology, Georgetown University, Washington, DC

[4]Department of Pediatrics, Thomas Jefferson University, Philadelphia, PA, USA.

Abstract

AIM—To assess global and regional brain matter variations associated with XYY syndrome by comparison with Klinefelter syndrome and typical development.

METHOD—We used two conceptually distinct voxel-based magnetic resonance imaging methods to examine brain structure in young males with XYY syndrome: (1) volumetric comparison to assess global grey and white matter volumes and (2) support vector machine-based multivariate pattern classification analysis to assess regional neuroanatomy. We assessed verbal, non-verbal, and spatial abilities with the Differential Ability Scales (DAS), and we measured autism diagnostic criteria in eight males with XYY syndrome using the Social Responsiveness Scale and the Autism Diagnostic Interview-Revised (ADI-R).

RESULTS—A comparison of 36 typically developing males (mean age 11y, SD 1y 9mo), 31 males with Klinefelter syndrome (mean age 9y 8mo, SD 1y 8mo), and eight males with XYY syndrome (mean age 11y 6mo, SD 1y 11mo) showed that total white and grey matter volumes were significantly, or nearly significantly, higher in males with XYY syndrome than in males belonging to the other two groups (grey matter: XYY males vs typically developing males, $p<0.006$; XYY vs males with Klinefelter syndrome, $p<0.001$; white matter: XYY males vs typically developing males, $p=0.061$; XYY males vs males with Klinefelter syndrome, $p=0.004$). Voxel-based multivariate pattern classification analysis indicates that, after controlling for global volumes, regional brain variations in XYY syndrome are more like those found in Klinefelter syndrome than those occurring in typical development. Further, visualization of classification parameters suggests that insular and frontotemporal grey matter and white matter, including known language areas, are reduced in males with XYY syndrome, similar to what is seen in Klinefelter syndrome. In males with XYY syndrome, DAS verbal and non-verbal scores were significantly lower than in typically developing participants (both $p<0.001$). DAS scores were not

Correspondence to Dr Allan L Reiss at Center for Interdisciplinary Brain Sciences Research MC 5795, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA. areiss1@stanford.edu.

significantly different between XYY and Klinefelter syndrome groups. In five of eight males with XYY syndrome, the Social Responsiveness Scale score exceeded the cut-off for a likely diagnosis of autism spectrum disorder (ASD). In three of eight males with XYY syndrome, the ADI-R score met the cut-off for ASD diagnosis; in another two, ADI-R scores within the social and communication domains met the cut-off values for a diagnosis of ASD.

INTERPRETATION—The results suggest that genetic variations associated with XYY syndrome result in increased brain matter volumes, a finding putatively related to the increased frequency of ASDs in individuals with this condition. In addition, frontotemporal grey and white matter reductions in XYY syndrome provide a likely neuroanatomical correlate for observed language impairments.

XYY syndrome is a genetic disorder characterized by an additional Y chromosome. Affecting only individuals who are phenotypically male, XYY syndrome is a common sex chromosome aneuploidy condition in humans, occurring in approximately one in 1000 live male births.[1] XYY syndrome has been associated with subtle physical features including tall stature[2] and increased head circumference,[3–5] though not all studies have observed the latter finding.[6] XYY syndrome is also associated with cognitive-behavioural deficits, most notably impairments in language and motor ability,[3,5–7] and is thought to entail increased risk of autism spectrum disorders (ASDs).[3,8–10]

In contrast, Klinefelter syndrome is a genetic disorder characterized by an additional X chromosome. Also affecting only individuals who are phenotypically male, Klinefelter syndrome has an estimated prevalence of one in 600 live male births[1] and often manifests with a characteristic physical phenotype, which includes reduced head circumference,[6] tall stature, and hypogonadism.[11] Individuals with Klinefelter syndrome exhibit impairments in language and motor ability similar to those observed in XYY syndrome,[5] raising the question of why two disorders with identifiably disparate genetic bases produce partially overlapping cognitive phenotypes. The present study addressed this question by highlighting regional neuroanatomical similarities and disparities between the two groups.

Though several neuroimaging studies have revealed abnormal brain structure associated with Klinefelter syndrome, to our knowledge, only one neuroimaging study has specifically addressed XYY neuroanatomy.[12] Gross neuroanatomical variation associated with Klinefelter syndrome most prominently includes reduced total brain volume,[12–14] though some report no significant difference.[15,16] Other independently replicated anatomical imaging findings in Klinefelter syndrome include reduced frontal and temporal grey matter[13,14,17] and either increased or spared parietooccipital grey matter.[17,18]

In the present study, we used conceptually distinct approaches to compare the neuroanatomy of eight males with XYY, 31 males with Klinefelter syndrome, and 36 typically developing males. First, we analysed total tissue volume using volumetric methods. Second, we explored patterns of regional grey matter and white matter difference using pattern classification analysis. We hypothesized that males with XYY syndrome would have increased total tissue volume, given previous reports of increased head circumference in individuals with XYY syndrome. Because of reports that males with XYY syndrome exhibit impairments in language and motor ability similar to those exhibited in Klinefelter

syndrome, we also expected males with XYY syndrome to exhibit patterns of regional brain variation more similar to those observed in males with Klinefelter syndrome than in typically developing males.

