MRI of Prepubertal Boys with Klinefelter Syndrom: A Voxel-based Morphometric Study

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Introduction: Klinefelter Syndrome (KS), characterized by the abnormal karyotype 47,XXY, is a relatively common (1/500 males) but very much understudied genetic disorder that serves as a homogeneous model for studying both androgen deficiency and learning disability in childhood. The KS phenotype is distinguished by testicular failure and childhood androgen deficiency [1]. The KS neurocognitive phenotype includes impaired motor function, language-based learning difficulties, and attention/working memory deficits [2]. The purpose of this study was to investigate the structural brain differences between boys with KS (8-12 years) and age-matched control boys in order to obtain insight of the underlying neuroanatomy of the KS cognitive phenotype. We hypothesize that boys with KS have smaller brain volumes in regions related to language, sensorimotor function and memory retrieval/working memory.

Method: Participating subjects included 16 boys with KS and 12 age- and socioeconomic status-matched normal boys. All were prepubertal. MR data were acquired using a Philips 3.0T whole-body clinical MRI system and a 8-channel SENSE head coil. Conventional high resolution anatomical images were acquired using a three-dimensional (3D) T1-weighted (T1WI) fast gradient echo sequence (TR/TE/α = 25ms/2.1ms/30^o, 1mm^3 isotropic voxels, 160 contiguous 1-mm slices (AC-PC aligned), acquisition time 6 min 9 seconds). The 3D T1WI datasets were analyzed using a robust automatic voxel-based morphometry (VBM) technique which combines a fully automated spatial normalization approach, dubbed HAMMER (Hierarchical Attribute Matching Mechanism for Elastic Registration) [3], in conjunction with a tissue mass preserving framework called RAVENS (Regional Analysis of Volumes Examined in Normalized Space) [4]. Six consecutive steps were carried out: removal of non-brain voxels, tissue segmentation, spatial normalization to a standardized template, generation of a mass-preserving tissue density map (i.e. RAVENS map) for each tissue type, measurements of brain structures' volumes, and voxel-wise statistical analysis (t-map) of tissue density maps.

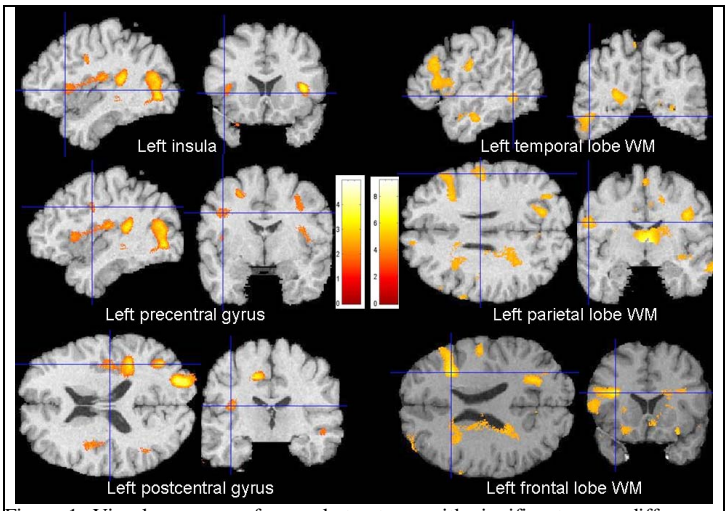

Figure 1: Visual summary of several structures with significant group differences between the KS and control groups (control > KS). The detected clusters have higher densities in the RAVENS maps in the control group, indicating that the underlying structures have larger volumes in the controls. Detection of group difference was based on the RAVENS maps of the KS and control groups that were compared pixel-by-pixel using SPM, after applying a Gaussian filter of a kernel size of 10mm to smooth the maps. Only the voxels with significant group differences, i.e., the corrected P-values exceeding a significance threshold 0.001 (WM) or 0.05 (GM), are shown. WM= white matter, GM = gray matter.

Results: Figure 1 and Table 1 summarize brain regions with significantly different regional brain volumes in KS compared to controls. Reduced brain volumes were found in the KS group relative to control boys (after correcting for total brain volume), for both gray matter and white matter regions.

Discussion and Conclusions: Related to our hypothesis, the left insula, frontal lobe WM, temporal lobe WM, and parietal lobe WM, [language function], the bilateral anterior limb of the internal capsule (ALIC), globus pallidus, pre and post-central gyri and corpus callusum [for bimanual motor function], and the left hippocampus and orbital-frontal gyrus [memory function] showed reduced volumes in the KS compared to the control group. Compared with most previous morphometric analysis methods that rely on manual segmentation of the structures of interest, thus suffer from subjectivity, low efficiency and reproducibility, the automated VBM method used in this study represents a powerful approach for quantitative measurement of regional volume differences between the KS and normal boys.

Table 1: Summary of structures with significant groups differences between KS and controls.

	KS (n=16)		Control (n=12)		P-value*
	Mean	SD	Mean	SD	
Age (years)	10.0	1.6	10.4	0.9	0.19
Socioeconomic status	50	13	58	7	0.08
GRAY MATTER (volume, mm^3)					
left insula	7446	1165	8653	1144	0.01
left hippocampal formation	3538	549	4113	704	0.02
left precentral gyrus	15030	1760	20222	5782	0.002
right precentral gyrus	17302	1979	22095	5462	0.003
left post central gyrus	15851	3187	19682	3111	0.004
right post central gyrus	11228	2242	12101	1467	0.25
left globus pallidus	1277	223	1541	305	0.01
right globus pallidus	1334	219	1665	258	0.01
left fronto-orbital gyrus	2805	434	3354	614	0.01
WHITE MATTER (volume, mm^3)					
left frontal lobe	106000	14121	121727	9484	0.003
left parietal lobe	42614	7157	51571	6285	0.002
left temporal lobe	521445	7839	61537	7361	0.003
left anterior limb of internal capsule	4261	895	6263	846	0.001
right anterior limb of internal capsule	3415	506	4349	669	0.001
corpus callosum	10141	1144	11640	2052	0.02

* t-test, comparing group means of KS and controls

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