Magnetic Resonance Microscopy of a Mouse Model of Attention-Deficit-Hyperactivity Disorder: Role of D4 dopamine receptors

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Introduction: Attention-Deficit-Hyperactivity Disorder (ADHD) is an early-onset neuro-psychological condition marked by inattention, hyperactivity and impulsivity. Although there is clear evidence of dopamine transporter and dopamine receptor D4 gene involvement in ADHD as well as documented morphological volume differences in brain regions, its underlying neurobiological mechanisms is still unclear. Given the wide variety of genetic polymorphisms and the high prevalence of the disorder, animal models, especially genetically engineered mouse models, are of importance in studying ADHD. Here, we characterized a recently developed mouse model of ADHD developed by Avale et al. [1], which involves neonatal disruption of the essential central dopaminergic pathways with 6-hydroxydopamine (6-OHDA) in CF-1 outbred male mice. In adolescence, these mice exhibit clear behavioral characteristics of ADHD [1]. To also investigate the role of the D4 receptor in ADHD behaviors, neonatal lesions in dopamine D4 receptor knockout ($Drd4^{-/-}$) mice were studied. We used MR microscopy (MRM) and 3D anatomical mouse brain atlas MRM templates [2] to extract accurate quantitative 3D neuro-anatomical information. **Methods**: High-resolution (40μm isotropic) MRM mouse brain images of perfusion fixed mice brains (in skull to prevent deformation) were acquired with the 750MHZ, 17.6T. 3D gradient-echo pulse sequence was used (TE = 10ms; TR = 150ms; Flip angle = 25 degree; Number of excitations = 2; Matrix = 625x350x300; FOV = 2.5x1.4x1.2cm; Acquisition time = 8.75 hours). The MRM images were segmented into 20 neuro-anatomical structures using a recently developed semi-automatic procedure based on image registration [2]. Figure 1 shows a representative outlining of the segmented structures (color contours) superimposed on the MRM image. The structure volumes and surface areas were quantified.

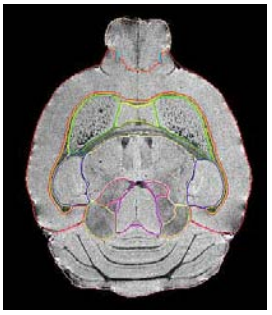

Figure 1

Results and Discussion: Our preliminary data show reductions in both surface areas and volumes of several structures including cerebellum, caudate putamen, globus pallidus, thalamus and hippocampus in the 6-OHDA neonatal lesioned group compared with controls (Figure 2a). These findings are consistent with a number of human morphometry studies demonstrating smaller volumes of the cerebellum, caudate putamen, globus pallidus and the whole brain in children with ADHD [3]. Volume and surface area reductions also were shown in the $Drd4^{-/-}$ group even though only a mild ADHD behavioral phenotype has been observed in $Drd4^{-/-}$ mice with 6-OHDA lesion (Figure 2b). These preliminary morphological phenotypic findings underscore the complicated link between neurotransmitter deficiencies, neuroanatomical alterations and behavior, while demonstrating the ability of MRM to interrogate subtle structural changes quantitatively. Further confirmations of these findings are in progress by collecting and analyzing more data.

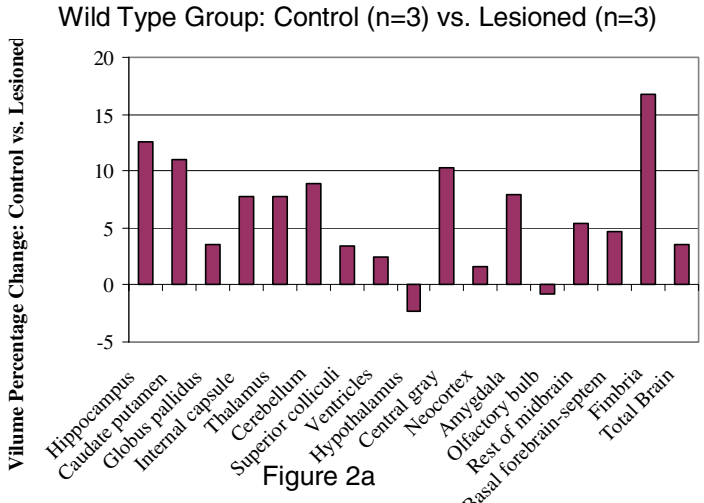

Figure 2a

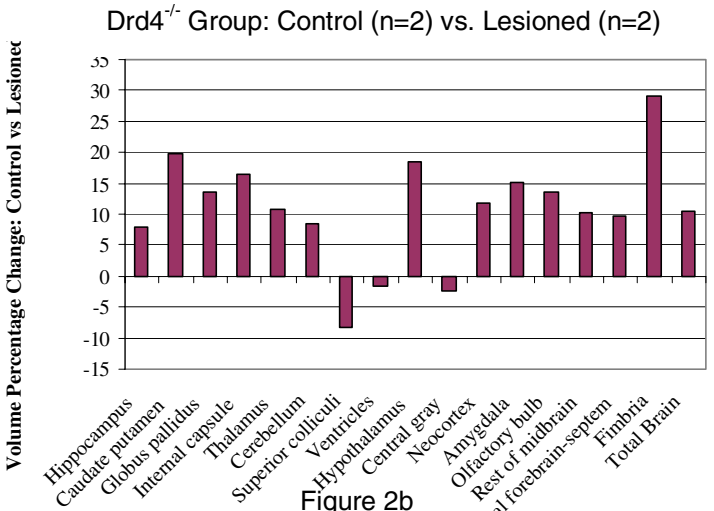

Figure 2b

1. Avale, ME, Falzone TL, Gelman DM, Grandy DK And Rubinstein M, Molecular Psychiatry 2004; 9 :718-726.
2. Ma Y, Hof PR, Grant SC, Blackband SJ, Bennett R, Slatest L, McGuigan MD and Benveniste H., Neuroscience 2005;135(4):1203-15
3. Castellanos et al. Am J Psychiatry 1994 ; 151(12):1791-6