ACcd Dysfunction In Brain Activation Between Subjects With ADHD And Controls

Brian Bateman

A. Study Purpose and Rational

Attention deficit/ hyperactivity disorder (ADHD) is syndrome that manifests in early childhood and is characterized by symptoms of impulsivity, inattentiveness, and hyperactivity that are inappropriate to a child's developmental stage.[i] [ii] Approximately 7% of American children ages 6-11 carry the diagnosis,[iii] making it one of the most common pediatric illnesses. The illness profoundly impairs cognitive, academic, emotional, and social functioning[iv] [v] [vi] [vii]. For a high percentage of patients with ADHD, these impairments continue into adulthood.[viii] Given the significant morbidity associated with this illness, it is important to elucidate its neurobiological basis.

Substantial work has been done to characterize the neurological abnormalities associated with ADHD[ix] [x] [xi] [xii] [xiii]. However, while ADHD is frequently diagnosed in early childhood (particularly the predominantly hyperactive-impulsive subtype of ADHD, which is most often diagnosed at age six or seven), the studies that have been done to date have generally included older children, adolescents, and/or adults as subjects, and sample pools have been frequently contaminated with subjects who have been exposed to pharmacologic treatments for the disorder. The neurobiological understanding of ADHD that emerges from data collected from such individuals may not accurately represent the fundamental abnormalities that initially cause ADHD, but rather may represent processes that attempt to compensate for the fundamental deficits. Further, long term exposure to psychoactive medications may markedly alter individuals' neurobiology, representing an important confounder in these data.

In light of the limitations of these earlier studies, we propose an fMRI study that will compare 6 or 7 year old subjects who are newly diagnosed with ADHD (the predominantly hyperactive-impulsive subtype) and who have never been exposed to psychoactive medications, with a matched control group. Such a study provides the advantage of imaging subjects at the earliest point possible in their disease course and before exposure to medication.

We plan to image the subjects and controls while they are engaged in the Simon Spatial Compatibility Task. This task requires subjects to look at a screen divided into even right and left halves by a vertical line. A series of rightward of leftward pointing arrows are projects onto the screen. Subjects are charged with pressing a button with the first finger of their right hand if the arrow is on the left side of the screen and with pressing a different button with the second finger of their right hand if the arrow is on the right side of the screen. In ninety-five percent of the projections the stimulus will be congruent (e.g. a rightward pointing arrow will be on the right side of the screen), but in five percent of projections the stimulus will be incongruent (e.g. a leftward pointing arrow will be on the right side of the screen). Presenting an incongruent stimulus creates a cognitive interference effect by presenting a task-irrelevant stimulus that is inconsistent with a task-relevant stimulus, as demonstrated by the fact that subjects' response times to incongruent stimuli are markedly delayed relative to congruent stimuli.[xiv] [xv]Resolution of this interference effect requires selecting the correct stimulus from two competing streams of input (an attention dependant task), as well as inhibiting a response to the incorrect stimulus (an impulse control dependant task). Thus the Simon Spatial Compatibility Task specifically taxes the cognitive functions whose deficit is a core feature of ADHD. Indeed studies have demonstrated poor performance on the Stroop Word-Color Task (a task that creates a similar type of interference and engages similar brain regions as the Simon[xvi]) by subjects with ADHD.[xvii]

The Simon Task is an excellent instrument for probing with fMRI the brain regions involved in the resolution of cognitive interference, as it allows all of the physical attributes of the task (including the percentage of left and right pointing arrows, and the percentage of left and right lying arrows) to be

equally balanced between the congruent and incongruent stimuli. Thus, subtracting the summed fMRI activation during congruent stimuli from the summed activation during incongruent stimuli should reveal differences in activation related only to interference effects. The Simon Task is also particularly useful for studying young children, as it is a spatial task that does not place linguistic demands on the subjects and controls who are at an age at which reading is not fully automated (a demand of the Word-Color Stroop Task).

A previously published study used fMRI to compare 8 unmedicated adults with ADHD with 8 matched controls while they performed the Counting Stroop. This study found robust differences between the activation maps of subjects and controls, with subjects failing to activate the anterior cingulated cognitive division, a brain region thought to be important in impulse control and attention.[xvii]i

We hypothesize that our study may similarly reveal ACcd dysfunction, as well as other previously unidentified differences in brain activation between subjects with ADHD and controls. The significance of this study lies in the fact that it will provide the first fMRI imaging of an interference task for subjects with ADHD who are very early in their disease course and who have not been exposed to medication.

