Neuromodulation of Decision Making in Young and Middle-Aged Adults: Part II

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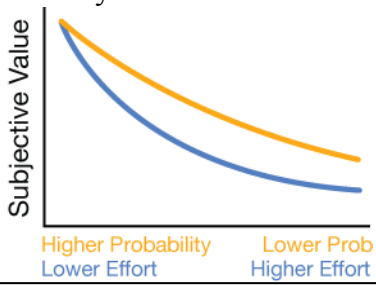
1.0 Background & Rationale

Over the past century we have witnessed the most rapid increase in life expectancy in human history, but for the last several decades the average age of retirement has not increased [18]. These biological and cultural trends combined with the current retirement wave of baby boomers will continue to put tremendous strain on public programs like Social Security and private pension accounts [19]. A common solution raised in public policy debates is to increase the retirement age [19]. However, it is not currently clear whether individuals approaching retirement age will maintain the motivation to continue working. Vital financial decisions are made during this pre-retirement age that can influence financial well-being for the rest of an individual's life. Most individuals in their 60s must determine if they should keep working and continue to save or retire and start spending down their savings. However, very little psychological and neurobiological research has examined financial decision making in pre-retirement age. As global demographics shift, it is vitally important to improve our understanding of the basic mechanisms underlying decision making across adulthood [13-15] – from the beginning of working careers in young adulthood to the pre-retirement period in late middle age.

Emerging theories suggest that changes in cognition, emotion, motivation, and experience across adulthood influence age differences in decision making [20-24]. However, the vast majority of empirical studies on decision making across adulthood simply document age differences in behavior or choice without investigating the underlying psychological, computational, and neural mechanisms. To move forward, a more mechanistic account is necessary [25]. An overarching goal of this grant is to begin to construct a more comprehensive model of the specific psychological and neural mechanisms that support financial decisions in young adulthood and late middle age. Our integrative approach includes measurement of cognitive and affective individual differences, decision-making behavior, functional and structural brain imaging, and pharmacological manipulations of neural systems. This work is primarily focused on effort-based decision making, but we will also examine sensitivity to reward magnitude and probability.

In our attempts to maximize wellbeing, the decisions we make require the integration of a number of features. For example, nearly all decisions require the weighing of expected benefits with any associated costs, which involves taking into account factors such as the exertion of effort required to achieve various outcomes or the probability of the outcome of a choice [26-28]. Depending on an individual's preferences, these features may systematically diminish the subjective value of decision outcomes (Fig. 1). Importantly, preferences may change across adulthood and differentially influence decisions. As reviewed below, recent studies have begun to examine changes in preferences with age and associated neural function, but there are large gaps and a number of methodological limitations of the existing literature.



FFigure 1. Decision features such as effort demands and probability may decrease the subjective value of a fixed amount of reward.

Effort. In animal research, effort-based decision-making paradigms have been widely used to study motivation [29] and the tolerance for physical costs in order to obtain a goal [30,31]. These paradigms involve repeated choices in which an animal must choose between a freely available, but smaller or less palatable food reward (Low-Cost/Low-Reward, LC/LR), as compared to a larger or preferred food reward, for which the animal must expend effort to obtain (High-Cost/High-Reward,

HC/HR). Effort expenditure in these paradigms has included scaling a barrier or engaging in repeated lever-pressing. Healthy animals show an overwhelming preference for HC/HR options, while various forms of interference with corticostriatal brain systems result in a shift towards more LC/LR choices. Forms of interference that result in a preference for LC/LR options include 6-OHDA lesions of nucleus accumbens (NAcc) dopamine (DA) terminals, blockade of NAcc DA D2 receptors, lesions of the anterior cingulate (ACC), DA D1-receptor blockade in the ACC, suppression of excitatory signaling from amygdala to ACC [32], or disruption of excitatory signaling from ACC to NAcc [33].

In order to assess effort-based decision making in humans, we developed the Effort Expenditure for Rewards Task (EEfRT or "effort"), which has been carefully modeled after effort-based paradigms developed by Salamone and colleagues [34]. Briefly, subjects perform repeated trials in which they choose between expending more effort (in the form of speeded manual button presses) to achieve a greater monetary reward (HC/HR), or less effort for a smaller reward (LC/LR). Individual trials vary in terms of the reward magnitude offered for the HC/HR option, as well as the probability of receiving a monetary reward for a given trial. This task has been previously shown to be sensitive to individual differences in trait anhedonia, such that individuals reporting greater anhedonic traits on the Chapman anhedonia scale [35] or the Beck Depression Inventory anhedonia scale made fewer HC/HR choices [16]. Studies in psychiatric populations are ongoing, but have strongly indicated changes in the context of affective disorders. Importantly, the EEfRT provides a means of assessing not only *whether* individuals choose HC/HR options, but also the subject's sensitivity to variables that influence these decisions, such as reward magnitude and reward probability. As in animal studies, EEfRT performance is modulated by manipulations of the DA system. Critically, we have demonstrated that release of DA induced by administration of d-amphetamine (dAMPH) dose-dependently increases the proportion of HC/HR choices [17]. Further, we have demonstrated in young subjects that EEfRT performance is related to measured DA functioning [36].

