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Automated morphometric study of brain variation in XXY males

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This paper studies brain morphometry variation associated with XXY males (Klinefelter's syndrome) by using an automated whole-brain volumetric analysis method. The application to 34 XXY males and 62 normal male controls reveals pronounced volume reduction in the brains of XXY males, relative to the brains of normal controls, localized at the insula, temporal gyri, amygdala, hippocampus, cingulate, and occipital gyri. Most of these statistically significant regions are in the gray matter structures, with the exception of one cluster of atrophy involved in white matter structure, i.e., right parietal lobe white matter. Compared to previous findings documented in the literature, our findings provide a better spatial localization of the affected regions. In addition to the reduction of local volume, overall enlargement of ventricles and overall volume reduction of both white matter and gray matter are also found in XXY males.

Keywords: XXY brain; 47,XXY brain; Sex chromosome aneuploidy; Klinefelter's syndrome; Morphometric study; Volumetric analysis

Introduction

XXY chromosome arrangement, instead of the usual male arrangement (XY), appears to be one of the most common genetic abnormalities known, occurring in an estimated 1:600 live male births (Patwardhan et al., 2000). The presence of an extra X chromosome is often related to atypical physical, cognitive, and behavioral features (Patwardhan et al., 2002). In particular, XXY males are more likely than other males to be overweight and lack physical coordination, and also tend to be taller than their fathers and brothers (Robert, 1993). XXY males are usually at risk of developmental delay, including language and learning impairment (Graham et al., 1988). For example, most XXY males perform normally on tests of nonverbal abilities and general intelligence, but are often impaired on measures of language skills. Studies also show that XXY males have passive personalities and are less assertive, social, and active than euploid males (Theilgaard, 1984). Additionally, XXY males have higher rates of mental illness than that observed in the general population (Warwick et al., 2003).

Many neuroimaging studies have investigated the differences between XXY brains and normal control brains, by comparing whole brain and regional brain volumes (Patwardhan et al., 2000, 2002; Warwick et al., 1999). Different studies found different alterations in brain morphology. In one study, Patwardhan et al. (2000) reported no significant difference in whole brain volume; however, significant decreases in left temporal lobe and right and left superior temporal gyri were found. In another study, Patwardhan et al. (2002) reported no significant decrease in whole brain volume and in hippocampus; however, a significant decrease was found in amygdala. Warwick et al. (1999) found a significant decrease in whole brain volume and enlarged ventricles. Giedd et al. (unpublished data) found larger lateral ventricle volume and smaller total cerebral volume (TCV). Also, except for parietal white matter, all regional volumes were significantly smaller in the XXY brains. When adjusted for the TCV difference, frontal and temporal gray matter remained significantly smaller in the XXY brains.

Most previous volumetric analysis methods rely on the manual delineation of regions of interest (ROIs), followed by statistical analysis of the volumes of those ROIs. These methods suffer from many well-known drawbacks, including high demand for human effort, which limits the number of subjects and ROIs to be examined, subjectivity and lack of reproducibility, and the need for a priori knowledge of ROIs. The latter is an important limitation, because it is often not possible to know in advance which regions might be affected by a disease or might differ between two groups. Even if the approximate regions were known, the ROIs are likely to include other surrounding regions, thereby confounding the results and reducing statistical power.

The purpose of this paper is to describe an automated method for voxel/regional parcellation and volumetric analysis. Automated methods are able to validate hypotheses, as well as generate new hypotheses on regional dysfunction in the brains of XXY males. This is a significant advantage of automated volumetric analysis methods, compared to manual delineation methods. However, if automated methods are not sufficiently accurate, they will create spatial normalization errors that wash out the actual regional

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differences between the two groups. We have previously developed a relatively accurate spatial normalization approach, called Hierarchical Attribute Matching Mechanism for Elastic Registration (HAMMER) (Shen and Davatzikos, 2002, 2003), and have validated it on various brain structures such as the hippocampus, precentral gyrus, superior temporal gyrus, and ventricles. This fully automated spatial normalization approach, along with tissue mass-preserving deformation (Goldszal et al., 1998, 2001), is employed in this paper for volumetric analysis of XXY brains.

