

# Multimodal brain imaging of methylphenidate treatment in patients with ADHD

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## Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders, thought to affect 6 million children in the United States alone [1]. The symptoms of the condition can include hyperactivity, impulsivity, problems with attention, self concept, and memory, which can make succeeding in school and careers challenging. It is estimated that more than a third of children with ADHD will still have ADHD symptoms in adulthood [2]. Despite the prevalence and persistence of this disorder, there is a paucity of data identifying predictors of treatment response in ADHD in children and adolescents. Subsequently, there are few biomarkers for use in development of novel ADHD medications. The pilot data presented are part of our efforts to identify non-invasive brain imaging biomarkers related to response to methylphenidate (MPH) in ADHD. Our strategy is to compare cognitive performance, brain activity during cognitive tasks, and brain metabolites after MPH and placebo.

## Objectives

1. Determine dose-dependent changes in functional MRI (fMRI) cognitive task-related neural activity after acute methylphenidate in patients with ADHD.
2. Determine changes in brain glutamate after acute methylphenidate in patients with ADHD using high field strength magnetic resonance spectroscopy (MRS).

## Materials and Methods

### Study Design

- Double-blind cross over of a single dose of methylphenidate (10 or 15 mg) and matching placebo.

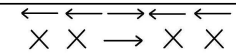
### Subjects

- 8 right-handed adults with ADHD, 18-36 years, not currently taking a stimulant medication and free of any other Axis 1 psychiatric disorders.

### fMRI

Blood oxygenation level dependent (BOLD) fMRI completed in a 3T Phillips dStream Ingenia Elition scanner. Tasks measured included the Flanker task, N-back task, and a visual declarative memory task. Results here focus on the No-Go condition of the Flanker task, which measures brain activity during response inhibition, known to be impaired in ADHD [3]. Figure 1 shows the go and no-go conditions of the flanker task.

Figure 1. (top) incongruent 'go' condition. (bottom) no-go response inhibition condition.



### MRS

MRS was completed on the Philips Achieva 7T scanner. The high magnet strength allowed for enough spectral resolution to separate similar neurotransmitters such as glutamate and glutamine. The LCModel was used for data analysis and 19 different metabolites were measured in 4 different brain regions: centrum semiovale (white matter), and parietal, anterior cingulate, and prefrontal cortices. This preliminary analysis focuses on glutamate, but other metabolites will be examined in future analyses.

### NIH Toolbox

The adult cognition battery of the NIH Toolbox was utilized for assessment of multiple cognitive domains including executive function, processing speed, and working memory.

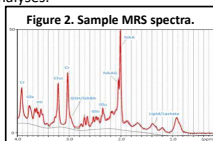
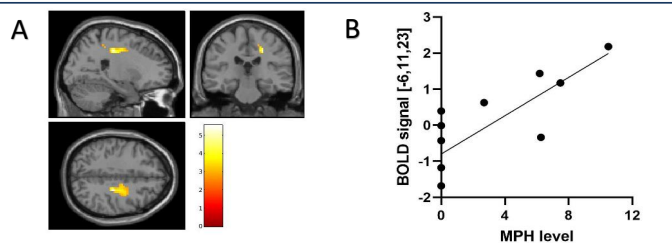
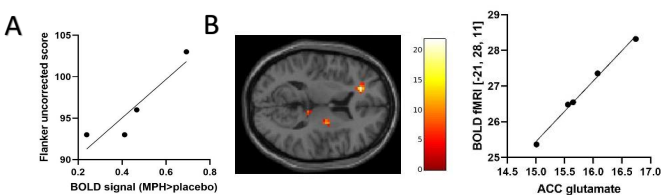


Figure 2. Sample MRS spectra.

