

SUMMARY STATEMENT
(Privileged Communication)

Release Date: 07/16/2013

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Application Number: 1 R01 AG043458-01A1

Principal Investigator

ZALD, DAVID H PHD

Applicant Organization: VANDERBILT UNIVERSITY MED CTR

Review Group: ZRG1 PSE-D (58)

Center for Scientific Review Special Emphasis Panel

PAR Panel: Social Neuroscience and Neuroeconomics of Aging

Meeting Date: 07/02/2013

RFA/PA: PAR11-337

Council: OCT 2013

PCC: 3DCLMMW

Requested Start: 12/01/2013

Project Title: Dopaminergic Neuromodulation of Decision Making in Young and Middle-Aged Adults

SRG Action: Impact Score: 17 Percentile: 3 #

Next Steps: Visit http://grants.nih.gov/grants/next_steps.htm

Human Subjects: 30-Human subjects involved - Certified, no SRG concerns

Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Gender: 1A-Both genders, scientifically acceptable

Minority: 1A-Minorities and non-minorities, scientifically acceptable

Children: 1A-Both Children and Adults, scientifically acceptable

Clinical Research - not NIH-defined Phase III Trial

Project Year	Direct Costs Requested	Estimated Total Cost
1	443,374	652,779
2	438,244	645,226
3	440,261	648,196
4	443,332	652,717
5	196,496	289,301
<hr/> TOTAL	<hr/> 1,961,707	<hr/> 2,888,219

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

1R01AG043458-01A1 ZALD, DAVID

RESUME AND SUMMARY OF DISCUSSION: This application seeks to explore age-related changes in dopamine function and dopamine transporter (DAT) receptor function and to relate these to changes in fMRI activity and behavior on reward-related tasks. The reviewers agreed during the discussion that the study will have high impact. The study is significant because it will advance knowledge of how age-related changes in dopamine function affect reward-related behavior. The principal investigator is a leader in the field and has assembled an outstanding investigator team. The study is exceptionally innovative because of the focus on late middle age; combination of PET, fMRI, and behavioral measures; and investigation of individual differences. These also contribute to a strong approach. Additional strength in the approach comes from the basis in existing literature and theory; demonstrated feasibility; well-established measures and tasks; and hypothesis based aims and analyses. The environment is outstanding. The reviewers concluded that the study is exceptionally strong with essentially no weaknesses.

DESCRIPTION (provided by applicant): Vital financial decisions are made during pre-retirement age that can influence financial well-being for the rest of an individual's life. However, very little psychological and neurobiological research has examined financial decision making in this pre-retirement late middle age range. 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. All aims seek to understand adult age differences in cost-benefit decisions and the specific role of dopaminergic neuro-modulation in supporting these preferences in young and late middle-age adults. We particularly focus on decisions with effort costs, but we will also examine the influence of dopamine (DA) on risky choice. A single multimodal neuroimaging study will examine age and individual differences in basic cognitive and motivational variables, decision making behavior, neural reward circuits using fMRI, multiple aspects of the DA system collected across three radio-ligand PET imaging sessions, and behavioral sensitivity to the drug amphetamine. Using radioligand PET imaging of D2-like receptors and release with [¹⁸F]allypride and DA transporters (DAT) with [¹⁸F]FECNT, the project will provide the first examination of the specific role of multiple aspects of DA function in supporting the core motivational processes underlying cost-benefit decision making in healthy young and middle-aged adults. We expect to observe differential age effects in both functional neural activity assessed with fMRI and DA function assessed with PET. Across imaging methods, we expect to observe some level of preservation of function in the ventral striatum and midbrain in late middle age. However, we expect to observe larger age differences in lateral cortical D2 receptors, striatal and ventromedial prefrontal DA release, and DAT expression. We expect these neurobiological age differences, especially in medial prefrontal and striatal networks, to be associated with decision making, such that individual differences in the function of these systems are associated with individual differences in the tolerance of effort costs. We will also include an amphetamine challenge to examine the influence of DA release on decision preferences. This will be the first study of human age differences in DA release, and the first study of DA drug effects on decision making across adulthood. The parallel use of the DAT ligand [¹⁸F]FECNT will allow us to uniquely assess the relative and possibly synergistic impact of presynaptic and postsynaptic DA variables, and to further provide a unique assessment of the relations between DAT expression and amphetamine-induced DA release and the behavioral effect of amphetamine. Beyond contributions to the study of human aging, the work will clarify the neural substrates of cost-benefit decision making across adulthood. This multimodal, adult developmental approach has the potential to more precisely characterize the neurobiological systems involved in motivation and decision making, and has the potential to identify focused targets for future interventions.

