Neuroimaging the Expectancy versus Pharmacotherapy Effect of Adderall on Cognitive Performance

Study Protocol

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Study Summary

Title	Neuroimaging the Expectancy versus Pharmacotherapy Effect of Adderall on Cognitive Performance
Methodology	Double blind, within subjects, balanced placebo, randomized controlled clinical trial.
Study Duration	Estimated duration for the main protocol (e.g. from start of study to finishing the study) is approximately 1 year.
Study Center(s)	The University of Alabama at Birmingham – Highlands Hospital and the Sparks Center, Birmingham, AL
Objectives	To further explore the relationship between stimulant medication and its effect on cognitive function, specifically whether participants' expectations regarding the benefits of stimulant medication affects their performance on neurocognitive tasks.
Number of Subjects	10 (4 to complete the study, and 6 alternate participants).
Diagnosis and Main Inclusion Criteria	**Inclusion Criteria** - Age (18-24) - College student with at least average IQ - Willingness to standardize caffeine intake to 100mg on day of study **Exclusion Criteria** - Diagnosis of ADHD - Unwillingness to comply with caffeine specifications - Regular use of Adderall - Pregnant/breastfeeding - History of substance use disorders - Illicit stimulant use within the last year - Contraindications to stimulants (i.e., tics, Tourette's, cardiac disease, hypertension) - Uncontrolled medical illness - Active contagious infection
Study Product, Dose, Route, Regimen	**Study Product:** Dextroamphetamine-amphetamine & Placebo, **Dose:** 10mg **Route:** Oral **Regimen**: One dose in the AM at Imaging visits

1. Introduction

1.1 Background

The conceptualization of prescription stimulant medications as cognitive enhancers is weakly supported by science. Nonmedical use of prescription stimulants for the purpose of academic enhancement is rampant in institutes of higher learning with potent negative public health implications. A recent series of recent military studies of healthy subjects comparing prescription stimulants to the ubiquitous caffeine and less abuse-prone modafinil demonstrated equivalent benefits between stimulants in sustaining alertness and attention during fatigue states. No improvement in higher order thinking skills (aka. cognitive enhancement) was noted for any stimulant. Nevertheless, 44% of healthy college students see prescription stimulants as superior to caffeine for cognitive enhancement (Franke, 2012). Evidence for prescription stimulants as cognitive enhances is lacking: two studies found dextroamphetamine improved a single measure of verbal memory, however, a number of studies have demonstrated that a 60-90 minute nap resulted in consolidation of memory on multiple measures.

Young adults have misconceptions about prescription stimulants. The majority of undergraduate students overestimated the prevalence of non-medical use of prescription stimulants (70.2%) among peers on their campus. Additionally, opinions about the use of illegally acquired substances were partly based on evidence based medical facts, but were also strongly influenced by their individual preferences of substances used for cognitive enhancement (Frank 2012). Among college students, actual self-reported non-medical use of prescription stimulants rates range from 1.5% to 31% between survey studies (Mcabe, 2008) with the majority reporting that the primary reason for use was to improve academic performance. (Bogle, 2009) In one survey, 11.3% of students in health care professional schools admitted to nonmedical prescription stimulants use for the purpose of: enhancing alertness/energy (65.9%), to improve academic performance (56.7%), to experiment (18.2%), and to use recreationally/get high (4.5%) (Bossier, 2013). The lifetime prevalence of prescription stimulant use in a sample of 144 medical students was 20%, with 15% using during medical school. 83% reported using them specifically for cognitive performance enhancement such as studying more effectively and staying awake longer. (Webb, 2013) (Arria). Substance abuse in late adolescence is more dependent on peer exposure to drug-abusing peers than intrinsic factors. (NIH, National Institute on Drug Abuse Website www.drugabuse.org)(Gerstein and Green 1993; Dishion et al. 1999). Accurate differentiated empiric data about the true benefit/risk ratio of prescription stimulants to caffeine and in healthy subjects vs. ADHD subjects could reduce nonmedical use resulting from peer-peer misinformation (Hawkins et al. 2002) (Frank, 2012).

