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A case-control study of brain structure and behavioral characteristics in 47,XXX Syndrome

Rhoshel K. Lenroot, MD¹, Jonathan D. Blumenthal, MA², Gregory L. Wallace, PhD², Liv S. Clasen, PhD², Nancy Raitano Lee, PhD², and Jay N. Giedd, MD²

¹University of New South Wales and Neuroscience Research Australia, Sydney, NSW, Australia

²Child Psychiatry Branch, National Institute of Mental Health, NIH, DHHS, Bethesda, MD, USA

Abstract

Trisomy X, the presence of an extra X chromosome in females (47,XXX), is a relatively common but under-recognized chromosomal disorder associated with characteristic cognitive and behavioral features of varying severity. The objective of this study was to determine whether there were neuroanatomical differences in girls with Trisomy X that could relate to cognitive and behavioral differences characteristic of the disorder during childhood and adolescence.

MRI scans were obtained on 35 girls with Trisomy X (mean age 11.4, s.d. 5.5) and 70 age- and sex- matched healthy controls. Cognitive and behavioral testing was also performed. Trisomy X girls underwent a semi-structured psychiatric interview. Regional brain volumes and cortical thickness were compared between the two groups.

Total brain volume was significantly decreased in subjects with Trisomy X, as were all regional volumes with the exception of parietal gray matter. Differences in cortical thickness had a mixed pattern. The subjects with Trisomy X had thicker cortex in bilateral medial prefrontal cortex and right medial temporal lobe, but decreased cortical thickness in both lateral temporal lobes. The most common psychiatric disorders present in this sample of Trisomy X girls included anxiety disorders, (40%), Attention-Deficit Disorder (17%), and depressive disorders (11%).

The most strongly affected brain regions are consistent with phenotypic characteristics such as language delay, poor executive function, and heightened anxiety previously described in population-based studies of Trisomy X and also found in our sample.

Address correspondence to: Jonathan Blumenthal, Child Psychiatry Branch, NIMH, NIH, Building 10, Room 4C110, MSC-1367, 10 Center Drive, Bethesda, MD 20892, [jb364e@nih.gov], 301-435-4516, 301-480-8898 (fax).

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Rhoshel K. Lenroot and Jonathan D. Blumenthal: Dr. Lenroot and Mr. Blumenthal conceptualized and designed the study, coordinated and supervised data collection, carried out the analyses, drafted and revised the initial manuscript, and approved the final manuscript as submitted.

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Keywords

Trisomy X syndrome; XXX; sex chromosome aneuploidy; magnetic resonance imaging; brain; children; adolescents; X chromosome

Introduction

Sex chromosome combinations other than XX or XY occur in approximately 1 in 400 live births (Nielsen & Wohler, 1990, Ratcliffe, 1994). The most common of these sex chromosome variations (SCVs) in females is the occurrence of an extra X chromosome (47,XXX), also known as Trisomy X, estimated to occur in approximately 1/1000 female births (Jacobs, 1979, Jacobs *et al.*, 1959, Nielsen & Wohler, 1990). Despite the high incidence compared to many genetic disorders, 47,XXX is rarely recognized because the relatively subtle and nonspecific physical characteristics of the phenotype do not routinely prompt genetic testing (Otter *et al.*, 2010). The additional X chromosome in females with 47,XXX syndrome appears to exert a much more prominent effect on cognitive and behavioral development, including slightly decreased IQ compared to socioeconomically matched peers or siblings (Netley, 1986, Otter *et al.*, 2010, Ratcliffe, 1999), impairments in language development in up to 75% of affected individuals, and deficits in attention and working memory (Leggett *et al.*, 2010). In longitudinal studies, behavioral phenotypes included poor interpersonal relationships, irritability, shyness, anxiety, and poor self-esteem, with a tendency to require greater levels of parental support and to take lower-skilled employment than would have been expected for their cognitive ability levels or educational achievement (Bender *et al.*, 1999).

