Precis

Attention Deficit hyperactivity disorder (ADHD) is the most common behavioral disorder of childhood, affecting an estimated 5-10% of the general population (Solanto et al., 2001). ADHD is characterized by difficulty paying attention and by inappropriate hyperactivity and impulsive behavior (Kaplan et al 1995). The exact cause of ADHD is unknown, but genetic influence is high with estimates of up to 85% (Levy et al., 1997). Dopamine pathways in the brain are thought to play a vital role in the etiology of this disorder, and psychostimulants, agents known to affect the dopaminergic pathway, are the treatment of choice. There is considerable public controversy about the validity of this diagnosis and its treatment.

Both healthy children and children with ADHD have the same behavioral response to psychostimulants (Rapoport et al., 1980, 1981; Rapoport and Germain, 2003) which had seemingly put to rest the notion of "paradoxical" response to stimulants in ADHD. With the advent of brain imaging techniques, a better understanding of the underlying mechanisms of ADHD has emerged, most consistently implicating frontostriatal systems. Two recent brain imaging studies have again raised the question of whether brain response to stimulants is "paradoxical" for ADHD (Langleben et al., 2002; Vaidya et al., 1998). In these studies, the ADHD and healthy groups had different brain activation patterns at baseline and different patterns of response to stimulant medication. However, these studies were small, and did not attempt to discriminate between the influence of state and trait. Moreover, confounding factors in these studies (such as differences in performance) might have spuriously led to the appearance of a paradoxical effect.

To address the important issue of a unique central response to stimulants in ADHD, this study includes a double blind, placebo-controlled challenge with a single, low oral dose of 0.10 mg of amphetamine. Subjects include 14 healthy control children and 14 children with ADHD matched for age and sex, and 12 pairs of monozygotic twins discordant for ADHD and 12 pairs of same sex dizygotic twins discordant for ADHD. Following a practice session using the "stop task", a motor inhibition task widely used in ADHD research (Logan, 1994; Oosterlaan, 1998), counterbalanced placebo or amphetamine will precede functional MRI scanning using the stop task and the attentional task of Casey (1997) used in Vaidya et al (1998).

Radiation involved in most neuroimaging techniques precludes application to children, but functional MRI represents an important exception in this regard, as the procedure relies on magnetic fields rather than radioisotopes. Previous experience with single dose challenge in healthy children and studies of treated ADHD and learning disabled children did not indicate any long-term adverse effects, or an increased risk of abuse.

If children with ADHD or their siblings exhibit differential activation of the fronto-striatal regions of the brain than do control children, at baseline and/or after stimulant treatment, these response patterns will be examined in relation to clinical severity and to genetic relatedness to the ADHD patient.

II. Introduction

A. Type of Protocol: This protocol examines the neural effects of a single dose of stimulant on children who have ADHD and on healthy children. As such, this protocol is designed to study the neural mechanisms of therapeutic psychostimulant medication.

B. Background: This section reviews four issues relevant to the current proposal: 1.Imaging studies delineating the functional brain differences between normal individuals and those with ADHD. 2. Studies combining psychostimulant medication and brain imaging. 3. Informative functional MRI tasks in ADHD. 4.The rationale for twin populations.

1. Brain Imaging Studies: Several studies have concluded that the brains of children with ADHD have subtle anatomical and functional differences from the brains of healthy children (relevant imaging studies are summarized in Appendix I).

- **a. Anatomical MRI studies**: Using magnetic resonance imaging (MRI), over fifteen anatomical studies have shown that ADHD children have subtle reductions in volume in the prefrontal cortex, caudate nucleus, globus pallidus, and a sub-region of the cerebellar vermis (Solanto et al., 2001).
- **b. SPECT and PET studies**: (See Appendix Ia.) Two (of three) SPECT studies in children show decreased frontal activation in ADHD. Two (of two) PET studies with adults and teenagers also indicate that subjects with ADHD show decreased frontal activation. Further, hypoperfusion in parietal and temporal regions was noted using SPECT (1/3 studies) with children with ADHD as compared to controls.
- **c. Functional MRI (fMRI) studies**: (See Appendix Ib.) Of three fMRI studies, one has shown decreased activation in the anterior cingulate, one has shown a decrease in prefrontal activation, and one has shown decreased activation in the caudate nucleus. Taken together, the above studies provide evidence for brain differences between healthy volunteers and patients with ADHD. However, to date, none of the tasks utilized during fMRI have controlled for performance differences between individuals with ADHD and healthy controls.
- **d. Dopamine and ADHD:** (See Appendix Ic &Id.) Genetic studies have shown ADHD to be associated with the dopamine transporter gene DAT1 (Swanson et al., 2000). Four (of six) SPECT studies and one (of three) PET study have concluded that ADHD is characterized by an overexpression of the dopamine transporter (DAT) in the striatum or basal ganglia, presumably lowering dopamine concentration in the synaptic cleft. One (of six) SPECT study has found no difference in DAT between ADHD and controls, and one found lower DAT levels in adults with ADHD. Three (of three) PET studies have concluded that there is dopaminergic dysfunction at the level of the dopaminergic nuclei in ADHD.

2. Medication Effects:

SPECT and PET studies: (See Appendix Id.) Three (of four) SPECT studies and one (of one) PET study have shown that following Methylphenidate (MPH) administration, either DAT density in the caudate, putamen, and/or striatum decreased or dopamine levels in the striatum increased. It is believed that target medications such as psychostimulants increase exogenous dopamine by blocking the DAT (Volkow et al., 1998). Amphetamine and MPH both raise extracellular dopamine levels by blocking DAT; in addition, amphetamine directly releases dopamine (Seeman and Madras, 1998). Volkow and colleagues (1999, 2001) predict that there is

a certain optimal range for dopaminergic D2 receptors. By studying the responses of healthy subjects to MPH, while at the same time measuring D2 receptor levels, the following was hypothesized: too few receptors may not allow individuals to respond effectively to a salient stimulus, while too many receptors may be aversive. Since stimulants affect the behavior of children with ADHD and of healthy children in a similar manner (Rapoport et al., 1980; Rapoport and Germain, 2002), it may be that the same brain regions are involved in response to stimulants, but the baseline physiology and activation patterns of these regions may differ between the groups.

Brain Imaging With Psychostimulant Administration to Children: To date, two studies have combined imaging, psychostimulants, and a pediatric control population.

Langleben et al.: Using SPECT, Langleben et al. (2002) examined the effects of MPH discontinuation on cerebral blood flow in 22 boys with ADHD and 7 healthy controls. The researchers used a stimulus-controlled version of the go/ no-go task as in Vaidya et al (1998), discussed below. Unfortunately, task performance data were not reported, and therefore it is unknown whether performance differed between the on- and off-MPH conditions. However, because abnormal performance on go/no-go tasks is among the most consistent findings in ADHD, one might expect such differences in this study. The investigators found that when children with ADHD were not taking MPH, their regional cerebral blood (rCBF) flow was higher in the motor, premotor, and anterior cingulate cortices compared to the on-MPH condition. Surprisingly, there were no significant differences in blood flow in any region between patients with ADHD and healthy controls either in the on-MPH or in the off-MPH state. Also, there were no differences between controls in the off-MPH or on-MPH state. Exact results were not provided, and hence it is unknown how the rCBF of the controls and ADHD subjects compared. Perhaps the small number of control subjects (n=7) limited any conclusions.

Vaidya et al.: This is the only fMRI study to image both healthy and ADHD children during a go/no go task with and without MPH (Vaidya et al., 1998). Both children with ADHD and healthy controls performed a stimulus-controlled and a response-controlled version of the go/no-go task (Casey et al 1997). At baseline, children with ADHD showed decreased striatal activation compared to controls. Both groups showed improved performance on MPH on the stimulus-controlled task, but only the children with ADHD showed improvement with MPH on the response-controlled task. By examining fMRI data during the stimulus-controlled task, this study concluded that although the behavioral response to MPH is identical across all subjects, the brain's response was not; MPH increased striatal activation in children with ADHD but reduced striatal activation in controls. The findings were interpreted as highly novel, and no neurophysiological model was presented in an effort to explain this result. This study used a block-design, and performance differed between the ADHD and comparison subjects. Hence, the study could not determine whether between-group differences in activation patterns were confounded by between-group differences in performance. An event-related design would address this confound.

3. **Informative functional MRI tasks**: An fMRI task must be well-characterized and effective at engaging circumscribed brain regions and systems, produce robust signals in every individual, and show variance across individuals (Hariri and Weinberger, 2003). Vaidya's imaging paradigm does not allow researchers to control for performance or to examine the degree to which neural structures are engaged by specific types of events. If performance differed between ADHD patients and controls, any differences in activation could either be attributed to deficits in performance (e.g. neural responses to more errors in affected subjects) or to deficits in the degree to which one or another brain region (e.g. striatum) is engaged.

Alternatively, we have used the stop task and an event-related design to study motor inhibition in the fMRI environment (Protocol 02-M-0036). The stop task controls for performance and the event-related design allows investigators to contrast activations between trials involving successful inhibition and those involving unsuccessful inhibition. In the stop task, the subject is asked to perform a fast reaction time task, denoted as the primary task. Occasionally, a stop signal is presented, which requires the child to inhibit response to the primary task. In a sense, then, the stop task is a variant of the go/no go task. However, in the stop task, a "go" appears on every trial, and subjects are instructed to respond unless a stop signal also appears; the timing of the stop signal varies depending on the individual's performance on the previous stop trial. Thus, the stop task adjusts for inter-individual differences in motor execution. Since the timing of the stop signal is tailored to individual motor performance, inhibitory and motor execution processes are effectively dissociated and error rates are equated across different groups of subjects. The estimated speed of the inhibitory process, termed SSRT or stop signal reaction time, is calculated. Performance on this task differs between children with ADHD and healthy controls; seven of eight studies show that children with ADHD have, on average, a 103 ms longer SSRT than healthy controls, indicating that children with ADHD are slower to inhibit a response (Oosterlaan et al, 1998). Results from this meta-analysis suggest that this is a moderate-to-large effect. Moreover, children with a familial form of ADHD are more likely to have a prolonged SSRT than children with non-familial ADHD (Crosbie and Schachar, 2001). Studies in both healthy individuals and individuals with ADHD have found that SSRT is significantly shorter on MPH treatment than on placebo (Uftring et al., 2001, Tannock et al., 1989, 1995, Bedard et al., 2002). Hence, like the go/no-go task, the stop task is sensitive to stimulant effects in both impaired and healthy individuals. However, unlike the go/no-go task, the stop task produces similar rates of "incorrect" responses in impaired and healthy subjects. Therefore, the task eliminates confounds associated with differing error rates, and their associated neural concomitants, across impaired and healthy subjects.