METHOD

Participants

The study included 31 males with Klinefelter syndrome (mean age 9y 8mo, SD 1y 8mo), 36 typically developing participants (mean age 11y, SD 1y 9mo), and eight males with XYY (mean age 11y 6mo, SD 1y 11mo). All participants were male, as Klinefelter syndrome and XYY affect only males. Participants with Klinefelter syndrome and XYY were recruited from the Thomas Jefferson University Pediatric Endocrine Clinic, were self-referred, or were referred by other physicians. Typically developing participants were recruited through Internet notices and by referrals from other families in research studies. All participants were recruited at 7 to 14 years of age, and the participants with Klinefelter syndrome and typically developing participants were matched for prepubertal status. Pubertal status was determined using standard clinical methods assessing testicular volume.[19] Half of the eight participants with XYY had pubertal testicular enlargement. Participants with known history of testosterone replacement therapy were excluded from the analysis. One of the eight participants with XYY had cavum velum interpositum but was retained in the analyses. To assess the possibility that inclusion of this participant inordinately influenced results, we performed support vector machine (SVM) analyses on a subsample with this participant excluded (36 typically developing participants, 31 participants with Klinefelter syndrome, and seven participants with XYY syndrome).

Genetic diagnoses of Klinefelter syndrome (47, XXY) and XYY syndrome (47, XYY) were confirmed by karyotype in each participant. A postnatal G-banded peripheral blood karyotype was obtained for all participants. Each karyotype included analysis of at least 20 cells. Of the males with Klinefelter syndrome, two had low levels (<20%) of mosaicism for a 46, XY cell line and were excluded. Participants were given a standard battery of psychological measures including the Crovitz–Zener test for measuring handedness[20] and the Differential Ability Scales (DAS) for verbal, non-verbal, and spatial abilities.[21] Head circumference was also measured and converted to standard deviation scores using population norms.[22] Table I reports details and between-group statistics.

The institutional review boards at Thomas Jefferson University and Stanford University approved the study. Informed consent was obtained from all parents and assent was obtained from all participants.

To assess whether males in the XYY syndrome group met criteria for ASD, parents of these participants completed the Social Responsiveness Scale[23] and the Autism Diagnostic Interview-Revised (ADI-R;[24] diagnostic algorithms for 4- to 5y-old children). The ADI-R is a developmental history interview that is based on the DSM-IV criteria for autism. Of the eight males with XYY, five had Social Responsiveness Scale total scores in the ‘severe’ range (2.6SD above population mean), which is strongly associated with a clinical diagnosis of ASD.[23] In addition, three of the eight males met the ADI-R score cut-off for ASD

diagnosis whereas another two met ADI-R ASD criteria on the Social and Communication domains of this instrument (but not for the restricted/repetitive behaviour domain).[24] Of the five males with XYY syndrome whose scores on the Social Responsiveness Scale were in the 'severe' range, four had ADI-R Social and Communication scores that surpassed the cut-off for ASD. Three of the eight males had received a prior clinical diagnosis of ASD. Complete scores are reported in Table II.

Of the 106 participants for whom structural magnetic resonance imaging (MRI) data were available, 75 participants (36 typically developing, 31 with Klinefelter syndrome, eight with XYY syndrome) were included. Twenty-six scans were excluded (five of typically developing participants, 17 of participants with Klinefelter syndrome, and four of participants with XYY) due to excessive in-scanner motion, as determined visually by experienced investigators (FH, ALR). Five additional participants with Klinefelter syndrome were eliminated in accordance with exclusion criteria (two for prior testosterone replacement therapy, two for mosaicism, and one for XXYY karyotype).

MRI data acquisition

All MRI was carried out on a Philips 3.0T whole-body clinical MRI system (Achieva; Philips Medical Systems, Best, the Netherlands) equipped with a Quasar Dual high-performance gradient system capable of on-axis (*x*, *y*, and *z*) peak gradient of 80 mT/m and 200 mT/m/ms slew rate, and an eight-channel SENSE (sensitivity encoding) head coil.

Structural images were obtained using a conventional, high-resolution three-dimensional T1-weighted (T1WI) fast gradient echo sequence (repetition time/echo time/angle=25ms/2.3ms/30°, 0.96×0.96×1mm^3 voxels, 160 contiguous anterior commissure-posterior commissure-aligned slices of 1mm thickness, acquisition time=6min 9s).