However, despite the evidence of adverse effects on cognitive, behavioral and emotional function, relatively few data are available regarding the effects of an additional X chromosome on brain development in females. Two 47,XXX neuroimaging studies have been conducted, both of adult subjects who had participated in the longitudinal birth cohort studies. One study of twelve subjects with 47,XXX (Warwick *et al.*, 1999) and matched controls found significantly smaller whole brain volumes and increased rate of white matter hyperintensities in the 47,XXX group. A second study of whole brain, amygdala, and hippocampus volumes in ten women with 47,XXX and matched controls (Patwardhan *et al.*, 2002) again found significantly smaller total brain volumes in the women with 47,XXX; amygdala and hippocampus were not different after controlling for overall brain tissue volume.

47,XXX is of particular interest in terms of understanding genetic influences on brain development, as the X chromosome contains many genes important for neural development and cognitive function (Skuse, 2005), and studies of 47,XXX are not confounded by the hypogonadism characteristic of males with an extra X chromosome (Giedd *et al.*, 2007). The goals of the current study were to examine the effects of an extra X chromosome on brain and behavioral development in females by performing an MRI study and in-depth psychiatric interview in a large pediatric sample of girls with 47,XXX and matched controls. Based on previous research, we hypothesized decreased brain volumes in 47,XXX, and,

more specifically, both decreased brain volume and thinner cortex in the temporal lobes, consistent with the high prevalence of language and auditory processing deficits found in this group.

Materials and Methods

We recruited 35 participants with 47,XXX (ranging in age from 5.0 to 24.8 years) nationwide with the help of the 47,XXX Support Group and two parent advocacy groups: the American Association for Klinefelter Syndrome Information and Support (AAKSIS) and Klinefelter Syndrome and Associates (KS&A). During their visit to the National Institutes of Health (NIH), subjects underwent physical, psychiatric, and neurocognitive assessment. IQ scores were obtained using the Wechsler Abbreviated Scale of Intelligence (WASI) for all but one of the girls with 47,XXX, who, at the time of testing, had recently completed the Wechsler Adult Intelligence Scales III (Wechsler, 1991, Wechsler, 1999, Wechsler & Corporation, 1989). The presence of 47,XXX was confirmed with karyotype testing on all subjects. High resolution G-band karyotyping was performed on phytohemagglutinin-stimulated patient peripheral blood cultures. A minimum of 50 metaphases were analyzed, and 3 karyotypes per patient were produced (all karyotyping was performed by the Cytogenetics Laboratory, Department of Obstetrics and Gynecology, Georgetown University Hospital.) Subjects were included on the basis of a 47,XXX karyotype and not on the presence of specific clinical features. Developmental history of subjects with 47,XXX, including delayed milestones, language delay, or use of special education services, as well as presence of psychiatric syndromes, was assessed by a doctoral-level clinician through a semi-structured clinical interview with the participant and a parent. The Kiddie-Schedule for Affective Disorders and Schizophrenia (K-SADS) (Kaufman *et al.*, 1997) was used for participants younger than 18, and the Structured Clinical Interview for DSM—IV-TR Axis 1 Disorders Patient Edition (First, 2002) was completed for the five subjects who were over 18 years of age.

70 healthy females (46,XX; ranging in age from 5.2 to 25.4 years) matched in age to the 47,XXX participants were selected as controls from a population of healthy volunteers recruited from the community as previously described (Giedd *et al.*, 2007). Exclusion criteria included psychiatric diagnosis in the subject or a first-degree relative and head injury or other conditions that might have affected gross brain development.

Because healthy control participants were taking part in an ongoing longitudinal study of brain development, several different versions of the Wechsler IQ tests were used depending on the time of assessment. Fifty-four controls completed the WASI, three completed the WPPSI-III, and 13 completed a 2-subtest (vocabulary and block design) short form of one of the Wechsler scales, scored by using Sattler's technique (Sattler, 1992).