B. Study Design and Statistical Analysis

Twenty male subjects ages 6 or 7 who are newly diagnosed with ADHD (subtype predominantly hyperactive-impulsive) by DSM IV criteria at the Columbia University Child Psychiatry Clinic will be recruited to undergo fMRI imaging while performing the Simon Spatial Compatibility Task. The subjects will all be male, as ADHD (subtype predominantly hyperactive-impulsive) has a 4:1 male to female predominance. Since sex can impact functional activation, we choose to image only males to avoid this confounder. Subjects are to be invited to an imaging session immediately after their initial diagnosis and before medication treatment is initiated

Twenty controls will be drawn from 6 to 7 year old male patients, without a known psychiatric diagnosis, attending the Columbia University Pediatric Clinic for well-child check-ups.

After the Simon task is explained to the subjects, they will be imaged in an MRI scanner while performing the Simon task. Activation maps for each subject and control will be generated by subtracting mean activation during the congruent stimuli from mean activation during incongruent stimuli (after accounting for the lag in hemodynamic response) on a pixel by pixel basis. The activation maps for subjects and controls will then be compared for differences in activation once the brains have been warped into standardized Talairach space.

The number of subjects selected was somewhat arbitrary. The only previous fMRI study which used a cognitive interference task to compare controls and subjects with ADHD had 8 subjects and 8 controls. With this number they were able to demonstrate statistically robust differences between subjects and controls in multiple brain regions.[xix] We speculate that if the same differences in activation between adults with ADHD and normal controls are present in 6 and 7 year olds, then our study will be able to detect these differences. Further, we speculate that by increasing our subject number to 20, we will be able to detect more statistically significant regional differences in brain activation than this previous study. A general principle in fMRI research is that as the number of subjects increases, the number of subtle differences in activation detected will also increase. We set our number at 20 subjects and 20 controls, because to further increase the number of subjects would be financially unfeasible.

C. Study Procedure

Subjects and controls will perform the Simon Task while being imaged in a 1.5 T MRI scanner. Subjects will lie flat inside the scanner and the stimuli will be projected on a screen as has been previously described.[xx] Subjects will use individualized "bite bars" to minimize head movement during the experiment. Each trial of the Simon task will consist of a 1300 msec stimulus presentation followed by a 350 msec interstimulus interval. The incongruent stimuli will occur pseudorandomly, once in every

13-16 congruent stimuli (resulting in a spacing of 21.45 to 26.40 seconds), to allow the hemodynamic response to the previous incongruent stimuli to dissipate. The subject will register the side of the screen on which the stimulus appears as was previously described. Each run will consist in 102 trials and will last 2 minutes 48 seconds. A total of nine runs will be collected for each subject. The research assistant will ask the subject if they are feeling "o.k." between each run and the subject will be instructed to respond by pressing one of the buttons.

D. Study Drugs

N/A

E. Medical Devices

N/A

F. Study Questioners

N/A

G. Study Subjects

Inclusion criteria for subjects: Boy, age 6 or 7, newly diagnosed by a board certified child psychiatrist at the Columbia University Child Psychiatry Clinic with ADHD (subtype predominantly hyperactive-impulsive) by DSM IV criteria

Inclusion criteria for controls: Boy, age 6 or 7, never diagnosed with a psychiatric disorder, seen for well child care at the Columbia University General Pediatric Clinic.

Exclusion criteria: Ferromagnetic implants, metal braces or retainers as ascertained by Standard Metal Screening Questionnaire and clinician verbal report; IQ<85 as ascertained by Wechsler Abbreviated Scale of Intelligence; a DSM IV Axis I diagnosis as ascertained by clinician verbal report and parent self-report; birth at <37 weeks gestational age as ascertained by parent self-report; history of concussion, seizure disorder, or other neurological illness as ascertained by parent self-report; and claustrophobia as ascertained by patient/parent self report.

H. Recruitment of Subjects

Subjects will be recruited at the Columbia University Child Psychiatry Clinic by a research assistant. Permission will be obtained to recruit subjects from the attending psychiatrists present at the clinic.

Controls will be recruited at the Columbia University General Pediatric Clinic by a research assistant. Permission will be obtained to recruit subjects from the attending pediatricians present at the clinic.

I. Confidentiality of Study Data

All data will be kept in a locked file cabinet assessable only to the study PI and research assistants. All subject information will be coded and will not contain any identifying information.

J. Potential Conflict of Interest

None.

K. Location of the Study

Imaging will be performed at the NY State Psychiatric Institute, in the MRI suite.

L. Potential Risks

There no known risks to MRI imaging.

