A DTI study of structural integrity of white matter in Prader-Willi syndrome

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Introduction

Prader-Willi Syndrome (PWS) is well-known as a genetic cause of childhood obesity, characterized by infantile hypotonia, mental retardation, short stature, hypogonadism, early-onset obesity and hyperphagia[1]. Increasing evidence from functional and structural imaging studies suggested abnormalities in the developmental trajectory of white matter (WM) in PWS while almost no studies have investigated the structural integrity. Diffusion tensor imaging (DTI) is capable of providing information about the organization of fibers in white matter tracts in vivo[2]. The purpose of this work was to detect white matter abnormalities in PWS by comparing one of the most commonly used measurements in DTI: fractional anisotropy (FA) between groups. FA is known as a normalized measure of diffusion anisotropy that provides information about the degree of fiber organization and integrity.

Materials and Methods:

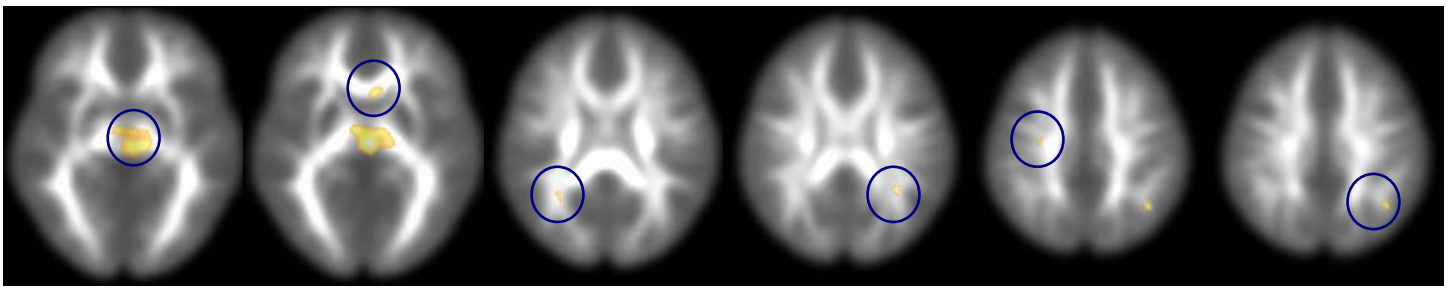
Eight patients (2M, 6F, aged 3.25□1.1) with PWS and eight age- and gender-matched controls (2M, 6F, aged 4.3□1.9) were recruited for this study. MRI data were acquired from all participants using a 3T-head dedicated Siemens Allegra MRI scanner (Siemens, Munich, Germany). First routine clinical scans (T1, T2, and fluid-attenuated inversion recovery) were taken to rule out any incidental pathologic abnormalities. For DTI acquisitions, 12 diffusion gradients were applied in 12 non-collinear directions and the b value was 1500 s/mm x mm . The thickness of each slice was 4mm, without skip, and 28 slices were acquired, paralleled to the AC-PC line. FOV was 220mm x 220mm and the size of the acquisition matrix was 128x128.

After preprocessing, the diffusion of every voxel was evaluated, and the FA value was calculated. After normalization and smoothing (FWHM = 6mm), FA maps were transformed to the same coordinate based on a template which was the mean data of all of our subjects. First, a voxel-based two sample t-test was done between groups using SPM5, then according to the literature, six regions of interest (ROI) were selected for further investigation of the integrity of WM, which were the hypothalamus, right and left internal capsule, right and left cerebellum. We also studied the corpus callosum (CC) in details by subdividing it into 5 sub-regions[3] (shown in Fig. 3).

Results and Discussion.

We found a significant reduction in FA values in a number of brain regions in PWS than in controls (Table 1 and Fig. 1) based on a voxel-wise approach using SPM5. These regions showing the differences were relevant to the previous MRI studies of PWS [4]. However, some areas, such as the hypothalamus, internal capsule and cerebellum, have not shown any significant change between these two groups. Further we conducted an ROI-based analysis of FA changes in the following regions: the hypothalamus (HYP), right and left internal capsule (RIC and LIC), right and left cerebella (RC and LC) and all of the sub-region of CC (I, II, III, VI and V); I, II and V of CC were found to have a significant reduction in FA in PWS as well the hypothalamus and the right internal capsule. There was no significant change in the left internal capsule and the cerebellum.

In sum, using DTI we have demonstrated the focal abnormalities of WM in PWS. Future study will focus on the WM pathways using fiber tracking to provide more information regarding the pathology of PWS.



A B C D E F

Fig. 1 The brain regions (A to F) with significant FA reduction in PWS relative to the control subjects. (p<0.05 with FDR correction, and cluster size >200)

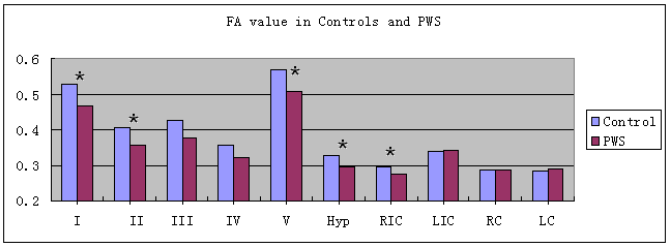


Fig. 2 Comparison of FA values; * indicating a significant change ($P < 0.05$).

Table 1 The brain regions showing significant differences of FA between the subjects with PWS and controls. (p<0.05 with FDR correction, and cluster size >200)

Location	Side	*P*	k
A Sub-lobar, thalamus / extra - nuclear	L	0.025	4198
B Sub-lobar, corpus callosum	L	0.026	216
C Parietal lobe, sub-gyral	R	0.029	224
D Parietal lobe, sub-gyral	L	0.025	436
E Frontal lobe, sub-gyral	R	0.029	212
F Parietal lobe, inferior parietal lobule	L	0.025	554

Reference list

[1] Miller et al. (2006), *J. Pediatrics* **149**:192-8.
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[3] Hofer et al. (2006), *Neuroimage*, **32**,989-94.
[4] Miller et al. (2007), Am. J. Med. Gene. (A)**143**: 476-83.

Acknowledgment

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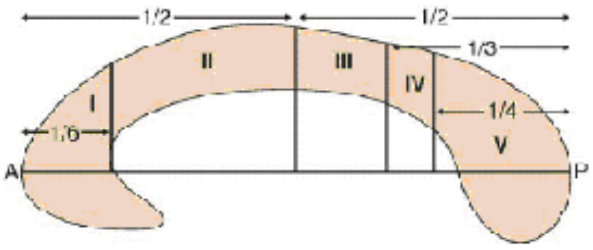

Fig.3 The proposed subdivisions of segmented corpus callosum by Hofer et al [3].