NeuroImage: Clinical 8 (2015) 133–139

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Brain and behavior in 48, XXYY syndrome

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ARTICLE INFO

Article history:
Received 21 January 2015
Received in revised form 23 March 2015
Accepted 8 April 2015
Available online 15 April 2015

Keywords:
Sex chromosomes aneuploidy
48, XXYY
Brain anatomy
White matter lesions

ABSTRACT

The phenotype of 48, XXYY syndrome (referred to as XXYY) is associated with characteristic but variable developmental, cognitive, behavioral and physical abnormalities. To discern the neuroanatomical phenotype of the syndrome, we conducted quantitative and qualitative analyses on MRI brain scans from 25 males with XXYY and 92 age and SES matched typically developing XY males. Quantitatively, males in the XXYY group had smaller gray and white matter volumes of the frontal and temporal lobes. Conversely, both gray and white matter volumes of the parietal lobe as well as lateral ventricular volume were larger in the XXYY group. Qualitatively, males in the XXYY group had a higher incidence of colpocephaly (84% vs. 34%, $p \leq 0.001$), white matter lesions (25% vs. 5%, $p = 0.007$), and thin posterior body of the corpus callosum (28% vs. 3%, $p = 0.001$). The specificity of these findings may shed light on the role of the X and Y chromosomes in typical and atypical brain development and help provide direction for future studies of brain–behavior relationships in males with XXYY syndrome.

1. Introduction

XXYY syndrome (referred to as XXYY) is a form of sex chromosome aneuploidy (SCA) originally described as the "double male," due to the addition of an X and Y chromosome to the already complete 46, XY karyotype. The first description of XXYY appeared in a 1960 letter to the editor of *The Lancet* (Muldal and Ockey, 1960). Studies of live births in the late 1970s and 1980s reported the incidence of XXYY between 1:18,000 and 1:50,000 (Sørensen et al., 1978; Nielsen and Wohlert, 1990).

XXYY is unique among other forms of SCA in its origin and in the 1:1 ratio of supernumerary X and Y chromosomes. The low incidence rate can be partly attributed to the paternal origin of XXYY. A mere 1–2% of spermatozoa contain an aneuploidy of sex chromosomes, compared to more than 20% in oocytes (Martin, 2008). While it is possible to produce an XXYY karyotype through nondisjunction during mitosis of a normal fertilized egg, evidence from parental origin studies of XXYY in seven published cases over the past two decades has consistently indicated that the triploid gamete ($X_pY_pY_p$) is of paternal origin (Rinaldi et al., 1979; Lorda-Sanchez et al., 1992; Leal et al., 1994; Iitsuka et al., 2001; Balsera et al., 2013). The origin of the supernumerary chromosomes is important due to a process known as genomic imprinting, wherein the manner in which certain genes are expressed depends upon the parent of origin. Because XXYY is the only form of SCA with an equal ratio of X and Y-chromosomes in which each supernumerary chromosome is likely to have originated paternally, this presents a unique opportunity to examine brain anatomy in the context of polysomy, genomic imprinting and sexual dimorphism.

The phenotype of XXYY shares features common to other forms of SCA such as impairments in cognitive, affective and social functioning, developmental delays, hormonal irregularities, and atypical physical features. The only published neuroimaging study of XXYY syndrome used qualitative assessment to identify abnormalities in 35 males with XXYY (Tartaglia et al., 2008). Structural MRI was completed in each case due to concerns such as cognitive or developmental issues, hypotonia or seizures. Major findings included focal white matter lesions and enlarged ventricles (46% and 23% of the sample respectively). Scans from age-matched controls were not included for comparison. While these findings offer some insight, it is difficult to disentangle the potential interactions between the incidental findings and the concerns that prompted the MRI (e.g., seizures) from XXYY syndrome. Further complicating the interpretation of these findings is the lack of data on brain abnormalities such as white matter (WM) lesions, particularly in a genetically typical reference sample of children and young adults. The cause of WM lesions cannot be determined from MRI. However, WM lesions are indicative of damage to tissue structure (Taylor et al., 2001). To date, the largest sample of typically developing children and adolescents qualitatively assessed for the presence of WM lesions that

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http://dx.doi.org/10.1016/j.nicl.2015.04.009

we are aware of included 42 males aged 5–17 (Blumenthal et al., 2013). When compared to males with 49, XXXXY, the number of males with WM lesions found in each group was not significantly different than expected. Furthermore, while 50% of males with 49, XXXXY had WM lesions ($n = 14$), 2% of males in the control group also shared this finding. The clinical significance of these WM lesions is unclear, and further study is warranted to identify characteristics of lesions uncommon to a normative sample.

The present study adds to the emerging understanding of XXYY through the first quantitative and qualitative comparison of brain anatomy in 25 XXYY males and 92 age and SES matched controls.