Handedness was assessed using the Physical And Neurological Examination for Soft Signs (PANESS) (Denckla, 1985). Socioeconomic status (SES) was measured using the Hollingshead scale (Hollingshead, 1975). Pubertal maturation was quantified using Tanner stages, as assessed by a questionnaire given to the participants or their parents (Petersen *et al.*, 1988). Height was adjusted for age and sex and reported as Z-scores, as was body mass

index. The norms for the 20-year-old group were used for the subjects between 21 and 25 years of age (Kuczmarski *et al.*, 2000).

We obtained verbal or written assent from the child and written consent from the parents for their participation in the study. The National Institute of Mental Health Institutional Review Board approved the protocol.

Statistical Analysis

The native MRI scans were registered into standardized stereotaxic space using a linear transformation (Collins *et al.*, 1994) and corrected for non-uniformity artifacts (Sled *et al.*, 1998). The registered and corrected volumes were segmented into white matter, gray matter, and CSF using a neural net classifier (Zijdenbos *et al.*, 2002). Region of interest analysis was performed by combining tissue classification information with a probabilistic atlas. Total cerebral volume included volumes of gray matter, white matter, and the lateral ventricles. We included brain volumes that have been validated by comparison with other methods: lateral ventricles, total gray and white matter volumes, frontal lobes, parietal lobes, and temporal lobes (Collins *et al.*, 1995). The laterality index was computed as the difference between the two hemispheres divided by their average. Cortical thickness was measured using the MNI CIVET image-processing software as previously described (Giedd *et al.*, 2007): in brief, white and gray matter surfaces were fitted using deformable models (Macdonald *et al.*, 2000), resulting in two surfaces with approximately 40,000 vertices per hemisphere; cortical thickness was defined as the distance between linked gray and white matter vertices. The thickness measurements are obtained in native space and blurred with a 30 mm surface based diffusion smoothing kernel (Chung *et al.*, 2003).

Demographic and IQ differences between groups were assessed with independent samples t-tests. Outlier analysis on morphometric data found no extreme outliers (defined as 3 or more SD from the mean). Two-tailed significance levels were employed at $p < 0.05$. In order to identify differences between groups in cortical thickness at each vertex, t-tests were utilized; multiple comparisons were controlled via the previously described False Discovery Rate (Genovese *et al.*, 2002, Giedd *et al.*, 2007).

Brain morphometric data were analyzed using ANOVA with diagnosis as the between-group factor, as well as ANCOVA adjusted for: (1) GW (total gray matter plus total white matter); and (2) GW and IQ. As overall brain volumes were expected to be smaller in the XXX group, analysis of data with and without adjustment for GW provide complementary measures: analysis without GW describes absolute differences, while analysis with adjustment indicates which areas are different once effects of global differences in brain volume are removed. Age was not included as a covariate because the samples were matched on an individual level by age. Analyses were performed with and without IQ as a covariate because groups were not matched on cognitive ability. The optimal control group for identifying brain differences associated with neurodevelopmental disorders that are associated with cognitive impairments is not straightforward: some studies emphasize using a functionally or cognitively matched control group, in order to attempt to control for effects of intellectual impairment, while others would argue that the cognitive impairment is part of

the genetic phenotype, and so a healthy control group is best. Since the IQ of participants with 47,XXX in our study was only slightly decreased and still fell within the normal range we felt a healthy control group was appropriate, but also reported results with IQ as a covariate as a method of describing what differences were present when IQ was included in the analysis.

In addition to demographic characteristics across the whole sample, we have provided demographic data separately for prenatally and postnatally diagnosed participants (see Table 1). As postnatally diagnosed subjects may have had genetic testing because of clinical concerns, they may be more likely to have impairments than the population of 47,XXX as a whole. The breakdown into participants diagnosed after birth and those diagnosed as part of prenatal screening was done to allow comparison of clinical characteristics between groups.

Results

Age distributions were closely matched (see Table 1 for demographic characteristics). The two groups also did not differ on SES, average Tanner stage, body mass index, or handedness (83% of both groups were right-handed). The ethnic composition of the 47,XXX group was 30 white, 3 Hispanic, 1 African-American, and 1 biracial. The ethnic composition of the control group was 65 white, 3 Hispanic, 1 African-American, and 1 biracial. Subjects under 13 years of age and those equal to or greater than 13 years were compared separately in order to assess differences before and after the pubertal growth spurt; the 47,XXX group was significantly taller in the older age range but not the younger.