The stop task can be used to identify brain regions involved in motor inhibition. As noted above, a contrast of particular relevance to psychopathology compares brain activation during stop trials in which subjects inhibit successfully ("stop correct") to activation during stop trials in which they do not ("stop incorrect"). Preliminary work from our group indicates that, in healthy adults, successful inhibition is referentially associated with activation of left inferior and bilateral medial prefrontal areas (Leibenluft et al., submitted). In other analyses, attempted inhibitions, whether or not they are successful, are associated with broader areas of activation, encompassing aspects of the basal ganglia, parietal, and prefrontal cortices. Rubia et al. (1999) found that when executing a similar stop task, children with ADHD, compared to controls, had lower power of response in the right mesial prefrontal cortex, right inferior prefrontal cortex, and left caudate than did controls. However, this study, like the Vaidya et al. (1998) study, used a block design, which does not allow for contrasts based on task performance.

In the present study, Vaidya's stimulus response task (developed by Casey et al 1997) and the stop task will be given. The two tasks will be used to examine which neural systems distinguish children with and without ADHD during the process of motor inhibition. Functional MRI, which uses no ionizing radiation, is ideal for testing children. It is essential to be able to study children because the deficits observed in adults with ADHD may not be the primary pathological defect but may rather result from an interaction of the primary neural deficit with maturation and aging processes. If time permits, the Durston (2003) Go-No-Go task will also be attempted, which has a parametric design. Even if the Durston task can not be incorporated however, there is a parametric component to the stop task (the stop signal delay) which will be examined.

4. Benefits of using twins: If ADHD subjects differ from controls in their pattern of response to stimulants, the basis for this difference is not clear as stimulants almost invariably improve performance, and placebo response is rare. Twin designs can, with certain assumptions, reveal the extent to which diagnostic differences can be attributed to genetic and non-genetic "state" factors. For most purposes, monozygotic (MZ) twins can be taken to be genetically identical whereas dizygotic (DZ) twins share 50% of their genes, on average. By using both MZ and DZ twins discordant for ADHD, the question of state versus trait influence on stimulant-related brain activation can be addressed. Statistical techniques on anatomic brain mapping have shown the usefulness of twin design in mapping genetic disease-related brain patterns (Thompson et al., 2002). These have already been adapted for analyses of functional activation patterns (Paul Thompson, personal communication).

C. The research question for the current protocol: Although healthy and ADHD children react in the same behavioral manner to psychostimulants, there may be differences between healthy children and those with ADHD in the brain circuits that mediate the behavioral response to medication. Imaging studies suggest that the difference lies in the frontal-striatal brain regions important for inhibitory control and in the striatal response to psychostimulants. However, no studies have examined the activation differences between healthy and ADHD children with a task that accurately controls for error rates in task execution and that allows for separate analyses of trials with successful and unsuccessful inhibition. Also, by using subjects at different degrees of genetic risk for the disorder, this study aims to untangle state and trait measures. The overall goal of this study will be to better understand the pathophysiology of ADHD while focusing on three specific aims: 1.To study brain activation patterns during response inhibition tasks in children with ADHD and in healthy controls. 2. To simultaneously examine the central and behavioral effects of a single-dose of amphetamine versus placebo in the two groups. 3. To examine (using monozygotic and dizygotic twins) brain activation patterns in relation to both clinical state and to the degree of genetic relatedness. Based on the data reviewed above, this protocol tests three hypotheses concerning the relationship between brain region activation, genetic relatedness, and ADHD diagnosis.

Hypothesis 1a: At baseline, children with ADHD will exhibit poorer performance on cognitive tasks compared to controls: specifically, those with ADHD will make more errors of commission on the go/no-go task and they will have a longer SSRT on the stop task.

Hypothesis 1b: On placebo, prefrontal cortex and striatal activation will be higher in controls than in children with ADHD during both tasks. On placebo, activation in three prefrontal ROIs (namely: medial, inferior, and dorsal) will be lower in children with ADHD than in controls, again, during both tasks.

Hypothesis 2a: After the amphetamine dose, both healthy controls and children with ADHD will show improved performance on the cognitive tasks, as evidenced by fewer errors of commission on the go/no-go task and a faster SSRT on the stop task.

Hypothesis 2b: On the stop task, both healthy children and those with ADHD will show increased striatal activation following the amphetamine dose. In contrast, as in Vaidya et al. (1998), on the go-no-go task, striatal activation will increase in children with ADHD and decrease in healthy controls following the amphetamine dose.

Hypothesis 3: Brain region activation response pattern will be related to ADHD symptom level rather than to degree of genetic relatedness.

D. Background of Approach: It is assumed that psychostimulants affect the behavior of healthy children and those with ADHD in the same manner (Rapoport et al., 1980; Rapoport and

Germain, 2002). As a result, it was assumed that brain activation in response to amphetamine was likely to be identical as well. Two recent controlled imaging studies with stimulants given to healthy and ADHD children have cast doubt on this (see section IIB). Langleben et al. (2002) found that psychostimulants lower cerebral blood flow in the anterior cingulate cortex and motor cortex in children with ADHD but have no such effect in healthy children. These results may explain why MPH helps relieve the symptom of locomotor hyperactivity. Vaidya et al. (1998) conducted the only fMRI controlled study in which MPH was administered both to children with ADHD and to healthy controls. Without MPH, striatal activation was greater in controls than in ADHD subjects. Both controls and children with ADHD improved significantly in the stimulus-controlled task while on MPH. During the stimulus-controlled task, MPH increased striatal activation in ADHD children but reduced it in healthy controls. Studies in animal models show that striatal engagement relates to appropriate execution of a planned motor response (Hikosaka et al., 2002). In Vaidya et al. (1998), between group differences in task performance show that children with ADHD and healthy children did not perform equally well: children with ADHD make more inappropriate motor responses. Therefore, one could argue that observed differences in activation patterns are secondary to observed differences in performance. However, the two studies (Langleben et al., 2002 and Vaidya et al., 1998) do raise the strong possibility that brain activation in response to psychostimulants is different in ADHD children than in controls. Both studies had small sample sizes and used less-than-optimal tasks, generating higher rates of inappropriate motor responding in patients than comparisons. Neither addressed the question of state versus trait. By using twin samples discordant for ADHD, unrelated children with ADHD, and unrelated controls, a larger sample size, and a more revealing task, differences in brain activation in response to psychostimulants can be examined. The study can not be carried out with adults as there is evidence for change in brain anatomy in ADHD late in adolescence (Castellanos), and adult ADHD samples differ significantly from childhood ADHD with respect to gender, co-morbidity and symptom pattern (Shaffer, 1994).

E. Qualifications of the Investigators: Three aspects of the investigators' extensive previous research are relevant to the current protocol. These include studies of: a) behavioral effects of amphetamine in ADHD and healthy children; b) stop tasks and other cognitive tasks in children; and c) fMRI in healthy and psychiatrically disordered children.

III. Study Design and Methods

A. Study Design Descriptive Statement: Following initial assessment for eligibility, the study will use a double-blind placebo-controlled crossover design, wherein all subjects undergo two drug challenges: a single dose of dextroamphetamine sulfate and of a placebo. Procedures for randomization will be implemented with the NIH pharmacy. All subjects will undergo fMRI one hour after each dose. Subjects with ADHD already receiving psychostimulant medication will withhold medication for 36 hours prior to each drug challenge.

B. Overview Summary: This study examines the behavioral and neural response to dextroamphetamine sulfate in four groups of children, namely unrelated children with ADHD; unrelated, healthy controls; monozygotic twins discordant for ADHD; and dizygotic twins discordant for ADHD. The twins will be selected in part from an already existing sample used previously for examination of clinical characteristics (Sharp et al., 2002). The healthy controls and children with ADHD will be recruited from nearby communities. Following telephone and mail screening, all groups will undergo three days of study, one involving a trial practice of the fMRI tasks, one involving placebo, and the third involving dextroamphetamine sulfate.

Procedures will be implemented using a double-blind, placebo-controlled crossover design with the placebo/dextroamphetamine order determined randomly. During both the placebo and dextroamphetamine days, subjects will undergo fMRI scanning, during which time two cognitive tasks will be administered. We considered randomizing task order, but we elected to administer the stop task second in all children. This allows us to more directly attempt to replicate prior results in Vaidya et al. (1998). Thus, the first task will be a stimulus-controlled go/no-go task as in Vaidya et al. (1998). The second task will be the stop task (Logan et al, 1994). Both tasks will test response inhibition, a cognitive process that is disrupted in children with ADHD. fMRI scans will be performed approximately one hour after placebo or psychostimulant is administered. Both tasks are needed to be relevant to the literature (Vaidya) and to better control for performance (stop task).

C. Study Phases: This study will have two phases. During phase I, all subjects will be screened for inclusion and exclusion criteria using procedures outlined below and will practice the cognitive fMRI tasks. During phase II, all subjects will receive both a single dose of dextroamphetamine and a dose of placebo in random order, using a double-blind cross-over design.

D. Sample Stratification: The sample will be stratified into four groups, based on genetic relatedness and on ADHD diagnosis. This will include a group of twin pairs: discordant (for ADHD) monozygotic twins, discordant dizygotic twins, unrelated healthy children, and unrelated children with ADHD. The inclusion of a genetically-unrelated healthy control group is required because, as shown in a previous study, unaffected siblings of children with ADHD may be genetically predisposed to exhibit the same abnormalities in brain activation patterns that are observed in children with ADHD (Vaidya et al., 1998).