Based upon the previously discussed findings we expected to find: (1) quantitative differences in total brain tissue (TBT), gray matter (GM) and WM; (2) qualitative abnormalities of WM and the ventricles; (3) decreased IQ; and (4) greater problems in social, emotional and behavioral functioning.

2. Materials and methods

2.1. Participants

Males in the XXYY group were recruited nationally via advertisements on the websites of several support groups which have since merged to become the Association for X and Y Chromosome Variations. Parents of XXYY individuals were screened by telephone. Individuals having a karyotype-confirmed diagnosis of XXYY were enrolled in the study. Persons with a history of conditions known to affect brain development (e.g., severe head injury) were excluded from participation.

Males in the control group (46, XY) were recruited locally from the Washington, DC area and nationally for participation in a longitudinal study of typical brain development via advertisements in newspapers and the NIH clinical trials website. Participants were excluded from the sample based upon the following criteria: psychiatric or learning disability diagnosis, history of severe head injury, or other condition affecting brain development.

Written consent was obtained from all participants age 18 and older. Written parental consent and child assent were obtained for all participants under the age of 18. The Institutional Review Board of the National Institute of Mental Health approved the protocol.

The ethnicity of the 25 males in the XXYY group included 23 non-Hispanic whites, one Hispanic white, and one multiracial non-Hispanic. Ages spanned from 4.9 to 28.3 years. Handedness within the group included 21 right-handed, three mixed-handed, and one left-handed participant. Of the 14 males age 13 years or older, eight were undergoing testosterone-replacement therapy (TRT) and six were not. None of the 11 males under age 13 were undergoing TRT. All participants were diagnosed with XXYY postnatally.

The ethnicity of the 92 males in the control group included 80 non-Hispanic whites, five black, five multiracial and two Hispanic white males. Eighty-three participants were right-handed, three were left-handed, five were mixed-handed and the handedness for one participant was unavailable.

2.2. Measures

2.3.1. Physical and genetic assessments

Karyotype testing was completed to confirm the presence of XXYY in all aneuploidy participants. Lymphocytes were cultured with phytohemagglutinin prior to high-resolution G band karyotyping. Three karyotypes per participant were produced, and 20 or 50 metaphase cells were analyzed. Chromosomal analyses were conducted at Quest Diagnostics or the Cytogenetics Laboratory in the Department of Obstetrics and Gynecology at Georgetown University Hospital.

Karyotyping analyses confirmed the presence of XXYY in all sampled cells for 23 participants. Samples from two participants produced cell lines containing 47, XXY in addition to 48, XXYY. The first participant produced a total of 50 metaphase cells, three of which contained 47, XXY. The second participant had a low mitotic index, yielding a smaller sample of 28 cells. One cell contained 47, XXY; the remaining 27 contained 48, XXYY. False-positive mosaicism is known to occur in G-banding when differing cells comprise less than 10% of cells in the sample (Okada et al., 1999; Okada et al., 2001). Therefore, these participants were not classified as mosaic, and remained in the sample.

Development of secondary sex characteristics was measured using Tanner stages (Tanner, 1962). Handedness was assessed using the Physical and Neurological Examination for Soft Signs (PANESS) (Denckla, 1985).

2.3.2. Assessments of cognitive, behavioral, emotional and social functioning

Neuropsychological assessments along with height, weight, and pubertal development measurements were completed at the National Institutes of Health (NIH) in Bethesda, MD. Intellectual functioning was measured using the Weschler Scales of Intelligence.

Twenty-four XXYY participants completed all four subtests of the Weschler Abbreviated Scales of Intelligence (WASI) (Weschler, 1999). Verbal IQ (VIQ) was comprised of scores from the Vocabulary and Similarities subtests. Performance IQ (PIQ) was comprised of scores from the Block Design and Matrix Reasoning subtests. One XXYY participant's verbal abilities were not sufficient to complete the WASI, so this participant was assessed using the Peabody Picture Vocabulary Test (PPVT-4) (Dunn and Dunn, 2007) instead.

Sixty-four control participants completed all four subtests of the WASI. Because the data were collected over many years, 24 participants completed different age–appropriate versions of the Weschler scales. These included the Wechsler Intelligence Scale for Children – Revised (Weschler, 1974) ($n = 19$), Wechsler Preschool and Primary Scale of Intelligence (Weschler, 1967) ($n = 3$), Wechsler Adult Intelligence Scale – Revised (Weschler, 1981) ($n = 1$), and the Wechsler Intelligence Scale for Children – Third Edition (Weschler, 1991) ($n = 1$). IQ in these 24 participants was estimated from Vocabulary and Block Design scores. Data were unavailable for four participants.