Controls had higher Full-Scale IQs and Vocabulary and Block Design subtest scores than subjects with 47,XXX. However, it should be noted that the 47,XXX group's mean IQ is in the average range, and that the significant IQ difference between the 47,XXX and control groups is due largely to the high mean IQ of the control group (assuming population average IQ to be 100). Given that the exclusion criteria for controls in our study are stricter than those on which the IQ tests were normed, the higher than average mean for our control group is not unexpected.

Consistent with the extant literature (Bishop *et al.*, 2011, Leggett *et al.*, 2010, Otter *et al.*, 2010, Tennes *et al.*, 1975), parent report revealed that 83% of the subjects with 47,XXX in our sample had been diagnosed with speech and/or language delays. 51% reported delayed development of language, motor function, or both, and 77% had received some type of special education (see Table 2). Results of the KSADs semi-structured psychiatric interview revealed that the subjects with 47,XXX had high levels of several types of psychopathology, primarily Attention Deficit and Hyperactivity Disorder (ADHD), anxiety, and depression (see Table 3).

Table 4 provides details of group comparisons of brain volumes. Total gray and white matter (GW) was 8% smaller in the 47,XXX group. White matter volume was 8% smaller in the 47,XXX group, and gray matter volume was 7% smaller, while the lateral ventricles were 50% larger (see Figure 1). Without correction for IQ or GW, all regional volumes were significantly smaller in the 47,XXX group, with the exception of parietal gray matter, which

was not different. Laterality and the ratio of gray to white matter volumes were not significantly different.

After adjustment for GW, the frontal and temporal white matter reduction remained significant, as did the larger volumes of the lateral ventricles. Parietal gray matter was significantly larger in the 47,XXX than in the controls, while frontal and temporal gray matter volumes were not different.

Since IQ was different between the groups, we carried out an additional ANCOVA covarying for IQ, and for the regional volumes, covarying for both GW and IQ. GW remained significantly smaller in the 47,XXX group after covarying for IQ. Total gray matter, frontal, and temporal gray matter volumes were not different between the groups. Parietal gray matter remained significantly larger in the 47,XXX group. Lateral ventricle volumes remained larger in 47,XXX. All white matter volumes except parietal were also smaller in the 47,XXX group.

Figure 2 contains maps of cortical thickness at each surface vertex. The top panel shows regions in which the cortex is significantly thicker in the 47,XXX group, including the right inferomedial temporal lobe and bilateral medial frontal cortices. The second panel shows regions in which the cortex is thinner in the 47,XXX group, including regions in the lateral temporal lobes and left inferior frontal cortex. For comparison, the third panel shows regions in which the cortex is thinner in the 47,XXY male group.

Discussion

Despite the high incidence compared to many genetic disorders, 47,XXX is rarely recognized because the relatively subtle and nonspecific physical characteristics of the phenotype do not routinely prompt genetic testing (Otter *et al.*, 2010). Congenital abnormalities may include occasional mild clinodactyly, epicanthal folds, and increased interpupillary distance in some individuals. Increased growth spurt velocity between ages 4 and 8 results in height typically above the 75th percentile and increased leg length. Overall sexual maturation occurs normally and fertility is not impaired (Otter *et al.*, 2010, Tartaglia *et al.*, 2010, Tennes *et al.*, 1975). However, fine and gross motor development is frequently delayed, and poor coordination and fine motor skills may persist into adulthood. Cognitive and behavioral features can show more marked differences, suggesting that brain development may be more vulnerable to the effects of the additional chromosome.

We found that an additional X chromosome in female children and adolescents is associated with decreased brain volumes for both gray and white matter in all brain regions except the parietal lobe. While the smaller brain volume was consistent with our prediction and with previous studies, the more pronounced effects on white rather than gray matter were a novel finding. This, together with the previous reports of increased white matter hyperintensities associated with additional numbers of X chromosomes (Garcia-Cazorla *et al.*, 2004, Warwick *et al.*, 1999), suggests that further study of the effects of supernumerary X chromosomes on white matter development is needed.