Materials and methods

Subjects

Totally 34 XXY males and 62 normal controls were used in our study.

The XXY group consisted of 34 XXY males ranging in age from 5.3 to 19.2 years (Table 1). Thirty-two were nonmosaic XXY; one was XXY/XY mosaic (24% XXY/76% XY); and one had a translocation of the Y-chromosome to the short arm of one of the two X chromosomes. Of the 18 XXY boys age 13 and over, 10 were undergoing testosterone replacement therapy (TRT) and 8 were not. None of the 16 XXY boys age 12 and younger was undergoing TRT.

The ethnic composition of this group was 32 White; 1 African-American; and 1 Hispanic. They were recruited nationwide with the help of two Klinefelter Syndrome support groups: The American Association for Klinefelter Syndrome Information and Support (AAKSIS) and Klinefelter Syndrome and Associates (KS&A). Parents of XXY boys initially were interviewed by phone and asked to report their child's health, developmental, and educational history. Children with head injuries or other conditions that might have affected brain development were not accepted into the study. During their visit to the NIH, they underwent a physical and neurological assessment.

A total of 62 normal XY male controls ranging in age from 5.3 to 20.8 were recruited from the community through the National Institutes of Health Normal Volunteer Office, newspaper advertisements and outreach to Washington, DC, area schools. The ethnic composition of this group of normal control boys was 58 White, 2 African American, and 2 African American and White.

Normal controls were screened via an initial telephone interview and parent and teacher rating scales (Achenbach and Ruffle, 2000), and underwent a physical and neurological assessment. Those with a suspected psychiatric diagnosis, first-degree relatives with psychiatric diagnoses, head injury, or any conditions that might have affected brain development were not accepted into the study.

Because braces have been found to cause distortions in MRI images, all parents whose children had braces on their teeth were asked to delay their visit until their children's braces were removed.

Table 1
XXY and normal control (NC) demographics

	XXY	NC	*P*
Age	12.60 ± 4.30	12.90 ± 4.30	0.72
Height	62.50 ± 10.1 in.	61.90 ± 8.90 in.	0.78
Weight	123.1 ± 62.6 lbs.	113.9 ± 42.8 lbs.	0.45
SES	51.00 ± 24.1	38.90 ± 21.3	0.02

The differences between the XXY boys and normal control boys on age, height, and weight were nonsignificant (Table 1). Control families had a somewhat higher mean socioeconomic status than the families of XXY boys (Hollinshead and Redlich, 1999; a lower Hollingshead score indicates higher SES).

Image acquisition

All subjects were studied on the same 1.5-T GE Signa scanner, with GE Head coil. T_1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained using three-dimensional spoiled gradient recalled echo in the steady state. Imaging parameters were echo time 5 ms, repetition time 24 ms, flip angle 45°, acquisition matrix 256 × 192, number of excitations = 1, and 24 cm field of view.

Image processing and analysis protocol

MR images of brains were analyzed by a voxel-based morphometric protocol that consisted of five continuous steps: removal of nonbrain voxels (Goldszal et al., 1998; Shen and Davatzikos, 2002, 2003), tissue segmentation (Pham and Prince, 1999), spatial normalization to a standardized template (Shen and Davatzikos, 2002, 2003), generation of a mass-preserving tissue density map for each tissue type (Davatzikos et al., 2001; Goldszal et al., 1998; Shen and Davatzikos, 2002), and voxel-wise statistical analysis (*t*-maps) of tissue density maps (Friston et al., 1995). These five steps are detailed next.