Behavioral, emotional, and social functioning was assessed using several questionnaires. Participants or their parents completed age–appropriate versions of all measures.

The Social Communication Questionnaire (SCQ; Rutter et al., 2003) is a parent report measure which assesses characteristics of autism over their child's lifetime. Scores ≥ 15 on the SCQ are highly sensitive and specific to diagnoses of autism in comparison with other developmental and intellectual disorders (Berument et al., 1999). This measure was administered only to the XXYY group due to their known elevated risk for autism spectrum disorders (Tartaglia et al., 2008).

The Social Responsiveness Scale (SRS; Constantino and Gruber, 2005) assesses behavior characteristic of ASD, with higher scores indicating more autistic behaviors. While SRS data were collected for nearly all males in the XXYY group ($N = 23$), only thirty-five of the healthy controls in the current sample completed the measure. This was due to our having introduced the measure to our longitudinal healthy control study long after it had begun.

The Child Behavior Checklist (CBCL; Achenbach and Ruffle, 2000) assesses emotional and behavioral competencies. The CBCL provides individual scale scores, a total score, and composite scores for Internalizing and Externalizing problems. Twenty-two males in the XXYY group and sixty-five males in the control group completed the CBCL. Data were missing from a small number of participants in each group on the Social Problems scale of the CBCL.

2.3.3. MRI acquisition

A General Electric 1.5 T Signa scanner (Waukesha, WI) located in the Nuclear Magnetic Resonance Center at NIH was used to collect all images using a steady-state 3-dimensional spoiled gradient-recalled echo sequence (3D SPGR). This sequence produced high-resolution anatomical definition with 124 contiguous 1.5 mm thick slices in the

axial plane (echo time = 5 ms; repetition time = 24 ms; flip angle = 45°; acquisition matrix = 256 × 192; number of excitations = 1; field of view = 240 mm; acquisition time = 9:52). For clinical evaluation a dual echo fast spin-echo imaging sequence (yielding proton density weighted and T2 weighted images) was also acquired.

2.3.4. Quality control of images pre- and post-processing

Reliable raters (JDB and LSC) assessed motion artifacts in the SPGR images, categorizing the degree of motion as (1) none, (2) mild, (3) moderate or (4) severe (Blumenthal et al., 2002). Scans with a rating of ≥3 were excluded from the sample. After images were rendered in 3-D via an automated image-processing pipeline, a group of reliable raters visually inspected the quality of the 3-D renderings, and categorized the degree of distortion. 3D renderings were rated in half-point increments ranging from one to five according to the degree of distortion (mild, moderate or severe) and number of lobes affected. Scans with ratings of ≥3.5 were excluded from the sample.

Motion ratings were slightly higher in the XXYY sample ($M = 1.12$, $SD = 0.33$) than in the control group ($M = 1.02$, $SD = 0.15$; $F = 4.75$, $p = 0.031$). However, the impact of this difference on scan interpretation is negligible because the means for both groups is a rating of 1, indicating motion artifacts were not detectable on the scan. Ratings of 3-D image distortion post-processing were also low, and not statistically significant ($F = 3.03$, $p = 0.084$) between the XXYY group ($M = 2.22$, $SD = 0.65$) and the control group ($M = 2.5$, $SD = 0.63$).

2.3.5. Qualitative evaluation of images

A neuroradiologist (EHB) reviewed all images to identify potential abnormalities of brain anatomy. The presence of global features such as skull shape and atrophy of the cerebrum and cerebellum were assessed. Specific structures such as the ventricles, cerebellar tonsils, and corpus callosum were evaluated with regard to shape, prominence and position. The presence and location of white matter anomalies such as lesions, cysts, and abnormalities of neural migration were also evaluated and recorded. In a few cases, it was not possible to make a determination about a specific abnormality due to image quality or artifact. These cases are identified below with the corrected sample size.

2.3.6. Quantification of whole brain and lobar volumes

MRI images were processed and transformed into quantitative data using the automated CIVET pipeline developed at the Montreal Neurological Institute. Native SPGR images were linearly transformed and registered into standardized stereotaxic space (Collins et al., 1994), then corrected for radio frequency transmission inhomogeneity of the scanner (Sled et al., 1998). The volume of brain tissue was then classified as gray matter (GM), white matter (WM) or cerebral–spinal fluid using an artificial neural network and tags (Zijdenbos et al., 2002). Classified tissue data were then combined with a probabilistic brain atlas to determine regions of interest. The regions chosen for analysis have been validated against other established segmentation methods. These regions include gray and white matter volumes, frontal, parietal and temporal lobes, and lateral ventricles (LV) (Collins et al., 1995). Total brain tissue (TBT) volume, defined as the sum of white and gray matter volumes, was also analyzed.

