DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institute of Health National Institute of Mental Health

Intramural Research Program

10 Center Drive M.C. 1381

Bldg. 10, Room 4N-222

Bethesda, Maryland 20892

Date: September 8, 2003

From: Director, Intramural Research Program, NIMH

To:

Subject: New Protocol Entitled "Effects of Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study"

Your new protocol entitled, "Effects of Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A Functional Magnetic Resonance Study" has been reviewed by the CSRP and was approved for submission to the IRB for review. Please address the attached comments from the CSRP and submit to the IRB for review.

Robert Desimone, PhD

cc.: Dr. Rosenstein

Dr. Rubinow

Effects of single dose dextroamphetamine in ADHD: fMRI study P1: Rapoport

This was an excellent protocol.

The overall aim of this study is to better understand the pathophysiology of ADHD by evaluating the response to amphetamine in ADHD kids. Specifically, whether the response is similar or different in ADHD and normal children when performance is equated on a measure of inhibitory control.

The sample will consist of 14 healthy children and adolescents (9-18 yrs. old), 14 ADHD, 12 pairs of dizygotic is concordant for ADHD, 12 pairs of monozygotyic twins disconcordant for ADHD. The design is a double-blind, placebo-controlled challenge using a single dose for all subjects — 0.25 mg/kg amphetamine). Children currently receiving psychostimulants will have a 36 hour wash-out period prior to the study.

Two fMRl experiments will provide the main dependent measures. Both tasks are considered to be measures of inhibitory control and are commonly used in the ADHD literature. One is a go: no-go paradigm that has been used previously to study dextroamphetamine effects in fMRI, thus allowing them to compare their results to previous findings. This tests last approximately 5 minutes. The second procedure will use the "stop task". The advantage of this task is that, unlike to go: no-go task, performance is equated by titrating the timing of the stop signal based on previous trials. This will allow for the critical, across group comparison without the confound of performance

differences. The analyses of the brain imaging data will be based primarily on an ROl analysis directed at the striatum and specific regions of prefrontal cortex.

This is a clearly described study. The design is appropriate and tasks well motivated. We received 2 out-side reviews. One rated it as outstanding, the other as excellent, although the numerical scores were nearly identical, 1.4 and I .5. each had some questions and comments that the investigators might want to think about.

At the meeting the Board members agreed that this was an excellent submission. I trust that in addition to the ROl analysis, careful attention will be paid to other brain regions (e.g., see reviewers

comments on the cerebellum). It also might be worth-while to consider whether a task could be implemented that would allow for parametric manipulation of difficulty in response inhibition to directly compare performance curves and regional changes in the BOLD signal.

Perhaps more importantly, a number of questions and concerns were raised that may be critical for the IRB approval. One issue concerns substance abuse. Specifically, it might be necessary to describe your plan for determining level of substance abuse and smoking in the children, how these data might be used scientifically for data analysis, and whether it is necessary to inform the parents. A second issue _____

was to provide a justification in the body of the protocol as to why the study could not or should not be done in adults. Finally, on page 19 _____

(Benefits of study participation) and in the consent and assent forms it should state in the first sentence of the benefits section that the study does not provide direct benefit to the subjects and the indirect _____

benefits should be toned down somewhat

Review of “Effects of Single Dose of Dextroamphetamine in Attention Deficit Hyperactivity Disorder: A functional magnetic resonance study”.

Investigator name:

1) Does the protocol articulate a clear and testable question or hypothesis?

The protocol sets forth three clearly formulated hypotheses. The hypotheses are logically based on prior work in field. The hypotheses are critical questions in the area of neuroimaging of ADHD. Even if the hypotheses are refuted, the field will be substantially advanced.

2) Will the experiments covered by the protocol allow the question under study to be answered?

The experiments relate directly to the hypotheses. Four groups will be compared:

unrelated ADHD children, dizygotic twins discordant for ADHD, monozygotic twins discordant for ADHD, and healthy controls. Subjects will undergo two functional M studies in a double blind placebo controlled crossover trial of amphetamine. The Go/No

Go and Stop Signal task, well established measures of inhibitory control, will be performed during the MRI. Drug X diagnosis X genetic relatedness interactions will be examined for in the brain regions of interest. In summary, the experiments are well designed and straightforward.

3) The main purpose of this committee is to review the protocol for scientific merit, not human subject concerns. However, if you have human subject concerns that you believe should be brought to the attention of our IRP, please indicate those here:

No concerns. The single dose amphetamine (.25 mg/kg dose) is well within the clinical range and has been administered safely to controls in previous studies. The MRI is without major medical risk.

4) Please indicate below a category and a numerical priority score for the work. Would you describe the experiment as: Outstanding 1.4

5) In two pages or less, please provide specific comments or feedback for the investigator.