Nonbrain voxels of an individual MR image were removed via an automated skull-stripping method that elastically warps a mask of the template brain to the individual and therefore removes the nonbrain voxels in the individual brain volume (Shen and Davatzikos, 2002, 2003). Cerebrospinal fluid around the brain volume was kept in the final skull-stripping results to make sure that no brain tissue was removed. Then, brain voxels were segmented into gray matter (GM), white matter (WM), or cerebrospinal fluid (CSF), by a fuzzy segmentation method (Pham and Prince, 1999), which simultaneously corrected for inhomogeneities in the image.

Tissue-segmented images were transferred to a standardized stereotaxic space for group analysis, using a high-dimensional spatial normalization process (Shen and Davatzikos, 2002, 2003). Importantly, this step of spatial normalization accounts for inter-individual morphological variability and allows the direct superposition and comparison of images from a large group of individuals voxel by voxel in the stereotaxic space, thereby enabling image statistics calculation. Many methods determine the high-dimensional spatial deformation field by attempting to match the intensities of the warped image with those of the target image. While these approaches are attractive because of their fairly straightforward implementation, they do not guarantee that anatomically meaningful matches are generated, as similarity in image intensities does not necessarily imply anatomical correspondence. We have developed a spatial transformation approach, called HAMMER, which partly overcomes the limitations of several existing spatial normalization methods and has been extensively validated on many brain structures (Shen and Davatzikos, 2003).

Spatial normalization changes the anatomy to be measured, in an effort to place this anatomy into a standardized stereotaxic space. To account for such anatomical changes, a mass-preserving tissue density map was generated for each tissue type, to ensure

that no local volumetric information is lost during the warping procedure (Davatzikos et al., 2001; Goldszal et al., 1998; Shen and Davatzikos, 2003). Specifically, three tissue density maps were generated, one for each tissue type, via mass-preserving transformations. If the warping transformation locally applied contraction to an individual's brain image to bring it into conformation with the template's brain, the local tissue density was increased accordingly, so that the total amount of tissue locally remains unchanged. This procedure guarantees that the total amount of tissue is identical in any structure or substructure of an individual's brain before and after spatial normalization. Spatial normalization fields provided by an extensively validated HAMMER warping approach (Shen and Davatzikos, 2002, 2003) are directly used here to create tissue density maps. Because the tissue density maps are spatially co-registered, local differences or changes in volume can be directly quantified by respective changes in the resulting tissue density maps. In Davatzikos et al. (2001) and Goldszal et al. (1998), we called this approach Regional Analysis of Volumes Examined in Normalized Space (RAVENS). Using this approach, a total of three tissue density maps are created, corresponding to WM, GM, and CSF, respectively.

Group differences between the spatially normalized tissue density maps of XXY males and normal controls were statistically measured by voxel-wise t tests provided by the widely used statistical parametric mapping (SPM) software (Friston et al., 1995), after spatial smoothing with a customary Gaussian filter of full-width-half-maximum equal to 10 mm. Correction for multiple comparisons was performed by the methods embedded in the SPM software. This step of statistical analysis was performed for WM, GM, and CSF density maps, respectively. Finally, the clusters with the corrected P values exceeding a significance threshold in each tissue density map are reported in this paper.

Results

Performance of HAMMER-based spatial normalization approach

To visually evaluate the accuracy of this image warping approach, an average of 96 spatially normalized images, analyzed in this paper, was formed and compared with the template in three cross-sectional views (Fig. 1). It is worth noting that this average of the images is still very clear, because the individual brains have been accurately co-registered. To further demonstrate the registration accuracy, we can also calculate a variance map for each tissue, after spatial normalization of 96 tissue-segmented brains. For convenience, only a WM variance map is color-coded and provided in Fig. 1c, which shows the high overlay of WM labels after spatial normalization, as red represents 100% overlay. The color-coded quantity is computed for each voxel, and it is the percentage of voxels (across 96 subjects) that have the same WM label. This experiment indicates the accuracy of the HAMMER image warping approach, which is directly related to the accuracy of the regional volumetric measurements.