2.3.7. Statistical analysis

Males in the control group were matched with males with 48, XXYY based on age and socioeconomic status (Hollingshead, 1957). Differences between groups on all measures were evaluated via one-way analysis of variance (ANOVA), with diagnosis as the between-groups factor. Outliers were defined as data points ≥2 standard deviations above the mean. The removal of outliers identified in cognitive, behavioral and quantitative MRI measures did not alter the significance of the findings in preliminary analyses. Therefore, outliers remained in the sample.

Analysis of covariance (ANCOVA) was also completed adjusting for TBT and IQ. Rates of brain abnormalities found upon qualitative review were compared using chi-squared analyses. Two-tailed significance levels for all statistical tests were set at alpha = 0.05.

3. Results

3.1. Demographics, tanner stage and IQ

Statistically significant differences were not found between groups on age, height, SES, or handedness, but differences were statistically significant between groups in weight, stage of pubertal development and cognitive functioning (Table 1). The XXYY group mean was almost a full Tanner stage below the mean of the age-matched controls. In addition, the XXYY group means in composite IQ, VIQ, and PIQ were also lower than those of the control group.

3.2. Social, emotional and behavioral functioning

As shown in Table 2, the mean scores of the XXYY group were higher and statistically different from the mean scores of the control group on all measures of social, emotional and behavioral functioning. Seven males with XXYY scored at or above the cutoff score, 15, on the SCQ, which correlates strongly with a diagnosis of autism spectrum disorder.

3.3. Quantitative brain measures

Analyses of quantitative MRI data are shown in Table 3. TBT volumes were 4.6% smaller in males with XXYY compared to the control group ($F = 4.9$, $p = 0.028$). XXYY group volumes of both GM and WM were smaller in the frontal ($F = 4.4$, $p = 0.039$; $F = 8.2$, $p = 0.005$) and temporal lobes ($F = 5.9$, $p = 0.017$; $F = 8.9$, $p = 0.003$). XXYY group volumes were larger for parietal GM ($F = 8.0$, $p = 0.005$), and for lateral ventricles with increases of 72.9% in the left lateral ventricle ($F = 24.3$, $p \leq 0.001$), 58.5% in the right lateral ventricle ($F = 27.2$, $p \leq 0.001$), and 66.1% in total combined lateral ventricles ($F = 17.2$, $p \leq 0.001$).

Because TBT was statistically smaller in the XXYY males than the control group, we completed ANCOVA analyses for all quantitative MRI measures with TBT as a covariate. After controlling for TBT, the left hemisphere of the XXYY group was 2.8% ($F = 73.3$, $p \leq 0.001$) smaller, and the right hemisphere was 2.7% ($F = 67.7$, $p \leq 0.001$) smaller compared to the control group. WM in the parietal lobe (0.7%) was statistically larger than in the control group after controlling for TBT ($F = 7.1$, $p = 0.009$).

Because IQ is statistically lower in males with XXYY we completed an ANCOVA including both TBT and IQ as covariates. As is shown in Table 3, the smaller volume of the left and right hemispheres ($F = 68.9$, $p \leq 0.001$; $F = 61.0$, $p \leq 0.001$) along with larger volume of WM in the parietal lobe ($F = 40.8$, $p \leq 0.001$) remained statistically different from the control group. Additionally, larger volumes of parietal GM ($F = 40.8$, $p \leq 0.001$), total lateral ventricle ($F = 27.5$, $p \leq 0.001$), left

Table 1
Demographics, Tanner stage, and IQ measures.

	XXYY			XY			ANOVA	
	Mean	*SD*	*N*	Mean	*SD*	*N*	*F*	*p*
Age (years)	14.5	6.5	25	14.5	5.9	92	0	0.994
Height (in.)	63.5	10.2	24	62.1	8.6	90	1.1	0.426
Weight (lbs.)	127.2	59.6	25	122.3	47.8	92	2.4	**0.007**
SES[a]	50.6	22.5	25	47.2	21.1	92	0.5	**0.493**
Tanner stage	2.5	1.5	25	3.3	1.6	89	5	**0.027**
Full scale IQ	85.4	12.2	24	116.2	13.1	88	107.5	**<0.001**
Verbal IQ	80.3	11.4	24	113.2	14.8	66	97.3	**<0.001**
Performance IQ	93.8	12.7	24	114.3	12.7	66	45.6	**<0.001**

Statistically significant *p* values have been highlighted in boldface type.
[a]SES = socioeconomic status (Hollingshead, 1957).

Table 2
Social, emotional and behavioral questionnaires.

