Tract Specific Analysis reveals the impact of childhood manganese exposure on the corpus callosum

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INTRODUCTION: Chronic Manganese (Mn) exposure is known to cause neuromotor and cognitive deficits [1,2,3]. In particular, a voxel-based analysis (VBA) of brain diffusion tensor imaging (DTI) images of adult wielders have shown significant alterations of the corpus callosum (CC) and frontal white matter (WM) from long-term Mn exposure [3]. However, white matter structures may not be accurately mapped in traditional voxel-based studies due to low accuracy of standard fractional anisotropy (FA) based whole-brain registrations. Additionally, methods that zoom in on particular white matter structures may provide better localization of areas that are affected by Mn. Here we use a more recent semi-automated method-Tract Specific Analysis (TSA) [4], which begins with a registration on the whole diffusion tensors[5] and is followed by a tract-based statistical analysis on manually-delineated tracts to quantify white matter changes. While the above studies were performed on adult humans and rats, we look at the effects of Mn on brain white matter microstructure in children chronically exposed to Mn through drinking water.

METHOD: Brain diffusion tensor images (DTI) of 9 (Mean age:11.78 years; SD:1.92 years) children with chronic exposure to Mn and 14 (Mean age:12.50 years; SD: 1.29 years) age and gender-matched controls were acquired with a 3T Philips scanner using a 15 directions, echo planar imaging sequence. All DTI scans were preprocessed using TTK [6], and registered to a template using DTITK[5]. Subsequently, TSA was performed on the corpus callosum using three different measures: the fractional anisotropy (FA), axial diffusivity (AD) and radial diffusivity (RD). 10000 permutations were employed in all the cases for multiple comparison correction.

RESULTS AND DISCUSSION: The left column of Fig. 1 displays significantly decreased FA in a broad area of the CC in the exposed group(corresponding to significantly decreased AD and increased RD, see middle and right columns), which is a typical sign of WM damage. The FA results are consistent with the findings in [3] in adult welders. In rodent DTI studies, decreased AD and increased RD have been associated with axonal injury and demyelination, respectively [7]. Our AD and RD results differ from those of [3] , which found significantly greater RD in the CC, but negligible AD changes. The discrepancy may be due to the difference age of the subjects between our study and [3]. One potential explanation may be that axonal connections are more vulnerable to chronic Mn exposure during neurodevelopment, before the CC is fully myelinated [8]. We also found areas with increased AD in the genu of the CC, which houses more high-density, small-diameter fibers compared with other parts of CC[9]. This may suggest an effect of adaption in response during neurodevelopment, similar to the findings present in studies of lead exposure[8].

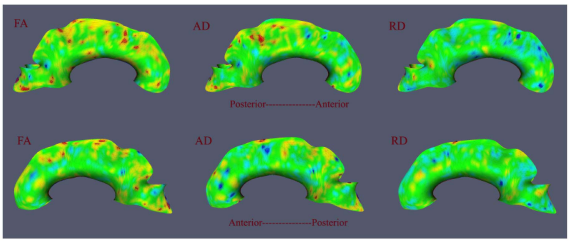

Figure 1: TSA results for FA(left column), AD(middle column), and RD(right column) on left CC(top row) and right CC(bottom row). Areas in blue represent an increase of the corresponding DTI parameters in exposed compared with non-exposed subjects, while areas in red show a decrease of these parameters in exposed compared with non-exposed subjects. Significant areas with $p<0.01$ are circled with a solid black line.

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