Motivated behavior in adults with and without ADHD

NCT 02630017

9/6/2018

Study Title: Motivated behavior in adults with and without ADHD (MOBE)

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Background and Rationale

The number of attention-deficit hyperactivity disorder (ADHD) diagnoses has increased dramatically in the last decade, and methylphenidate (MPH) – a common medication for ADHD – is at risk of being over-prescribed. While some patients experience significant symptom improvement from MPH, as many as 90% of adults discontinue use within one year [1]. The clinical presentation of ADHD is heterogeneous, and this heterogeneity may arise from differences in the underlying neurobiology of ADHD symptoms. These symptoms are believed to arise from either hypo- or hyperactive dopamine (DA) and/or norepinephrine systems. This etiological complexity presents a challenge in prescribing appropriate medication to ADHD patients, but patients whose behavioral problems stem from DA-ergic deficits may gain the most benefit from MPH, which indirectly increases extracellular DA in the brain. However, there are no noninvasive tools currently available that can identify DA dysfunction, despite an urgent need for improved classification of ADHD subtypes in order to maximize treatment efficacy. This proposal seeks to refine the clinical heterogeneity of ADHD symptoms based on a neurobiological mechanism.

ADHD has been proposed to consist of 2 subtypes, one subtype consists of disordered thought and action typified by poor inhibitory control, and the other subtype consists of decreased motivation typified by delay aversion [2]. There is direct evidence that decreased motivation in ADHD is specifically related to hypoactive DA function. In particular, trait motivation scores among ADHD participants positively correlated with biological markers of DA function [3]. However, obtaining biological markers of DA function is expensive, invasive, and not a feasible diagnostic tool. There are also some well-established behavioral reinforcement deficits of the motivation subtype, including failure to delay gratification, impaired response to partial schedules of reinforcement, and preference for small immediate rewards over larger delayed rewards. However, delay discounting/aversion paradigms have not been directly linked to DA function in ADHD [4], nor do they offer predictions about the underlying neurobiological mechanisms of these behaviors. An excellent paradigm of behavioral reinforcement that provides a theoretically-driven model of DA function, and has been directly linked to DA function, is the explore/exploit trade-off. This paradigm could be used to characterize ADHD subtypes based on DA function; however, behavior on this paradigm has not yet been investigated in the context of ADHD.

The explore/exploit trade-off is a decision between exploiting a known source of reward versus exploring the environment for a new source of reward with potentially greater value, in order to maximize long-term reward. This trade-off plays a fundamental role in survival and many species have been shown to follow predictable rules of reward maximization [5]. DA regulates the explore/exploit trade-off by modulating the extent that reward information biases behavioral activity: Diminished DA biases behavior towards exploitation of known rewards, whereas enhanced DA favors exploration [6]. Furthermore, diminished DA increases the sensitivity to costs and/or delays associated with obtaining rewards, which is consistent with the reward delay aversion typical of the decreased motivation ADHD subtype. Importantly, trait- and state-based enhancement of DA function has been shown to increase exploratory behavior [6-8], suggesting that this behavior could be modulated by both ADHD (i.e., trait-based hypoactive DA function) and MPH (i.e., state-based enhanced DA function).

The explore/exploit trade-off could have vital importance to psychiatry as a behavioral measure of DA function and predictor of MPH efficacy; however, more research is needed to establish the distribution of explore/exploit behavior among ADHD patients and healthy controls, and to demonstrate that explore/exploit behavior is sensitive to changes in brain DA function. This proposal seeks to address these points by administering a paradigm of explore/exploit

behavior known as the 6-armed bandit task (6ABT) [9] to individuals with and without ADHD. Inattention deficits, in particular, have been related to trait motivation [3] and will be the primary ADHD symptom of interest. The 6ABT will be administered at baseline and during 2 testing sessions in which participants will receive MPH or placebo in a counter-balanced, double-blind design. During the testing sessions, participants will be administered a battery of neurocognitive tests in addition to the 6ABT.