	XXYY			XY			ANOVA	
	Mean	*SD*	*N*	Mean	*SD*	*N*	*F*	*p*
Social Communication Checklist	11.1	7.4	23	—	—	—	—	—
Social Responsiveness Scale (Raw)	79.6	22.3	23	25.5	17.9	35	104.1	<**0.001**
Child Behavior Checklist								
Total problems	66.6	6.8	22	41.6	8.3	65	161.4	<**0.001**
Externalizing problems	58.9	8.1	22	43.5	8.3	65	57.6	<**0.001**
Internalizing problems	64.6	8.5	22	42.9	8.3	65	111.0	<**0.001**
Anxious/depressed	61.7	8.9	22	51.1	2.6	65	74.1	<**0.001**
Withdrawn	63.4	9.3	22	51.7	4.1	65	65.7	<**0.001**
Somatic	64.0	10.5	22	51.9	3.8	65	64.1	<**0.001**
Social problems	68.2	6.9	17	51.1	3.0	63	234.8	<**0.001**
Thought problems	67.3	6.8	22	50.9	2.2	65	290.4	<**0.001**
Attention problems	69.4	10.2	22	50.4	1.1	65	223.4	<**0.001**
Rule breaking/delinquent behavior	59.8	5.3	22	51.5	3.7	65	66.1	<**0.001**
Aggression	58.9	8.5	22	51.3	3.4	65	36.3	<**0.001**

Statistically significant *p* values have been highlighted in boldface type.

lateral ventricle ($F = 31.3$, $p \leq 0.001$), and right lateral ventricle ($F = 18.9$, $p \leq 0.001$) remained statistically different from the control group across all the levels of analysis.

Statistically significant differences were not found between measures of volume in laterality, ratio of GM to WM, total GM or total WM.

3.4. Qualitative MRI assessment

Brain anatomical findings for the two groups are summarized in Table 4. Abnormalities of brain anatomy are categorized and described by affected structure, composition, and functional system.

3.5.1. General morphology of the skull, cerebrum and cerebellum

Among the males with XXYY syndrome, three (12.0%) had a skull deformity including two cases of plagiocephaly and one case of brachycephaly. Two males (8.0%) had cerebral atrophy, and two (8.0%) had abnormal positioning of the cerebellar tonsils and cerebellar vermis combined with underdevelopment of the tonsils and/or vermis, producing a Dandy–Walker variant. Type I Chiari malformations were not observed in any males with XXYY syndrome.

Two of the males in the control group (2.2%) had abnormally shaped skulls, one each with scaphocephaly and plagiocephaly. Cerebral atrophy was noted in four males (4.3%) and one had a distorted left temporal lobe secondary to an arachnoid cyst. Abnormalities of the cerebellum were noted in seven males, with four classified as Type I Chiari malformations (4.3%), one Dandy–Walker variant, and one case of cerebellar tonsil ectopia.

Table 4
Qualitative Brain Findings.

	XXYY			XY				
	Count	Total	%	Count	Total	%	χ^2	*p*
General morphology								
Skull shape	3	25	12.0	2	92	2.2	4.6	**0.031**
Cerebral atrophy	2	25	8.0	4	92	4.3	0.5	0.463
Cerebellar abnormalities	2	25	8.0	7	92	7.6	0.0	0.948
Type I Chiari malformation	0	25	0.0	4	92	4.3	1.1	0.289
Dandy–Walker variant	2	25	8.0	1	92	1.1	3.8	0.052
White matter								
White matter lesions	6	24	25.0	4	89	4.5	9.8	**0.007**
Prominent perivascular spaces	3	25	12.0	4	92	4.3	21.0	<**0.001**
Thin corpus callosum	4	25	16.0	0	91	0.0	15.4	<**0.001**
Dysmorphic corpus callosum	6	25	24.0	3	92	3.3	11.9	**0.001**
Ventricle and periventricular abnormalities								
Colpocephaly	21	25	84.0	31	92	33.7	20.1	<**0.001**
Periventricular cysts	2	24	8.3	0	91	0.0	8.6	**0.014**
Other anatomical findings								
Mega cisterna magna	3	25	12.0	1	92	1.1	7.1	**0.008**
Arachnoid cysts	5	25	20.0	15	88	17.0	0.1	.733

Statistically significant *p* values have been highlighted in boldface type.

3.5.2. Focal white matter signal abnormalities

Within the XXYY group, small WM lesions were noted in six out of 24 males (25.0%). Within this subgroup, the majority had three or more lesions. Overall, lesions tended to be located in the periventricular areas of the frontal and parietal lobes, and involved the left hemisphere more frequently than the right. Prominent perivascular spaces were observed in three males (12.0%). While perivascular spaces are a non-pathological normal variant, their appearance can be difficult to differentiate from small white matter lesions due to motion artifacts, low resolution, and thick image slices generated by the 1.5 T scanner. Thinning of the corpus callosum was noted in four males with 48,

Table 3
Whole-brain brain volumes (cm^3).