The cognitive effect of prescription stimulants on normal healthy adults has not been

characterized definitively. No studies have shown that cognitive gains from prescription stimulants exceed the benefits from caffeine, a less risky and legal product. Since caffeine is well known to enhance attention and vigilance during fatigue states, subjects desirous of cognitive enhancement are presumably seeking to enhance high order thinking such as learning and memory. In a double blind placebo-controlled crossover study, 19 healthy young male volunteers were tested after a single dose of placebo or methylphenidate. Declarative memory consolidation was significantly improved relative to placebo for the 20 and 40 mg methylphenidate states as measured by a word-learning test, but not on spatial working memory or a planning task. (Linnsen, 2012). Another double-blind, cross-over placebo controlled study assessed healthy controls on 13 measures of cognitive abilities and found no cognitive enhancement from stimulant medication. However, subjects in this study believed their performance was enhanced by the stimulant medication (Illieva, Boland, & Farah, 2013).

A previous study conducted by the principal investigator and one of the co-investigators of this proposed study involved the administration of a neurocognitive battery to healthy controls after receiving either stimulant medication or placebo. Participants were either accurately or inaccurately informed whether they received medication or placebo. Out of 31 subtests, participants only showed improvement on two of the subtests during active medication. Expecting stimulant medication was associated with improved cognitive performance and expecting placebo was associated with worse cognitive performance, regardless of the type of medication given. The results of this study demonstrated that individuals' expectancies influenced cognitive performance while the use of stimulant medication did not (Cropsey et al. 2017).

2. Study Objectives

To further explore the relationship between stimulant medications and its effect on cognitive function, specifically whether participants' expectations regarding the benefits of stimulant medication affects their performance on neurocognitive tasks. We were interested in examining feasibility and acceptability of administering Adderall and neuroimaging while completing tasks in the scanner.

3. Study Design

3.1 General Design

This is a within subjects 2 x 2 design, in which all participants will experience all four conditions during four sequential weeks. Medication administered (Adderall vs. placebo) will be crossed with instructional set (truth vs. deception) and participants' performance on neurocognitive tasks will be compared across these groups. For example, participants will be told either accurately or inaccurately that they are receiving Adderall or placebo. This creates four conditions that will be delivered over four weeks (see table below). The presentation of these conditions will be counter-balanced across the four weeks for each of the participants, such that they will not

receive the same ordering of conditions.

3.2 Primary Study Endpoints

Feasibility and acceptability of imaging college-age participants administered Adderall or placebo.

4. Subject Selection and Withdrawal

4.1 Inclusion Criteria

- Age (18-24)
- College student with at least average IQ
- Willingness to standardize caffeine intake to 100mg on day of study

4.2 Exclusion Criteria

- Diagnosis of ADHD
- First degree relative with ADHD
- Unwillingness to comply with caffeine specifications
- Regular use of Adderall
- Pregnant/breastfeeding
- History of substance use disorders
- Illicit stimulant use within the last year
- Contraindications to stimulants (i.e., tics, Tourette's, cardiac disease, hypertension)
- Uncontrolled medical illness
- Active contagious infection

4.3 Study Recruitment and Screening

Advertisements posted around campus will include tear-off slips of paper with contact information. The study investigators have been able to recruit healthy controls in this age group in previous studies of a similar nature without going to TV or radio advertisements. A telephone pre-screen interview will be designed to capture the most obvious exclusion criteria so that potential screen failures can be eliminated prior to an office visit.

Self-referred potential subjects will have a pre-screen telephone interview. If self-referred potential subjects meet criteria from this pre-screen telephone interview, a screening appointment will be scheduled.