MRI analysis

Analysis of T1-weighted MRI was performed using Statistical Parametric Mapping, version 8 (http://www.fil.ion.ucl.ac. uk/spm). After image conversion to Nifti format using r2aGUI (http://r2agui.sourceforge.net/) and alignment to anterior commissure–posterior commissure axis, T1-weighted images were bias corrected and segmented to grey matter, white matter, and cerebrospinal fluid using Statistical Parametric Mapping, version 8, default tissue probability maps and the 'New Segment' tool, which also included an affine regularization to warp images to the included International Consortium for Brain Mapping template, producing rigidly aligned tissue class images. Inter-participant registration was achieved with diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL), using default settings. Jacobian-scaled ('modulated'), warped tissue class images were created with the DARTEL 'normalize to MNI space' tool, which spatially normalized images to Montreal Neurological Institute (MNI) space, converted voxel sizes to 1.5×1.5×1.5mm^3, and smoothed images with a standard Gaussian filter of full-width at half-maximum equal to 8mm.

Total grey matter volume (TGMV) and total white matter volume (TWMV) measures were extracted using the Statistical Parametric Mapping, version 8, built-in 'get totals' function,

passing the segmented images, generated by the 'new segment' step above, as parameters. Table I reports measures of TGMV and TWMV, after controlling for the effects of age.

Owing to the small number of available participants with XYY, we did not perform typical voxel-based morphometric statistical comparisons of regional grey matter and white matter among the three groups. An extensive comparison of regional grey matter and white matter differences between participants with Klinefelter syndrome and typically developing males in this same sample was reported in a recent study.[17] To compare total grey and white matter volumes, a three-group, one-way analysis of variance (ANOVA) was performed using Tukey's honestly significant difference test as a post-hoc assessment of each between-group difference (Table I). Comparisons of mean were performed using SPSS (IBM Corporation, Armonk, NY, USA) statistical software.

Multivoxel pattern analysis

In order to classify grey matter and white matter regional volumetric differences in XYY as more like those of Klinefelter syndrome or typically developing children, multivoxel pattern analysis was conducted with an in-house MatLab-based (Mathworks, Natick, MA, USA) multivoxel pattern analysis toolbox, which adopts LIBSVM (a library for support vector machines),[25] and has been used successfully in several earlier studies.[26–29] For example, Tanaka et al.[30] recently used these same methods and multivoxel pattern analysis toolbox in a study of dyslexia to classify one group of impaired readers as more like another group of impaired readers or more like typical readers. Their study illustrates the ability of this method to reveal important additional information about the group of interest.

We began multivoxel pattern analysis with the images resulting from the 'normalize to MNI space' step, described above, i.e. the smoothed, modulated, warped tissue class images. The search regions were restricted to grey and white matter regions using custom grey matter and white matter masks, which were created using participants' grey matter and white matter images. Images were downsampled to 4×4×4mm voxels excluding NaN (not-a-number) voxels and were converted to a matrix.

To control for differences in age and total grey or white matter volumes, we used linear multiple regression, with each voxel value as a dependent variable and TGMV (or TWMV) and age as independent variables. We obtained unstandardized residuals for each voxel (i.e. a residualized data matrix). The residualized matrix was then normalized so that the mean and standard deviation were 0 and 1 respectively. This correction for age and brain matter volume occurred before performance of principal components analysis and application of SVM, which are both addressed below. It is important to note that preprocessing occurred on an initial matrix that included data from all three groups. So, when analyses were performed with images from seven individuals with XYY syndrome, instead of eight, as noted above, the initial matrix and all regressor vectors had one fewer participant entries. As a result, subsequent preprocessing steps, including normalization, relied on slightly different values, and optimal Klinefelter syndrome–typically developing classification changed accordingly.

Before classifying the participants in the XYY syndrome group as more like those with Klinefelter syndrome or typically developing participants, we determined the pattern that best discriminated participants with Klinefelter syndrome from typically developing participants. To do this, principal components analysis was performed to reduce the number of dimensions in the residualized, normalized matrix to N–1 eigenvectors, where N–1 is the maximum number of eigenvectors possible and N is the total number of participants in the matrix.

SVM analysis was performed with recursive feature elimination, where features (eigenvectors) with the lowest absolute values of their weights were eliminated in 30% increments until performance began to degrade. Leave-one-out cross-validation was used for the entire procedure so that information from the test set was not used to train a linear support vector pattern classifier (regularization parameter C=1). To visualize the pattern that yielded the best classification between participants with Klinefelter syndrome and typically developing participants, we converted the new matrix back into an image and viewed it in MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron; Fig. 1).