	XXYY ($N = 25$)		XY ($N = 92$)		ANOVA		ANCOVA (TBT)		ANCOVA (TBT + IQ)	
	Mean	(*SD*)	Mean	(*SD*)	*F*	*p*	*F*	*p*	*F*	*p*
Total brain tissue	1325.4	113.5	1389.4	131.1	4.9	**0.028**				
Left hemisphere	518.7	47.4	533.7	53.7	1.6	0.207	73.3	<**0.001**	68.9	<**0.001**
Right hemisphere	514.9	45.2	529.3	53.0	1.5	0.216	67.7	<**0.001**	61.0	<**0.001**
Laterality	0.0	0.0	0.0	0.0	0.2	0.631	0.6	0.456	0.8	0.384
GM/WM ratio[a]	1.7	0.2	1.7	0.2	0.1	0.759	0.1	0.752	0.0	0.924
Total GM	831.2	89.4	868.0	92.1	3.2	0.077	0.1	0.759	0.0	0.960
Frontal GM	224.7	25.4	237.7	28.0	4.4	**0.039**	0.2	0.677	0.3	0.556
Temporal GM	192.3	21.7	204.3	22.0	5.9	**0.017**	1.0	0.332	1.9	0.170
Parietal GM	132.1	15.8	121.8	16.3	8.0	**0.005**	46.8	<**0.001**	40.8	<**0.001**
Total WM	494.2	57.3	521.4	67.5	3.4	0.069	0.1	0.759	0.0	0.960
Frontal WM	166.4	21.4	182.1	25.0	8.2	**0.005**	3.2	0.077	1.9	0.166
Temporal WM	92.0	10.0	100.7	13.5	8.9	**0.003**	3.8	0.053	2.6	0.110
Parietal WM	95.3	11.0	94.6	12.7	0.1	0.793	7.1	**0.009**	8.2	**0.005**
Lateral ventricles	18.6	9.2	11.2	5.8	24.3	<**0.001**	29.1	<**0.001**	27.5	0.000
Left lateral ventricle	10.2	4.7	5.9	3.3	27.2	<**0.001**	32.2	<**0.001**	31.3	<**0.001**
Right lateral ventricle	8.4	4.9	5.3	2.9	17.2	<**0.001**	20.6	<**0.001**	18.9	<**0.001**

Statistically significant *p* values have been highlighted in boldface type.
[a]GM = gray matter; WM = white matter.

XXYY (16.0%), and abnormal morphology was noted in six males in this group (24.0%), three of whom had small splenia.

WM lesions were noted in four out of 89 control group males (4.5%). One male in this subgroup had six periventricular lesions; the other males had single subcortical lesions. All subcortical lesions occurred in the frontal lobe, with the remaining periventricular lesions evenly distributed in the parietal, temporal and occipital lobes. Lesions occurred slightly more frequently in the left hemisphere. Prominent perivascular spaces were observed in four control group males (4.3%). Thinning of the corpus callosum was not identified in any of the control group males; however, three males in the control group (3.3%) had either large or slightly small splenia. The corpus callosum was completely formed in all males in both the XXYY and control groups.

3.5.3. Colpocephaly and ventricular abnormalities

Colpocephaly, defined as disproportionate enlargement of the occipital horns with the remaining ventricular system maintaining normal size and configuration, was observed in 21 males (84%) in the XXYY group. Overall, the majority of cases occurred unilaterally, with approximately equal numbers of cases involving only the left or right hemisphere. However, enlargements in the right hemisphere were primarily minimal, whereas enlargements in the left hemisphere were primarily moderate. Cavum of the septum pellucidum and cavum vergae were noted in seven males with 48, XXYY (28.0%) but only one (4.0%) was large, beyond the normal variation in size. Periventricular cysts were found in two of 24 males with XXYY (8.3%).

Within the control group, 31 instances of colpocephaly were identified (33.7%). Most were minimal and isolated to the left hemisphere (15.2%). However, a sizable proportion of cases rated as minimal involved both hemispheres (10.9%). All 31 cases of cavum of the septum pellucidum in the control group (33.7%) were small, which is considered a normal variant. Medium-sized cavum vergae was observed in three males (3.3%), while periventricular cysts were not found in any control group males.

3.5.4. Other clinical observations

Arachnoid cysts were observed in five males in the XXYY group (20.0%). Mega cisterna magna was found in three males in this group (12.0%). Within the control group, arachnoid cysts were noted in 15 of 88 (17.0%) males. Mega cisterna magna was found in one male in the control group (1.1%). Neither heterotopia resulting from abnormal neural migration nor cerebellar atrophy was present in any participant.