The cortex showed areas of both increased and decreased thickness in 47,XXX. As predicted, thinner cortex was found in the lateral temporal lobes, possibly related to the language problems and auditory processing abnormalities frequently observed in 47,XXX (Leggett *et al.*, 2010). The finding of increased thickness in the medial temporal and medial prefrontal cortices was unexpected. The medial prefrontal cortex is an area that has been associated with social cognitive function (Adolphs, 2009, Blakemore, 2008). The region of increased thickness in the medial temporal lobe is in the vicinity of the amygdala, another region important for social cognition and also strongly linked to anxiety (Adolphs, 2009). These specific regions could be related to the often-present difficulties with social interactions and high levels of anxiety symptoms.

Comparison of the reported effects of an additional X chromosome in females with an additional X chromosome in males (47,XXY disorder, also known as Klinefelter's syndrome) (Klinefelter *et al.*, 1942) shows some intriguing similarities and discrepancies. Although the range of function can vary widely, the characteristic cognitive and behavioral pattern of 47,XXY, similarly to 47,XXX, includes slightly decreased IQ compared to matched controls or siblings, and increased rates of language difficulties, attention problems, poor self-esteem, and anxiety. In males, however, unlike females, an additional X chromosome also results in progressive degeneration of the testes, resulting in hypogonadism with accompanying decreased testosterone levels and infertility (Aksela *et al.*, 2006, Robinson *et al.*, 1990).

We previously characterized brain volumes and cortical thickness using the same methods in a sample of males with 47,XXY of approximately the same age range as the participants in the current study (Giedd *et al.*, 2007). Although the ability to draw firm conclusions is limited without direct comparison of data from the two groups, the similarity in methods prompts some observations. While brain volumes in the 47,XXY sample were also globally decreased, gray matter volumes were significantly smaller in the 47,XXY group, even after covarying for GW, unlike what we found in females with 47,XXX. This was reflected in more widespread regions of cortical thinning. These more pronounced gray matter deficits may be related to the effects of low testosterone levels on gray matter volumes. However, as seen in Figure 2, panel 3, the regions of cortical thinning in the females with 47,XXX are highly similar in location to those in the males with 47,XXY, despite the lack of testosterone effects in the female group. This raises the possibility that the location of these deficits may relate instead to the dosage effects of the X chromosome, consistent with the similar deficits in language and auditory processing seen in both groups. Parietal lobe volumes were also relatively spared in both groups, suggesting that the effects of the additional X chromosome are affecting brain structure at the level of lobar volume similarly. These results are consistent with recent findings of a study by Bishop *et al.* comparing effects of an additional X or Y chromosome in males and females, which found that an additional X chromosome conferred elevated risk for language impairments in either sex (Bishop *et al.*, 2011). A strength of this study was that subjects were all identified prenatally, decreasing the likelihood that subjects had been diagnosed postnatally due to language problems or other clinical features. Interestingly, this study reported that males with an additional X

chromosome were more likely to meet criteria for an autism spectrum disorder, while in females communication difficulties were not associated with other features of autism

This study adds to the scarce data from in-depth diagnostic interviews in children and adolescents with 47,XXX. We found that nearly half (40%) of the participants either had or currently met criteria for an anxiety disorder. Although the exact type of anxiety disorder varied, the most frequent diagnoses were Separation Anxiety and Social Phobia, with a common pattern of early Separation Anxiety disorder followed by persisting anxious traits, Social Phobia, and/or Generalized Anxiety Disorder. The second-most frequent diagnosis was Attention Deficit Disorder, affecting 17%; notably, all cases were of the Inattentive subtype. Depressive disorders began to appear in the adolescent group. These findings confirm previous reports suggesting anxiety and poor attention to be prominent in this cohort (Ottesen *et al.*, 2010). Given the frequency with which both inattentive ADHD and anxiety disorders are under diagnosed in children, these results would suggest vigilance in assessing their contribution to learning difficulties and overall functioning in this population is warranted.