E. Sample Size Justification: FMRI studies examining the effects of dopaminergic manipulations on the BOLD signal have noted large effect sizes (standardized differences [Cohen's d] of 1.0-1.2) (Rubia et al., 1999; Bush et al., 1999). Therefore, with sample sizes as small as n=14 per cell, assuming alpha = .05 two-tailed, we would have power of >.80 to detect between-group differences. We note that in Vaidya et al., 1998, the only other study that examined activation differences after stimulant administration in patients with ADHD and controls, significant between-group differences were found with a sample size of 10 patients and 6 controls. Our study will have more than twice as many healthy controls.

F. Data Analysis:

1. Cognitive Response to stimulants: Relative to placebo treatment, dextroamphetamine treatment is hypothesized to produce improvements in performance on the go-no-go and stop tasks (i.e. fewer errors of commission on the go/no-go task and shorter SSRT on the stop task). To test this hypothesis, we will contrast study groups using ANOVA/random effects regression models, one for each of the two tasks. Each of these analyses will have one between subject factor (ADHD vs. control) and one within-subject factor (stimulant vs. placebo). In each analysis, the continuous dependent measure from a given task (Y_{jkl}) is predicted by the following model: $Y_{jkl}= \beta_{0k} + \beta_{1j} + \beta_{2l} + \beta_{3lj} + \varepsilon_{jkl}$, where j indexes group (ADHD vs. control), k indexes person, and l indexes treatment (stimulant vs. placebo). As shown in the model, β_{0k} indexes the person-specific mean (random effect), β_{1j} indexes the overall mean difference for the dependent measure between ADHD vs. comparison subjects (fixed effect), β_{2l} indexes the overall mean difference across the two treatment conditions (fixed effect), β_{3lj} indexes the interaction between the two previous effects (β_{1j} & β_{2l}), and ε_{jkl} is a random effect for error. We will assess significance of

β_3 (group-by-treatment interaction) to evaluate the differential effects of stimulant treatment on task performance across our two study groups.

2. fMRI Response to stimulants: Because we enter this study with regionally-specified a priori hypotheses, fMRI analyses will examine changes in BOLD signal within pre-specified regions-of-interest (ROIs). Identification of ROI's will use established methods for cortical and subcortical parcellation on high resolution T1 weighted images. ROIs will comprise subcomponents of the striatum and PFC, as defined in our prior studies (Castellanos et al., 2002; Castellanos et al., 1996; Castellanos et al., 2001; Szeszko et al., 1999a; Szeszko et al., 1999b; Szeszko et al., 2001). Two methods will be used to analyze fMRI data. For the components of the striatum, including the caudate nucleus and globus pallidus, average BOLD intensity in the entire structure will be used as the dependent measure. This method will be used due to the small size of these structures. Moreover, similar methods have been used in Vaidya et al. (1998) and other recent fMRI studies of striatal activations during inhibitory tasks. For larger ROIs within the PFC, voxel-based methods with small volume correction will be used.

As in prior publications from our group (Monk et al., 2003; Nelson et al., 2003; Pine et al., 2002), analyses will begin with realignment and motion correction. Data from any subject with movement greater than 2 mm in any direction will be discarded. Stereotactic normalization, resampling, and spatial smoothing will use methods in SPM '99 (8 mm smoothing kernal). Smoothing will not be employed for the analysis of striatal activity. Results are co-registered on either individual subject scans or averaged, spatially/stereotactically normalized images for presentation of group results.

Striatum: Single values will be generated for each subject in each striatal subregion to quantify the magnitude of response in these ROIs, both during the placebo-day scan and during the stimulant-day scan. To examine between group differences in stimulant response, these sets of values will be submitted to the same type of random regression/ANOVA analysis, as noted above, used to examine stimulant-induced changes in cognition. To examine baseline differences, values will be used only from the placebo scan, and terms for a treatment effect and group-by-treatment interaction will be excluded from the model.

Larger ROIs: Hypotheses on task-associated changes in larger PFC ROIs will be tested using random effects regression models in SPM '99 to analyze task effects on the hemodynamic response. As in prior studies, procedures will draw on the expertise of Eric Zarahn, Ph.D. to model effects on BOLD activity of specific events occurring within larger blocks of events. Full details of the application of these approaches to our work appear in recent publications (Monk et al., 2003; Nelson et al., 2003; Pine et al., 2002).

In brief, these analyses will test secondary hypotheses concerning response to stimulants within three PFC sub-regions, comprising medial, inferior, and superior components. These regions will be defined based on anatomical criteria (Szeszko et al., 1999a; Szeszko et al., 1999b; Szeszko et al., 2001), as in our prior fMRI studies (Monk et al., 2003). Cerebellar regions will also be examined bilaterally (Indovina and Sanes, 2001).

We provide further details for one specific contrast in the go/no-go task (parallel models test hypotheses for other contrasts). Specifically, for the go/no-go task, we will first compute for each subject the interaction of a task factor (e.g. "no-go" vs. "go") and a "medication" factor (stimulant vs. placebo), yielding a "double difference" ("no-go" during stimulants – "go" during stimulants) – ("no-go" during placebo – "go" during placebo). Selection of the specific "task factor" contrasts is based on prior data documenting task-related activation in the contrast, either from Vaidya et al. (1998) for the current contrast or from data in our group for the stop task. These individual-subject data will then be submitted to a second, group-level "random effects" analysis in SPM '99, where we will use the small volume correction to determine a ROI-wise α=.05 threshold for each of the specific ROIs. This provides a group level significance map for

precise PFC regions where activations during stimulants vs. placebo are hypothesized to differ in ADHD vs. comparison subjects.

G. Justification for use of medication washout: As outlined in Section II, compelling scientific data point to the importance of studying the neurophysiological effects of amphetamine versus placebo in children with ADHD and healthy controls. As such, it will be necessary for children with ADHD currently on stimulant medication to temporarily withhold it. Since drug holidays are often recommended for patients with ADHD and since temporarily withholding stimulant medication is standard practice in over 100 outpatient studies of ADHD, it is unlikely that this will present a problem. If the family finds this unacceptable, the children will not be entered.

IV. Subject Enrollment

A. Recruitment – sample composition and characteristics:

The sample will consist of: 14 healthy children and adolescents, 14 subjects with ADHD, 12 pairs of dizygotic twins (n=24) discordant for ADHD and 12 pairs of monozygotic twins (n=24) discordant for ADHD.

ADHD subjects: Determination of ADHD phenotype will be made based upon the Structured Interview and Rating Scales (with a parent and separately with the patient if the patient is older than 9), Conners Teacher Rating Scale, and the Teacher Report Form (Conners, 1997).

Healthy controls: Subjects will be assessed for inclusion and exclusion criteria. Screening will include a telephone interview, parent and teacher rating scales and an in-person assessment that will include physical and neurological examinations, structured psychiatric interview using the K-SADS (Kaufman et al., 1997), and Child Behavior Checklist. History of ADHD in all 1st degree relatives will be investigated using the Family Interview of Genetic Studies. Individuals who meet inclusion criteria will be contacted to schedule the necessary imaging sessions.

Discordant twins: Each individual will be assessed for inclusion and exclusion criteria. Healthy twins will undergo the same screening as healthy control subjects and twins with ADHD will complete identical screening as other subjects with ADHD.

B. Inclusion criteria:

ADHD subjects: a) hyperactive, inattentive, and impulsive behaviors that were impairing in at least 2 settings (home, school, or during testing and/or interviews), b) a Conners' Teacher Hyperactivity rating greater than 2 SDs above age mean, c) a DSM-IV diagnosis of ADHD based upon the K-SADS, the Conners Teacher Rating Scale, and the Teacher Report Form.

Healthy controls: Subjects will be included as healthy controls using the following criteria: no current psychiatric or medical conditions revealed during screening and with the K-SADS with exceptions listed below. Mild past anxiety disorder or depressive episodes will not be exclusionary.

All subjects must be between 9 and 18 years of age, be able to give consent, and have a minimum IQ of 80.

C. Exclusion criteria:

ADHD subjects: Any DSM-IV psychiatric diagnosis with the exception of Oppositional Defiant Disorder or mild learning disabilities that are often comorbid with ADHD. Any subject who has a history of substance abuse or smoking (based on parent report or K-SADS interview)

will be excluded. Any subjects who may not tolerate a drug holiday during testing will be excluded. Past history of mood or anxiety disorders will not be exclusionary. Subjects will be excluded with a full-scale WISC-III IQ score less than 80.

Healthy controls: Any medical or neurological disorders on exam or by history, any developmental disorders or ADHD in a first-degree family member.

Any subject who is taking medication will be excluded as well as any subject who meets general MRI exclusion criteria. Any subjects with a body weight below 25 kg will be excluded.

D. Study initiation and screening methods:

1. Sample: Preliminarily, 10 healthy subjects will be piloted on the two tasks. For the protocol: ADHD subjects age 9-18 will be recruited locally and may also include ADHD subjects who have participated in previous studies. Healthy controls will be recruited locally. Discordant twins have been and will be recruited nationally through patient advocacy groups, mothers of twins groups and from pools of available subjects from previous studies (Castellanos et al., in press; Sharp et al., 2003).

2. Screening methods: Subjects will be assessed using three sets of procedures. These procedures will be completed over two visits, though there will be some flexibility in this schedule to accommodate families.

a. Psychiatric History: All subjects will be screened for lifetime history of psychiatric disorders using the K-SADS Interview administered by a trained clinician. This measure requires one-to-two hours to complete. Families will also be assessed for family history of psychopathology, through an interview with at least one parent.

b. Physical Exam: All subjects will receive a medical history and physical examination from a licensed physician. The exam will assess all relevant inclusion/exclusion criteria. This measure requires 30 minutes to complete.

c. Neuropsychological Assessment: Subjects will undergo full WISC-III testing by a trained clinician during a medication-free period. Diagnostic interviews with parents require two hours to complete.