The proposed study is of high significance. There is great public interest in the matter of stimulant treatment of ADHD. Clarifying the mechanisms of stimulant action would be

very helpful in dispelling myths about ADHD and its treatment, and would be move us closer to understanding the pathophysiology of the disorder.

The study is innovative in that it combines techniques from both genetics and neuroimaging. It will be the first study that directly compares dizygotic and monozygotic twins on functional brain imaging studies. This strategy has been useful in schizophrenia studies in teasing out environmental and genetic factors on brain anatomy. There are many strengths to the study: the diagnostic and neuropsychological batteries are well designed and the inclusion and exclusion criteria are logical. The sample should be quite representative of ADHD children in the general population.

Use of the Go/No Go study is useful so that the results can be compared to prior studies. The Stop Signal Task is also a very specific measure of inhibitory control; the tracking version of the task will equate performance and thus remove a possible confound.

The technical aspects of the FMRI appear appropriate. The investigators are highly experienced in this area.

Only minor weaknesses are noted. There is no healthy twin group, so if twins share some brain function differences compared to non-twins this might be difficult to resolve. The investigators do not mention perinatal history (prematurity, etc) as a factor and how it might be more common in twins. They do not mention history of prior treatment as a factor. Apparently treatment naïve subjects, those with a positive response to stimulant in the past and those with a non-response to stimulant will be included. This data should be gathered, for use as a possible covariate in the analyses.

The sample is too small for any definitive genetic analysis, but will provide a first look as to whether any ADHD genotype is related to the imaging variables.

The tables in the appendix were most informative and would very useful if published as a review paper. The investigators should consider this, if they have not already done so.

New Protocol Review Investigator name:

1) Does the protocol articulate a clear and testable question or hypothesis?

Yes, the proposal is a very sound and logically based one to examine the effects

of a single dose of dextroamphetamine in children and adolescents with Attention

Deficit Hyperactivity Disorder using functional magnetic resonance imaging

2) Will the experiments covered by the protocol allow the question under study to be answered?

Yes, the investigators have included both behavioral and functional imaging assays that tap the relevant neural circuitry (basal ganglia and prefrontal cortex), and that realistically relate to the symptoms of this disorder (inattention and impulsivity). The proposed double blind, placebo controlled design is appropriate and the inclusion of monozygotic and dizygotic twins discordant for the disorder will help constrain explanations of individual differences in response to treatment.

3) The main purpose of this committee is to review the protocol for scientific merit, not human subject concerns. However, if you have human subject concerns that you believe should be brought to the attention of our IRP, please indicate those here:

There are no human subject concerns. The investigators are trained in the methods proposed and with interacting with patient populations in this context. Moreover, the findings may significantly impact, diagnosis, treatment and intervention for these disorders.

4) Please indicate below a category and a numerical priority score for the

work.

I would rate the proposal 1.5.

5) In two pages or less, please provide specific comments or feedback for the investigator.

This is a very sound and logically based proposal to examine the effects of a single dose of dextroamphetamine in children and adolescents with Attention Deficit Hyperactivity Disorder using functional magnetic resonance imaging. A few minor constructive comments for the investigators follow:

The large age range of 9 to 18 year olds may confound the results of the study in that there are developmental changes in the dopamine system across these ages. The proposal may be strengthened if age were thus treated as either a subject variable of interest and/or covariate in explaining the response to the pharmacological challenge.

Performance differences between groups is a confound the investigators raise in their review of the literature on functional imaging studies of ADHD. The ability to equate behavioral performance was a strong basis for the selection of the proposed tasks. Yet the go/nogo task proposed does not allow for equation of performance across groups. Even if the investigators only analyze correct trials, should the ADHD subjects make several misses and false alarms, the degree of inhibitory control needed to perform the task is diminished and therefore not comparable across groups. A parametric design titrating

task difficulty by varying the number of go trials preceding a nogo trial may be a better task design (see Durston et al., 2002 Dev Science; 2003 Bio Psychiatry)

The proposed studies target frontostriatal circuitry, but this group has shown the most compelling differences between children with and without ADHD in MRI based measures of the cerebellum. A number of manipulations to the proposed tasks in manipulating the timing of a stimulus in the go/nogo or stop signal task could effectively activatethis region. Yet, this region is not discussed or included

as part of the region of interest analysis. The proposal would be strengthened and most likely more informative if such manipulations and analyses were done.

The appropriate citation for the go/nogo task they are using - developed in the branch of the P1 and exported to the Stanford cite for the Vaidya et al. study - is 1997J Cogn Neuro.

Overall this is a very strong proposal and the investigators are well positioned with the technical skill and theoretical background to successfully carry them to completion.