The primary goal of this preliminary study is to collect data to perform power analyses for a larger project.

Specific Aims

Aim 1: Relate explore/exploit behavior to ADHD symptomatology.

Hypothesis 1a: At screening, nonmedicated ADHD participants will make fewer exploratory choices than controls.

Hypothesis 1b: At screening, the number of exploratory choices among nonmedicated ADHD participants will negatively correlate with inattention symptom severity and positively correlate with trait motivation.

Aim 2: Relate explore/exploit behavior to dopamine function and medication efficacy

Hypothesis 2a: At testing, ADHD and control participants will make more exploratory choices after MPH compared to placebo.

Hypothesis 2b: At testing, neurocognitive improvements from placebo to MPH among ADHD participants will negatively correlate with the number of exploratory choices made at screening.

Study Design and Procedures

Overview: This study has a mixed between- and within-subject design. Participants are young adults (aged 18-45) with ADHD and non-ADHD matched controls. They will be recruited from locations around the community, consented, screened for eligibility, then scheduled for 2 study days. Study days will be at least 48 hours apart. Thus, there will be a total of 3 lab visits across a 3 week period. Participants will be administered 40 mg methylphenidate (MPH) on one study day and placebo on the other study day. They will complete a battery of cognitive/behavioral tasks and answer questionnaires on both study days.

Recruitment/Screening: We will advertise on internet, flyers, and in the newspapers for volunteers for the study. Participants who qualify over the phone and are interested in participating will be scheduled for further screening at the study site. We are submitting a HIPAA Waiver for the purposes of conducting this phone screen. The informed consent and screening session will last approximately 3 hr. All aspects of the study will be described and informed consent will be obtained by the PI or study coordinator. Breath and urine samples will be collected in order to screen for drug use and recent alcohol use. Women of child-bearing potential will undergo urine pregnancy testing. Detailed inclusion/exclusion criteria are described below in the Study Population section. ADHD participants will meet DSM-IV criteria for a primary diagnosis of ADHD. The non-ADHD group will be age, education level, and sex matched to the ADHD group by targeted recruitment or selective enrollment.

During the informed consent process and prior to participation, participants will be informed that they will receive drugs that are commonly used to treat ADHD (i.e MPH) and/or placebo. Participants will be told that the purpose of the study is to measure the effects of stimulants used to treat ADHD and to see how these drugs affect mood and behavior. Other than receiving this general information about MPH versus placebo, participants will be unaware

of the type of drug administered. Participants will be given no instructions regarding what they are "supposed" to do or what outcomes might be expected.

As part of the screening, all participants will undergo standardized diagnostic procedures for ADHD, including the Conners Adult ADHD Rating Scales to assess ADHD status (all participants) and the Conners Adult ADHD Diagnostic Interview for DSM (prospective ADHD participants only). Participants will be administered the MINI International Neuropsychiatric Interview to assess the presence of other Axis I disorders. The ADHD diagnostic interview will be administered by the Principal Investigator or the study coordinator, under the supervision of the study physician. The MINI will be administered by the Principal Investigator or study coordinator. Any answers given by the participant that may indicate the presence of an Axis I disorder will be further reviewed by the study physician.

Participants will also complete a physical examination of their vital signs (height, weight, pulse, blood pressure) and complete a medical history to screen for contraindications for MPH administration. The participants will also complete a drug use history interview. This exam, medical, and drug use history will be overseen by the study physician. The study physician will follow-up with questions about family history of heart disease or other illnesses as necessary.