V. Procedures

A. Details of method: A general overview of the procedures and description of data analytic methods appear in Section III. This section summarizes methods for assessments, the drug challenge, and fMRI portions of the study.

B. Details of assessment by study phase:

1. **Schedule of visits:** Children and parents are seen as shown below by psychiatrists or psychologists for 30-40 minutes. A list of procedures at each visit appears below.

				Schedule			
Form	Informant	Time (min)	Interviewer	Screening	Day 1	Day 3	Day 8
KSADS	C, P	120	Therap	X			
Neuropsych Testing	C	60-120	RA	X			
FMRI Assessment	--	60-90	--			X	X

Physical Exam	C	20	MD	X			
Amphetamine/Placebo	C	60	MD			X	X
Cognitive Tasks (stimulus-controlled go/no-go task & stop task)	C	25	RA		X	X	X
Cheek swab for DNA	C, (twins only)	2	MD	X			
Post-task survey	P	5	RA		X	X	X

Key for abbreviations in table appearing above: "KSADS" full = Complete Kiddie SADS; Therap = trained, non-medical researcher or social worker, RA = research assistant, MD = child psychiatrist or pediatrician, P = parent, C = child.

2. Drug Challenge Procedure:

Subjects are enrolled into a double-blind, placebo-controlled crossover drug challenge study and are randomly assigned to either an amphetamine drug challenge first and placebo second or placebo first and amphetamine second. To avoid carryover effects, a period of at least 2 days between each drug challenge will be established. We will use a single dose of dextroamphetamine sulfate at therapeutic levels; all children will 0.10mg p.o. of dextroamphetamine. A single dose is chosen because amphetamine response is related more to rate of absorption and relatively less to blood level. The dose/per kg would be expected to vary therefore from .4 to .12 mg/kg across our age range.

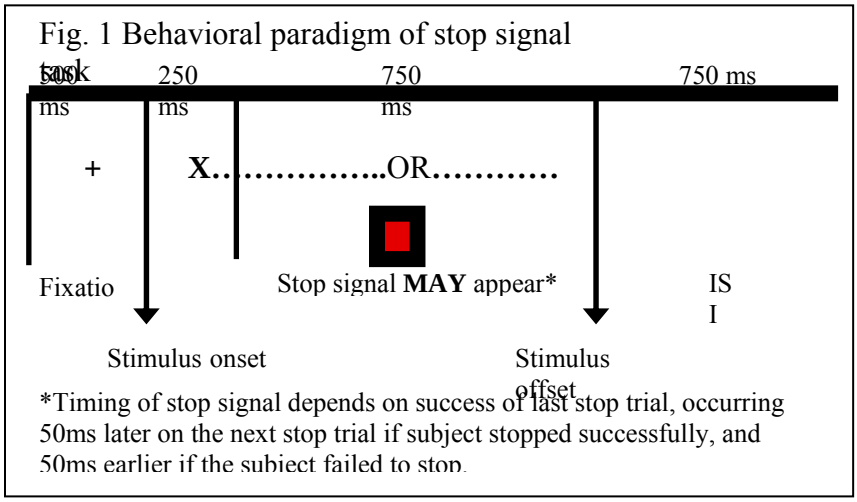
The effects of dextroamphetamine versus placebo on performance will be evaluated by administering the two cognitive tasks one hour after the subjects receive a placebo dose and one hour after an amphetamine dose.

3. fMRI Paradigms:

a. Stimulus-controlled go/no go task: Subjects will perform a stimulus-controlled version of the go/no-go task. The task will last for 5 min and consist of six alternating go and no-go blocks, each 25 s long. Each block will begin with the presentation of the task instruction ("press for all letters" for go blocks and "do not press for X" for no-go blocks) followed by a consonant letter on each trial. For go blocks, subjects will press a button for every letter. "X" will not be presented and "C" will occur in 50% of the trials; no other letter will be repeated within each block. For no-go blocks, subjects will press the button for every letter except "X"; "X" will occur in 50% of the trials and no other letter will be repeated within each block. Go and no-go blocks will be equated for the rate of presentation (exposure duration = 500 ms, inter-trial interval = 1.4 s) and number of trials but differ in the number of key presses (12 in go blocks, six in no-go blocks) (adapted from Vaidya et al., 1998 and Casey et al 1997.)

b. Stop task: The stop task, developed to measure response inhibition, has been used extensively in behavioral and in fMRI studies. The task is based on previous published work (Logan et al., 1994). Subjects are trained to proficiency prior to entering the scanner. In the scanner, subjects complete four blocks, each with 64 trials (32 go, 16 stop, and 16 blank trials). As in prior fMRI studies, blank trials provide an implicit background against which to contrast other events. The three trial types are distributed randomly throughout each block.

During go and stop trials, a white fixation cross appears on a black background for 500 ms; it is replaced by an "X" or "O" for 1000 ms (Fig.1). Trials are separated by 750 ms. During stop trials, the stop signal is indicated by a change of the black background to red after the "X" or "O" appears. Using a button box, subjects indicate "1" for "X" and "2" for "O", but are told to not respond if the background color changes to red. Subjects are told that they must respond before the "X" or "O" disappears from the screen (i.e. within 1000 ms).



On the first "stop" trial, the stop signal appears 250 ms after the "X" or "O". Subsequent stop signal timing is determined by performance on the previous stop trial. If the subject successfully inhibited, the next stop signal appears 50 ms later, making inhibition more difficult. If the subject did not successfully inhibit, the signal appears 50 ms earlier on the next stop trial, making inhibition easier.

c. In addition, if time permits, we will implement the Go-No-Go task described in Durston et al 2003 This task is conceptually identical to the task described above in (a). However the Durston et al task uses an event related design and a parametric manipulation.

C. Details of secondary procedures: The main secondary measure we will collect consists of genetic relatedness to proband. For all twin pairs, zygosity will be determined by DNA analysis using the following markers: DIS80 (20 alleles), DI7S30 (13 alleles), *apo*B (20 alleles), COL2A1 (10 alleles), *v*WA (9 alleles), and HUMTH01 (6 alleles). Assuming an average heterozygosity rate of 70% per marker, this procedure will falsely classify a DZ pair as MZ in approximately 1/482 cases. DNA will be obtained by cheek swab.

Subjects will complete a survey after each imaging session that will measure their motivation to complete the required tasks during the fMRI scans. This survey will require each subject to rate the strength of several emotions (e.g. "boring", "tiring", "interesting", "difficult") felt during the tasks on a scale from one to ten. Data from these surveys will be used to analyze the effect of dextroamphetamine on motivation and to analyze the saliency of the tasks.

D. Relationship to other studies proposed: Drs. Leibenluft and Pine are conducting fMRI studies using the stop task in normal adults (Leibenluft et al, submitted) and adolescents (Protocol 02-M-0036), as well as in children with bipolar disorder with and without comorbid ADHD (protocol #00-M-0198). These data will later be examined in relation to data from the present study.

VI. Provision of Care to Research Subjects

A. Concomitant clinical care: During their participation in this study, subjects will have access to a variety of clinical care and resources. A medical doctor will supervise all procedures and will provide medical care to any subject who feels discomfort or pain during any part of the

study. All subjects with ADHD will have the option of consultation with a licensed clinician to discuss treatment options and current psychiatric status. Participation in this study may provide the opportunity for a subject to assess the effectiveness of a dextroamphetamine treatment on his/her ADHD symptoms compared to his/her current treatment. A certified clinician will be available during the study to discuss medication adjustments based on the effectiveness of the dextroamphetamine treatment used in this study and on the treatment history of the subject. All data obtained from each subject will be available to the subject and his/her family for clinical application.

B. After care, including plans after completion of protocol, after discharge from study and during follow-up: Outpatient consultation will be available to all ADHD subjects for 3 months following the conclusion of the study. For ADHD subjects, if desired, these visits would provide meetings with a licensed clinician expert in ADHD to adjust treatments and to discuss medication options and the current psychiatric status of the subject. Follow-up consultations with NIH clinicians will not be a requisite part of the study protocol; these visits will be scheduled solely to provide further consultation for subjects who are seeking more information. It is expected that many ADHD subjects will prefer to see their treating pediatricians and will not utilize this follow-up resource. Healthy subjects will be given the phone number of the study physician to contact in case of any concerns. All healthy subjects will be contacted one week after the completion of testing to make sure that the subject and his/her family have no additional questions about the study.

C. Reasons for discontinuation from study including any required transitional care: Participation in this protocol is voluntary. Parents may withdraw their children from this study at any time without negative repercussion, and children may withdraw assent. Subjects who have withdrawn from the study will be eligible for consultation with clinical staff as described above.

The research team may discontinue the participation of a subject at any time. This discontinuation may be the result of an unexpected reaction, because the subject failed to follow directions or because of the termination of the study.

D. Toxicity criteria: Any subjects exhibiting adverse effects of dextroamphetamine will be seen by a clinician if desired. At the dose prescribed only mild restlessness, anxiety, loss of appetite, or insomnia is anticipated. All subjects will be monitored by a clinician throughout the imaging sessions and will be available for immediate medical assistance if necessary. Clinicians at the NIH will be available for 24 hours after the completion of an imaging session to treat any adverse events associated with dextroamphetamine treatment.

VII. Human Subject Risks and Protections

A. Consent & assent documentation: The current study examines brain function and response to a single stimulant dose in both psychiatrically healthy children and adolescents, and children and adolescents with ADHD. For the healthy control groups, volunteers will be solicited from the community.

Parents of healthy volunteers will be informed of the nature of the assessments, medications and imaging procedures included. Participants will be informed about the purposes of the research. They will be advised that the information obtained will utilize a confidential code and can only be accessed by Drs. Rapoport and Tossell, and will be treated to group statistical analyses only.