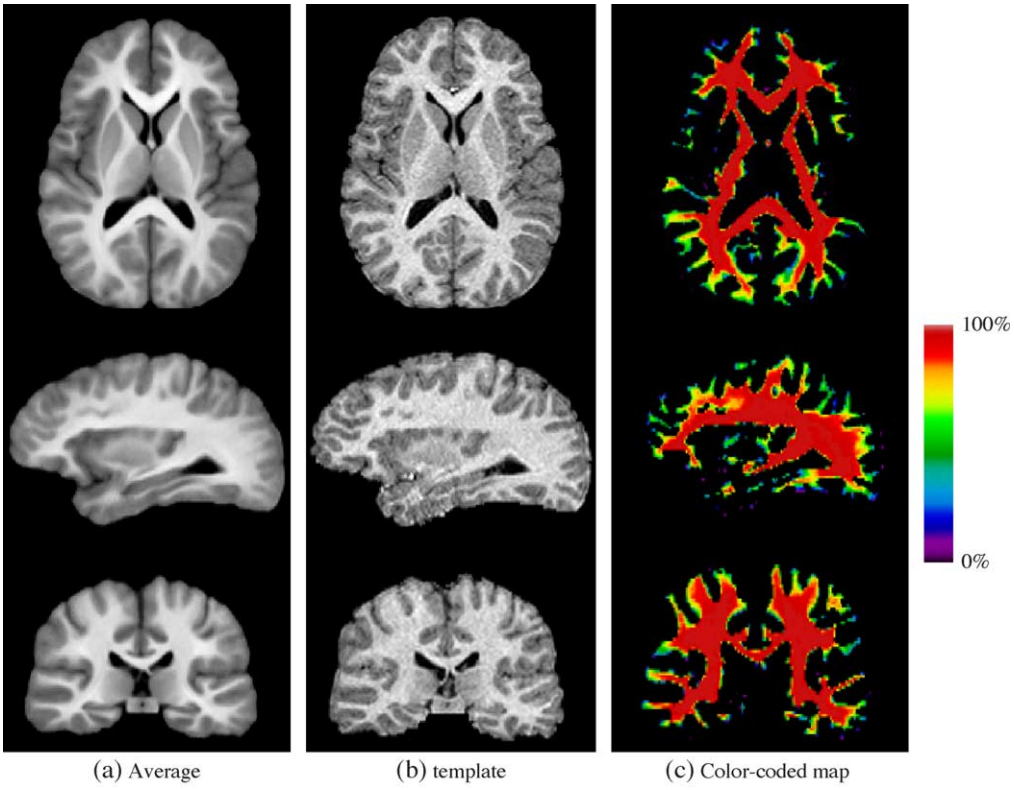

Fig. 1. Average of 96 spatially normalized subjects in (a), compared to the template in (b). The clarity of the average reflects a high accuracy of the underlying image warping approach, and therefore of our morphological measurements. A color-coded WM variance map of 96 spatially normalized subjects is also provided in (c), to further demonstrate the accuracy of our registration algorithm. The color-coded quantity is computed for each voxel, and it is the percentage of voxels (across 96 subjects) that have the same WM label. Red represents 100% overlay, according to the color bar on the right.

Global group differences

Global group differences between XXY and normal control brains were obtained by statistically comparing the total brain tissue volumes of GM, WM, and ventricular CSF, which were computed by counting the number of voxels with same labels after tissue segmentation. The average global volumes and standard deviations of GM, WM, and ventricular CSF are 535 ± 49.6, 322 ± 52.2, and 9.67 ± 4.76, respectively, for normal controls; 493 ± 39.5, 298 ± 50.8, and 13.8 ± 10.0, respectively, for XXY brains. The unit is cm^3. GM and WM volumes in normal controls were, respectively, 8.52% and 8.05% larger than those in the XXY group. In contrast, ventricular CSF volume in the XXY group was about 42.7% larger.