Despite the ubiquity of effort-based decisions, and increasing attention to effort-based decision making in studies and theories of psychopathology [37], there are currently no published studies of preferences for effort in middle-aged or older adults. Yet, effort is a rapidly growing area of interest in both clinical psychology [16,37] and decision neuroscience [17,29,38]. Stereotypes of pre-retirement age as a time of shifting preferences toward physical relaxation and leisure might suggest that tolerance of physical effort declines across adulthood. Although there is not yet any available empirical evidence related to effort and decision making in late middle age, age-related declines in DA may contribute to a lower tolerance for effort [26]. This lowered tolerance may be further exacerbated by an increase in physical motor limitations and ease of muscle fatigue with age [39], although these peripheral effects are likely more influential later in old age. Together this leads us to predict a reduced tolerance for physical effort in late middle age. We also expect middle-aged adults to show a larger difference in neural activation in mesolimbic DA target areas for higher relative to lower effort choices during fMRI of an effort-based decision task.

Probability. The impact of dAMPH on the EEfRT is notable in that its strongest impact is on the low probability trials, when there is a significant chance of not obtaining a reward [17]. Despite popular stereotypes of older adults being more risk averse than young adults in the face of uncertainty, a quantitative meta-analysis conducted by a member of our research team reveals that behavioral risk preferences (tolerance of low probabilities) do not globally differ between younger and older adults [40]. Although different patterns of risk taking or risk aversion emerge for certain

classes of decisions [40], these differences appear to be more related to cognitive limitations than true preferences. Such findings suggest the possibility of dissociations between changes in effort and probability discounting. However, there are currently no existing studies that have examined relationships between effort and probability preferences in young and middle-aged adults.

Subjective Valuation and Neural Systems

The work reviewed thus far has focused on how features of decision options (tolerance for effort and probability) may influence choice differentially across adulthood. Importantly, age and individual differences in goals and preferences directly influence the *subjective value* of a decision option. For some decisions, it is possible to compute a mathematical expected value (independent of an individual's preferences), in dollars, for each choice. In contrast, the subjective value of an option is just that, subjective. The value or utility of an option to a given individual is dependent on their preferences. Observable decisions reflect these subjective values people hold about the outcomes. This concept of subjective valuation has been a strong focus of recent decision neuroscience research.

Neuroimaging work suggests that there is a unitary neural system supporting subjective valuation [41-43]. This work is just beginning to focus on effort cost integration [44], with more work examining related decision costs such as uncertainty and temporal delays [41-43] in healthy young adults. The medial prefrontal cortex and ventral striatum lie at the core of this system. Preferences for risk and ambiguity are reflected in a shared mesolimbic subjective valuation system [43]. There is also some evidence for domain generality such that a shared aspect of this core subjective valuation system underlies risky decisions about both primary rewards (food, water) and money [41]. Such data raise the possibility that influences on subjective valuation may provide a pervasive impact on decision making regardless of the type of cost. With one recent exception [45] regarding uncertainty, this prior neuroimaging work has exclusively used fMRI, which cannot fully address the specific neurochemical modulation of these signals. However, these regions of the striatum and medial prefrontal cortex are primary targets of ascending midbrain DA projections. Thus, it has been argued that subjective valuation is dependent on these more ventromedial aspects of the DA system.

In Part I of this study we are examining behavioral and neural sensitivity to monetary reward and physical effort costs in young adulthood and late middle age**.** In a sample of healthy young (ages 20–30) and late middle-aged (ages 50–60) adults, we are using functional MRI to examine basic aspects of reward processing using the Monetary Incentive Delay (MID) task and sensitivity to effort costs using the Effort Expenditures for Reward Task (EEfRT). Participants in Part 1 of the study are also screened for eligibility for Part II of the study.

In the present (Part II) portion of the study, we will use positron emission tomography (PET) imaging to determine whether individual differences in DA functions are related to the decision-making and fMRI measures collected in Part 1 of the study. DA imaging will include striatal and extrastriatal baseline D2 receptor availability, amphetamine-induced DA release (a marker of DA system responsivity) and DA transporter levels. This approach provides a more comprehensive evaluation of DA functions than in prior studies attempting to link individual differences in dopamine to behavioral, cognitive or decision-making functions. In addition to allowing us to test key hypotheses about DA and behavior, this study will also allow us to address several questions about age-related and individual differences in DA functions, including 1) whether age related declines in striatal and extrastriatal D2 receptor levels covary with changes in DAT, 2) whether there are age related changes in DA system reactivity to amphetamine, and 3)

whether individual differences in baseline levels of DAT uptake are associated with the amount of amphetamine-induced DA release (which is predicted given that DAT is the target site for amphetamine, but has never been tested in humans. Additionally, we will be able to examine whether baseline differences in DAT are related to the behavioral effects of amphetamine

2.0 Specific Aims:
There are three specific aims of this phase of the study
Aim 1: To test the hypothesis that multiple aspects of mesolimbic DA function are uniquely associated with age differences in decision behavior.
Based on preliminary data, we expect to observe larger age differences in DA D2-like receptor availability in the pallidum and frontal cortical regions, but smaller (but measurable) declines in the ventral striatum. We hypothesize that middle-aged adults will show significantly lower levels of DA release in the striatum and medial prefrontal cortex and DAT expression in the striatum compared to younger adults. Across both groups, we expect individuals with greater DA release in the ventral striatum and ventromedial prefrontal cortex to be more tolerant of effort costs.

Aim 2: To examine the influence of individual and age-related differences in DAT on dAMPH-induced DA release. Given that DAT is the primary site on which dAMPH acts, we will test the hypothesis that individual differences in DAT expression substantially predict DA release and the subjective effects of dAMPH. Because DAT declines with age, we additionally hypothesize that dAMPH-induced DA release will be lower in the middle aged than the young adult sample. We additionally predict that the combination of DA midbrain autoreceptor levels and striatal DAT levels will predict dAMPH induced DA release better than either index in isolation.

