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Cortical anatomy in human X monosomy

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ABSTRACT

Turner syndrome (TS) is a model for X chromosome influences on neurodevelopment because it is most commonly caused by absence of one X chromosome and associated with altered brain structure and function. However, all prior *in vivo* magnetic resonance imaging studies of the brain in TS have either used manual approaches or voxel-based morphometry (VBM) to measure cortical volume (CV). These methods, unlike surface-based morphometry (SBM), cannot measure the two neurobiologically distinct determinants of CV– cortical thickness (CT) and surface area (SA) – which have differing genetic determinants and may be independently altered. Therefore, in 24 adults with X monosomy and 19 healthy female controls, we used SBM to compare (i) lobar CV, CT and SA; (ii) an index of hemispheric gyrification; (iii) CT throughout the cortical sheet; and (iv) CT correlation between cortical regions. Compared to controls, females with TS had (i) significantly increased CT and decreased SA in parietal and occipital lobes (resulting in no significant difference in lobar CV); (ii) reduced hemispheric gyrification bilaterally; (iii) foci of significantly increased CT involving inferior temporal, lateral occipital, intraparietal sulcus (IPS), cingulate and orbitofrontal cortices; and (iv) significantly reduced CT correlation between the left IPS and cortical regions including supramarginal and lateral occipital gyri. Our findings suggest that females with TS have complex, sometimes "opposing", abnormalities in SA/gyrification (decreased) and CT (increased), which can result in no overall detectable differences in CV. Thus, haploinsufficiency of X chromosome genes, may differentially impact the distinct mechanisms shaping SA (e.g. cortical folding) and CT (e.g. dendritic arborization/pruning). CT disruptions are maximal within and between cortical regions previously implicated in the TS cognitive phenotype.

Introduction

Turner syndrome (TS) is a neurogenetic syndrome seen in approximately 1/2000 live female births (Stochholm et al., 2006). Turner syndrome arises due to partial or complete absence of one X chromosome, with the most common karyotype being X monosomy [45,XO]. Since, in karyotypically normal [46,XX] females, almost all of one of the X chromosomes in each cell is randomly "silenced" through an epigenetic process known as Lyonization (Lyon, 1961), the TS phenotype may be due to haploinsufficiency of those X chromosome genes that escape inactivation (Zinn and Ross, 1998). Effective X-linked gene haploinsufficiency in TS is also influenced by the "parent of origin" of the intact X chromosome, as the expression of some X chromosome genes differs systematically depending on which parent the chromosome is inherited from through a process known as imprinting (Barlow, 1995). X chromosome haploinsufficiency in TS is also associated with ovarian failure and related estrogen and androgen deficiency, which may in themselves contribute to the TS phenotype.

Compared to the TS physical phenotype (Ogata and Matsuo, 1995), the behavioral–cognitive and neuroanatomical phenotypes remain less well described. A better understanding of how brain and behavior are altered in TS could shed light on how X-linked genetic and epigenetic influence human neurodevelopment.

Females with TS typically show an uneven cognitive profile with pronounced deficits in visuo-spatial skills alongside verbal abilities within the normal range. Deficits are best documented for tasks involving mental rotation, visual construction and number manipulation. There are also reports of deficits in other domains such as

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Table 1
Magnetic resonance imaging studies in Turner syndrome.

Author (year)	Sample details				Method/measure	Findings	
	Turner syndrome (TS)		Controls			TS<C	TS>C
	Number (XO/other)	Mean age, year (SD/range)	Number	Mean age, year (SD/range)			
Murphy et al. (1993)	18 (9/9)	30 (7/–)	19	30(7/–)	Manual	BIL hippocampus, caudate, lenticular nucleus, thalamus, parieto-occipital lobes	–
Reiss et al. (1995)	30(27/3)	10(3/6–17)	30	10(3/6–17)	Semi-automated/"lobar" volumes	BIL "parietal region" combined grey and white matter volumes	R "pareito-occipital region" combined grey and white matter volumes
Brown et al. (2002)	26(26/–)	13(–/8–17)	26	13(–/9–17)	Semi-automated/lobar volumes	BIL parietal grey matter, BIL occipital white matter volumes	BIL cerebellar grey matter volumes
Fryer et al. (2003)	27(27/–)	13(4/7–20)	27	13(4/7–20)	Semi-automated mid-sagittal area	Genu of corpus callosum, pons, cerebellar vermis lobules VI-VII	–
Good et al. (2003)	21(21/–)	25(9/–)	17	25(9/–)	VBM	–	BIL amygdala and orbitofrontal cortex grey matter volume
Molko et al. (2003)	14(10/4)	25(6/18–36)	14	24(–/20–27)	Automated sulcal morphometry VBM	Maximal depth R intraparietal sulcus GREY: L primary motor cortex, R intraparietal sulcus CV.	– GREY: L parieto-occipital region, R primary motor cortex CV
Kesler et al. (2004)	30(30/–)	15(6/7–33)	29	15(6/6–32)	Manual—amygdala and hippocampus only	R hippocampal grey and R hippocampal white matter	L amygdalar grey
Molko et al. (2004)	14 (10/4)	25(6/18–36)	14	24(–/20–27)	Automated sulcal morphometry VBM	Length and depth BIL superior temporal sulcus Grey: CV in BIL anterior cingulate, lingual and orbitofrontal. R insula, postcentral gyrus, intraparietal sulcus, supramarginal gyrus L postcentral and superior temporal White: adjacent to R head of caudate, postcentral sulcus, body of caudate and supramarginal gyrus. Adjacent to L superior temporal sulcus, lingual gyrus, head of caudate, occipito-parietal junction, body of caudate	– Grey: BIL orbitofrontal, lingual, temporal pole CV and caudate grey matter. R postcentral and fusiform CV White: adjacent to R anterior cingulate and intraparietal sulcus. R external capsule and body of corpus callosum. Adjacent to L anterior cingulate, superior temporal gyrus and body of corpus callosum.
Rae et al. (2004)	9(9/–)	27(8/–)	20	27(7/–)	Manual—temporal lobe	–	CV in BIL superior temporal sulcus, middle temporal gyrus
Cutter et al. (2006)	27(27/–)	27(8/–)	21	27(7/–)	Manual region of interest	BIL parieto-occipital lobes combined (grey and white) matter, R hippocampus and caudate volumes	Total cerebellar volume
					VBM	Grey: BIL parieto-occipital, inferior temporal, caudate and thalamus volumes. L prefrontal CV. White: R occipital, superior parietal, external capsule, body of corpus callosum and cerebellum. L occipito-frontal fasciculus.	Grey: BIL cerebellar and anterior putamen grey matter volumes. White: BIL middle temporal, orbitofrontal, genu of corpus callosum. R precentral and centrum semi-ovale
Holzapfel et al. (2006)	10 (10/–)	16(5/7–24)	10	15(5/7–24)	VBM of white matter only	White: BIL internal capsule, L superior temporal gyrus, superior frontal gyrus, inferior and middle temporal gyri, inferior parietal lobule and temporoparietal junction	–

Abbreviations: TS, Turner syndrome; C, controls; BIL, bilateral; L, left; R, right; CV, cortical volume.
Summary of all structural magnetic resonance imaging studies comparing cortical anatomy between turner syndrome and typically developing controls that were available at the time of publication.