B. Risks of study participation by phase with means for minimizing risks:

1. Psychiatric assessment: Based on our research and clinical experience with children of this age group to date, no adverse reactions are anticipated as a result of the assessment procedures. For most of our studies, the task of completing the face-to-face interviews, tests, and scales will require a maximum of three hours for both parents and children. It is highly unlikely that a study participant will become upset about the questions or interview process used in the study. Each measure has been used extensively in hundreds of children without adverse effects. Children may refuse study participation at any time, and the standard interviewing and data collection procedures will cease, should any adverse reactions be noted. All subjects completing the interviews and questionnaires will be provided with phone numbers so that they can have any questions answered that they feel have not been satisfactorily addressed. The investigative team has extensive interview experience, and they will determine if there is a need for clinical intervention; if necessary, arrangements for appropriate clinical services will be made.

2. Functional MRI (fMRI): Recently, new methods for functional brain imaging have been developed that use MRI to observe activity-related, hemodynamic changes with high spatial and temporal resolution. The most promising method, as is used in the current protocol, examines changes in blood oxygenation. Because of the different magnetic properties of oxy- and deoxyhemoglobin, increased levels of blood oxygenation are associated with increased signal for some MR imaging methods, including T2*-weighted gradient echo imaging and echo-planar imaging. Increased neural activity is associated with this increased signal, presumably because local, activity-related increases in blood flow are greater than increases in oxygen extraction, resulting in higher ratios of oxy- to deoxyhemoglobin. Because the change in signal is due to properties inherent in normal blood constituents, injection of contrast agents or tracers and sampling of plasma are unnecessary.

All studies in the current protocol involve presentation of visual stimuli while the subject is in the scanner, and the subject responds by pressing buttons with the thumb of his dominant hand. These studies will be performed in a GE 3 Tesla scanner, though the GE Sigma 1.5 Tesla scanner may also be used on occasion. All scanners are located in the In Vivo NMR Center in the Clinical Center. During a scan the subject hears a loud rhythmic tapping or banging sound. This noise is caused by the switching of the gradient coils that is necessary to produce the image. Subjects are warned of this prior to scanning, and most do not find it to be objectionable.

MRI is widely regarded as a safe, noninvasive procedure for visualization of brain tissue in both adults and children. The risks involved with fMRI are the same as those involved in standard anatomic MRI, since these procedures rely on the same physical properties of brain tissue. As noted above, this study will be performed on an FDA approved 3T scanner at the NIMH. FDA standards for minimal risk MRI require that four criteria be met: 1) a static magnetic field no greater than 4T; 2) specific absorption rates a) no greater than 4W/kd for the entire body for 15 minutes, b) no greater than 3W/kg over the head for 10 minutes, and c) no greater than 8W/kg in any gram of tissue in the head or torso or 12W/kg in any gram of tissue in the extremities for five minutes; 3) a time rate of change in the field that does not produce physical discomfort or painful nerve simulation; and 4) a peak sound pressure level that does not exceed 140 dB or A-weighted R.M.S. pressure level that does not exceed 99dBA with hearing protection. Each of these guidelines will be monitored throughout the study to insure that none are exceeded.

MRI at 1.5 Tesla is a routine clinical procedure, and issues regarding radio frequency deposition, time varying magnetic fields, and the static field at 1.5 Tesla do not require detailed discussion. MRI at 3 Tesla is not used for clinical scanning but is now widely used for research

with healthy human subjects. This includes studies with healthy children. The gradients for the GE 3 Tesla scanner are higher performance, in terms of gradient strength and slew rate. The gradients for the 3T scanner have a maximum gradient strength of 4 G/cm, which is greater than the 2 G/cm gradient strength of the 1.5 T scanners at the NIH. Gradient strength allows for higher resolution and for study of water diffusion in tissue. No studies have documented any detrimental effects of gradient magnitude. The maximum slew rate, the maximum rate at which the gradients change in magnitude, of the gradients on the 3T scanner is 150 mT/m/sec, which is greater than that on the 1.5T scanners (120 mT/m/sec). A higher maximum slew rate allows for faster imaging which is generally better because the shorter readout window (time to collect an image) causes images to be less contaminated by susceptibility or motion artifacts. It is well known that if the gradients are switched too rapidly, peripheral nerve stimulation can take place. The 3T scanner has identical safeguards as the 1.5 T scanner in that the maximum allowable slew rate is 66% of the FDA limit. Lastly, because of the higher radio frequencies associated with the 3T scanner, (i.e. at 1.5 T protons have a resonance frequency of 63 KHz and at 3T protons have a resonance frequency of 125 KHz), larger amounts of energy are deposited into the tissue during scanning. Tissue heating becomes a concern for certain pulse sequences at higher field strength. Again, the operating system for the scanner has built-in safeguards that only allow scanning with specific absorption rates (SAR) of radio frequency that are well below guidelines established by the Bureau of Radiological Health, FDA. The operation system limits radio frequency deposition in the head to an average rate of 10 watts, < 4 w/kg, which has been shown to raise the average core temperature approximately 0.3 deg. C. These temperature changes are within the normal diurnal rhythms (+/- 1 deg. C.) found in human core temperatures or a change associated with a brisk 20-minute walk (+/-1 deg. C.).

Based on pilot work, fMRI in children and adolescents has been considered a minimal risk procedure by the IRBs at New York State Psychiatric Institute (NYSPI), by the Center for Advanced Brain Imaging (CABI), the Nathan Kline Institute (NKI), and in previous protocols at the NIMH. These are institutions where Dr. Pine has conducted previous fMRI studies. Prior fMRI studies by our group and by other groups document the innocuous nature of these procedures. Each child who undergoes fMRI in our laboratory trains in a similar device to increase familiarity and reduce any stress associated with the novelty of the procedure. We also interview each child who completes our fMRI studies following the study. Children rate a set of negative emotions (e.g. “scared”, “angry”, “grouchy”) using 10-point scales, with a score of 1 indicating “no” degree of negative emotion and a score of 10 indicating extreme degrees of negative emotion. No child in our studies has rated the procedures as anything more extreme than a 3, in terms of negative experiences. Of note, the tolerability of fMRI in our studies, as well as our ability to generate usable data, may relate to our use of an fMRI simulator device. Each child studied in our laboratory undergoes training on our simulation to reduce any apprehension concerning the procedures of the study.

3. Single dose usage of stimulant: One significant ethical consideration is whether the administration of a single dose of stimulant to a healthy subject might psychologically encourage future recreational use of the drug. There are several reasons why this is unlikely. Dextroamphetamine and methylphenidate, when used to treat children and adolescents with ADHD, are administered at consistent, low doses for several years. During this type of treatment, no sensitization to the medication is observed. In addition, long-term follow up of subjects from the 1980 NIH study (Rapoport et al., 1980) in which psychiatrically healthy children were administered a single dose of amphetamine revealed no adverse effects or increased risk of drug abuse in subjects followed for at least five years after the conclusion of the study (n=14). The low potential for sensitization and abuse of oral stimulants has been

illustrated by a series of studies that followed ADHD patients treated with stimulants during childhood and/or adolescence. Three published studies have found that stimulant-treated ADHD patients had a reduced rate of later substance abuse compared to ADHD patients who were not treated (Total sample size = 1393) (Barkley et al., 2003; Biederman et al., 1999; Wilens et al., 2003). Only one study found an increased rate of substance abuse among the stimulant-treated group for tobacco (increase of 50.2% with over 1 year of stimulant treatment; n=84 medicated ADHD, 81 non-medicated ADHD) and cocaine (82.6% increase with over one year of stimulant treatment; n = 84 medicated, 81 non-medicated ADHD) (Lambert and Hartsough, 1998). Most recently, a study followed 100 psychiatrically healthy children with mild reading disabilities for 16 years after they had completed a 16-week treatment of either methylphenidate or placebo (Mannuzza et al., in press). There was no significant difference in the rate of substance abuse at follow-up between those treated with methylphenidate and those treated with placebo.

Methylphenidate and dextroamphetamine have been shown to block dopamine transporters (DATs) resulting in an increase of extracellular dopamine in several areas of the brain including the striatum and frontal lobe (Volkow, 2002a). Chronic administration of methylphenidate or amphetamine has, however, been shown to induce stimulant sensitization in mice and rats (Achat-Mendes et al., 2003; Battisti et al., 2000; Brandon et al., 2001; Gaytan et al., 2000; Sokolov et al., 2003). All 6 of these studies introduced the stimulants using intraperitoneal or intravenous injections; this method results in a much more rapid uptake and shorter half-life than when the drug is introduced orally (Volkow et al., 2002b). The longer half-life observed during oral administration suggests that oral stimulants have a lower potential for abuse and fewer reinforcing effects than administrations using intravenous or intraperitoneal injections (Oldendorf, 1992).

A second issue involving the use of stimulants relates to reports of insomnia and loss of appetite during stimulant treatment. Treatment with stimulants causes a statistically significant increase of insomnia and appetite suppression over a placebo (Ahmann et al., 1993; Fine and Johnston, 1993; James et al., 2000). Although there is risk for these adverse effects, limiting the exposure of the subjects to a single dose of stimulant should reduce the possibility of any subject experiencing more than a few hours of side effects from the medication. Moreover, with the proposed low dose to be used, the effect of these side effects on children will remain well within the range of physiological, affective, and cognitive effects regularly experienced by children in their every day lives. There are a range of other concerns associated with stimulant use including constipation, diarrhea, nausea, and confusion. These effects have never been observed after a single dose of stimulant and will not be further discussed in this protocol. We have considerable experience in the use of psychostimulants among both healthy and impaired children. In a previous NIH healthy volunteer study using doses of 0.35 mg/kg there were no significant adverse effects (Rapoport, 1980). Due to the sensitive ethical issues in this study, dosage for this study will be limited to 0.25 mg/kg in an effort to further minimize any side effects while still inducing measurable pharmacological effects on behavior and brain activation patterns. At this dosage level, adverse effects from a single-dose of dextroamphetamine will fall within the normal experience of a child's life and therefore will pose minimal risk.