Aim 3: To examine the influence of dAMPH-induced DA release on cost-benefit decision making in young adulthood and late middle age.

We recently demonstrated that dAMPH increases tolerance of physical effort costs in healthy young adults. Young and middle-aged adults will complete a behavioral version of the effort-based task in two sessions (placebo, dAMPH). We expect that tolerance of physical effort will be increased under dAMPH in both age groups, with differences in the extent of modulation correlating with measures of baseline DA functioning and DA release.

3.0 Recruitment and Inclusion/Exclusion Criteria

3.1 *Recruitment*: Subjects are recruited directly as part of IRB#141812 Neuromodulation of Decision Making in Young and Middle-Aged Adults Part I. No recruitment external to that study are planned. Participants in IRB#141812 are recruited through online advertisements including the Dept. of Psychology Paid Subject Pool (Sona Systems), ResearchMatch and Craigslist, and fliers posted around the Vanderbilt campus or in local community organizations or handed out at health related events).

3.2. *Criteria for inclusion and exclusion and procedures used to determine eligibility*:

Inclusion: a) Be between the ages of 20-30 or <u>50-65</u>
b) Be able to give informed consent
c) Have an estimated intelligence quotient of greater than 80
d) Fluent English speaker

Exclusion:

a) History of substance dependence (or prolonged substance abuse lasting more than 2 years) or positive urine drug screen
b) Use of any psychostimulants (other than caffeine) in the last 6 months or more than 4 times in lifetime
c) Current tobacco (or nicotine use), or alcohol intake greater than 8 ounces of whiskey or equivalent per week
d) Any psychotropic medication for the past 6 months other than benzodiazepines for sleep
e) History of major psychiatric illness (including recurrent major depressive episodes or a depressive episode in the past 10 years, any anxiety disorders in the last 10 years, any history of bipolar disorder or dysthymia, any psychotic disorder, or any eating disorder in which symptoms persisted for more than two years)
f) History of neurological disorder (excluding headaches or problems limited to peripheral nerves), or history of head trauma (other than a single concussion)
g) Significant untreated or unregulated major medical condition deemed likely to influence cognitive functioning, dopaminergic functioning or neuroimaging measures
h) Any condition which would interfere with MRI or PET studies, e.g. extreme obesity, claustrophobia, cochlear implant, metal fragments in eyes, cardiac pacemaker, neural stimulator, tattoos with iron pigment and metallic body inclusions or other metal implanted in the body which may interfere with MRI scanning.
i) Pregnancy, lactation or trying to get pregnant during the month during which the study is to take place
j) Anemia, a hematocrit below 34
k) Diabetes, hypoglycemia, or any condition that could would prevent the participant from fasting for 6 hours
l) Recent participation in studies involving radiation or routine occupational exposure to radiation.
m) High blood pressure (Systolic B.P. > 150), or an abnormal EKG indicating potential cardiac risk under conditions of increased blood pressure. <u>If subject is over 60, baseline B.P. > 145.</u>

Inclusion/Exclusion criteria are determined based on data obtained during IRB#141812 (with the exception of the plasma pregnancy exam for women of child-bearing potential which is collected within 48 hours prior to each PET scan. At any point in the study, the study PI (Zald), or one of the study physicians may withdraw a participant if they find new evidence that the participant has an exclusionary condition.

Up to 70 subjects may be consented for the study, with the aim of having 60 subjects total complete the PET studies. No more than 60 subjects (30 per age group, with equal gender representation). No subjects will be consented after the 60th participant is scheduled for a PET scan unless we have another withdrawal from the study.

4.0 Study Procedures

4.1 Primary Study Procedures: The study involves 4 sessions: Informed Consent, Fallypride PET + placebo, Fallypride PET + oral d-amphetamine, and PE2I PET. The 3 PET sessions will be conducted within a 6 week window, and whenever possible within a 2 week time period.

4.2. *Informed consent session*: Informed consent will be obtained by Dr. Zald or approved study personnel after inclusion and exclusion criteria have been reviewed. This will be done in the Dept. of Psychology at Vanderbilt University. Written consent materials are provided to the participant originally when they complete the related IRB protocol #141812. Although given to participants during Part I of the study, Participants only sign the consent for the 2nd part of the study after completing the prior study and passing inclusion and exclusion criteria assessed during that study.

In the present study, participants are given time to read (or reread) the written informed consent document in a quiet private room. They are asked if they have any questions about the protocol. If they have no questions or the researcher has any concerns about whether they understand the procedures, the researcher will briefly review the steps of the study. Because the participants will have already completed IRB #141812, the researchers will already have some knowledge of the participants level of cognitive functioning, and if there is a concern about the participants ability to understand the procedures based on their past performance on cognitive measures they will be excluded from the study.

After the potential participant indicates they have read the document, Dr. Zald or his associate will briefly review specific procedures and their risks (especially those related to administration of amphetamine and PET radioisotopes), and the subject will be given a chance to ask questions. The participants will only be asked to sign the informed consent document after any and all questions have been answered.

After signing the informed consent, participants will receive a brief training on how to perform the two-stage task (this will help reduce the amount of time needed for training on that task on the fallypride PET scan days). Participants will also complete the Tests of Vigilance and Attention (TOVA: http://www.tovatest.com/), which assesses attention abilities and motor impulsivity.

4.3 Specific procedures for female subjects of child-bearing potential: Premenopausal without hysterectomy or similar procedure, will need to have an additional blood draw within 48 hours prior to each PET session to rule out pregnancy (blood drawers will typically be scheduled within 36 hours preceding the planned time of radioisotope administration). Women who are premenopausal will be only studied within the first 10 days of their menstrual cycle.