Little is yet known about which genes on the X chromosome may be contributing to the dosage effects. Although approximately 85% of one X chromosome is randomly inactivated in each cell (Nguyen & Disteche, 2006), the potential for dosage effects remains because of the X chromosome genes that may escape inactivation. Most of these genes fall within the pseudoautosomal regions (PAR), areas at the tips of each X and Y chromosome containing homologous genes, which undergo recombination in a manner similar to autosomes. The number of genes escaping X-inactivation has been estimated at approximately 15% (Carrel & Willard, 2005), although a more recent analysis using next-generation sequencing found evidence of significantly more, also, predominantly located in the PAR regions (Zhang *et al.*, 2013). Among these were 22 that had been previously linked to intellectual disability syndromes (Gecz *et al.*, 2009), highlighting their role in brain development and possible relevance to the cognitive and behavioral phenotypes present in 47,XXX. Gecz *et al.* also found a high degree of individual variability in the degree to which genes escaped X-inactivation, which may help to explain the marked variation in clinical severity seen in this population.

One PAR gene escaping X-inactivation and thought to contribute to the clinical phenotype in both 47,XXX and 47,XXY is the SHOX gene, which was identified in Turner syndrome (45,XO) as the gene whose insufficiency resulted in the short stature characteristic of this condition (Clement-Jones *et al.*, 2000) and whose duplication is thought to be responsible for the characteristic increased height of 47,XXX and 47,XXY (Ottesen *et al.*, 2010). Genes coding for neuroligins are also found in the PAR region, and could be related to the social, cognitive, and language impairments frequently associated with a supernumerary sex chromosome (Bishop & Scerif, 2011). These genes, important for synaptic development, have been associated with neurodevelopmental disorders such as autism, which are also characterized by impaired social and language function (Jamain *et al.*, 2003).

Limitations of the present study include a possible ascertainment bias in this self-referred sample. However, clinical characteristics of this sample were similar to those from previous

large-scale prospective longitudinal studies. The structured psychiatric assessment used does not directly assess the presence of autism, limiting our ability to detect this clinical group, although no subjects presented with a history or previous diagnosis of autism. Another limitation of the current study is that validated measures of some brain characteristics that would be of interest are not provided by the automated image analysis method used here. Future studies using different image processing methods will be used to explore features such as amygdala volume or abnormalities in the development of white matter. Furthermore, given the suggestion reported here of convergent brain regions being affected in 47,XXX and 47,XXY syndromes, we plan studies explicitly designed to compare dosages of X and Y chromosomes across different sex chromosome disorders; for example see Raznahan et al., 2014.

In summary, a supernumerary X chromosome in females is a common but highly under-recognized genetic abnormality that has specific regional effects on brain development consistent with the behavioral and cognitive profile. While the associated physical phenotypic characteristics are typically mild, there is a stronger impact on cognitive and emotional capacities, consistent with the prominent role of genes on the X chromosome in neurodevelopment and cognitive function.

It should be emphasized, however, that as in other genetic conditions, the degree to which function is affected in females with an additional X chromosome varies widely, and the diagnosis of 47,XXX cannot be used in isolation to predict clinical outcome. However, early identification and better understanding of effects on brain structure and function may be helpful in guiding supportive interventions to improve quality of life for affected individuals.

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Abbreviations

SES	socioeconomic status
SCV	sex chromosome variations
GW	total gray matter plus total white matter

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Figure 1.

Scatterplot of total brain volume, gray matter, and white matter volumes for 35 47,XXX and 70 46,XX subjects.

Thicker cortex in XXX than XX females

T-statistic

Thinner cortex in XXX than XX females

T-statistic

Thinner cortex in XXY than XY males*

T-statistic

Figure 2.

Differences in cortical thickness associated with an additional X chromosome in females (panels 1 and 2) and males (panel 3). Colored regions are significantly different after FDR correction for multiple comparisons. *Adapted from Giedd et al., *Pediatrics* 2007.