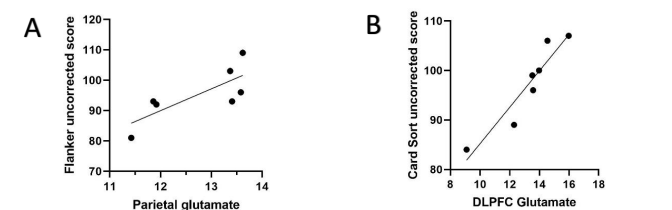
## Results



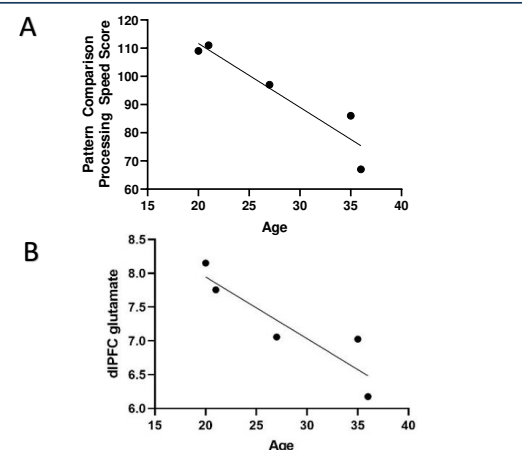
**Figure 3. Methylphenidate increases brain activity in the cingulate during response inhibition.** A) MPH increases cingulate activity during response inhibition (No-Go during Flanker task) in 5 young adults (two-sample t-test, MPH > placebo, whole brain threshold  $p < 0.01$  uncorrected,  $k = 10$  voxels). B) Higher MPH levels are correlated with greater BOLD activity during no-go (peak voxel [-6, 11, 23],  $p = 0.0057$ ,  $F = 13.03$ , slope = 0.074,  $r^2 = 0.59$ ).



**Figure 4. Brain activity during response inhibition positively correlates with task performance and anterior cingulate cortex (ACC) glutamate.** A) BOLD signal in peak voxel (MPH > placebo during No-Go predicts better performance on the Flanker task (uncorrected standard score) measured using the NIH Toolbox. B) ACC glutamate is positively correlated with frontal and cingulate cortical activity during response inhibition in regions where activity is greater after MPH compared to placebo (SPM12 IMCalc MPH-placebo), ( $p < 0.01$  uncorrected, frontal peak [-21, 38, 11],  $T = 21.68$ ,  $Z = 3.70$ ,  $k = 21$  voxels, cingulate peak [6, -25, 17],  $T = 13.05$ ,  $Z = 3.30$ ,  $k = 42$  voxels).



**Figure 5. Glutamate levels measured by MRS correlate with performance on cognitive tests.** A) Higher parietal glutamate levels after MPH correlate with higher flanker score ( $p = 0.04$ , slope = 7.174,  $r^2 = 0.60$ ). B) Higher DLPFC glutamate levels predicted higher scores on the card sort ( $p = 0.0016$ , slope = 3.676,  $r^2 = 0.89$ ) during the placebo visit. A similar relationship was found between higher ACC glutamate levels and higher scores on the card sort ( $p = 0.0038$ , slope = 7.273,  $r^2 = 0.84$ ) during the placebo visit. These data suggest that regional glutamate levels may contribute to differential regulation of performance on cognitive domains.



**Figure 6. Age is correlated with differences in processing speed and frontal cortical glutamate in young adulthood.** A) Younger patients with ADHD performed better on the pattern comparison processing speed test than the older patients with ADHD ( $p = 0.0171$ , slope = -2.266,  $r^2 = 0.8852$ , uncorrected scores). B) Younger patients with ADHD have higher glutamate in the dorsolateral prefrontal cortex (dlPFC) ( $p = 0.0339$ , slope = -0.091,  $r^2 = 0.82$ ). Higher dlPFC glutamate is associated with better processing speed ( $p = 0.0347$ , slope = 6.106,  $r^2 = 0.8188$ ).

## Conclusions

- We found an increase in brain activity and task performance after MPH as previously reported.
- Novel findings included correlations between brain glutamate and BOLD response changes after MPH, and correlations between regional glutamate levels and cognitive domains.
- We observed age-related changes in glutamate level and processing speed in our young adult patients.
- The methods utilized in this pilot study show promise as tools for use as biomarkers in the development of novel pharmacological therapies for ADHD.

## Future directions

Data collection is still ongoing to increase sample size. Further analysis will be done of additional fMRI tasks, MRS brain regions, and neurometabolites already measured. Future studies must measure fMRI and MRS in children and adolescents.

## References

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