4.4 Fallypride PET Sessions (with placebo or oral d-amphetamine).
Participants complete two [^{18}F]fallypride PET sessions, each lasting approximately 7 hours. Scan sessions will all start in the afternoon. Subjects will be instructed to have a moderate lunch with no more than a single cup of coffee or tea before coming to the PET center. If the scan is not expected to start until after 5 PM, a light snack may also be eaten. After determination of blood pressure, respirations, pulse, temperature, an intravenous line will be placed in the forearm, the subject will complete ratings of their mood (using the and PANAS and the Amphetamine Interview Schedule administered on a laptop computer), and participants will have a brief neurological exam conducted by one of the study MDs. An initial blood sample for genotyping or estradiol levels (women only) will be acquired.

The subject will then receive a 0.43 mg/kg oral dose of d-amphetamine or placebo. The investigational pharmacy will prepare capsules with 10 mg, and 2.5 mg with dosing rounded to the nearest 2.5 mgs (for instance an individual weighing 80 kg would be rounded up to a 35 mg dose). The drug dose and placebo, will be placed by the pharmacist in identical containers, labeled with the subject's ID and scan day number. A sealed envelope indicating whether the dose is d-amphetamine or placebo will be included in case there is a need to break the blinding. The study physician, can quickly access this information if there is appearance of an adverse drug effect. Otherwise the study physician and experimenters who have contact with the participant will remain blind until the participant has completed their second PET scan. If a participant has an adverse event that necessitates any medication, or other intervention, the blind will be broken to the participant.

Subjects will have blood pressure and pulse determinations every 30 minutes for the first 2.5 hours, prior to the start of PET scanning (around 175 minutes post-administration) and every 60-70 minutes thereafter until the subject's blood is in the normotensive range. In the event that the participant's blood pressure exceeds 180 mm Hg systolic, blood pressure will be measured every 15 minutes until it shows evidence of reducing (at least a 5 mm Hg decline). In the unlikely event that a subject's blood pressure should rise to greater than 200 mm Hg systolic B.P. for over 30 minutes, the patient may be treated with oral clonidine at the discretion of the study MD (see risk section below for specific details). We note that in our multi-year experience working with oral amphetamine, we have never required an intervention.

After .5, 1, 1.25, 1.5, 2, 3, hours post-dAMPH/placebo administration and after the first two PET scans, approximately 4 and 5 hours subjects will complete ratings of mood (with selected items from the Amphetamine Interview Schedule and PANAS) and the DEQ (which asks them to rate whether they feel the drug, feel high, like the drug, or want more of the drug). Subjects will make their ratings on a laptop computer.

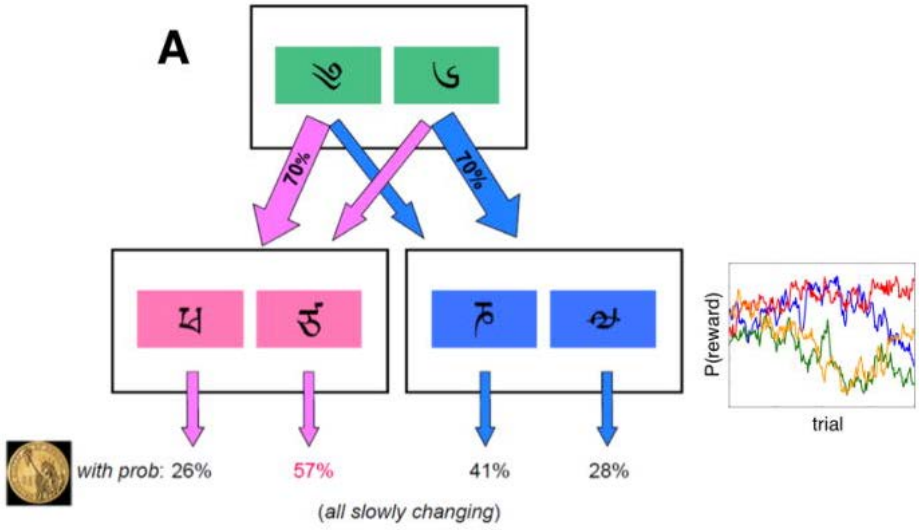
4.41 Cognitive Assessments. To further assess the cognitive specificity of dAMPH effects on cognition, participants will complete a battery of cognitive measures under placebo and drug. After the 60-minute post-administration blood pressure, mood ratings and blood draw, participants will begin performing the cognitive assessments tasks. Testing will include measures of speed of processing [WAIS-III Digit Symbol Coding and Symbol Search [115]], a measure of the speed of verbal associations [Controlled Oral Word Association Test [116]], and a measure of motor speed [finger tapping [151]] and a measure of working memory (2-back task). All tasks are included based on literature indicating that these functions are modulated by DA (e.g., [124,125]), with the tasks starting immediately following the amphetamine. The precise order of these tasks will vary, with brief tasks occurring during the 60-75 post-administration period, and the other tasks occurring following the 90 minute blood pressure and mood ratings.

4.42: Decision Making and Reward Learning Tasks. A 15-minute behavioral variant of the EEfRT task (which requires participants to make decisions about expending effort for rewards) will be performed starting 75 minutes after drug administration. In approximately half the trials the trial will terminate immediately after the decision phase, skipping both the effort expenditure and feedback phase. This approach allows us to complete significantly more decision trials during the 15-minute window.

