White Matter and Cortical Abnormalities in Williams Syndrome Detected by Diffusion Tensor Imaging.

A. V. Faria[1,2], B. Landau[1], K. O'Hearn[1], J. Zhang[1], K. Oishi[1], X. Li[1], H. Jiang[1], K. Akhter[1], K. Sakai[1,3], P. van Zijl[1,4], S. Mori[1], and M. I. Miller[5]

[1]Johns Hopkins Medical Institutes, Baltimore, MD, United States, [2]State University of Campinas, Campinas, SP, Brazil, [3]Kyoto University, Japan, [4]Kennedy Krieger Institute, Baltimore, MD, United States, [5]Center for Imaging Studies, Johns Hopkins University, Baltimore, MD, United States

INTRODUCTION: Willians Syndrome (WS) is a unique combination of striking behavioral abnormalities, such as hypersociability, and characteristic neurocognitive loss, such as severe visuospatial construction deficit, raising fundamental questions about the mechanisms of the brain modularity. Regardless of morphometric and functional studies accessing cortical differences in WS patients, there are only a small number of studies reporting the status of the white matter. Here, we combined DTI, DTI based brain atlas, and large-deformation diffeomorphic metric mapping (LDDMM) to access shape and diffusivity in various white matter structures in WS patients' brains. LDDMM achieves an accurate level of normalization that allows warping an anatomical atlas, thereby automatically segmenting the white and gray matter into many functional units. We applied this Atlas-based approach (ABA) and voxel-based analysis (VBA) to investigate the status of the cortex and white matter structures related to physiophatological and clinical findings characteristics of this disease.

METHODS: 8 patients with WS (3 male, ages ranging from 12 to 27 years old, mean 18.4) and 8 healthy controls paired by age and gender were included in this study. Images were acquired using a 1.5T scanner with b=700s/mm^2. Nonlinear transformations between each subject's data and a single subject atlas were obtained using fractional anisotropy (FA) and b0 based (dual contrast) LDDMM. The atlas contains detailed parcellation of 176 white and gray matter structures. By warping our atlas to each subject original space we measured size, FA, apparent coefficient diffusion (ADC), parallel diffusivity ($\lambda_{||}$, the primary eigenvalue) and perpendicular diffusivity ($\lambda_{\perp}$, the average of the secondary and tertiary eigenvalues). The same parameters were analyzed by VBA. We used the Jacobian determinants of the LDDMM matrix to access differences in size. Wilcoxon Rank Sum test was carried out to access differences between groups with *p* value less than 0.1 after correction for multiple comparisons by false discovery ratio.

RESULTS: Total brain, CSF, and cortex volume were significantly smaller in WS. In both VBA and ABA (Figure 1), cortical regions in parietal and occipital lobes, supra orbital and middle frontal gyrus, basal ganglia, diencephalon, left internal and external capsulas, portions of corona radiate and genu of corpus callosum were smaller in WS. Two focal regions, in pre-cuneus and forceps major at left and in the projection of superior longitudinal fasciculus (SLF) at right, were bigger (Figure 1 and 2). ABA showed increased FA in the projection of SLF, inferior longitudinal fasciculus (ILF), posterior thalamic radiations, fronto-occiptal fibers and supra-orbital gyrus at right, cortex of superior temporal gyrus at left and caudate nucleus, bilaterally. Right SLF and cingulum also had significantly increasing of $\lambda_{\perp}$ (Figure 3).

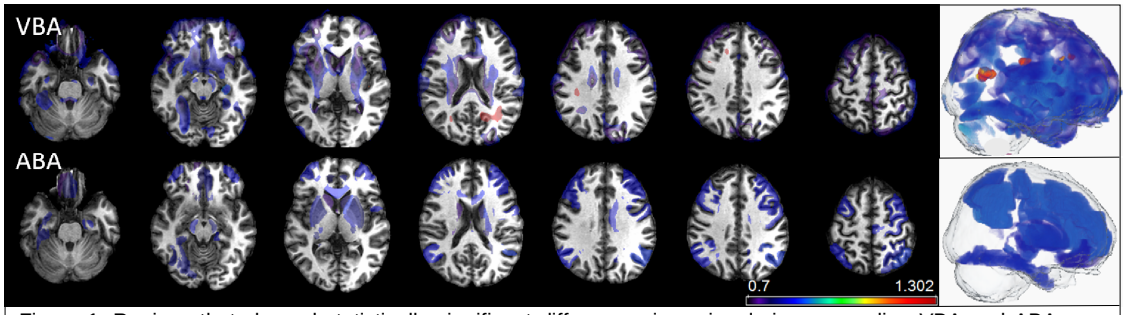

Figure 1: Regions that showed statistically significant differences in regional sizes according VBA and ABA. Colors represent the ratio WS/controls.

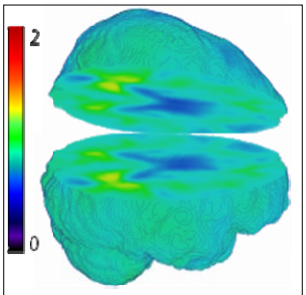

Figure 2: Ratio of brain size means (WS / controls)

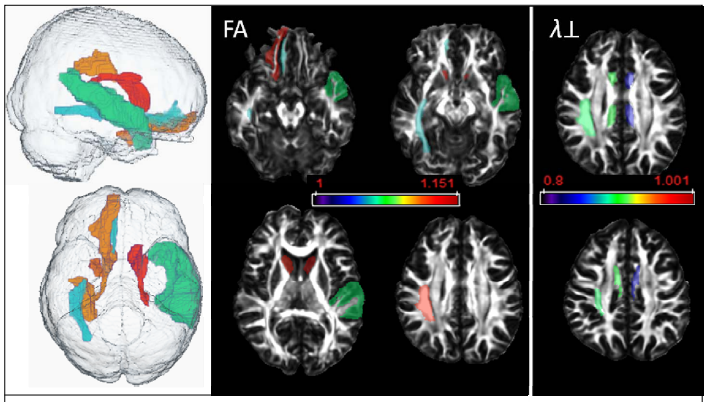

Figure 3: Regions that showed statistically significant differences in FA (3D view and right panel) and $\lambda_{\perp}$ (left panel) according ABA. Colors represent the ratio WS/controls.

DISCUSSION: Reduction in parietal, occipital and orbital cortex was described before in WS, associated with debilities in fronto-occipital circuit and with anomalous parietal lobe gyrification. The enlargement of right SLF and other regions associated to visuospatial function were not reported in the past. Increased FA of the right SLF was showed in a previous study and confirmed here. The known reduced leftward asymmetry of the planum temporal in WS can be responsible for these findings as well as the FA increase in other parts of right fronto-occiptal tract and superior temporal cortex at left. The reduction of basal ganglia and FA increase in caudate, this latter also unexpected, can be related to alterations in fronto-striatal connections described in WS. Changes in cingulum diffusivity are in accord with functional studies where abnormal activation occurred in areas involved with social behavior.

CONCLUSION: Based on DTI and highly nonlinear normalization methods, we observed abnormalities in cortical and white matter regions in the WS population. These findings are compatible with the physiophatological and clinical characteristics of this disease, which include impairment of functional systems responsible for abilities such as visuospatial notion, language and socio-comportamental behavior.

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This study was supported by NIH grant F05NS059230 (AVF), P41RR015241 (PVZ), AG20012 and RR015241 (SM).