Screening Appointment (1-2 hours): During the consent process, the purpose of the study, its risks and benefits, the rights of the participants, and what will be required of participants will be discussed. The participants will be given time to ask questions and have their questions answered by trained research staff. A pregnancy test will be obtained for all non-sterile female participants and a urine drug screen will be obtained for all participants at the screening interview. Positive results on either will result in immediate disqualification from the study. Results will be read

prior to giving any medication to a subject. These procedures will not be repeated during the study unless considered clinically necessary based on history or signs and symptoms at the discretion of the study physicians. Participants will review the MRI safety questionnaire to ensure that it is safe for them to be scanned. Participants will then fill out a demographics sheet, MRI Safety Questionnaire, Prescription Stimulant Expectancies Questionnaire (PSEQ-II), and an ADHD screener, the Adult Self-Report Scale (ASRS) Symptom Checklist. Medical and psychiatric history will be reviewed. The absence of an ADHD diagnosis will be confirmed by a physician investigator.

4.4 Early Withdrawal of Subjects

4.4.1 When and How to Withdraw Subjects

Students will be informed they may withdraw from the study at any time, for any reason, before it is completed. They will be informed that their participation will not affect their class standing or grades at UAB. They will not be offered or receive any special consideration if they take part in the research. Employees will be informed that taking part in the research is not part of their UAB duties and refusing to be a part of the study will not affect their job or relationship with UAB. They will not be offered or receive any special job-related consideration if they take part in this research.

5. Study Drug

Dextroamphetamine-amphetamine & Placebo

6. Study Procedures

Study Appointment (2-3 hours): Pulse and blood pressure will be measured before medication is administered. If pulse and blood pressure are within acceptable limits, medication will be administered. A potential side effect checklist (attached) will be reviewed after the period of time in which medication effects would become active. Any reported side effects will be addressed prior to continuation of the session. The MRI safety questionnaire will be reviewed and signed at each scanning visit. This questionnaire will be filed at the CINL. Any abnormal findings will be discussed with physician investigator who will determine if the subject is fit to participate in the study.

The participant will be given either a placebo or Adderall depending on randomization. Each participant (N = 4) will either be told that he/she is receiving Adderall or placebo, as indicated on pre-labeled medication bottles to preserve the double-blind nature of the study. The participant will either receive medication or placebo as they are informed, not receive medication when they believe they are receiving medication, or will receive medication when they believe they are not receiving medication. This will allow for measurement of expectancy, which is a core measure for this study. This study design makes the comparison of cognitive performance based on actual versus perceived benefit possible. Presented below is an example table of study conditions.

Conditions will be counterbalanced across participants to control for order effects.

	Week 1	Week 2	Week 3	Week 4
Expecting	Adderall	Adderall	Placebo	Placebo
Medication	Adderall	Placebo	Placebo	Adderall

(Expecting refers to whether participants are told that they are taking Adderall or a placebo pill. Medication refers to the pill that participants are actually receiving.)

Before the medication is administered and after the MRI scan, participants will complete the POMS (Profile of Mood States) to measure mood and euphoria (attached). Participants will also self-report on their perceived mental acuity pre-dose and after each cognitive task (described below) performed in the scanner on a scale of 0-100with 100 indicating "more sharp than normal."

Cognitive testing will be timed to begin 45 minutes after medication or placebo is given.

Participants will then start the magnetic resonance spectroscopy scanning portion of the session, which will take one hour. The MRI scan will not include the use of a contrast agent. A 3 Tesla Siemens Prisma scanner and 20-channel head coil will be used. Scan sequences are listed below:

- Auto-align scout (1 min): to determine brain orientation and slice prescription. Will use 260mm field of view (FOV), 160 x 160 matrix, 3.15ms repetition time (TR), 1.37ms echo time (TE), 1.6mm slice thickness, no gap. The scout data are not used in post-scan analyses, so processing and analysis steps are not described.
- T1-weighted magnetization prepared rapid gradient echo (MPRAGE) high-resolution scan (10 min): for anatomical localization and to achieve standard space for group analyses. Will use 230mm FOV, 256 x 256matrix, 2000ms TR, 2.51ms TE, 0.9mm slice thickness, and no gap, yielding 0.9x0.9x0.9mm voxels.
- Functional MRI (60 min): Axial T2*-weighted images will be acquired using an echo-planar sequence – 220x220 FOV, 64x64 matrix, 2000ms TR, 28ms TE, 3mm slices, yielding 3x3x3 mm voxels. Heart rate and respirations will be measured continuously in the scanner.
    - Participants will complete a "resting state" scan in which they are instructed to close their eyes and rest.
    - While undergoing fMRI scans, participants will complete three different cognitive tasks measuring aspects of sustained attention, new learning, and working memory. Participants will receive a short explanation of each task, as well as sample items, prior to entering the scanner, and will be able to have their questions answered. Specific task instructions will also be presented on screen inside the scanner prior to each task.
    - The first task will utilize a paced serial addition paradigm. Participants will be

presented with a string of single digits (0-9), one every three seconds, for approximately 12 minutes. The digits will be presented in auditory form via headphones. Participants will be asked to add the two most recently presented digits in their mind, and will respond with a button press each time the two digits add up to 10. The task does not require participants to maintain a running total of all digits, meaning that participants can resume the task at any point in case of set loss. We will measure the accuracy of participants' responses.

- During the second task, a sustained attention task, a row of 5 left- or right-pointing arrows will be presented on each trial. The participant will be required to indicate the direction of the central arrow (left or right) by pressing one of two buttons. The target arrow in the center of the row will be flanked by two non-target stimuli on either side, which point either in the same direction as the target, the opposite direction, or will be circles. The row of arrows will be presented in rapid succession and the participant is to indicate their response as quickly as possible on each trial by pressing the button. The task will last no longer than 15 minutes.
- During the final task, a visual version of a paired associates learning task, participants will be presented with 50 word pairs on screen, and will be asked to memorize both words in each pair. The pairs will be presented individually, at a rate of one word pair per three seconds. The 50 word pairs will be presented three times in the same order, for a total of 7 minutes and 30 seconds. Words in each pair will be everyday objects of neutral emotional valence, and will be limited to 8th grade reading level (e.g. rose – bag; elephant – glass). fMRI scans will be acquired during the learning phase of this task, although no response is required from participants during this time. Immediately following completion of the learning phase, participants will be presented with the first word from each pair on screen, and will be asked to name the second word in the pair. No brain scans will be acquired during the recall phase, but the accuracy of participants' responses will be recorded by a member of the research team.
- Each task will take no longer than 15 minutes to complete, and participants will be given short periods of rest between tasks, as needed. Participants will not receive feedback about the accuracy of their performance.

After the MRI portion of the session is complete, an additional neuropsychological battery will be administered to participants:

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS): Measures various domains including immediate and delayed memory, visuospatial/constructional, language, and attention

Debriefing: After all four weeks of the protocol, a research assistant will conduct the debriefing portion of the session to inform participants about the deception aspect of the study. Following a manipulation check, the research assistant will disclose whether the participant received Adderall or placebo during each session. The research assistant will discuss the participants' feelings

about the deception, use this as a chance to educate them about cognitive enhancers, and more fully explain the reasons for doing the study. Participants will be given as much time as deemed clinically appropriate to answer all questions and concerns or address any feeling of betrayal in an accepting way.

Prior to leaving, the side effect checklist will be completed a final time and blood pressure and pulse rechecked by trained study staff. Stable subjects will be allowed to leave. Any subjects experiencing side effects will be observed longer, or in the rare event of more moderate to severe adverse events (most commonly hypertension < 160/110), will be referred to the ER at the discretion of the physician and PI. Orange juice will be kept on site for use in subjects experiencing negative symptoms, as acidifying urine increases amphetamine excretion. A study physician will be available at all times.