M. Potential Benefits

Although the imaging will not be read by a neuroradiologist, if there is a suspected lesion observed on the imaging obtained, the subject will be referred to a pediatric neurologist.

N. Alternative Therapies

There is no therapeutic benefit to participation in the study and thus no alternative.

O. Compensation to Subjects

Subjects' parents will be paid $150 for their time.

P. Cost to Subjects

None.

Q. References

i. Attention-deficit and disruptive behavior disorders. In: Diagnostic and Statistical Manual of Mental Disorders, 4th ed, Text Revision, American Psychiatric Association, 2000.
ii. Clinical practice guideline: diagnosis and evaluation of the child with attention-deficit/hyperactivity disorder. American Academy of Pediatrics. Pediatrics 2000; 105:1158.
iii. Pastor, PN, Reuben, CA. Attention deficit disorder and learning disability: United States, 1997-98. National Center for Health Statistics. Vital Health Stat 10(206). 2002.
iv. Merrell C, Tymms PB. Inattention, hyperactivity and impulsiveness: their impact on academic achievement and progress. Br J Educ Psychol. 2001 Mar;71(Pt 1):43-56.
v. Seidman LJ, Biederman J, Faraone SV, Weber W, Ouellette C. Toward defining a neuropsychology of attention deficit-hyperactivity disorder: performance of children and adolescents from a large clinically referred sample. J Consult Clin Psychol. 1997 Feb;65(1):150-60.
vi. Klorman R, Hazel-Fernandez LA, Shaywitz SE, Fletcher JM, Marchione KE, Holahan JM, Stuebing KK, Shaywitz BA. Executive functioning deficits in attention-deficit/hyperactivity disorder are independent of oppositional defiant or reading disorder. J Am Acad Child Adolesc Psychiatry. 1999 Sep;38(9):1148-55.
vii. Bagwell CL, Molina BS, Pelham WE Jr, Hoza B. Attention-deficit hyperactivity disorder and problems in peer relations: predictions from childhood to adolescence. J Am Acad Child Adolesc Psychiatry. 2001 Nov;40(11):1285-92.
viii. Biederman, J. Attention-deficit/hyperactivity disorder: a life-span perspective. J Clin Psychiatry 1998; 59 Suppl 7:4.
ix. Castellanos FX. Toward a pathophysiology of attention-deficit/hyperactivity disorder. Clin Pediatr (Phila). 1997 Jul;36(7):381-93.

x. Tannock R. Attention deficit hyperactivity disorder: advances in cognitive, neurobiological, and genetic research. J Child Psychol Psychiatry. 1998 Jan;39(1):65-99.

xi. Durston S. A review of the biological bases of ADHD: what have we learned from imaging studies? Ment Retard Dev Disabil Res Rev. 2003;9(3):184-95.

xii. Swanson J, Castellanos FX, Murias M, LaHoste G, Kennedy J. Cognitive neuroscience of attention deficit hyperactivity disorder and hyperkinetic disorder. Curr Opin Neurobiol. 1998 Apr;8(2):263-71.

xiii. Zametkin AJ, Liotta W. The neurobiology of attention-deficit/hyperactivity disorder. J Clin Psychiatry. 1998;59 Suppl 7:17-23.

xiv. Simon JR. Reaction toward the source of stimulation. J. Exp. Psychol. 1969;81 174-176.

xv. Simon JR, Berbaum K. Effect of conflicting cues on information processing: the 'Stroop effect' vs. the 'Simon effect'. Acta Psychol (Amst). 1990 Mar;73(2):159-70.

xvi. Peterson BS, Kane MJ, Alexander GM, Lacadie C, Skudlarski P, Leung HC, May J, Gore JC. An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. Brain Res Cogn Brain Res. 2002 May;13(3):427-40.

xvii. Barkley RA, Grodzinsky G, DuPaul GJ. Frontal lobe functions in attention deficit disorder with and without hyperactivity: a review and research report. J Abnorm Child Psychol. 1992 Apr;20(2):163-88.

xviii. Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, Rosen BR, Biederman J. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. Biol Psychiatry. 1999 Jun 15;45(12):1542-52.

xix. Bush G, Frazier JA, Rauch SL, Seidman LJ, Whalen PJ, Jenike MA, Rosen BR, Biederman J. Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the Counting Stroop. Biol Psychiatry. 1999 Jun 15;45(12):1542-52.

xx. Peterson BS, Kane MJ, Alexander GM, Lacadie C, Skudlarski P, Leung HC, May J, Gore JC. An event-related functional MRI study comparing interference effects in the Simon and Stroop tasks. Brain Res Cogn Brain Res. 2002 May;13(3):427-40