4. Stimulant-Free Period: Participation in this study will require that ADHD subjects who are taking psychostimulants be off these drugs for at least 36 hours prior to all neuropsychological testing and imaging sessions. These periods are necessary to allow for a medication "wash-out" so that all subjects are clear of psychostimulants at the time of their treatment and imaging for this study. This inconvenience may result in an increase in inattentive and hyperactive behavior for some affected subjects during these stimulant-free periods. If there

is any concern about the ability of a subject to tolerate a stimulant holiday, he/she will be excluded from this study.

5. Confidentiality: Every necessary step will be taken to prevent identification of study participants of violations of confidentiality of the data. Information will be stored using a confidential code and data will be treated only as groups. All data entered into a database will appear only in coded form. Members of the research team will have access to these coded data. Only staff directly involved in the care of each subject will have access to clinical documents that contain identifying information. This will include research assistants, clinical staff, and the study psychiatrist.

6. Safety Monitoring: All procedures will be performed under the supervision of a medical doctor. If at any point in the study a subject feels any discomfort or pain, the procedure will be stopped and the subject will be given medical attention. Families of the subjects will be provided with phone numbers for emergency coverage, 24-hours/day in case of adverse effects of medication.

7. Emergency Treatments:

- **a. Assessment Phase:** If, during the course of interview and assessment procedures, study staff identifies any condition that should require immediate clinical intervention or official reporting (e.g., suicidality, child abuse), all necessary steps will be taken. In the case that staff determines that the child is at significant risk for self- or other-destructive behavior, the parent will be notified, any mental health or professional persons currently treating the child and family will be contacted (with parental permission), and necessary treatment steps (e.g., hospitalization, referral to a care provider, etc.) will be offered.
- **b. Imaging Phase:** If, during the course of the study, a subject's condition deteriorates significantly, the subject will be removed from the study. At this point or any other point where subjects are removed from the study for non-emergent reasons, short term clinical care will be provided by staff within the Child Psychiatry Branch, under the direction of the study physician, Dr. Julia Tossell.
- **c. Clinical Care After Study:** The total amount of time that out-of-study psychiatric consultation will be provided is expected to vary, given the diverse clinical needs of these patients. Consultations about treatment options and psychiatric condition by the study psychiatrist will be available for up to three months following the conclusion of the study.

8. Procedures for minimizing risk:

- **a. Recruitment and Assessment Procedures:** To reduce subject fatigue, the recruitment and assessment procedures may be spread out over two visits, with breaks interspersed to reduce any discomfort. If, in the opinion of the study staff, PI, subject, or his/her family, the assessment procedures or study participation is adversely affecting the subject's emotional well-being, the clinical circumstances will be reviewed to determine what additional steps should be taken.
- **b. FMRI Procedures:** We routinely use a series of procedures to minimize the risk for upset in children and adolescents who participate in our prior and proposed studies. Prior to screening, through the use of a simulator,

subjects are habituated to the MRI environment. The procedures are conducted in the presence of a trained clinician and subjects will have ready access to the team should they experience any problems. During scanning the subject can be seen at all times by a person standing in front of the bore or through the window between the control room and the scanner room. The subject can communicate with the control room personnel via an intercom at the operating console and can be removed immediately from the scanner if necessary. Subjects wear earplugs to minimize exposure to excessively loud noises, and the length of each MR study will not exceed 90 minutes. Each subject is interviewed immediately following the procedure to detect any problems.

c. **Stimulant Treatment Procedures:** The risks associated with exposure to psychostimulants will be minimized in two ways. First, exposure to stimulant treatment will be limited to a single dose. Second, stimulant treatments will be administered orally. Oral administration lengthens the half-life of the drug and effectively prevents any psychological "high" or stimulant sensitization. In addition, a trained clinician will be present during stimulant treatment to supervise and, if necessary, provide assistance.

C. Benefits of study participation:

There are no direct benefits of the study for any group. Indirect benefits vary for each group of subjects:

Healthy controls: Healthy children may learn about the experience of being in a scientific research project; they will learn about the research process and about brain imaging. Some children may receive some sort of science credit or create a science fair project out of the experience.

ADHD subjects: Participation in this study may help these subjects better understand the effects of their own medication. The involvement of these subjects in the experiment may also teach them about clinical research and the experimental process. Their participation in this study may also provide these subjects with an opportunity to examine the effectiveness of this medication on their ADHD symptoms. Participation in this study will also involve free consultation from a licensed clinician at NIMH for all subjects in this group.

Healthy twins: Many of the healthy twins may participate in this study to help further the understanding of their sibling's condition. The involvement of these children and adolescents may provide this group with an opportunity to experience first-hand the effects of the medication that their twins may be taking.

ADHD twins: Participation in this study may help these subjects better understand the effects of their own medication. The involvement of these subjects in the experiment may also teach them about clinical research and the experimental process. Their participation in this study may also provide these subjects with an opportunity to examine the effectiveness of this medication on their ADHD symptoms. Participation in this study will also involve free consultation from a licensed clinician at NIMH for all subjects in this group.

D. Investigator conflicts of interest: None.

E. Privacy and confidentiality provisions: Information will be stored using a confidential case number, and no identifiers (name, address, phone number, etc.) will be used that could allow direct linking of database information to individual subjects. Where temporary linking of information with identifiers is needed, such identifiers will be temporarily attached to the data, and will be removed after information has been encoded. Information will be stored using a confidential code and data will be treated only as groups. All data entered into a database will appear only in coded form. Members of the research team will have access to clinical documents that contain identifying information. This will include research assistants, clinical staff, and the study psychiatrist.

F. Adverse event reporting: Adverse events associated with assessment, placebo and amphetamine administration, and fMRI scanning will be monitored during each visit. All clinically significant adverse events will be immediately reported to the IRB. A summary of all adverse events will be provided to the IRB during each yearly review of the protocol.

G. Data and safety monitoring process: The IRB and clinical director will decide if we need to establish a Data and Safety Monitor (DSM) for this study. The Data and Safety Monitor would monitor and report unexpected or serious adverse events associated with this study. The Data and Safety Monitor would follow the guidelines of the NIH and HHS. These duties do not obviate the responsibility of the Principal Investigator to report serious adverse events directly to the IRB, but it allows a further layer of protection and supervision for the subjects. If a DSM is chosen for this study he/she will report any unexpected adverse events to the IRB within 24 hours.

H. Subject compensation:

All subjects who participate in any part of this study will be compensated. Financial compensation will be as follows:

Screening Session - $70
- 3 Hours
- K-SADS: 1 Inconvenience Unit (IU)
- Physical Exam: 1 IU
- WASI: 1 IU

Visit 1 - $250
- 4 Hours
- fMRI Session: 13 IU
- Placebo Treatment: 1 IU

Visit 2 - $250
- 4 Hours
- fMRI session: 13 IU
- Amphetamine Treatment: 1 IU

Total possible study compensation: $570

VIII. Pharmaceutical, Biologic, and/or Device Information

A. Source: Preparation of the placebo and dextroamphetamine treatments for the "blind" will be completed by the Clinical Center pharmacy. During this preparation, the pharmacy will keep all records of treatment randomization; neither the subject nor the research team will be able to identify any given treatment. A double-blind preparation is preferable to an open trial

because of the minimization of bias. Dextroamphetamine and placebo treatments will be prepared as liquids so that proper doses can be administered to each subject based on his/her body weight.

B. Relevant pharmacology: The current study will utilize a single-dose treatment of dextroamphetamine for both the subjects with ADHD and the healthy control group. Amphetamine treatment is widely administered to children and adolescents with ADHD and effectively increases attention and decreases hyperactivity in individuals who have been diagnosed with ADHD. Dextroamphetamine is well absorbed after oral ingestion and reaches peak blood concentrations within two hours of administration. Mean half-life for dextroamphetamine elimination is approximately 10 hours and the drug is excreted from the body in urine. Appropriate dosage for this study will be determined by body weight (0.25 mg/kg.) and will be comparable to therapeutic dosage. Amphetamines act as psychostimulants by facilitating the release and blocking the reuptake of biogenic amines, specifically dopamine, norepinepherine, and serotonin. This mechanism results not only in psychostimulation, but can also induce insomnia and loss of appetite at the dosage required for this study. Amphetamines also inhibit the enzyme monoamine oxidase. Amphetamines, when administered chronically, have potential for abuse and can be habit forming.

C. Toxicity: Symptoms of dextroamphetamine overdose include the following: constipation, panic, over-stimulation, restlessness, rapid respirations, and tremor. Stimulation of the central nervous system can be followed by depression and/or fatigue. Acute amphetamine overdose can result in convulsions, coma, and death and requires emergency medical support of body systems with attention to amphetamine elimination. Adverse effects are rarely seen at dosages below 20 mg. Subjects in this study will be administered a single low, therapeutic-level dose of amphetamine that is not likely to induce toxic effects. A minimum weight requirement (25 kg) will be established for all subjects. This requirement will prevent the administration of significant dextroamphetamine doses to children with low body weights. In the previous NIH healthy volunteer study using these doses there were no significant adverse effects. Any adverse effects that result from the dosage levels utilized in this protocol will fall within the experience of a healthy child's life and will pose minimal risk.

D. Incompatibilities: Volunteers on other medications will be excluded from this study.

E. Administration Procedures: Single doses of amphetamine will be administered orally to all subjects. Oral administration of amphetamine is commonly used to treat children and adolescents who are afflicted with ADHD. Oral administration is favorable to intravenous or intraperitoneal injections due to the longer half-life associated with oral stimulants (Volkow, 2002). Due to the increased half-life of this type of administration, oral stimulants produce no psychological "high" and are less likely to be abused than injected stimulants. In addition to the psychological benefits of this type of administration, giving the drug orally also eliminates the exposure of the subjects to needles that would administer intravenous or intraperitoneal stimulants.