Local group differences

Statistical comparison of three types of tissue density maps between normal control group and XXY group reveals some pronounced and fairly localized group differences, with the XXY group displaying relative atrophy with respect to normal controls. In particular, the main group differences, represented as local volume reduction in XXY group, are localized in insula, temporal gyri, amygdala, hippocampus, cingulate, and occipital gyri. The left hemisphere contains more localized clusters of volumetric differences, compared to the right hemisphere. Moreover, most of the statistically significant clusters were localized in GM structures, with only one cluster localized in the WM structure, i.e., right parietal lobe WM. Additionally, no region of significant volume increase was found in XXY group. Our significance level was $P < 0.005$ after correction for multiple comparisons.

Table 2 lists all regions of localized clusters with significant group differences, and their P values after correction for multiple comparisons. Fig. 2 visually shows the color-coded t maps on several representative regions with statistically significant group differences ($P < 0.005$). The t maps are color-coded according to the values of the t statistic, after SPM's correction for multiple comparisons. The underlying image is the template that we used for spatial normalization of XXY and normal control brains.

Table 2
Summary of the clusters with significant group differences, obtained by voxel-wise statistical analysis of the tissue density maps of XXY brains and normal control brains

Tissue	Cluster		Corrected P value
GM	Temporal lobe	insula, left	0.0034
		superior temporal gyrus, left	0.0007
		superior temporal gyrus, right	0.0009
		inferior temporal gyrus, left	0.0029
		middle temporal gyrus, left	0.0031
		medial occipitotemporal gyrus, right	0.0040
		lateral occipitotemporal gyrus, left	0.0006
	Limbic system	amygdala, right	0.0035
		cingulate region	0.0009
		hippocampal formation, left	0.0018
	Occipital gyri	middle occipital gyrus, left	0.0044
		superior occipital gyrus, right	0.0044
WM	Parietal lobe	parietal lobe WM, right	0.0035

In each tissue density map, the clusters with the corrected P values exceeding a significance threshold (0.005) are listed.

Discussion

An automated morphometric whole-brain study has shown pronounced and localized group differences between XXY and normal control brains. The clusters of significant atrophy are localized in the regions of insula, temporal gyri, amygdala, hippocampus, cingulate, occipital gyri, and parietal lobe WM. Abnormalities of these structures in XXY brains are potentially linked to deficits known in XXY children, which typically includes verbal and language abilities (insula, temporal gyri), memorization, and regulation of emotional behavior (medial limbic system: amygdala, hippocampus, and cingulate), and spatial perception (visual system: occipital gyri, occipitotemporal gyri, and parietal lobe WM).

Some of our findings are consistent with previous findings documented in the literature (Patwardhan et al., 2000, 2002), while others are different from previous findings. For example, there are no significant decreases in whole brain volume and hippocampal volume found in Patwardhan et al. (2002). This is probably due to the use of different data sets and also very different image analysis protocols. Our spatial normalization algorithm has been extensively validated on various structures such as hippocampus, ventricle, precentral gyrus, and superior temporal gyrus (Shen and Davatzikos, 2003). It is reasonably accurate in spatially normalizing brain images, thereby potentially enabling the detection of localized group differences between XXY and normal control brains.

Firstly, a set of foci of atrophy were in areas involving verbal and language processing, i.e., in the prominent clusters of left insula, left/right superior temporal gyri, left middle/inferior temporal gyri, and left-lateral/right-medial occipitotemporal gyri. The insula are believed to be involved in the limbic belt and body sense; but lesion studies and functional imaging have suggested a broad range of roles, ranging from *speech* to attention, gestation, and visceral control (Wise et al., 1999). Part of the superior temporal gyrus is part of the Wernicke language area. Temporal association cortex, including middle and inferior temporal gyri in the inferior aspect, seems especially concerned with memory in relation with the mechanism of language (memory of names of persons, places, etc.) (Henri et al, 1999). Therefore, our finding of atrophy in these areas is consistent with the previous finding of written and spoken language impairment in most XXY males (Graham et al., 1988). In particular, a volume reduction in left temporal lobe gray matter has been reported (Patwardhan et al., 2000) using manual delineation of ROIs in XXY MR brains, and we replicated this finding in our study. In addition, our study provides a better spatial localization of this atrophy, due to its voxel-based nature.

