

Effect of psychostimulants on basal ganglia structures in young ADHD children

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Background: ADHD is one of the most common neuropsychiatric disorders with a prevalence of 5-10% in school-aged children. The role of the basal ganglia in ADHD has been well-documented and PET studies have shown significant binding of stimulant medication to dopamine transporters in this region. However, very few studies have reported a relationship between the medication history and volume of basal ganglia structures.

Materials and Methods: Subjects in this study were composed of three groups of children between the ages of 7-11 years. Group 1 was 20 medication-naïve ADHD children, Group 2 was 11 medicated ADHD children, and Group 3 was 25 healthy controls (HC). Subjects were matched on age ($p=.2$), sex ($p=.1$), ethnicity ($p=.24$), SES ($p=.3$) and IQ ($p=.37$). All analyses were two-tailed, co-varying for total brain volume with $\alpha=0.05$. Images were obtained on a GE 1.5 T magnet using the 3D SPGR T1 weighted sequence and obtaining contiguous images of the whole brain. The caudate and putamen were extracted using the Feature-Based Metrics algorithm provided by ANTS software^[1]. The algorithm includes a landmark matching metric and two point-set metrics which can accommodate point sets of different cardinality. Reliability and validity of extracted caudate and putamen volumes using this method is reported by Avants et al^[1]. Using this reliable, automated registration routine, caudate and putamen structures were automatically extracted in the subject space of all three groups.

Results: A GLM multivariate analysis, co-varying for total brain volume, was performed to compare med-naïve and medicated ADHD patients to their demographically matched HC. Although the ADHD med-naïve group consistently presented with slightly larger volumes compared to HCs and the medicated group had volumes similar to the HC, no significant differences were observed for the right and left basal ganglia structures (caudate and putamen) for between group analysis. Subsequent partial correlations (controlling for brain volume) of the basal ganglia volumes with Conners' hyperactivity raw scores showed a robust correlation for the right caudate in med-naïve ADHD subjects (Fig. 1) and no correlation for the medicated or HC groups. Based on this, despite the small number of medicated ADHD children in our group, we carried out an exploratory analysis to examine the effect of stimulants on basal ganglia volumes.

Medication History and Basal Ganglia Volume: Correlation analyses were carried out between the duration of medication exposure in the medicated group and their basal ganglia volumes, controlling for total brain volume. Results showed a negative partial correlation for the left caudate ($r=-0.61$; $p=0.032$) and the right caudate ($r=-0.51$; $p=0.06$) with medication duration, with a longer duration of medication corresponding to a smaller caudate. No significant partial correlations were observed for putamen volumes and medication duration.

Conclusions: Results from our exploratory analysis suggest that the basal ganglia, especially the caudate nucleus, play a key role in the neurobiology of ADHD and the underlying mechanism of stimulant effect on the brain. It is difficult to draw a causality conclusion from the small sample size; further, no information was available on the medicated group's pre-medication, baseline basal ganglia volumes. However, these preliminary results are exciting and support the need for a controlled longitudinal study to further explore the effect of ADHD stimulant medication on brain structure.

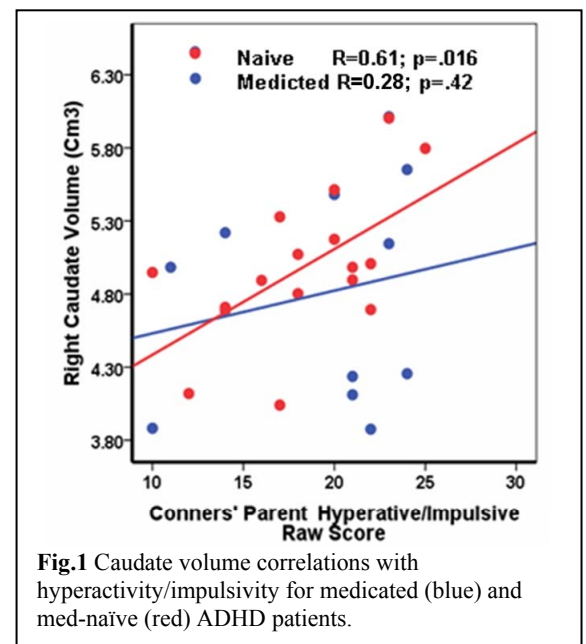


Fig.1 Caudate volume correlations with hyperactivity/impulsivity for medicated (blue) and med-naïve (red) ADHD patients.

1. Avants BB, Tustison NJ, Song G, Cook PA, Klein A, Gee JC (2010) A reproducible evaluation of ANTs similarity metric performance in brain image registration. *NeuroImage*, in press. 10.1016/j.neuroimage.2010.09.025