Study days: Participants who meet all eligibility criteria will complete baseline behavioral tasks (see below) and some questionnaires, and will then be scheduled for their 2 study days. Each study day will be scheduled at the same time of day (either morning or afternoon). Participants scheduled for the morning session will be asked to skip breakfast, participants scheduled for the afternoon session will be asked to skip lunch. A small meal will be provided (e.g., 2 granola bars and a fruit cup) for all participants after capsule administration. On each study day, participants' blood pressure and pulse will be measured and they will fill out a mood questionnaire (Positive and Negative Affect Schedule: PANAS). Women will provide a urine sample for a urine pregnancy test due to potential increased risks of stimulant drug administration. Women who return a positive pregnancy test will be excluded from further participation and will meet with the PI or study physician to provide appropriate follow up. Participants who continue to meet eligibility criteria will be administered 40 mg immediate-release MPH (MPH IR, Ritalin, Novartis) or a matching placebo with 8oz of water using a double-blind, counterbalanced design. Participants will sit quietly in a private waiting room while the drug is absorbed and eat the provided meal. After 60 min, participants will be administered a battery of behavioral tasks. Then, participants will complete questionnaires regarding mood, side-effects, and drug effects. Additional measurements of blood pressure and pulse will be taken approximately every 60 min after capsule administration and before participants are dismissed (4x per study day). Each study day will last approximately 3 hours.

Behavioral Tasks:

Bandit Task. Participants are shown a computer screen with 6 slot machines depicted. Each machine, when selected, will pay off points around a mean probability that changes randomly and independently from trial to trial. Participants must actively sample from a machine to discover its pay-out. As the average pay-out changes across trials, participants must decide whether to continue to exploit the current machine, or explore other machines. This task takes approximately 15 minutes to complete.

Patchy Foraging Task. Subjects choose between 2 targets on each trial. Choosing to stay in the current patch yields a short delay (0.5 s) and reward whose value diminishes on each trial. Choosing to leave the patch yields no reward and a long delay (travel time) whose duration is indicated on screen while participants make their selection. Choosing this option resets the value of the current patch. This task takes 8 min to complete.

Effort Expenditure for Reward Task (EffRT). This task measures effort-based decision making. On each trial, participants choose between two different task difficulty levels to obtain monetary rewards. For all trials, participants make repeated manual button presses within a short amount of time. Each button press raises the level of a "bar" viewed onscreen. If the bar is raised to the top within the allotted time period, the participants wins the points for that trial. Each trial offers a choice between two levels of difficulty: a "hard" task and an "easy" task. Hard task trials required the subject to make 100 button presses using the non-dominant little finger within 21 seconds, while easy task trials require the subject to make 30 button presses using the dominant index finger within 7 seconds. Completion of easy task trials will earn 1 point. Hard task trials could earn between 1.24 and 4.30 points. However, the probability of earning the points for successful task completion is 88%, 50%, or 12%. The probability of earning points is indicated onscreen at the start of each trial. At the end of each trial, participants are shown whether they completed the task on time or not, and earned the points or not. Participants have 20 min to play as many trials as they can.

Motivated Memory Task (MMT): This task measures the effects of reward motivation on expectancy violation processing. The design of this task is based on the monetary incentive delay task and is described in detail in Murty & Adcock, Enriched encoding: Reward motivation organizes cortical networks for hippocampal detection of unexpected events (Cerebral Cortex 2013). Each trial consists of 3 phases: 1) a cue indicating whether the participant could earn a high ($2) or low ($0) reward, 2) a variable delay during which color images are flashed on the screen 10 or 11 times, and 3) the formerly color image is presented in grayscale (the target image), which signals to the participant to make a speeded button press to earn a reward. During phase 2: the color images are either control (all images are identical) or expectancy violation trials, in which a novel distractor image is presented among the serial presentation of a color image. During phase 3: participants will perform a 2-alternative forced-choice recognition computerized memory task for images that constituted expectancy violations for both the high-reward and low-reward trials. This task takes 20 min.

Conner's Continuous Performance Task (CPT). This task measures sustained attention and inhibitory control. Subjects are asked to press a space bar on a computer as letters are sequentially displayed on the computer screen (unless an "x" appears). Subjects are asked to inhibit their response whenever an "x" appears. This task lasts approximately 15 minutes.