Once the optimal discriminating feature set between participants with Klinefelter syndrome and typically developing participants was determined, we used the resulting classifier to determine if brain morphometry in individual participants with XYY syndrome resembled that of participants with Klinefelter syndrome or of typically developing participants. All classifiers created during the cross-validation procedure were applied to the eight participants with XYY syndrome, and the proportion of instances in which XYY syndrome was classified as Klinefelter syndrome versus typically developing was calculated. For example, if, for 57 of 67 (males with Klinefelter syndrome+typically developing males; n=67) models, seven out of eight males with XYY syndrome were classified as having Klinefelter syndrome and then, for the remaining 10 models, only six out of eight males with XYY syndrome were classified as having Klinefelter syndrome, this would yield a classification percentage of 85.63%, which is (57×7+10×6)/(67×8). Classification accuracies were statistically compared using permutation analyses (i.e. class labels [diagnoses] were randomly permuted and analyses were repeated more than 1000 times to obtain the distribution of data).

RESULTS

Total tissue volume

Participants with XYY syndrome had significantly increased total tissue volume, including individually increased TGMV and TWMV, relative to both participants with Klinefelter syndrome and typically developing participants (Table I and Fig. 2). In contrast, neither TGMV differences nor TWMV differences were significant between the participants with Klinefelter syndrome and typically developing participants.

Head circumference

Males with XYY syndrome had larger mean head circumference SD scores than typically developing males, but the difference was not significant (Table I). Males with XYY

syndrome did have significantly larger mean head circumference SD scores than males with Klinefelter syndrome.

Multivoxel pattern analysis

In the assessment of regional grey matter volumetric patterns, SVM with two features (eigenvectors) yielded optimal performance, accurately distinguishing participants with Klinefelter syndrome and typically developing participants 82.1% ($p<0.001$) of the time. In assessment of white matter patterns, SVM with 25 features yielded optimal performance, accurately distinguishing participants with Klinefelter syndrome and typically developing participants 80.6% ($p<0.001$) of the time. Figure 1 shows image-converted versions of these optimal classification matrices, demonstrating that pattern classification of participants with Klinefelter syndrome compared with typically developing participants includes contributions of positive weights in insular and frontotemporal regions and negative weights in parieto-occipital regions. Visual inspection reveals that brain regions used in optimally distinguishing Klinefelter syndrome and typical development are similar in location and extent to those regions showing significant differences between Klinefelter syndrome and typical development in a univariate, voxel-based morphometry study of this same sample.

After controlling for the effects of TGMV and age, regional grey matter patterns in males with XYY syndrome were classified as more like those of Klinefelter syndrome 85.6% ($p<0.001$) of the time using the feature set that yielded optimal grey matter classification between participants with Klinefelter syndrome and typically developing participants. Similarly, after controlling for the effects of TWMV and age, regional white matter patterns in XYY syndrome were classified as more like those of Klinefelter syndrome 83.6% ($p=0.007$) of the time using the feature set that yielded optimal white matter classification between participants with Klinefelter syndrome and typically developing participants.

When analyses were performed on the subsample that excluded the one participant with XYY syndrome with cavum velum interpositum, the results were highly similar: SVM was able to distinguish Klinefelter syndrome and typically development with similar accuracy (85.07% using grey matter with 12 eigenvectors, and 79.10% using white matter with 25 eigenvectors), and males with XYY syndrome were classified as Klinefelter syndrome-like with higher probability (91.7% for grey matter, and 84.9% for white matter, using the feature sets that optimally discriminated Klinefelter syndrome from typical development).

DISCUSSION

In this study, we show that males with XYY syndrome have a distinctive pattern of neuroanatomical variation, relative to males with Klinefelter syndrome and typically developing participants. Specifically, males with XYY syndrome show significantly increased total grey matter and white matter, relative to both comparison groups. After statistically adjusting for global tissue volumes, males with XYY syndrome also show patterns of regional grey matter and white matter that are more similar to those of participants with Klinefelter syndrome than to those of typically developing participants, chiefly in areas associated with language and motor ability. These neuroanatomical

variations putatively represent the downstream correlates of abnormal Y-chromosome gene expression associated with XYY syndrome.

To our knowledge, increased TGMV and TWMV in XYY syndrome have not been reported previously. The only other neuroimaging study of XYY syndrome reported no significant total or regional volumetric differences associated with the condition.[12] This discrepancy probably arises from differences inherent in our samples, given that both were relatively small for neuroimaging studies, though the discrepancy may also arise from variations in neuroimaging acquisition and analysis methods, most notably differences in definition of whole brain volume.