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Appendix Ia: SPECT and PET Studies: Brain Abnormalities in ADHD

Author & date	Study Type	Sample	Method	Locus	Relevant Results	Comment
Kaya et al., 2002	Tc-99m HMPAO SPECT scan	13 ADHD children 7 healthy controls age 7-12 yrs old **None previously treated with stimulant medication**.	Conners teachers questionnaire rating; Du Paul parents and teacher questionnaire rating. SPECT imaging For each region of interest, ADHD patients were divided into two groups according to degree of hypoperfusion and compared with symptom rating scales.	Hypoperfusion in the right medial temporal cortex and the right lateral temporal cortex in children with ADHD when compared with controls.	↓ rCBF in right medial temporal cortex & right lateral temporal cortex : cerebellum ratio in ADHD. Hypoperfusion in right medial temporal cortex inversely correlated with Du Paul teachers' questionnaire rating scale.	Difficulty regulating response to stimuli in ADHD may be mediated by underfunctioning of the orbital frontal cortex and subsequent connection to the limbic system.
Amen and Carmichael, 1997	SPECT imaging scan using Certec (99m Tc hexamethyl-propylene amine oxime).	54 **medication-free** ADHD children and adolescents 18 medication-free controls from the psychiatric outpatient clinic w/o ADHD ages 6-18	A resting and on task brain scan were performed. For the task, patients performed a standardized continuous performance task 5 minutes before and 10 minutes after the isotope was injected.	Left prefrontal lobe decreased activity in children w/ ADHD.	↓ perfusion in prefrontal cortex with intellectual stress	Children with ADHD may not process attention tasks in the same manner. Large ADHD sample; however, choice of controls from among psychiatric population may not be best.
Sieg et al., 1995	N-Isopropyl Iodine-123 IMP SPECT scan	10 ADHD patients 6 patients from a non-ADHD mixed psychiatric group as controls age 6-16 **None of the patients were receiving psychotropic medications at the time of the scan**.	A resting SPECT scan.	↓ activity in frontal and parietal regions in ADHD patients.	↑ overall hemispheric I-123 IP uptake asymmetry in ADHD subjects. ↓ activity in left frontal and left parietal regions in comparison to controls.	Implicates regional cortical perfusion and metabolism abnormalities in areas that are involved in the control of attentional processes in children with ADHD.
Zametkin et al, 1993	PET and fludeoxyglucose F18 were used to study brain glucose metabolism	10 healthy teenagers 10 teenagers with ADHD Age 13-16 **7/10 ADHD patients had been previously treated w/ stimulants, but all had been medication free for 3 wks prior to PET scan.**	A computerized auditory-attention task (Continuous Performance Test) was performed.	↓ glucose metabolism in an area of the left anterior frontal lobe in children with ADHD.	Global/absolute metabolism the same. ↓ glucose metabolism in 6/60 specific brain regions, including an area in the left anterior frontal lobe in ADHD. ↓ metabolism in that specific region of the left anterior frontal lobe inversely correlated with symptom severity.	7/10 controls siblings of children with ADHD, but only 2 controls had ADHD affected siblings that participated in the study. Of ADHD group, 8 had an affected parent. Of control group, 6 had ADHD-affected parent.
Zametkin et al, 1990	PET and fludeoxyglucose F18 were used to study brain glucose metabolism	50 normal adults 25 patients w/ ADHD age 24- 48 **None of the patients had been treated at any time with stimulant medication.**.	A computerized auditory-attention task (Continuous Performance Test) was performed on all subjects during FDG uptake.	↓ glucose metabolism in premotor cortex & superior prefrontal cortex in ADHD	↓ global cerebral glucose metabolism in adults w/ hyperactivity. ↓ glucose metabolism reduced in 30/60 specific brain regions in ADHD. ↓ in premotor cortex and superior frontal cortex in ADHD.	Glucose cerebral metabolism differences especially in areas involving control of attention and motor activity.

Appendix Ib: Functional MRI Studies of Brain Abnormality in ADHD

Author & date	Study Type	Sample	Method	Locus	Relevant Results	Comment
Durston et al, 2003	FMRI study.	7 normal controls 7 ADHD age 6-10 **Subjects taking stimulant medication withheld dose on day of MRI.**	A go/nogo task, so that the number of go trials preceding a no-go trial is varied to tax the neural systems underlying cognitive control with increasing levels of interference.	↓ activation in region in left caudate nucleus in ADHD. ↑ activation in the right superior frontal gyrus (BA 10), right middle frontal gyrus (BA 9/46), right inferior parietal lobe (BA 40), bilateral posterior cingulated gyrus (BA 31), bilateral precuneues (BA 7), right superior temporal gyrus (BA 22), and the bilateral cortex (BA18) in ADHD.	Frontostriatal regions not activated in the same manner. Children w/ ADHD rely on a more diffuse network of regions, including more posterior and dorsolateral prefrontal regions.	Evidence for frontostriatal involvement in ADHD.
Bush et al., 1999	FMRI study.	8 adults with ADHD 8 normal controls age 22-47. **All 8 ADHD subjects had been exposed to ADHD medications. 3/8 ADHD subjects were unmedicated for >=3 months prior to scanning and the remaining 5 patients underwent a 5 half-life medication wash-out period prior to scanning.**	The counting Stroop, a Stroop variant, was used to examine the functional integrity of the anterior cingulate cognitive division (ACcd) in adults with ADHD.	No activation in the cingulate cortex of the ADHD group.	The ACcd, previously shown to play a central role in attentional processing, was not activated by adults with ADHD. Not caused by poor neuronal responsiveness.	Suggests ACcd hypoactivity during attentional tasks may be a characteristic of adults with ADHD when compared with controls.
Rubia et al., 1999	FMRI study.	7 males w/ ADHD 9 normal controls aged 12-18 The ADHD subjects were either **unmedicated or medication free for 1 week prior to testing**.	Brain activation was compared while performing two tasks. The stop task required inhibition of a planned motor response, and the motor timing task required timing of a motor response to a sensory cue.	↓ power of response in right mesial prefrontal cortex, right inferior prefrontal cortex, and left caudate in ADHD subjects.	↓ power of response in right mesial prefrontal cortex during both tasks and in right inferior prefrontal cortex and left caudate during the stop task.	ADHD may be associated with subnormal activation of the prefrontal systems which are responsible for higher-order motor control.

Appendix Ic: Studies without Psychostimulants that Indicate a Dopaminergic Role in ADHD

Authors	Study Type	Sample	Method	Locus	Pertinent Results	Comment
Bonab et al., 2003	PET scan using ^{11}C-Altropane.	6 adults w/ ADHD 6 healthy volunteers	A resting PET scan.	↑ DAT binding potential in left & right striatum in ADHD patients.	30% ↑ in DAT density in left striatum & 28% ↑ in DAT density in right striatum in ADHD patients compared with controls.	DAT binding is higher in ADHD; contradicts Volkow et al., 2003, see appendix Id.
Cheon et al, 2002	[123I]IPT SPET scan to study DAT density	9 children with ADHD 6 normal children age 7-13 Children with ADHD **had never been exposed to psychostimulants**.	A resting SPET study.	↑ DAT binding in basal ganglia in children w/ ADHD.	↑ specific/non-specific DAT binding ratio in basal ganglia in ADHD. No significant correlation between severity of scores of ADHD symptoms & specific/non-specific DAT binding.	Drug-naïve children with ADHD appear to exhibit a complex dysregulation of the dopaminergic neurotransmitter system.
Van Dyck et al., 2002	SPECT imaging using [^{123}I]2β-carboxymethoxy-3β-(4-iodophenyl)tropane ([^{123}I]β-CIT)	9 ADHD patients 9 healthy controls age 25-57 **8 patients were stimulant naïve, while one had not received stimulants for 14 years**.	A resting SPECT study	DAT binding n the striatum, diencephalon, or brainstem, did not differ between the two groups.	Striatal [^{123}I]β-CIT binding did not differ significantly between the ADHD and comparison subjects.	Contradictory to other studies, no differences were found in DAT levels.
Dougherty et al., 2000	SPECT images after injection of 5-7 mCi of ^{123}I altropane.	6 adults w/ ADHD 30 healthy controls age 21-51 yrs.	A resting SPECT study	↑ DAT density in the striatum in adults w/ ADHD.	Independently of age, DAT density ↑ 70% in patients w/ ADHD.	SPECT could be expanded to individualize treatment with psychostimulant drugs, to evaluate new drugs for treating ADHD, and to clarify the pathophysiology of ADHD and the mechanisms of action of antihyperactivity meds.
Ernst et al, 1999	PET and the tracer [18F]fluorodopa.	10 children with ADHD 10 healthy controls age 12-17 All comparison children had a sibling with ADHD, except for one child who had a sibling with a diagnosis of autism. **Subjects were medication-free for at least 2 wks prior to scanning. 8/10 ADHD children had a history of stimulant medication use.**	A 2 hr [F18]FDOPA PET session. [F18]FDOPA, an analog of DOPA, is transported into presynaptic neurons where it is converted by DOPA decarboxylase to [F18]FDOPA & kept in vesicles.	↑ [18F]DOPA in right midbrain in children w/ ADHD and correlated with symptom severity.	Accumulation of [18F]DOPA in the right midbrain was higher by 48% in the children with ADHD than in the controls. This was not statistically significant, but did correlate with symptom severity.	Suggests an abnormality in the dopamine pathway of children with ADHD. Results are weakened by the fact that there is no statistical significance.
Ernst et al, 1998	PET and the tracer [18F]fluorodopa	17 adults with ADHD 23 control adults age 23-45 yrs **Only 4 of the ADHD volunteers had ever been treated with stimulants. None were receiving treatment at the time of the study.**	A 2 hr [F18]FDOPA PET session was used.	↓ F18-ratios in ADHD in medial & left prefrontal areas.	Low DOPA decarboxylase activity in prefrontal cortex reflects a reduction in the activity of the enzyme, either *structurally*, i.e., decreased number of synapses, or *functionally*, i.e., inhibition of the enzymatic activity (decreased concentration or affinity).	The prefrontal dopaminergic deficits in ADHD adults may not be the primary pathological defect but rather result from an interaction of the primary neural deficit with maturation and aging processes