Participants will also complete a two-stage reward learning paradigm that follows the procedures by Daw et al. (2011). On each trial, participants make an initial choice between two

options labeled by Tibetan characters that lead probabilistically to either of two, second-stage "states," represented by different colors (see Figure 2). Each first stage choice is associated with one of the second stage states, and leads there 70% of the time. In turn, each of the second-stage states demanded another choice between another pair of options labeled by Tibetan characters. Each second-stage option was associated with a different probability of delivering a monetary reward (versus nothing) when chosen. To encourage participants to continue learning throughout the task, the chances of payoff associated with the four second-stage options is changed slowly and independently throughout the task, according to Gaussian random walks. In each stage participants have 2s to make a choice. Inter-stimuli and inter-trial intervals are 500ms and 300ms, respectively, and monetary reward is presented for 500ms. The task will take approximately 20 minutes to complete.

Participants keep any money won during the two decision-making tasks, which we estimate will be around $40 between the two tasks (range = $20-60).



4.43 Spontaneous Eye Blinks: During portions of the study procedure participants may be asked to wear eye tracking goggles capable of recording spontaneous eye blinks. If participants cannot wear the goggles comfortably (primarily due to interactions with prescription glasses), will not be asked to wear the goggles.

4.44 *Post administration blood draws*. 4 blood draws (3 ml each) are taken to measure plasma amphetamine levels. These are collected at 30, 60, 90, and 175 minutes post-amphetamine. In order to avoid a different blood draw schedule, blood draws will additionally be made on the placebo day and will be discarded using appropriate hazardous biospecimen procedures. The lab will receive a sealed form that indicates whether to analyze or discard the samples.

4.45 PET scanning and fallypride administration. Scanning will be accomplished with a GE Discovery STE PET/CT scanner. 5 mCi of [^{18}F]fallypride (specific activity > 3,000 Ci/mmol) will

be injected, and subjects will be scanned for 3.5 hours (with two 15 minute breaks) to allow estimates of both striatal and extrastriatal binding potential. Dots are placed on the subject's forehead and cheeks for periodic visual checks of alignment throughout the scan period, and for repositioning after breaks. Three CT scans will also be collected during each session for attenuation correction. Blood pressure will be taken during each break and mood ratings will be taken during each break. During the second break participants will be given a high fat meal to help improve elimination of the radioisotope. Participants will also be given fluids to drink and asked to void their bladder.

At the conclusion of each PET scan on drug and placebo day, vital signs-blood pressure, pulse, temperature and respirations – will be measured, a brief motor neurological examination performed, and an additional 3.5 ml of blood drawn for a CBC and a comprehensive metabolic panel (CMP). If neurological exam and vital signs are normal the participants will be released from the study. In the unlikely event that they are not normal, the participant will be asked to stay under medical supervision in the VUMC (in one of the rooms in the PET center) until these measures have normalized. At the time of release participants will be given instructions to drink fluids and void their bladder at least once every two hours for up to 6 hours after the time of the start of the PET session.

4.5 *FE-PE2I PET Session*

All participants complete one [^{18}F]FE-PE2I PET session lasting approximately 2 hours. Female subjects capable of childbearing will have a plasma beta HCG determination within 48 hours of the PET study. Subjects will be instructed to not eat or drink coffee within 2 hours of the scheduled appointment. After determination of blood pressure, respirations, pulse, temperature, an intravenous line will be placed in the forearm, and a 3.5 ml blood sample for CBC and CMP will be drawn.

Scanning will be accomplished with a GE Discovery STE PET/CT scanner. 5 mCi of [^{18}F]FE-PE2I (specific activity > NLT 457Ci/mmol) will be injected, and subjects will be scanned for 1 hour. Dots are placed on the subject's forehead and cheeks for periodic visual checks of alignment throughout the scan period. One CT scan will also be collected for attenuation correction.

At the conclusion of the PET scan, vital signs-blood pressure, pulse, temperature and respirations will be measured, and an additional 3.5 ml of blood will be drawn for a CBC CMP. Participants will be given a high fat snack or meal to help improve elimination of the radioisotope. They will also be given fluids to drink and asked to void their bladder. Participants will be given a neurological exam, and if both neurological exam and vital signs are normal, the participants will be released from the study. In the unlikely event that the neurological exam and vital signs are not normal, the participant will be asked to stay under medical supervision in the VUMC (in one of the rooms in the PET center) until these measures have normalized. At the time of release participants will be given instructions to drink fluids and void their bladder at least once every two hours for up to 6 hours after the time of the start of the PET session.

Participants may be asked to complete an extended [^{18}F]FE-PE2I scan in order to establish radiation-dosimetry. Our current estimates of [^{18}F]FE-PE2I uptake are based on nonhuman primate data. A small number of subjects will complete an extra hour of scanning, with no additional injection. For the extra PET scanning the scanner will be switched into whole body mode so as to scan the critical organs of the torso, including gonads). Participants will be exposed to one extra CT scan (covering the torso/gonads), and will have up to 14.5 additional blood drawn to measure the metabolites of [^{18}F]FE-PE2I.

5.0 Risks

Possible risks from the study include administration of radiopharmaceuticals and oral d-amphetamine, venipuncture, and the discomforts associated with PET scanning

Radiopharmaceuticals: Subjects are exposed to radiation from the two [^{18}F]fallypride scans and, the single [^{18}F]FE-PE2I scan, and the CT scans that are used for attenuation correction. The total radiation dose associated with one PET study is approximately 1900 mrem. This dose corresponds to the background radiation received in 6 years from the environment. Dosing at this level is within FDA guidelines, and large-scale studies of the long-term risk of radiation exposure (within FDA limits) have shown no increase in rates of cancer associated with this amount of exposure.