The Spatial Span consists of two parts: Spatial Span Forward and Spatial Span Backward. For each part, the examiner taps a series of cubes at the rate of about one cube per second. Following presentation, the examinee either taps the cubes in the same order as the examiner (Spatial Span Forward) or in reverse order (Spatial Span Backward). For both Spatial Span Forward and Spatial Span Backward, the test begins with series of two cubes and continues to a maximum of eight cubes. Examinees are given two trials at each series length, and the test continues until both trials of a series length are failed. One point is awarded for each trial the examinee answers correctly. The maximum possible score for the Spatial Span subtest is 32 (16 points each for Spatial Span Forward and Backward). This task takes up to 10 min.

Attention Network Test (ANT). This test measures different types of attention. At the start of each trial, a cue is displayed onscreen followed by flanker displays (i.e., horizontal arrows). There are four cue conditions and three flanker conditions. The task on each trial is to classify the central arrow as either pointing left or right. Participants respond using the computer keyboard. This task lasts 30 min.

Effort Discounting Task. Effort discounting is a computerized choice task designed to measure of the willingness to accept a smaller reward that requires less effort to obtain. During

this task, participants will be presented with a series of choices between a small, easy to obtain reward (between $0 and $20, available for no effort), and a larger reward requiring effort to obtain ($20, available after typing a number of words backward). The monetary value of the smaller reward and the effort (i.e., number of words) required to obtain the larger reward will be systematically varied across the series of choices in order to determine the participant's indifference point (i.e., the point at which the larger reward is no longer "worth it" to work for, and the preference switches to the smaller amount. Participants will be presented with each pair of options on a computer screen and will make their selections with a button press. Before beginning the task, participants will first type 5 words backward in order to gain experience with the effort. They will then complete the choice portion of the task. Participants will be instructed that one of their choices will be selected at random at the end of the task, and they will receive whichever that option. If the participant chooses the larger, effortful option, they will be required to type the specified number of words backward at the conclusion of the session before earning the reward. The task takes about 15 minutes to complete and will only be administered during the Screening/Baseline Day.

Table 1. Outline of planned study activities

Screen/Baseline	**Study Day 1 & 2**
20 min Consent & HIPPA brochure	5 min Measure BP & pulse. Urine pregnancy test (women only)
10 min Urine Drug Screen & pregnancy screen	2 min Mood questionnaire (PANAS)
10 min Drug Use History	5 min Administer capsule (placebo or MPH)
15 min Medical History & Physical Exam	Wait 60 min – eat meal while waiting
2 hours Conners Adult ADHD Diagnostic Interview and Rating Scales & MINI Psychiatric Interview	2 hours Tasks (Bandit Task, Patchy Foraging, EffRT, CPT, MMT, Spatial Span, ANT) BP/pulse/side effects taken every 60 min.
	5 min PANAS, side-effects, and drug effects questionnaires
1 hour Baseline Tasks (Bandit Task, Effort Discounting Task) & questionnaires	5 min Measure BP & pulse before dismissal

Study Interventions

Drug administration: Ritalin will be used to provide methylphenidate (MPH) in the methylphenidate condition. MPH is a mild central nervous system stimulant that blocks dopamine and norepinephrine reuptake. Ritalin was approved by the FDA to treat ADHD. In the central nervous system, 40 mg IR MPH results in a peak dopamine transporter receptor occupancy (at approximately 70%) between 1-3 hours after ingestion. This 40mg IR dose of methylphenidate has been administered to healthy adults previously by our research team and was well tolerated [10-13].