Appendix Id: Studies that Show Central Effects of Psychostimulants

Authors	Study Type	Sample	Method	Locus	Pertinent Results	Comment
Volkow et al., 2003	SPECT imaging using [^{11}C]raclopride	7 never-medicated adults w/ ADHD 7 healthy controls age 21-38	PET scan with & w/o 0.5 mg/kg of MPH.	↓ MPH induced DA changes in ADHD compared w/ controls. ↓ baseline DAT measures in striatum in ADHD.	↓ baseline DAT measures in striatum in ADHD. Baseline DAT measures negatively correlated w/ MPH-induced DA changes in ADHD but not in controls.	Lower baseline DAT levels in ADHD contradicts other studies (see Appendix Ic).
Vles et al., 2003	SPECT imaging using 123I-Ioflupane to measure DAT levels and post-synaptic D2-receptor integrity	6 boys with ADHD age 6-10 yrs **No current or previous pharmacological treatment**.	DAT levels and D2 receptor integrity were measured using a SPECT scan prior to any medication. After baseline SPECT studies, the boys received MPH at 0.25-0.6 mg/kg/day. After 3-4 months SPECT studies were repeated.	Left-right asymmetry (Ri>Le) in DAT activity in the caudate nucleus, not found in the putamen in the drug-naïve boys. DAT density increase in basal ganglia. D2 down-regulation after treatment.	MPH treatment resulted in a down-regulation of the post-synaptic dopamine receptor with a maximum of 20% and a down-regulation of the DAT with a maximum of 74.7% in the striatal system.	Although no control group, this is an important study because drug-naïve children are evaluated in a baseline reading, then treated with MPH for a long period of time (3-4 months), and then re-evaluated.
Volkow et al. 2001	PET and [^{11}C]raclopride (D2 receptor radioligand that competes with endogenous DA for binding to the receptor)	11 male healthy subjects age 23-37 yrs **None of the subjects were taking medication at the time of the study**.	Subjects had two scans; the first was performed 60 min after placebo and the second was performed 60 min after 60 mg of oral MPH. Subjects were blind to whether placebo or oral MPH had been administered.	↑ DA in striatum (putamen) after MPH	↑ extracellular DA in striatum by blockade of DAT after MPH. ↑ of weak DA signals in subjects w/ ADHD by MPH may enhance task-specific signaling, improving attention & decreasing distractibility; OR MPH-induced ↑ in DA may enhance the salience of a task, facilitating the "interest that it elicits" and thereby improving performance.	Dopamine pathway study. Single-dose MPH in adults. MPH significantly increased DA in brain. Suggests role of MPH in alleviating ADHD symptoms. Only healthy subjects.
Dresel et al., 2000	[99mTc]TRODAT-1 SPET scan	17 **untreated** patients w/ ADHD 14 healthy controls age 21-64 yrs	SPET scan before and after the initiation of MPH treatment (3*5 mg/ day) for 4 wks.	↑ DAT binding in striatum, caudate nucleus, & putamen in ADHD. After MPH treatment, DAT binding levels ↓ in all 3 areas.	↑ binding of [99mTc]TRODAT-1 to the DAT in untreated ADHD patients. Under MPH treatment, specific binding decreased significantly in all patients. May explain complex dysregulation of the dopaminergic system in ADHD patients and the effects of psychoactive drugs.	Provides further evidence for the role of the dopaminergic system in ADHD.
Krause et al., 2000	[99mTc]TRODAT-1 SPECT scan	10 **untreated** patients) w/ ADHD 10 healthy controls Age 21-63 yrs	SPECT scan before and after the initiation of MPH treatment (3*5 mg/ day) for 4 wks.	↑ DAT density in striatum (basal ganglia) of patients with ADHD than of controls.	↑ specific binding to the DAT at baseline in subjects w/ ADHD. After MPH treatment, specific binding of Tc-99m-TRODAT-1 to the DAT ↓ in all patients.	First study to show that MPH lowers increased striatal DAT availability in adults with ADHD.

Appendix Ie: Imaging Studies that Examine Central Effects of Stimulant Medication in ADHD

Author & date	Study Type	Sample	Method	Locus	Relevant Results	Comment
Schweitzer et al., 2003	PET [^{15}O]H_2 scans used to measure regional cerebral blood flow (rCBF)	10 men w/ ADHD Age 23-39 yrs **4 subjects had prior history of MPH medication; 2 as children and 2 as adults. Two had been stimulant free for approx. 10 yrs, one adult had been stimulant free for several months while the other had been stimulant free for 8 days before the off-medication scan was collected**.	MPH dose of 0.5 mg/kg/day 1st wk, 0.75 mg/kg/day for 2nd wk, & up to 1.0 mg/kg/day for 3rd wk, until optimal dose found, barring adverse side effects. Ave. dose 19 mg TID. MPH ingested 60 mins before scan.	↓ in rCBF bilaterally in the precentral gyri, in the left caudate nucleus, and in the right claustrum, & ↑ increase in rCBF in the cerebellar vermis after MPH treatment.	MPH-related changes were associated with a ↓ in rCBF in brain areas related to motor preparation and action, including bilaterally in the precentral gyri, in the left caudate nucleus, and in the right claustrum. Chronic MPH administration ↑ rCBF in cerebellar vermis. The degree of change in ADHD symptom ratings between off and on-medication states was negatively correlated with rCBF increases in the midbrain, cerebellar vermis, and the precentral and middle frontal gyri in the off-MPH condition.	**No healthy control group.** MPH appears to modulate brain regions associated w/ motor function to achieve reduction in ADHD symptoms.
Kim et al., 2001	99Tc-HMPAO-SPECT	32 male, never-medicated, ADHD patients aged 7-14 **The subjects had never been treated with stimulants or other psychiatric medication before.**	Various questionnaires, a psychometric test, & neuropsychological battery applied to the drug-naïve patients & parents. Patients then underwent SPECT scan. Subsequently, patients received MPH treatment for 8 wks, mean dosage of 0.7 g/kg. Then reevaluated w/ a second behavioral assessment & SPECT scan. MPH administered 90 mins before Tc-HMPAO injection.	↑ perfusion in caudate nuclei & frontal lobes after MPH treatment.	↑ rCBF in left & right prefrontal areas & caudate & thalamic areas post MPH treatment, suggesting that MPH affects the function of the fronto-striato-thalamic circuit, known to be the pathophysiologic site of ADHD.	Examines how never-medicated children with ADHD react to 8 wks of MPH treatment. **(no control group to examine if normal children react in the same way and children who didn't react to the stimulants weren't included)**
Matochik et al., 1994	PET scan with [18F] fluorodeoxy-glucose as a tracer	19 (age 21-50 yrs) subjects studied before and after MPH medication 18 subjects (aged 18-47 yrs) studied before and after d-amphetamine. All subjects were diagnosed with ADHD. **The subjects took no medication for at least one month before beginning the study, and most had never been treated w/ stimulants.**	Baseline PET scan. Subjects randomly put into daily doses of d-amphetamine sulfate group or of methylphenidate hydrochloride. Dose individually titrated for clinical effect. Starting dose was 5 mg b.i.d. for both MPH and d-amphetamine & dose was titrated within 3 wks to 5-25 mg b.i.d. for MPH and 5-15 mg b.i.d. for d-amphetamine. 2nd PET scan was obtained after chronic stimulant treatment was 6-15 wks. On day of 2nd scan, daily dose administered 90 mins prior to injection of glucose tracer.	No significant areas.	No significant main effect of drug or scan for global metabolism or for any of 60 regions of interest. Both drugs were associated w/ significant improvement in behavior.	There were no robust metabolic effects of stimulant treatment. This study did not have a control group.

Appendix Ie Continued: Studies that Examine the Underlying Neurophysiology of Medication Effects on ADHD

Authors	Study Type	Sample	Method	Locus	Pertinent Results	Comment
Langleben et al., 2002	99mTc-ethylcysteinate dimmer (ECD) SPECT scan.	22 boys w/ ADHD 7 healthy volunteers age 8-11 yrs ADHD candidates were treated with MPH for an average of 12 wk (range 8-16 wk) and demonstrated a clinical response.	Each subject had imaging sessions 1-3 wk apart; one on MPH & another off MPH. On-MPH: ADHD patients received usual prescribed dose of MPH (range, 10-30 mg) 2 hr before the imaging session & controls received single 10 mg dose. Off-MPH scan: MPH withheld for 36 hr prior to the scan for ADHD patients. Subjects completed stimulus-controlled version of the "go/no-go" task as in Vaidya et al.	↑ rCBF motor cortex & premotor cortex bilaterally; in Brodmann's area (BA) 4 and 6; & in the anterior cingulate gyrus (BA 32) in untreated ADHD subjects as compared to when treated w/ MPH.	When ADHD subjects were not taking MPH, rCBF was higher in the motor cortex and premotor cortex bilaterally; in Brodmann's area (BA) 4 and 6; and in the anterior cingulate gyrus (BA 32). No differences found in the control group.	Indirect support for prefrontostriatal dysfunction hypothesis since both motor cortex and the anterior cingulate receive inhibitory prefrontostriatal input. Study may have been underpowered.
Vaidya et al., 1998	FMRI study	10 children w/ ADHD 6 healthy controls age 8-13 yrs	Two go/no go tasks with & without MPH, 1 wk apart, with counterbalancing across subjects. **On-MPH: ADHD took regularly prescribed dose (range = 7.5-30 mg) & controls took 10 mg, 2-2.5 hrs before scanning. Off-MPH: ADHD subjects went off meds for 36 hrs before scanning.**	↑ striatal activation (head of the caudate, putamen) in ADHD subjects while a ↓ in controls post MPH treatment. Without MPH, striatal activation was ↑ in controls than in ADHD subjects.	Improved response inhibition in both groups on one task & only in ADHD subjects on the other. ↑ frontal activation equally in both groups, but ↑ striatal activation in ADHD while ↓ in controls after MPH.	This is the only study that uses fMRI to investigate response to MPH in **normal children** as well as children with ADHD.