In addition, there is a potential adverse response to the injections themselves. This risk is minimal because [^{18}F]fallypride and [^{18}F]FE-PE2I are injected at subpharmaceutical (tracer-level) doses, and procedures are in place to ensure quality control in terms of requirements for high specific activity, chemical purity and demonstrated sterility. Dr. Zald and colleagues have now performed over 200 [^{18}F]fallypride PET studies at Vanderbilt and have seen no laboratory abnormalities from administration of this radiopharmaceutical. The only adverse event seen in these studies was a single subject who became nauseous, but review of the case suggested that this may have related from hypoglycemia due to fasting before the study.

We lack past experience with injecting [^{18}F]FE-PE2I at Vanderbilt, but no reports of adverse events have been reported at other institutions using the radioligand, and qualifying runs have shown suitable specific activity, chemical purity and sterility. A nuclear medicine physician will be available within the Department of Radiology in case a problem arises that requires attention.

Administration of Amphetamine: The primary risks associated with the use of dAMPH include an increase in blood pressure, psychological effects (i.e. feeling jittery, anxiety, increased alertness and restlessness), and difficulty sleeping. Numerous studies of oral dAMPH in normal volunteers have been reported. A 0.5 mg/kg oral dose of dAMPH produced a mean elevation of 28 mm Hg increase in systolic blood pressure at 2 hours, i.e. a peak systolic blood pressure of 148 which decreased to a 14 mm Hg increase at 4 hours and returned to normal levels by 6 hours. The pulse rate remained unchanged [145,176]. Our own data in young adults exposed to our standard dose of 0.43 mg/kg indicates a mean increase of approximately 27 mm HG at peak (148 mm Hg) that occurs by 3 hours, and decreases substantially by completion of scanning. Based on these data we anticipate that a 0.43 mg/kg dose of dAMPH should produce blood pressure elevations of 25-30 mm Hg on average. To limit risk, we apply strict blood pressure restrictions on enrollment (systolic no more than 150 mm Hg). The average systolic blood pressure is 120 (average range: 108-133) for the age range 20-30, and 130 (average range: 116-144) for the age range 50-60. With an inclusion cutoff of 150 mm Hg, we do not anticipate many participants exceeding 180 mm Hg on dAMPH. This is within the normal range for systolic blood pressure for exercise (160 - 220 mm Hg). Participants with a reported history of labile hypertension will also be excluded, since they would be at increased risk for a blood pressure elevation. Participants will also be given an EKG and will be excluded if there are any abnormalities that would represent a risk under a condition of temporary elevation of blood pressure. Participants' blood pressure will be monitored by medical staff during their time in the study (every half hour), and standard of care intervention will be administered if there is a sustained elevation in blood pressure > 200 mm Hg

for more than 30 minutes. The default treatment strategy for sustained high blood pressure will be administration of 0.3 mg oral clonidine, which typically begins lowering blood pressure within 30 minutes. We note that in the unlikely event that the study physician felt a more rapid lowering of blood pressure was essential for patient safety, the study MD could select administration of intravenous nitroprusside as part of a standard of care treatment for a blood pressure emergency, but we do not anticipate any situations in which this should necessary. We note it in the protocol only for purposes of thoroughness – and any case where this would be necessary would warrant an adverse event report to the IRB. In all of our past studies intervention has never been necessary following amphetamine (although we note that the majority of subjects studied in our lab to date were under 40 years of age). A study medical doctor (Dr. Cowan or his surrogate) will be in the PET suite or the medical campus throughout all procedures and will be notified immediately if blood pressure exceeds 170 mm Hg systolic on any reading.

Psychological effects range from positive effects to some mild negative subjective emotional states including feeling jittery, anxious or restless. These negative emotional states resolve within a few hours of drug administration and are consistently gone by the time subject's leave the study. Participants are given a number to reach the investigators if they are experiencing any acute negative emotional events in the hours after they leave the study, although we have never had a participant feel the need to contact us following exposure to amphetamine. Participants may have difficulty falling asleep in the evening after amphetamine administration. They are advised of this, and told: 1) not to make any major decisions or drive following the study, and 2) not to schedule anything too early in the morning the next day. The study staff will make transportation arrangements in cases where someone does not have a ride option after the scans. We additionally try to start drug administration by 2 PM in the afternoon, so that 8-hours have passed by a typical bedtime.

There is a potential ethical concern regarding the administration of psychostimulant drugs to healthy non-drug using normal control subjects. We have relied on guidelines developed by the National Advisory Council on Drug Abuse (NACDA; appointed by the Secretary of Health and Human Services and Advisory to the National Institute of Drug Abuse). The entire report is available at: http://www.nida.nih.gov/funding/hsguide.html. In addition, we have relied on the "Human Subject Issues in Drug Abuse Research" published by the College on Problems of Drug Dependence (Adler, 1994) which states "There is no evidence that exposure to drugs in a research setting enhances the desire of an individual to use drugs, leads the individual to addiction, worsens the addiction of an individual, or makes an addict more difficult to treat". For the sake of thoroughness, we have provided pertinent excerpts from the most recent NACDA guidelines as a supplement to this application.

Venipuncture: There is a risk of local bruising and discomfort associated with venipuncture for obtaining blood samples and placement of IV lines for the PET studies. A small amount of bleeding may occur when an IV line is inserted or removed. While there is the possibility of infection associated with venipuncture, this is very unlikely. Participants with anemia are excluded in order to avoid problems associated with repeated blood draws.