The UAMS pharmacy facility will prepare the MPH and placebo capsules for the study. The matching placebos will contain lactose. The drug and placebo capsules will look identical, except the base of the bottles will be marked with two different letters, one denoting the MPH capsules and the other the placebo capsules. The PI will be unblinded during the study to both the MPH and the placebos, and will therefore be able to identify which capsule was used if there

are any significant adverse effects felt by the participant after administration. The PI will not have direct contact with the participants during the experimental visits. The MPH and placebo capsules will not be given to participants to take home. These two products will be obtained by the study team and used only in the research setting.

Questionnaires evaluating both participant and experimenter judgments about the capsule condition will be acquired. Should a participant report severe side effects associated with a high dose of MPH (e.g., nausea, headache) they will be reminded of their right to withdraw from the study. Any reports of unexpected or severe side-effects will be logged and reported to the IRB as adverse effects. Heart rate, blood pressure, and side-effects will be measured approximately every 60 min after drug administration and prior to dismissal.

Compensation: No compensation is provided for the phone screen or the screening session (including consenting, drug screening, medical exam, drug use history, CAARS questionnaire, and MINI). Prospective participants who undergo the CAADID interview will be compensated $10/hour. Participants who are eligible for the study will receive $45 for the baseline visit and $100 for completing each study day. In addition, participants can earn up to $15 on the baseline day and up to $20 on each study day based on behavioral task performance. Thus, the total compensation for completing all parts of the study will be $245-300. Participants that decide to withdraw from the study before completion will be compensated $20/hour of participation on a pro-rated basis for the part(s) of the study that they have completed.

Study Population

We propose to obtain consent from 150 individuals in order to find 80 eligible participants and obtain useable data from 60 participants (30 per group). Prospective participants, ages 18-45, will be recruited from the surrounding area. During an initial phone screen, they will be given a brief description of our studies and will be asked questions to determine interest and eligibility.

Inclusion criteria for all subjects:

1) Capable of informed consent and able to complete all aspects of the study.
2) between the ages of 18-45
   negative urine drug screen for drugs (other than those allowed for depression or anxiety) and negative breath alcohol concentration

Inclusion criteria for non-ADHD subjects:

1) do not meet criteria for ADHD diagnosis or any subtype as determined by the Conners Adult ADHD Rating Scale (CAARS) T-Score < 55 on Inattentive Symptoms, Hyperactive-Impulsive Symptoms, Total Symptoms or ADHD Index subscales of the CAARS.

Inclusion criteria for ADHD subjects

1) meet criteria for a primary diagnosis of ADHD, any subtype, based on the Conners Adult ADHD Diagnostic Interview for DSM-IV and the CAARS.

Exclusion criteria for all subjects:

1) inability to attend all required experimental sessions
2) significant health problems (e.g., current and uncontrolled liver, lung, or heart problems, current or past seizure disorder, serious head trauma)
3) primary diagnosis of Axis I psychiatric disorders other than ADHD with the exception of depression or anxiety
4) meet DSM-5 criteria for substance use disorder other than nicotine in the past 12 months

5) use of psychoactive medications in the past 6 months as indicated by self-report with the exception of first-line medications for depression or anxiety (e.g., selective serotonin reuptake inhibitors or benzodiazepines)
6) contraindications for MPH (including use of monoamine oxidase inhibitors, have motor tics, Tourette syndrome, severe anxiety, or glaucoma – based on self-report)
7) among women, nursing or a positive pregnancy test
8) ≤ 8th grade education
9) allergy to lactose
10) hypertension (If subject has blood pressure over 140/90)

Risks and Benefits

Women of childbearing potential: Due to unknown risks and potential harm to the unborn fetus, women of child-bearing potential will be screened with a urine pregnancy test at the beginning of the study. Positive pregnancy tests are exclusionary. At each study day visit, urine pregnancy tests will be administered.

Undiagnosed ADHD: We will provide comprehensive feedback to subjects who have undiagnosed ADHD. Appropriate referrals will be provided when necessary.

Methylphenidate Administration: The most salient risk to participants will be the possibility of side effects of the MPH. The most commonly reported side effects of MPH have been headache, decreased appetite, stomach ache, nervousness, trouble sleeping, and nausea.