7. Safety and Adverse Events

7.1 Definitions

Participants can experience adverse reactions to Adderall during the treatment. However, they have been screened carefully by experienced clinicians for the likely psychiatric and medical problems that lead to Adderall drug reactions, so severe reactions are very unlikely. Also, 10mg of Adderall is a standard adult starting dose, routinely and safely used in clinical practice. This dose is generally very well tolerated among most people. If participants do experience side effects they are likely to be mild and short–lived. This drug is very safe under medical supervision and more common side effects are generally mild.

Use of Adderall is associated with side effects such as:

- nervousness
- difficulty falling asleep or staying asleep
- dizziness
- nausea
- vomiting
- loss of appetite
- stomach pain
- diarrhea
- heartburn
- dry mouth
- headache
- muscle tightness
- drowsiness
- uncontrollable movement of a part of the body
- restlessness
- numbness, burning, or tingling in the hands or feet
- decreased sexual desire

The following are rarer but serious toxic effects from Adderall:

- fast, pounding, irregular heartbeat
- chest pain
- shortness of breath
- excessive tiredness
- slow or difficult speech
- fainting
- weakness or numbness of an arm or leg
- seizures
- changes in vision or blurred vision
- agitation
- believing things that are not true
- feeling unusually suspicious of others
- hallucinating (seeing or hearing voices that do not exist)
- motor tics or verbal tics
- depression
- abnormally excited mood
- mood changes
- erection that lasts longer than 4 hours that could result in penile injury (sexual activity is discouraged until evening time when medications should be largely excreted)
- numbness, pain, or sensitivity to temperature in the fingers or toes
- skin color change from pale to blue to red in the fingers or toes
- unexplained wounds on the fingers or toes
- fever
- hives
- rash
- blistering or peeling skin
- itching
- swelling of the eyes, face, lips, mouth, tongue, or throat
- hoarseness
- difficulty breathing or swallowing

7.2 Recording of Adverse Events

All adverse events that occur in the course of the study will be documented in the research record. Further, all adverse events will be compiled and reported in summary form on an annual basis to the IRB and at the conclusion of the study.

7.3 Reporting of Serious Adverse Events and Unanticipated Problems

Unanticipated (non-serious) adverse events will be reported to the IRB within 30 days via submission of the UAB IRB Adverse Event Report. Serious adverse events will be reported to the IRB within 24 hours by phone, email or fax; a completed UAB IRB Adverse Event Report will be submitted within 72 hours of initial IRB notification. All deaths will be reported to the IRB within 48 hours.

7.4 Medical Monitoring

During imagining sessions, the study physician will be on call in case of adverse or serious adverse events. If necessary, the study physician will arrive on site to address reported symptoms, and monitor and subsequently clear the participant to be released. Participants will be taken to the emergency room if deemed necessary.

8. Data Handling and Record Keeping

8.1 Confidentiality

The study records will be kept confidential to the extent provided by Federal, State, and local law. The records will be kept in a locked file by the research staff in offices maintained by the Department of Psychiatry and Behavioral Neurobiology. When a participant is enrolled in the study protocol, they are given a unique identification number that is used to identify all data associated with that person. All identifiers will be stored locally in secure areas of a computerized file system, with several levels of access security built in, thus assuring confidentiality. Unique identifiers can be linked to personal identifiers only by key study personnel with access to the personal identifier database protected by password.

9. Study Finances

9.1 Funding Source

The costs of the study will be funded by the Department of Psychiatry

9.2 Conflict of Interest

All involved study personnel declare no conflicts of interest.

9.3 Subject Stipends or Payments

Participants will receive $50 for the screening visit and $100 for the 4 scanning visits for a maximum of $450 per participant. If the participant does not complete the study, payments will be prorated to pay them for the visits they did complete. Payments will be processed after participants complete the study by mail.

10. Publication Plan

This is an acceptability/feasibility study. Given the small sample size, we do not anticipate publishing results.