The finding of increased TGMV and TWMV in individuals with XYY syndrome reported here deserves particular attention. First, the finding is consistent with previous reports of increased head circumference, often considered a proxy for total brain volume, in individuals with XYY syndrome,[3,4] though not all studies report increased head circumference in XYY syndrome.[6] However, males with XYY syndrome in our sample did not have significantly increased head circumference compared with typically developing participants, suggesting that head circumference may not be an adequate proxy for brain volume, at least in this case, and highlighting the importance of direct brain volumetric assessment using neuroimaging methods. Small sample size does temper these claims. Second, increased TGMV and TWMV may be related to increased risk of ASD, which has been described in XYY syndrome by independent research groups.[8,9] Increased head circumference and brain matter volume represent the most robust and consistent neural findings reported in individuals with autism.[31–33] More specifically, increased head circumference has been associated with greater severity of impairments in social functioning as well as delayed language onset in ASD.[32] However, it is important to note that, even within ASD populations, there is much variability in the neuroanatomical phenotype.[29] More generally, idiopathic ASD is a heterogeneous syndrome from the point of view of aetiological/risk factors and pathogenesis,[34–36] whereas XYY syndrome represents a relatively well-defined genetic condition, which may be one among many risk factors for ASD. As such, neuroanatomical differences associated with ASD and XYY syndrome may arise from distinct biological origins. Nevertheless, when considered in light of evidence that sex-differentiating mechanisms play an important role in the development of ASD,[37,38] the possibility that downstream neuroanatomical differences, aberrant Y-chromosome dosage, and increased risk of ASD are significantly associated deserves further investigation.

Though increased TGMV and TWMV in the group of individuals with XYY distinguishes XYY syndrome from Klinefelter syndrome, pattern classification analysis suggests that, after controlling for total brain tissue volumes, regional neuroanatomical variation in XYY syndrome is more like that of Klinefelter syndrome than of male typical development. In particular, pattern classification analysis suggests that reduced insular and frontotemporal regional volumes accompanied by increased or spared volumes of parieto-occipital regions represent a pattern of altered neurodevelopment characteristic of both XYY and Klinefelter syndrome. Considerations of brain– behaviour associations in these conditions can be only speculative at this time given the limited size of our XYY sample. However, Klinefelter

syndrome-like patterns of insular and frontotemporal grey matter and white matter could be associated with previously described language impairment in XYY syndrome[7] as well as our sample's significantly reduced performance on the DAS verbal assessment, which was very similar to the performance of the participants in the Klinefelter syndrome group (Table I).

Klinefelter syndrome- and XYY-specific pattern weights associated with brain matter differences in language-associated regions appear overtly similar, but it is important to keep in mind that these similarities may not reflect similarities in the pathogenesis of underlying language deficits. Pattern classification merely suggests that XYY syndrome may be similar to Klinefelter syndrome with regard to patterns of volumetric differences in grey matter and white matter and that this finding could provide a tentative description of neuroanatomical variation associated with general language impairment. Indeed, language deficits in these two disorders have been distinguished from one another with increasingly detailed behavioural metrics. For example, a recent study addressed these differences, suggesting that males with XYY syndrome have more severe and pervasive language impairment, specifically with greater deficits in higher-level meta-linguistic abilities.[5] Other studies have characterized variations in language ability and behavioural phenotype.[8] As such, it seems likely that the biological pathways mediating overall language impairment are at least partially distinct in these two common genetic disorders. However, the observation that patterns of grey matter and white matter difference in XYY syndrome in areas associated with language function are more like those of Klinefelter syndrome offers additional insight into possible neuroanatomical correlates of language impairment in XYY syndrome. Further discrimination of specific genetic risk factors and downstream biological mechanisms in XYY syndrome may contribute to a better understanding of gene– brain–behaviour associations underlying impairment in language, cognition, and behaviour in young children.

Though the present study offers new insight into neuroanatomical variation in XYY syndrome, it has some limitations worth noting. First, as is the case for many other studies of sex chromosome aneuploidies, ascertainment bias probably affects the composition of our sample. Participants with Klinefelter syndrome and those with XYY syndrome were mostly referred for clinical evaluation (of eight males with XYY syndrome, two were diagnosed prenatally), so it is likely that cases involving more severe outward manifestations are preferentially included. It is important to keep this in mind when interpreting the results, as many males with XYY syndrome or Klinefelter syndrome frequently go undiagnosed. Second, some participants with XYY syndrome and Klinefelter syndrome were excluded for in-scanner motion; thus, methodological limitations may have precluded assessment of neuroanatomical differences potentially linked to motion-inducing behaviours. Third, small sample size limits our ability to make inferences from our statistical analyses. In part to address limitations associated with small sample size and relative imbalance among sample sizes, we performed SVM-based pattern classification analysis. This allowed us to assess regional neuroanatomical differences indirectly by comparing them with those already observed in contrasts between Klinefelter syndrome and typical development.[17]

In addition, the SVM methods that were used here do not reveal XYY-specific regional morphometric differences. Rather, our SVM analyses were designed to determine which group the participants with XYY syndrome most resembled with regard to a

neuroanatomical pattern previously defined by comparing participants with Klinefelter syndrome and typically developing participants. Lastly, inclusion of a participant with XYY syndrome with cavum velum interpositum may have influenced results, especially as the optimal number of features discriminating Klinefelter syndrome from typical development was different in subgroup analyses with this participant excluded. However, analyses on that same subgroup yielded an XYY classification probability similar to that of the main analyses, suggesting that inclusion of the participant did not inordinately influence our conclusion, namely that regional patterns of neuroanatomical variation observed in XYY syndrome are more like those observed in Klinefelter syndrome than in typical development.