Table 1

Demographics

	XXX (N=35)		XX (N=70)		F	P
	Mean (SD)	N	Mean (SD)	N		
Age (years)	11.4 (5.5)	35	11.5 (5.4)	70	0.0	.94
Height Z-scores	0.9 (1.0)	35	0.3 (0.9)	69	11.6	.001 ^a
Height age < 13y	0.7 (1.1)	25	0.2 (0.9)	48	3.7	.06
Height age 13y	1.4 (0.6)	10	0.3 (0.8)	21	16.6	<.001 ^a
BMI ^b Z-score	0.2 (1.0)	35	0.2 (1.0)	69	0.1	.82
Tanner stage	2.5 (1.5)	35	2.5 (1.5)	68	0.0	.96
SES ^c	40.9 (16.6)	34	43.7 (20.6)	70	0.5	.48
FSIQ ^d	93.7 (15.8)	35	109.5 (11.4)	70	34.3	<.001 ^a
Vocabulary	8.5 (3.7)	35	11.7 (2.6)	70	27.4	<.001 ^a
Block design	8.7 (3.1)	35	11.2 (2.8)	70	17.2	<.001 ^a

	Prenatal Dx XXX (N=25)		Postnatal Dx XXX (N=10)		F	P
	Mean (SD)	N	Mean (SD)	N		
Age (years)	9.7 (3.5)	25	15.6 (7.2)	10	10.6	.003 ^a
Height Z-score	0.7 (1.0)	25	1.4 (0.7)	10	3.9	.06
BMI ^b Z-score	0.2 (0.9)	25	0.2 (1.0)	10	0.0	.85
Tanner stage	2.1 (1.3)	25	3.5 (1.6)	10	7.3	.011 ^a
SES ^c	40.7 (17.1)	25	41.2 (15.9)	9	0.0	.94
FSIQ ^d	96.9 (12.9)	25	85.8 (20.0)	10	3.8	.06
Vocabulary	8.6 (3.4)	25	8.2 (4.6)	10	0.1	.80
Block design	9.3 (3.1)	25	7.1 (2.8)	10	3.9	.06

^a Statistically significant.

^b BMI=body mass index.

^c SES=socioeconomic status.

FSIQ=full scale IQ,
 p

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Table II

Clinical conditions for Trisomy X

Clinical conditions	Number endorsing	Comments
Problems with language or articulation	29 (83%)	Most frequently problems with articulation or expressive language
Difficulties with anxiety	29 (83%)	Most common reported problems were separation anxiety and social phobia
Received special education including special placement, occupational, physical, or speech therapy	27 (77%)	
Neurologic abnormalities	19 (54%)	Included low muscle tone, abnormal sensitivity to sensory input, poor balance or coordination
Delayed developmental milestones	18 (51%)	
Difficulties with attention or organization	16 (46%)	
Other medical conditions		
Respiratory	11 (31%)	(environmental allergies, asthma)
Constipation	9 (26%)	
Dental	6 (17%)	
Seizures	4 (11%)	
Premature ovarian failure	1 (3%)**	
This subject also had idiopathic thrombocytopenic purpura (ITP) and systemic lupus erythematosus (SLE)		

* Some subjects met criteria for multiple diagnoses

** This percentage is only relevant to this sample, and should not be taken as indicative of overall risk in 47,XXX.

Table III

Psychiatric Diagnoses for 35 subjects with Trisomy X.

K-SADS Diagnosis**	Met Criteria in past or present	Comment
Any anxiety Disorder	14 (40%)	
Social Phobia	6 (17%)	
Separation Anxiety Disorder	6 (17%)	
Avoidant Disorder	3 (9%)	
Simple phobia	2 (6%)	
Panic Disorder	2 (6%)	
Post-traumatic Stress Disorder	1 (3%)	
Generalized Anxiety Disorder	1 (3%)	
Attention-Deficit/Hyperactivity Disorder	6 (17%)	All inattentive subtype
Dysthymia	2 (6%)	
Major Depression	2 (6%)	One individual met criteria for Major Depressive Disorder, Psychotic Disorder, Obsessive Compulsive Disorder, and Anorexia Nervosa
Psychotic Disorder NOS	1 (3%)	
Obsessive Compulsive Disorder	1 (3%)	
Anorexia Nervosa	1 (3%)	
Vocal Tic Disorder	1 (3%)	

* Some subjects met criteria for multiple diagnoses.