PUBLIC HEALTH RELEVANCE: The proposal aims to characterize individual and age differences in motivation and decision making in young and late middle-aged adults using multimodal neuroimaging

techniques. This work will form the basis of a translational research program on decision making over adult development, and has the potential to eventually facilitate identification of specific markers for suboptimal decision making in adults of all ages to inform the design of appropriate interventions. The long-term goal of this line of research is to improve the physical, emotional, and financial health of all adults by improving decision making at the individual level.

CRITIQUE 1:

Significance: 2
Investigator(s): 1
Innovation: 1
Approach: 3
Environment: 1

Overall Impact: The proposed study is significant and innovative. The investigators are exceptionally strong. The revisions made to the application in response to the previous round of review have strengthened the application considerably.

1. Significance:

Strengths

- The potential significance of this work is high as understanding how dopamine function changes with age in the striatum and prefrontal cortex is an underexplored area of research.
- The proposed studies could provide important new information about the role of modulatory neurotransmitter function in cognitive decline.
- Furthermore, the linking of dopamine function directly with performance on reward-related choice tasks could further our understanding of how dopamine function impacts reward-related behavior, as well as further understanding of how this relationship might change with age.

Weaknesses

- None noted

2. Investigator(s):

Strengths

- The principal investigator is a leading authority in PET studies of reward and motivation, and in the neurobiology of reward. The co-investigators and collaborators are all excellent and ideally suited to enabling this project to reach fruition.

Weaknesses

- None noted

3. Innovation:

Strengths

- The multiple PET assessments of dopamine function alongside fMRI studies on related tasks is a significant innovation.

- Tracking of age-related changes in dopamine function in this multi-modal approach is highly innovative

Weaknesses

- None noted

4. Approach:

Strengths

- The PET method seems thorough and feasible, especially given the principal investigator has published extensively using similar methods in the past.
- In the revised application the investigators have demonstrated that correlation between effort and reward magnitude is not an issue for the effort task.

Weaknesses

- The investigators have not adequately addressed the previously raised concerns about the Monetary Incentive Delay (MID) task as they have not supplemented this task with another task that does not have the weaknesses of the MID task in terms of motivational confounds (such that increased speed of response = increased probability of reward), and lack of sensitivity for prediction error. The fact that an attempt has been previously made to model prediction error signals on this task does not get around the fact that the task is not optimized to detect PE signals. The presence of a motivational confound is only a strength if one doesn't care about whether or not the signals being measured correspond to reward per se or motivation. It would seem important to separate out those variables given that both of these may independently depend on dopaminergic function.
- Inclusion of a cognitive battery helps to assess overall changes in cognitive function mediated by dopamine independently of reward and effort, although it is a shame such a task was not included in the neuroimaging battery as opposed to only being tested at the behavioral level: inclusion of a cognitive/executive task in the functional imaging battery would have enabled these functions to be compared and contrasted against reward/effort in terms of neural substrates.

5. Environment:

Strengths

- The facilities and support in place seem excellent. The MRI facilities are top-notch.

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

Resubmission:

- The revisions made to the application in response to the previous round of review have strengthened the application considerably.

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Significance: 2

Investigator(s): 1

Innovation: 2

Approach: 2

Environment: 1

Overall Impact: This is a highly significant and innovative application, addressing a question of high clinical and economic importance. The application focuses on late middle age, a time when complicated decisions about retirement, involving uncertainty and costs, are typically made. If successful these studies will contribute substantially to our understanding of age-related changes in dopamine function, and may lead to the development of pharmacological treatments. The team of investigators is outstanding, the approach is excellent, with a carefully thought-of design and analysis, and plenty of preliminary data to support the feasibility of the proposed studies. As a result the application is likely to have a high impact on aging research as well as on knowledge of the neural substrates involved in cost-benefit decision-making in general.

1. Significance:

Strengths

- The application addresses a problem of high clinical and economic importance.
- These studies are likely to contribute substantially to the understanding of changes in dopamine function in older adults and their association with changes in effort and probability attitudes.

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- An outstanding team with complementary expertise that cover all aspects of the application

Weaknesses

- None noted.