This study represents an important step towards understanding neurodevelopmental consequences associated with XYY syndrome. More generally, the research offers insight into the effects of a supernumerary Y chromosome on structural brain development, suggesting a putative relationship with language and motor abilities. In addition, the results suggest a relationship between Y-chromosome gene dosage and brain structural abnormalities that have previously been associated with ASD. In the future, we plan to conduct a voxel-based morphometry study of neuroanatomy in XYY with a larger sample. Continued research of this nature is important, both for its potential future benefit to individuals with XYY syndrome and for its ability to elucidate genetic influences on cognition, behaviour, and brain development.

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ABBREVIATIONS

ADI-R	Autism Diagnostic Interview-Revised
ASD	Autism spectrum disorder
DAS	Differential Ability Scales
SVM	Support vector machine
TGMV	Total grey matter volume
TWMV	Total white matter volume

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What this paper adds

- Our results reveal a unique picture of neuroanatomy related to XYY syndrome.
- It offers new insight into associations among sex chromosome gene expression, neurodevelopment, and cognitive-linguistic ability.
- Observed grey and white matter volume increases suggest avenues for further study of the link between XYY syndrome and ASDs.

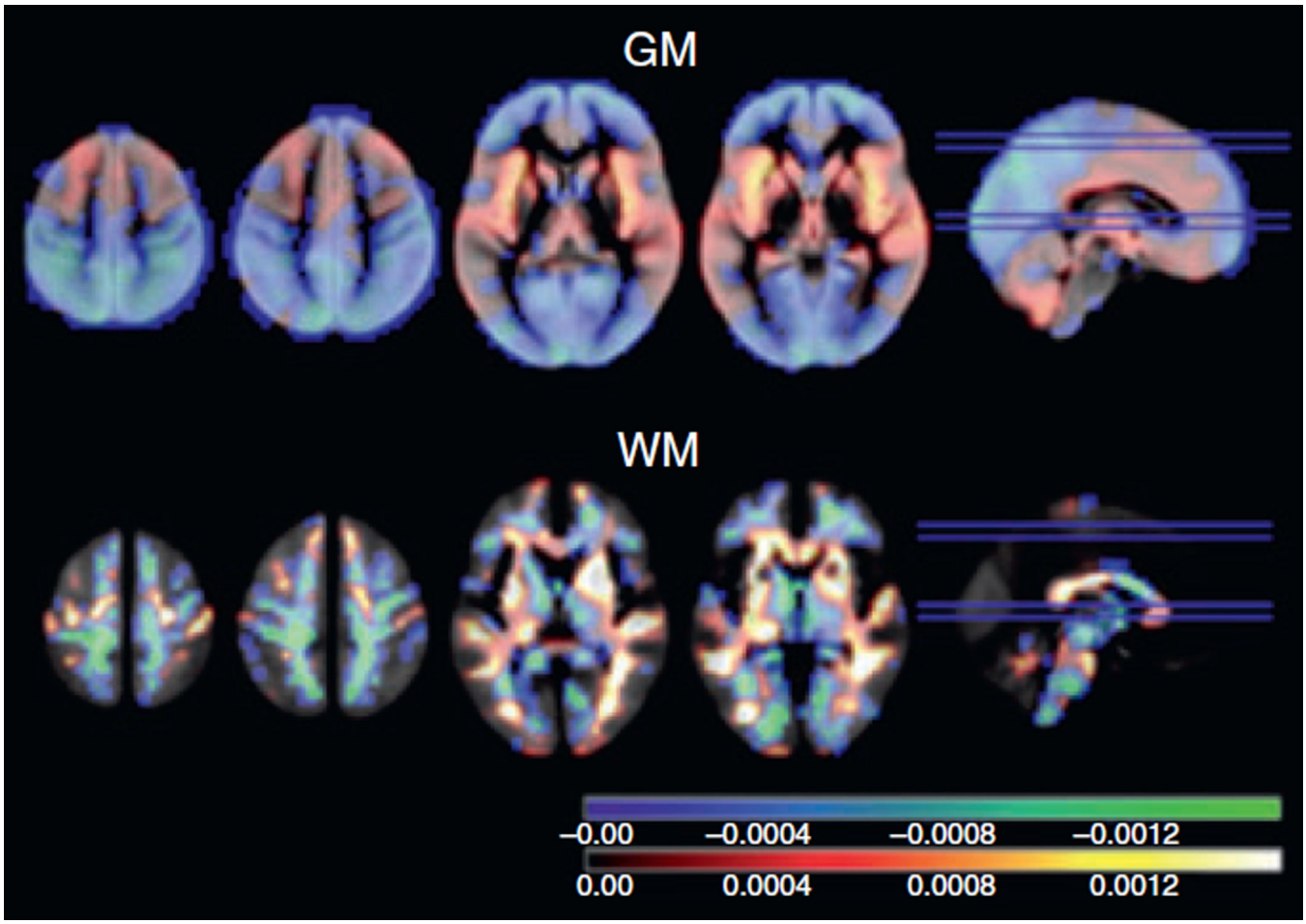

Figure 1.