Discomfort associated with PET scanning: Participants may experience some discomfort due to having to remain motionless for up to 70 minutes at a time during PET scanning. Participants are given pillows to help them get comfortable before the start of the scans.

5.1 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Each study will be monitored by Dr. Cowan or one of the approved study M.D.'s in his absence. The physician will monitor vital signs, physical and mental status, in real-time, to assess for adverse events and safety concerns. Subjects will be discharged with instructions to call immediately for any concerning signs or symptoms. Adverse events will be classified mild, moderate or severe as follows:

1) Mild – Adverse effects including events which do not produce functional impairment and do not require intervention or promptly respond to treatment.

2) Moderate – Moderate side effects include events and pharmacological effects which may affect function and pharmacological effects of drugs which do not respond promptly to treatment but are reversible over a period of hours.

3) Severe - Adverse effects are those which are life-threatening, incapacitate the subject, and in the case of pharmacological effects do not respond to treatment and do not resolve within hours.

Adverse events or unanticipated events will be attributed to the study as follows:

1) Probable: The adverse event is likely related to the study.

2) Possible: The adverse event occurs within 96 hours of the end of the study, but may be related to other factors.

3) Unrelated: The event occurs more than 96 hours after the end of the study and is more likely due to extraneous factors. Probable or possible serious adverse events will be reported to the IRB within 10 days.

All potentially serious adverse events will be reviewed on a real time basis. All adverse events will be reviewed with Dr. Warren Taylor during regular review meetings. Any adverse events that could be deemed moderate or greater, and probable or possible, will lead to a meeting with Dr. Taylor at his earliest possible schedule opening (within 48 hours of the event). All events that either the PI or Dr. Taylor consider to be severe adverse events, which are probably or possibly related to the study will be reported within 7 days to the IRB, and within 10 days to the FDA by Dr. Zald (and Jeffrey Clanton, MD, who is the physician in charge of the institutional IND), and NIA program officer by (Dr. Zald). Additionally, any unanticipated event that is considered moderate and possibly or probably related to the protocol will be reported to the IRB (but not the FDA or NIDA program officer) within 10 days. Annual reports of all adverse events (regardless of severity) will be made to the IRB (by Dr. Zald) and FDA (by Dr. Zald and Clanton). Note, non-pharmacological adverse events, such as vasovagal responses to the placement of the IV line, will not be included as part of FDA reporting as they are unrelated to the investigational drug.

Data and Safety Monitoring

The PI will meet with the data safety monitor on an annual basis to review participant data. Data to be reviewed will include any descriptions of impaired functioning reported by the medical staff involved in the project including pre- and post-administration neurological exam, pre- and post-administration vital sign, CBC and CMP. Any unanticipated adverse events will be reviewed with the data safety monitor within 48 hours of the event in order to evaluate the event, determine reporting requirements, and evaluate if protocol changes are necessary.

6.0 Study Withdrawal/Discontinuation

Subjects may elect to withdraw from the study at any point. The investigator may discontinue an individual's participation in the study for the following reasons:

1) The participant becomes pregnant.

2) The subject is found during screening to have laboratory results, physical findings, or psychiatric history that are exclusion criteria.

3) The subject has an adverse events of moderate severity or greater who, in the judgment of the principle investigator, may be unable to complete the study or whose health may be compromised by further participation. If an adverse event occurs, immediate treatment will be provided.

4) A subject cannot complete the study in a reasonable period of time, i.e. >3 months. Subjects will be informed of this possibility orally and then in writing prior to discontinuation.

If a subject is discontinued by the investigator during the initial session of the study or because of a failed drug screen, they will not be reimbursed for their time. If they are discontinued because of medical or psychiatric reasons, they will be compensated at a rate of $10 per hour spent in the study up to a total of $150. If the study was discontinued after administration of [^{18}F]fallypride, the subjects will be paid for the complete study.

7.0 Statistical Analysis Plan

Aim 1 tests the hypothesis that aspects of mesolimbic DA function are associated with age differences in decision behavior.

PET Analyses. A region of interest (ROI) approach will be used in the first set of analyses to examine age group differences in D2 binding (placebo BP_{ND}), DA release (ΔBP_{ND}), and DAT uptake in a set of eight brain areas. We will define subcortical (e.g., caudate, putamen, globus pallidus, thalamus) ROIs based on adapted methods developed for adults of various ages [173] by consultant William Jagust. We will define a lateral cortical ROI based on the results of a PCA (as in [153]) We will also anatomically define smaller key regions of interest in the midbrain (VTA/SN), ventral striatum (nucleus accumbens), and ventromedial prefrontal cortex using previously published guidelines [110,111] within individual subjects. For initial analyses all ROIs

will be averaged bilaterally, but follow-up tests will also be conducted to determine whether any ROIs warrant bilateral specification. D2 BP_{ND} (placebo) will be extracted for all eight ROIs, while DA release (ΔBP_{ND}) and DAT expression will be extracted from ROIs restricted to only those where there is substantial signal to noise (e.g., VTA/SN and striatal sites for DAT).

We will first test for expected age related differences in DA variables, using ANOVAs with Age group as the independent between subjects variable of interest. Separate analyses will be performed for $BP_{ND,}$ $\Delta BP_{ND)}$, and DAT measures. We will also test for interactions between age group and region to test the hypothesis that there will be larger age differences in DA D2-like receptor availability in the pallidum and frontal cortical regions, but smaller (but measurable) declines in the ventral striatum. We expect that middle-aged adults will show significantly lower levels of DA release in the striatum and medial prefrontal cortex and DAT expression in the striatum compared to younger adults.