MPH is not recommended for people with certain conditions or taking some medications. MPH should not be taken if the person is very anxious, tense, or agitated; has glaucoma; has tics or Tourette's syndrome, or a family history of Tourette's syndrome; is taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI; or is allergic to any of the inactive ingredients found in Ritalin (D&C Yellow No.10, lactose, magnesium stearate, polyethylene glycol, sucrose, talc, and tragacanth).

MPH use should be supervised by a doctor if the patient is taking any of these medications: anti-depression medicines including MAOIs; seizure medicines; blood thinner medicines; blood pressure medicines; and cold or allergy medicines that contain decongestants (information from http://www.fda.gov/downloads/Drugs/DrugSafety/ucm089090.pdf).

It is important to note that we will collect subjective effects data and vital signs throughout all experimental sessions and subjects will be discontinued from the protocol if significant adverse events occur. Moreover, the study physician will carefully screen participants for eligibility, including health and medication history, and will be on site or on call during all visits and can be consulted regarding AE's if they arise. Based on experience among our research team, we do not anticipate significant side events.

During the study, the study physician (Dr. Weiss) will be notified if there is an increase in pulse by more than 20 beats per minute from that day's baseline (i.e., vitals taken upon arrival), or if the pulse is greater than 120 beats per minute and the blood pressure is greater than 140/90, or if the participant complains of palpitations. If these symptoms occur or persist at the end of the study visit, the participant may be asked to remain in the lab for monitoring. The participant will be released or referred for treatment per Dr. Weiss' decision.

Placebo Administration: Placebo capsules will contain powdered lactose to match the color and consistency of the methylphenidate capsules. Lactose is a sugar found in milk and dairy products. People who are lactose intolerant may experience gas, abdominal pain, diarrhea, and bloating after ingesting lactose. People who are allergic to lactose may experience these

symptoms as well as swelling of the lips or throat and trouble breathing. For these reasons, people who self-report having lactose allergies will not be eligible for participation.

Costs to subjects: Subjects will not incur any costs associated with participating in the study. All the study costs, including any procedures related directly to the study, will be paid for by the study.

Confidentiality: There is a potential risk of loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and Recordkeeping section below.

Benefits: There will be no direct benefits to the study participants; however, knowledge gained from the study could potentially benefit patients in the future.

Data Handling and Recordkeeping

The Principal Investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of the data and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a locked file in the principal investigator's office. Only the study coordinator will have access to the code and information that identifies the subject in this study. At the conclusion of the study, the data will be permanently de-identified and retained for seven years after final reporting or publication of the project.

Data Analysis

We base our sample sizes on previous studies that have found within- and between-group differences with sample sizes ranging from 20 to 30 subjects. Based on a previous study [9], we will be adequately powered to detect at significant effects with this sample size. The goal of this preliminary study is to collect data to perform power analyses for a larger project. The primary variable of interest is exploratory performance on the Bandit task. Behavior and self-report data will be analyzed using SPSS (Chicago, Ill), with significance set to alpha = .05. We plan to compare ADHD symptomatology and behavioral performance across all subjects using Pearson correlations, and to compare performance between groups using independent-samples t-tests. The interaction between within-subject differences in performance between MPH and placebo and between-subject differences in ADHD status will be investigated using a mixed-design 2x2 ANOVA.

Ethical Considerations

This study will be conducted in accordance with all applicable government regulations and University of Arkansas for Medical Sciences research policies and procedures. This protocol and any amendments will be submitted and approved by the UAMS Institutional Review Board (IRB) to conduct the study.

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternate treatment(s), and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject, and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed

consent process will be documented in each subject's research record.

Dissemination of Data

Results of this study may be used for presentations, posters, or publications. The publications will not contain any identifiable information that could be linked to a participant.

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Appendices

None