Patterns of regional grey matter and white matter difference that yielded optimal support vector machine (SVM) classification between participants with Klinefelter syndrome and typically developing participants. SVM was performed on optimal features (eigenvectors) and matrices were converted back to voxels in image space. Warm colours represent positive weights and cool colours represent negative weights that best discriminate Klinefelter syndrome (class label=1) and typically developing participants (class label=−1). Scale bars illustrate weight values associated with each colour. GM, grey matter; WM, white matter.

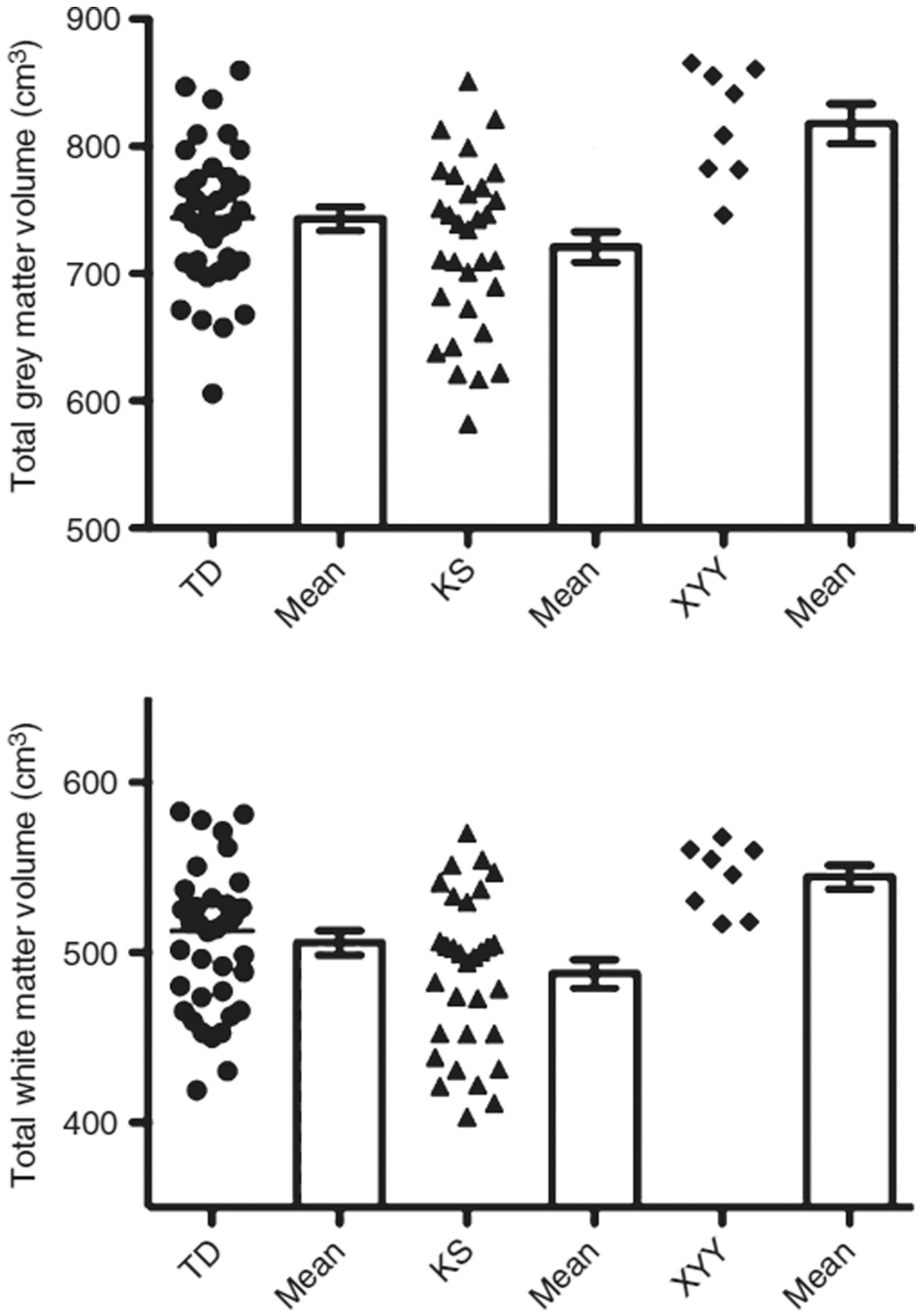

Figure 2.

