Inhibition Network Differences Between ADHD and Healthy Adults are Unbiased by Drug Use History

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Introduction: Attention Deficit Hyperactivity Disorder (ADHD) has been associated with deficits in inhibition during Go/NoGo tasks of varying complexity[1]. Differential activity in a number of regions, relative to controls, characterizes inhibition deficits in ADHD[2,3]. ADHD adolescents are at a higher risk for substance use disorders[4], and it has been suggested that impairment in inhibition may play a role in the increased risk of drug use among ADHD diagnosed young adults[5]. Functional activation during inhibition tasks is impacted by drug use including dose and age of use onset [6,7]. The goal of this study was to assess the single and combined effects of ADHD and cannabis use on cognitive deficits manifested in a Go/NoGo task as well as inhibitory-related activation patterns.

Methods: The study cohort consisted of 86 participants recruited from four sites participating in a NIDA funded Multimodal Treatment study of ADHD (MTA). Groups included individuals with ADHD (diagnostic status was determined in childhood) and without ADHD (Local Normative Control Group, CTRL) who do and do not use cannabis (SU) at least two to three times per month. It should be noted that all participants observed a 36-hour washout for cannabis prior to the scan. 12 subjects were removed based on two criteria: 1) behavioral performance below chance levels or 2) excessive motion (SFNR<65) coupled with a lack of significant activation in occipital cortex (z<1.96) (remaining $N_{ADHD,SU}$=26,$N_{ADHD,NSU}$=26,$N_{CTRL,SU}$=11,$N_{CTRL,NSU}$=11). Participants were instructed to press a button in response to target stimuli and inhibit their responses to non-target stimuli on an appetitive Go/NoGo task[3] collapsed across emotional content. Emotional content was balanced and pseudo-randomized for each subject. Behavioral responses were analyzed by averaging performance across the four runs administered and tested for significance in a two way ANOVA (Diagnosis, Substance Use) with interaction terms. Echo planar imaging was acquired over 154 volumes for a total of 5m12s (TR/TE=2000/30ms, 32 axial slices, TH=4mm, Slice Gap=1mm, In-plane resolution=3.4x3.4mm). T1 weighted imaging was performed for registration to a standard space template. B0 images were collected for distortion correction.

Images were slice time and B0 corrected prior to whitening, a high-pass temporal filter (Gaussian Weighted Least Squares, 50s), and a spatial filter were applied (Gaussian, FWHM=5mm). A GLM analysis for each run was performed using FSL and co-varying for motion and the time derivative of stimuli onset to account for differences in response time. Runs were collapsed using fixed effects into the visit level before calculating group statistics using FLAME 1. Collapsed group (ADHD vs CTRL, SU vs NSU) and inter-group (i.e. ADHD,SU vs ADHD,NSU) voxelwise analyses were performed. Due to a qualitatively observed large variation in ventricle size, striatal regions were segmented in native space using FreeSurfer and used as regions of interest (ROIs) for further inspection to account for registration errors near ventricle walls.

Figure 1. ADHD participants make more errors of commission than CTRL (p<.05). No significant effects of drug use were found behaviorally.

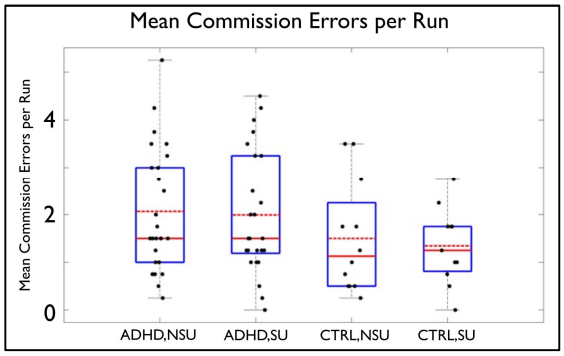
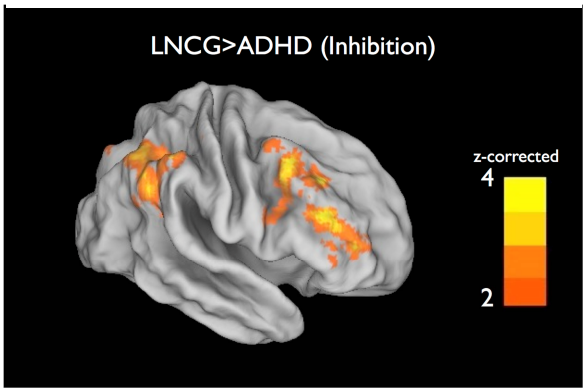


Figure 2. Right lateralized inhibition network difference map demonstrates deficits in ADHD. No significant effects of drug use were found in the voxelwise analysis.



Results: ADHD participants made more errors of commission (p<.05) compared to CTRLs (figure 1). No significant effects of drug use and/or the interaction with ADHD diagnosis were observed for errors of omission, d', or errors of commission. Group contrasts corrected for multiple-comparisons showed greater fMRI activation for CTRL than ADHD participants in the right lateralized cortical surface including the middle frontal, inferior frontal, angular and supramarginal gyrus along with the frontal pole (figure 2). Native space analysis of striatal ROIs showed significant group differences in the same direction (CTRL>ADHD) in right caudate (p<.01), right putamen (p<.05) and left pallidum (p<.05). No significant effects of cannabis use were found in imaging or ROI analyses, either within diagnosis, across diagnosis or when collapsing across diagnosis.

Discussion: Clear ADHD-related deficits in behavioral performance (errors of commission) and functional activation were present. Cannabis use was not significant in terms of behavior or cognitive function during this inhibition task, suggesting that cannabis use does not impair inhibition within this sample when collapsing across emotion. Networks identified by this study show both consistency and novelty with previous findings in ADHD literature[2,3]. As the largest reported sample to date of young adults with ADHD, these results may apply to the general ADHD population irrespective of past history of drug use.

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