Secondly, a set of foci of atrophy were involved in the limbic system, i.e., right amygdala, left hippocampus, and cingulate region. The involvement of this system in XXY brains agrees with the previous finding of the abnormalities of mood and behavior in XXY males (Bender et al., 1995; Mandoki et al., 1991; Walzer et al., 1991), since one of limbic system's main roles is the control of behavior and the memorization and regulation of emotional behavior. This finding has been replicated in several studies. For example, the behavioral studies have shown an increased incidence of psychiatric disorders in XXY males, including anxiety, depression, and conduct disorder (Bender et al., 1995; Mandoki et al., 1991), although in most cases these disorders are relatively mild in severity. Also, attention and impulse control difficulties were noted in XXY males (Walzer et al., 1991).

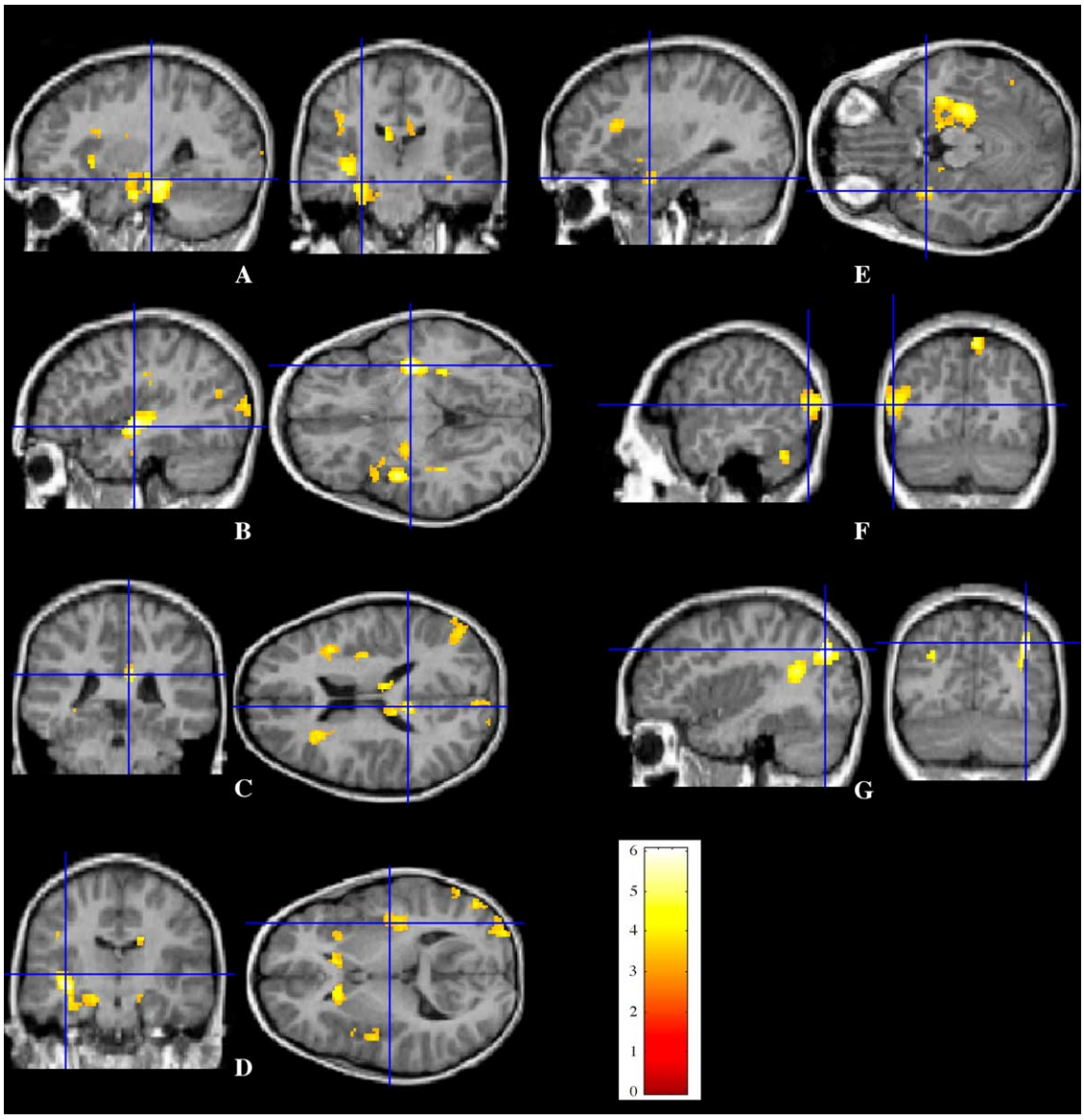

Fig. 2. Visual summary of several detected regions with significant group differences between XXY brains and normal control brains. The underlying image is the template that we used to normalize individual brains. Color-coding was based on the values of the t statistic. Only the voxels with significant group differences, i.e., the corrected P values exceeding a significance threshold 0.005, are shown. (A) Left hippocampal formation. (B) Left superior temporal gyrus. (C) Cingulate region. (D) Left Insula. (E) Right amygdala. (F) Left middle temporal gyri. (G) Right parietal lobe WM.

Thirdly, a set of foci of atrophy were found in visual association cortex of the occipital lobe, such as left middle occipital gyrus and right superior occipital gyrus, and in parietal association cortex of the parietal lobe, such as right parietal lobe WM. The superior visual system in the visual association cortex is involved in spatial perception such as localization and movements of an object, while the inferior visual system in the visual association cortex along with temporal association cortex (such as occipitotemporal gyri where we did find atrophy) is involved in visual localization of objects and color perception. Similarly, the parietal association cortex also involves functions of spatial perception, spatial memory, and spatial localization. Atrophy in these regions is likely to underlie the spatial processing impairment in XXY males.