Total grey matter volume and total white matter volume corrected for age. For each of the three groups (TD, typically developing participants [circles]; KS, participants with Klinefelter syndrome [triangles]; XYY, participants with XYY syndrome [diamonds]), individual participant values are shown alongside the group mean with error bars indicating standard error of the mean.

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Table I

Demographic information, cognitive testing, and brain matter volumes[a]

Characteristic	*n*	Klinefelter syndrome, mean (SD)	Typically developing	XYY syndrome, mean (SD)	For χ^2	*p*-value	Post-hoc: Tukey's HSD, *p*-values
Age							
KS	31	9y 8mo (1y 8mo)	11y (1y 9mo)	11y 6mo (1y 11mo)	6.289	0.003	KS vs TD: 0.008[b]; KS vs XYY: 0.024[c]; TD vs XYY: 0.702
TD	36						
XYY	8						
Head circumference SD score							
KS	31	0.3316 (1.32)	1.11 (1.56)	2.22 (0.95)	6.431	0.003	KS vs TD: 0.080[d]; KS vs XYY: 0.003[b]; TD vs XYY: 0.118
TD	32						
XYY	8						
Crovitz–Zener handedness							
KS	31	29 right, 2 left, 0 ambidextrous	28 right, 4 left, 2 ambidextrous	7 right, 0 left, 1 ambidextrous	χ^2 4.432	0.351	
TD	34						
XYY	8						
DAS (non-verbal cluster)							
KS	30	96.47 (15.76)	111.15 (13.68)	87.63 (13.03)	12.601	<0.001	KS vs TD: <0.001[e]; KS vs XYY: 0.284; TD vs XYY: <0.001[e]
TD	33						
XYY	8						
DAS (verbal cluster)							
KS	30	88.80 (14.15)	112.70 (14.50)	87.13 (7.88)	27.267	<0.001	KS vs TD: <0.001[e]; KS vs XYY: 0.950; TD vs XYY: <0.001[e]
TD	33						
XYY	8						
DAS (spatial cluster)							
KS	30	92.33 (15.22)	104.65 (14.84)	91.13 (16.48)	6.175	0.003	KS vs TD: 0.005[b]; KS vs XYY: 0.978; TD vs XYY: 0.067[d]

Characteristic	*n*	Klinefelter syndrome, mean (SD)	Typically developing	XYY syndrome, mean (SD)	For χ^2	*p*-value	Post-hoc: Tukey's HSD, *p*-values
TD	34						
XYY	8						
TGMV							
KS	31	720.89 (66.72)	743.14 (55.80)	817.83 (44.51)	8.405	0.001	KS vs TD: 0.287; KS vs XYY: <0.001[e]; TD vs XYY: 0.006[b]
TD	36						
XYY	8						
TWMV							
KS	31	487.43 (46.39)	505.68 (42.77)	544.26 (20.05)	5.847	0.004	KS vs TD: 0.196; KS vs XYY: 0.004[b]; TD vs XYY: 0.061[d]
TD	36						
XYY	8						
TTV (TGMV+TWMV)							
KS	31	1208.32 (111.97)	1248.82 (95.63)	1362.08 (60.57)	7.572	0.001	KS vs TD: 0.231; KS vs XYY: 0.001[b]; TD vs XYY: 0.014[c]
TD	36						
XYY	8						

[a] Head circumference measure is reported in standard deviations above the age-matched population mean. Brain matter volumes are corrected for age.

[b] <0.1.

[c] <0.05.

[d] <0.01.

[e] <0.001.

HSD, honestly significant difference; KS, Klinefelter syndrome; TD, typically developing; XYY, XYY syndrome; DAS, Differential Ability Scales; TGMV, total grey matter volume; TWMV, total white matter volume; TTV, total tissue volume.

Table II

Autism diagnostic scores for each participant with XYY syndrome

		SRS social					ADI-R		
Participant with XYY no.	**SRS Total (T score)**	**Awareness (T score)**	**Social cognition (T score)**	**Communication (T score)**	**Motivation (T score)**	**SRS autistic mannerisms (T score)**	**Reciprocal social interaction (cut-off 10)**	**Communication (cut-off 8)**	**Restrictive-repetitive behaviour (cut-off 3)**
1[a]	90	90	90	90	90	90	20	18	4
2(CVI)[a]	84	72	88	81	68	85	22	16	3
3	53	59	48	52	51	59	1	7	2
4[b]	87	75	85	84	78	85	10	11	0
5[b]	78	81	74	77	68	71	4	2	2
6	61	75	72	52	47	60	12	9	3
7	46	49	56	45	40	46	3	6	0
8[a]	76	62	72	77	68	76	14	13	0

[a] Autism spectrumdisorder diagnosis before the study.

[b] Prenatal diagnosis. SRS, Social Responsiveness Scale; ADI-R, Autism Diagnostic Interview-Revised; CVI, cavum velum interpositum.