3. Innovation:

Strengths

- Within-subject multi-model assessment of DA function is novel in general, and especially in examining age-related changes.
- Focus on late middle age is novel.

Weaknesses

- None noted.

4. Approach:

Strengths

- A combination of PET, fMRI and behavioral measures, as well as a pharmacological intervention (d-amphetamine) all within the same individuals
- Approach rooted in animal studies
- Pilot data support the feasibility of each stage of the proposed study

Weaknesses

- Although the required effort is tailored to each subject based on their maximal button press rate in an initial calibration, it is possible that older subjects get tired more easily than younger subjects. In this sense the physical effort used here is different from the types of effort it is meant to model, such as the effort required in order to continue to work and not retire. This is, however, a minor weakness, which does not lessen impact.
- Subjects will have to go through 5 sessions, including 3 long PET sessions, which may make it hard to recruit subjects, especially in the older group. This is also a minor weakness.

5. Environment:

Strengths

- Vanderbilt University provides an outstanding environment

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Adequate protections

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Adequate representation of both genders and minorities

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Acceptable

- Adequate protections

Resubmission:

- Adequate responses to most of the reviewers comments on the first submission

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Significance: 1

Investigator(s): 1

Innovation: 1

Approach: 2

Environment: 1

Overall Impact: Solid justification for the importance of this work is provided, and the work is also highly innovative. More specifically, the research plan was built from well-established basic procedures and practices, but here they are brought together in new ways to help increase understanding of how age impacts dopamine function and associated decision behaviors. The principal investigator and team of investigators are excellent, as is the environment for the research. The approach seems very strong and specific; experimental elements and predictions are guided by the experience of the investigators as well as a solid theoretical framework. Overall this research promises to have a very high impact on the field.

1. Significance:

Strengths

- the research addresses a very clear, very important problem of widespread relevance to the population, that is age-related changes in financial decision making

- imaging multiple aspects of dopamine system function will provide a comprehensive view of potential age-related changes
- behavioral and neural measures are integrated in the investigation, a priori (rather than this being simply an investigation of the "neural correlates of...")
- in addition to across group comparisons of behavior and neural function, planned investigation of individual differences within groups promises to add further information to the field
- specific focus on dopamine (as opposed to other candidate neurochemicals) seems appropriate and well-justified

Weaknesses

- None noted.

2. Investigator(s):

Strengths

- the principal investigator is an established investigator with a solid record of achievement and external funding in this area
- additional investigators and consultants provide excellent coverage of all relevant aspects of the project

Weaknesses

- None noted.

3. Innovation:

Strengths

- while yet building from well-established methods and well-supported concepts, the research plan incorporates several highly innovative aspects
- middle aged adults are woefully understudied in this field; they are a critical link between younger and "older" adult studies, particularly for the types of financial decisions that will be under investigation here
- sophisticated investigation of individual differences (other than age) is also relatively novel and a strength of the application
- although dopamine has been studied in the context of age-related changes in behavior, the present research aims to deepen the understanding of its role in several new ways
- the project is highly interdisciplinary; although this type of approach is becoming more of the norm, this particular application yet integrates knowledge and scientific approaches from many different disciplines in a very satisfying and thoughtful way

Weaknesses

- None noted.

4. Approach:

Strengths

- sampling procedures and sample size were carefully selected based on previous studies and the investigators have performed power calculations

- well-established individual difference measures will be administered
- behavioral tasks are well-suited for performance during fMRI signal acquisition
- planned analyses and hypotheses seem well-reasoned based on existing literature and theory

Weaknesses

- None noted.

5. Environment:

Strengths

- space, equipment, resources and institutional support all seem excellent and appropriate

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Acceptable

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

Vertebrate Animals:

Not Applicable

Biohazards:

Acceptable

- Management and safety plans appear acceptable

Resubmission:

- The investigators appear to be receptive to the substantive comments of the previous reviews. Relatively little actual study design has changed in this version. Rather, the investigators have attempted to clarify several issues and provide further justification in an attempt to address previous concerns. Overall they were very responsive and the application improved as a result.

Budget and Period of Support:

Recommend as Requested

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

Ad hoc or special section application percentiled against "Total CSR" base.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html>.

The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

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CENTER FOR SCIENTIFIC REVIEW
PAR Panel: Social Neuroscience and Neuroeconomics of Aging
ZRG1 PSE-D (58) R
July 02, 2013

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Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.

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