Fourthly, average WM and GM volumes in normal control brains are more than 8.0% larger than those in XXY brains. In contrast, the average ventricular CSF volume in XXY brains is 42.7% larger than that in normal control brains. This agrees with the findings documented in J. Giedd's unpublished data. Additionally, the left hemisphere has a greater number of clusters of atrophy, compared to the right hemisphere. This implies that the left hemisphere is significantly affected due to the presence of an extra X chromosome in XXY males.

Finally, most of the statistically significant atrophy regions were localized in the GM structures, and only one was localized in the WM of the right parietal lobe although a relatively large WM volume reduction has been found in XXY brains. The different findings regarding GM and WM atrophy might reflect an underlying difference in the way that neuronal bodies and axonal connections are affected by the disease. Also, it might be due to the limitations of standard T_1-weighted MRI to resolve

white matter structures. Future studies using diffusion tensor imaging will be able to resolve white matter anatomy in greater detail.

The results obtained from any voxel-based analysis methods, including our method, should be carefully interpreted. A negative result does not imply an absence of atrophy in the respective regions. This is because the statistical significance of group differences is dependent not only on true group differences, but also on spatial image normalization that brings the individual images to the template. Any errors in the spatial normalization will unquestionably lower the level of true group difference, thereby affecting the final detection of atrophy. Notably, spatial normalization accuracy is usually inversely proportional to the variability of the underlying regions. Therefore, our ability to detect group differences will be reduced to a greater extent in a more highly variable region than in a less variable region. Notably, the result of spatial normalization will be affected by errors in skull stripping and fuzzy segmentation, which are the two preprocessing stages for spatial normalization. Therefore, how those errors in preprocessing stages affect the final stage of spatial normalization should be studied. Future work in our laboratory involves a better understanding and quantification of spatial normalization errors as a function of spatial locations in the brain, which is important for better interpreting the findings. Also, we will investigate a correlation of particular atrophic areas to behavioral alterations or deficits attributed to those areas, such as atrophy of superior temporal gyrus correlating to language comprehension.

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