As is shown in Table 4, chi-squared analyses showed that when compared to males in the control group, males with XXYY have higher rates of abnormally-shaped skulls ($\chi^2 = 4.6$, $p = 0.031$), white matter lesions ($\chi^2 = 9.8$, $p = 0.007$), prominent perivascular spaces ($\chi^2 = 21.0$, $p = 0.000$), thinning of the corpus callosum ($\chi^2 = 15.4$, $p = 0.000$), abnormal morphology of the corpus callosum ($\chi^2 = 11.9$, $p = 0.001$), colpocephaly ($\chi^2 = 20.1$, $p = 0.000$), periventricular cysts ($\chi^2 = 8.6$, $p = 0.014$), and mega cisterna magna ($\chi^2 = 7.1$, $p = 0.008$).

4. Discussion

Previous findings in the context of sexual dimorphism, SCA and genomic imprinting indicate that the type, amount and paternal origin of sex chromosomes all influence TBT. Between genetically typical males and females TBT is approximately 10% larger in males than females throughout development (Giedd et al., 2012). In SCA additional X-chromosomes are associated with reductions in TBT compared to age-matched controls, and reductions tend to increase with the number of additional X chromosomes (Lenroot et al., 2009). For example, total brain volume in 47, XXY is 7–8% smaller than healthy age-matched controls (Giedd et al., 2007; Lentini et al., 2013), whereas Blumenthal et al. (2013) found reductions of 20% in males with 49, XXXXY compared to age-matched controls. In contrast, TBT in males with one additional Y-chromosome (47, XYY) is larger by 8% (Bryant et al., 2012; Lepage et al., 2013). This pattern of supernumerary X-related volume deficit is consistent in trisomy X (47, XXX), with an 8% smaller TBT compared to matched controls. Additionally, recent evidence from a genomic imprinting study in Turner syndrome (XO) shows smaller TBT associated with paternally-derived X chromosomes compared to maternally-derived X chromosomes (Lepage et al., 2013).

Accordingly, evidence also suggests that, in addition to the number and type of sex chromosomes, circulating sex hormones affect GM and WM volumes. Differences in cortical GM between genetically typical males and females are related to androgen receptor genotype and circulating levels of sex hormones (Giedd et al., 2012). In a comparison of 46, XX, 46, XY and 47, XXY Lentini et al. (2013) found that the number of X chromosomes was associated with smaller fronto-temporal WM volume and greater parietal GM volume, with parietal GM negatively correlated with circulating level of testosterone. Hypogonadism is part of the phenotype of XXYY, and testosterone replacement therapy (TRT) is often recommended to advance pubertal development to an age–appropriate stage (Tartaglia et al., 2008).

While little is known about the brain in XXYY, the developmental, cognitive, social, affective, and behavioral aspects of the syndrome are well documented. XXYY is most often diagnosed postnatally via genetic testing prompted by concerns regarding delayed development (Tartaglia et al., 2008). In XXYY neurodevelopmental disorders such as ADHD and autism occur at rates as high as 72% for ADHD (Tartaglia et al., 2008) and 28–50% for autism (Tartaglia et al., 2005; Tartaglia et al., 2008).

Cognitive abilities as shown by full-scale IQ scores range from intellectual disability to the lower end of average. Visual–spatial skills are often stronger than verbal abilities (Linden et al., 1995; Tartaglia et al., 2008), and are therefore considered a relative strength in XXYY. However, it is important to note that visual–spatial abilities are not stronger on average than those of typically developing peers.

Existing reports of emotional and behavioral difficulties suggest that on average males with XXYY have greater difficulties in both internalizing (i.e., anxiety and depressive symptoms) and externalizing (i.e., hyperactivity, aggression) domains, and have higher prevalence of mood disorders (Tartaglia et al., 2005).

4.1. Conclusions

This study presents the first comparison of quantitative and qualitative brain anatomy from a sample of males with XXYY syndrome to healthy age and SES matched males (46, XY), and replicates previously-reported findings in cognitive, emotional and social functioning. Overall, the XXYY brain is smaller than the brain of the genetically typical male, and more often has abnormalities in WM and in the ventricular system. Gray and white matter volumes show an inverse pattern of volumetric differences in the frontal and temporal lobes compared to the parietal lobe, with relatively disproportionate excess of GM and WM in the parietal lobe. Visual–spatial skills are a relative cognitive strength, while verbal skills are relatively weaker. Problems of affect and behavior are more common, along with social difficulties.

Considering previous findings of total brain volumes in other forms of SCA (Giedd et al., 2007; Bryant et al., 2012; Blumenthal et al., 2013; Lentini et al., 2013; Lepage et al., 2013), it appears that the additional X chromosome in XXYY syndrome contributes to reductions in overall brain volume. However, the magnitude of this reduction (relative to the number of supernumerary chromosomes) appears to be mitigated in the presence of the additional Y chromosome. The overall reductions found in XXYY were more similar to those found in studies of 47, XXY compared to 47, XYY or 49, XXXXY which suggests that the X chromosome influences overall brain volume to a greater extent than the number of sex chromosomes in total. Furthermore, these findings are in line with previous findings of reduced TBT associated with paternally-derived X chromosome (Lepage et al., 2013).