We will next test the whether the dopaminergic measures predict behavioral differences in decision making. Across both groups, we expect individuals with greater DA release in the ventral striatum and ventromedial prefrontal cortex to be more tolerant of effort costs.

Aim 2 examines the hypothesis that individual and age-related differences in DAT are associated with dAMPH-induced DA release. This will be studied using striatal ROIs and ANOVA with age group serving as a between subjects variable.

Aim 3: To examine the influence of dAMPH-induced DA release on cost-benefit decision making in young adulthood and late middle age. We expect that tolerance of physical effort will be increased under dAMPH in both age groups, with differences in the extent of modulation correlating with measures of baseline DAT functioning and DA release. This will be accomplished by ANOVA analysis with age group as a between subjects variable.

Mediation Analyses: In each of the above cases we will utilize a mediation analysis to test whether expected age differences in behavior (effort performance, responsivity to d-AMPH) are mediated by age related differences in regional DA functions.

*Exploratory voxel-wise analyse*s: Beyond the ROI analyses, more exploratory whole-brain voxelwise analyses will be conducted. For these analyses, individual difference measures (e.g., choice preferences, trait affect, cognitive ability, etc) and age will be mean-deviated and entered as regressors of interest to predict BP_{ND}. The resulting whole-brain maps will be thresholded at whole brain $p_{cluster\text{-}corrected} < 0.05$.

Relative Influence of Different DA Measures. By assessing multiple aspects of the DA system it will be possible to assess the relative influence of different aspects of the DA system on behavioral measures. We will first use a PCA analysis of ROI data for cortical and subcortical ROIs for binding potential, striatal and ventromedial prefrontal DA release, and striatal and midbrain DAT. We expect there to be a positive correlation between all of these variables, reflecting an overall integrity of the DA system, but for separate components to arise reflecting region and measure specific variance [153]. We will then assess the relative impact of the DA variables, by utilizing step-wise regression to determine which variables provide the strongest influence on the behavioral variable, and whether, as predicted, a combination of DA measures provides significantly greater explanation of the behavioral variable than the measures taken in isolation. Further, we expect the inclusion of each additional measure of DA function to reduce the significance of the age effect on differences in sensitivity to effort costs. We expect that a model that includes D2 receptors, DA release, and DAT expression will reduce the age effect to

non-significance, indicating that the age effects are mediated by the DA variables. We will also formally test a mediation model.

Control for Morphometry: When imaging the aging brain it is extremely important to address age differences in morphometry. Aside from common issues that arise with BOLD fMRI [108], findings from prior PET studies of aging may be limited by a lack of control for morphometric changes with age. Lacking information on morphometry, it is possible that observed declines in striatal D2 BP_{ND} could be partially due to changes in grey matter rather than a specific D2 deficit. An additional *innovation* of this project is that we will examine the role of morphometric change, by directly examining whether controlling for grey matter volume changes the results, applying partial volume averaging corrections for ROI analyses, and voxelwise procedures based on voxelwise morphometry techniques (see [154,174] for method details and feasibility).

Statistical Power: The analyses of age differences will be conducted with age as a dichotomous variable. The group difference effects that have been observed in relevant recent studies of decision making or corticostriatal brain activity [109-112] range from around d=0.75–1.5. To detect the lower extent of these effects, a total sample size of at least 60 (30 per group) is recommended for a power of .80 at $p < .05$ two-tailed. Across the sample and within age groups, we will examine relationships between continuous measures (e.g., task performance, cognitive ability, emotional traits, fMRI neural activity, PET DA measures). The individual difference correlations that have been observed in related studies range on average from r=0.3–0.6. To detect an average correlation of r=.5 within each age group (with up to two other covariates in the model), a sample size of at least 32 is recommended for a power of .80 at $p < .05$ two-tailed. Individual difference analyses that combine the age groups (N=64) will provide a power of over .95 to detect a correlation of $r = .50$ at $p < .05$ two-tailed (allowing for up to three covariates in the model). An r of this level is consistent with our past level of correlations between individual difference measures and DA BP_{ND} within healthy young samples [78,79]. We will also require this sample size to have sufficient power to detect interaction effects (see later hypotheses on age differences in DA measures).

8.0 Privacy/Confidentiality Issues

All subject information is kept in a locked file cabinet in the offices of PI and/or co-investigator. Image data are only accessible to study personnel on password-protected computers. Wherever possible, data is stored as a study ID number instead of with the subjects name in order to limit subject identification. This includes all genetic information, financial and credit report data, and drug screening data. Subjects are warned in advance and consent to the fact that oversight agencies (FDA, local IRB, etc.) may request and receive access to portions of their data. A certificate of confidentiality will be obtained from NIH prior to the start of the study in order to specifically protect participants from any forced disclosure of information related to past or present drug usage, psychiatric status, or genotyping information. All individuals who will come in contact with the patients or their data as part of this study are required to first pass a test on research with human subjects (approved by the Vanderbilt University Institutional Review Board) in order to ensure they understand the importance of confidentiality issues.

9.0 Follow-up and Record Retention

The initial study is estimated to last 3–5 years. If funding is obtained for longitudinal extension studies after the initial study period, the study could last longer (5+ years). All records and data

will be retained in locked cabinets and archived indefinitely following completion of the study. After 10 years, records that are not needed for FDA reporting may be discarded (shredded).

Participants may be recontacted after completion of the study in order to request they complete additional personality measures, and to measure their weight (based on evidence that dopamine functioning impacts body mass index). No other follow-up is planned. Participants may opt-out of any follow-up.

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