** Structured Clinical Interview for DSM—IV-TR Axis 1 Disorders Patient Edition was completed for the 5 subjects who were over 18 years of age.

Table 1V
Regional XXX and XX Brain Volumes (in cc), Unadjusted and Adjusted for GW, GW and IQ

Brain Structure	XXX (N = 35)		XX (N = 70)		Covariates for GW				Covariates for GW & IQ			
	Mean (SD)	Mean (SD)	ANOVA	F	XXX	XX	EMM (SE)	ANCOVA	XXX	XX	EMM (SE)	ANCOVA
GM+WM (GW)	1170.4 (110.3)	1268.9 (101.8)	20.6	<.001 ^a					1197.9 (18.6) ^b	1255.2 (12.6) ^b	5.8	.018 ^a
Gray matter	756.1 (85.0)	816.3 (80.9)	12.5	<.001 ^a					779.0 (14.5) ^b	804.9 (9.8) ^b	1.9	.17
Frontal gray matter	206.7 (27.2)	225.6 (25.2)	12.4	.001 ^a	220.9 (2.3)	218.5 (1.6)		0.7	221.8 (2.4)	218.0 (1.6)	1.5	.23
Temporal gray matter	175.4 (18.1)	189.6 (18.9)	13.5	<.001 ^a	185.7 (1.6)	184.4 (1.1)		0.4	186.2 (1.7)	184.2 (1.1)	0.8	.37
Parietal gray matter	114.4 (16.7)	116.2 (15.4)	0.3	.59	122.3 (1.8)	112.3 (1.2)		20.5	122.8 (1.9)	112.0 (1.2)	20.4	<.001 ^a
White matter	414.4 (42.1)	452.6 (47.1)	16.4	<.001 ^a					418.9 (8.5) ^b	450.3 (5.7) ^b	8.3	.005 ^a
Frontal white matter	141.2 (15.0)	159.5 (17.0)	28.9	<.001 ^a	148.3 (2.1)	155.9 (1.5)		7.9	147.7 (2.3)	156.2 (1.5)	8.3	.005 ^a
Temporal white matter	79.3 (9.0)	88.2 (9.2)	22.3	<.001 ^a	82.9 (1.3)	86.3 (0.9)		4.6	82.5 (1.3)	86.5 (0.9)	5.3	.024 ^a
Parietal white matter	78.3 (8.8)	82.1 (9.3)	4.1	.046 ^a	82.4 (1.1)	80.0 (0.8)		2.8	81.9 (1.2)	80.3 (0.8)	1.1	.30
Lateral ventricles	13.2 (6.9)	8.8 (4.0)	16.9	<.001 ^a	13.8 (0.9)	8.5 (0.6)		21.8	13.6 (1.0)	8.6 (0.6)	16.2	<.001 ^a
Left hemisphere	461.4 (48.0)	491.9 (42.2)	11.2	.001 ^a					472.8 (7.9) ^b	486.2 (5.3) ^b	1.8	.19
Right hemisphere	456.9 (46.1)	487.5 (41.2)	11.9	.001 ^a					467.7 (7.6) ^b	482.1 (5.2) ^b	2.1	.15
Laterality	-.009 (.013)	-.009 (.010)	0.0	.84					-.011 (.002) ^b	-.008 (.001) ^b	0.7	.42
GW ratio	1.8 (0.2)	1.8 (0.2)	0.1	.74					1.9 (0.0) ^b	1.8 (0.0) ^b	1.6	.21

EMM indicates estimated marginal mean.

^a Statistically significant.

^b Covaried IQ only for GW, GM, WM, Left hemisphere, Right hemisphere, Laterality, and GW Ratio.