Findings regarding the GM and WM between lobes also provide support for differential associations between the numbers of X chromosomes and the more general additive or multiplicative effects of aneuploidy. The frontal and temporal lobes in XXYY were characterized by deficits of both GM and WM. WM deficit in the frontal lobe was also reported in both 47, XXY and 47, XYY (Lentini et al., 2013; Lepage et al., 2013), suggesting a shared influence of the total number of supernumerary sex chromosomes rather than the additional X or Y specifically. In contrast, the divergence in WM findings of the temporal and parietal lobes suggests that a supernumerary X plays a greater role in the temporal lobe, and that a supernumerary Y exerts more influence in the parietal lobe. WM deficit in the temporal lobe is a finding common to both XXYY and 47, XXY, whereas excess WM in the parietal lobe is common to both XXYY and 47, XYY.

Differences in the WM and GM of the frontal and temporal lobes in XXYY are proportionate between lobes and between tissue types within each lobe. The parietal lobe however, shows disproportionate excess of GM (8.5%) relative to WM (0.7%). This finding is unexpected in the context of the parallel differences in WM and GM across groups of genetically typical males and females in comparison to males with 47, XXY (Lentini et al., 2013). While previous work has found a larger proportion of GM to WM in both males and females with smaller TBT, this finding was global (Leonard et al., 2008). The disparity of excess GM and WM in the parietal lobe could be related to qualitative findings of high prevalence of colpocephaly and smaller splenium in the corpus callosum, due to the majority of fibers crossing from the posterior corpus callosum to the parietal lobes. Additionally, excess GM in the parietal lobe was the only tissue finding that remained statistically different from controls across all levels of adjustment, indicating that it is a robust feature of whole-brain anatomy in XXYY.

Nonspecific WM lesions were observed in a much smaller proportion of our sample (25%, $n = 25$) than previous findings reported by Tartaglia et al. (2008) in a similarly sized sample (46%, $n = 35$). The prevalence of WM lesions found in XXYY is similar to the prevalence in adults aged 64 years (11–21%; Ylikoski et al., 1995), despite the much younger mean age of XXYY males with lesions ($M = 12.1$, $SD = 6.1$) and younger mean age of the group overall ($M = 14.5$, $SD = 6.5$). While the number of WM lesions was statistically greater than would be expected in the control group, the importance of this finding cannot be interpreted without considering the lack of published data describing the prevalence, development and clinical significance of WM lesions in healthy children and adolescents. Therefore, our finding that WM lesions were present in 4.5% of genetically typical males ($n = 4$) between the ages of 6 and 18 ($M = 9.5$, $SD = 6.0$) contributes toward understanding the development and consequences of WM lesions. The young ages of the control group males with WM lesions is particularly interesting in light of recent evidence suggesting that focal WM lesions develop gradually (deGroot et al., 2013).

Limitations of the study include potential ascertainment bias, lobar level of brain measurement, and lack of data regarding paternal origin of supernumerary chromosomes and circulating levels of sex hormones. First, ascertainment bias due to postnatal diagnosis could impact study results. Participants diagnosed as a result of investigating other developmental concerns may represent a more severe form of the phenotype. However, while it is not uncommon for certain cases of sex chromosome trisomy such as 47, XXY to remain undetected (Okada et al., 1999), it is unlikely that non-mosaic tetrasomy would remain undetected. This is because physical dysmorphology is typically more noticeable in cases of tetrasomy and pentasomy compared to trisomy. Secondly, brain volumes were not measured beyond the lobar level (e.g., regions) and therefore, did not permit a meaningful analysis of brain–behavior correlations. Future studies using more sophisticated image quantification techniques, such as surface- and voxel-based morphometry, should expand upon these preliminary findings by investigating regions of interest to identify potential brain–behavior relationships. Thirdly, while overwhelming evidence suggests that the supernumerary X and Y in XXYY are both paternal in origin, we did not investigate parental origin within this study. While this does not diminish the value of the descriptive study, it restricts the interpretation of the findings with regard to genomic imprinting. Finally, because the level of circulating testosterone impacts aspects of brain development in both genetically typical and SCA populations, lack of data in this area restricts the interpretation of findings. Future studies incorporating measures of testosterone are warranted.

Acknowledgments

The Intramural Research Program of the NIMH supported this research. The authors were solely responsible for the study design; collection, analysis and interpretation of data; the writing of the report; and the decision to submit for publication. We thank the families who participated in this research, and the Association of X and Y Chromosome Variations for their assistance with recruitment of participants.

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