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**SUMMARY STATEMENT**  
( Privileged Communication )

*Release Date:* 07/14/2010

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*Application Number:* 1 F32 AG039131-01

Samanez Larkin, Gregory R  
Vanderbilt University  
111 21st Avenue South  
301 Wilson Hall, PMB 407817  
Nashville, TN 37240-7817

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*Review Group:* ZRG1 F02A-J (20)  
Center for Scientific Review Special Emphasis Panel  
Fellowships: Behavioral Neuroscience

*Meeting Date:* 06/24/2010

*Council:* OCT 2010

*PCC:* 2BCOGJK

*Requested Start:*

*Dual IC(s):* MH

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*Project Title:* Imaging the human reward system across the adult life span

*Requested:* 3 years 1 month

*Sponsor:* Zald, David H  
*Department:* Psychology  
*Organization:* VANDERBILT UNIVERSITY  
*City, State:* NASHVILLE TENNESSEE

*SRG Action:* Impact/Priority Score: 52  
*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

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**1F32AG039131-01 Samanez Larkin, Gregory**

## **SCIENTIFIC REVIEW OFFICER'S NOTES**

**RESUME AND SUMMARY OF DISCUSSION:** The research proposed seeks to characterize associations between dopamine receptor availability and reward processing and behavioral control and to explore age-related changes in components of the reward system using PET and fMRI techniques. The applicant is exceptional; one reviewer noted that he was the best applicant he'd seen in 10 yrs of reviewing. The applicant has 10 publications including some in high impact journals such as Nature Neuroscience and the Journal of Neuroscience. The sponsor, Dr. David Zald, has a strong training record, ample funding for the work, and the appropriate expertise. The research proposal will certainly allow the applicant to learn valuable neuroimaging techniques. This a particular strength because few researchers are adept at multiple neuroimaging techniques. Despite the strengths of the applicant and sponsor and the training opportunities presented, significant weaknesses in the proposal suggest limited training potential. First, the research is entirely too focused on techniques, to the extent that no hypotheses are presented, no pitfalls/alternative approaches are discussed, and the aims are poorly connected.

**DESCRIPTION (provided by applicant):** Increases in human life expectancy over the twentieth century will continue to expand the proportion of older adults in the global population, magnifying the relative economic impact of their health-related and financial decisions. Thus, it is increasingly imperative to better characterize and understand age-related changes in reward processing and decision making across the adult life span. New in vivo brain imaging techniques using magnetic resonance imaging (MRI) and positron emission tomography (PET) now allow more precise measurement of the human reward system. Highly detailed visualization of structures across the brain is now possible using ultra high field strength 7-Tesla MRI scanners. The use of high-resolution protocols (i.e., slice prescriptions that selectively measure a subsection of the brain) at high field strength has the potential to both structurally and functionally dissociate individual nuclei in the reward system. Measurement of dopamine receptor availability in both striatal and extrastriatal (e.g., midbrain, frontal cortical) regions is now possible using the radioligand [ $^{18}\text{F}$ ]fallypride in PET imaging. These imaging techniques facilitate previously unavailable in-depth measurement across the brain. The main objective of this fellowship grant is to train the applicant in the use of novel methods for imaging the human reward system across the adult life span. Training will also include broadening the applicant's base of knowledge through directed reading, honing teaching and mentoring skills, and building grant writing skills to ensure productivity and success throughout the applicant's career. The specific aims are to train the applicant to (1) optimize and utilize techniques for structural and functional imaging of individual nuclei in the adult midbrain using high-resolution and ultra high field strength (7-Tesla) MRI, (2) combine [ $^{18}\text{F}$ ]fallypride PET and functional MRI to characterize associations between dopamine receptor availability and aspects of reward processing and behavioral control in healthy adults, and (3) explore age-related structural (MRI) and functional (radioligand PET, fMRI) changes in specific components of the reward system over the first half of adult development. The fellowship will support the next stage of directly mentored training on the applicant's path to becoming an independent psychological scientist in the cognitive neuroscience of aging. After completion of training, the applicant's goal is to combine these new methods to not only more precisely quantify age-related change in the human reward system but also to investigate the implications of these changes throughout the adult life span. The long-term goal of the applicant's career is to conduct basic scientific research that contributes directly to interventions aimed at easing the cognitive strain and improving emotional and economic health in the daily lives of aging adults.

**PUBLIC HEALTH RELEVANCE:** This research training plan aims to use cutting edge neuroimaging technology to expand understanding of processes underlying learning and decision making over the

adult life span. This work has the potential to facilitate identification of markers for suboptimal decisions in older adults in order to provide appropriate interventions. The long-term goal of this line of research is to improve the financial and emotional health of older adults by improving learning and decision making at the individual level.

### **CRITIQUE 1:**

Fellowship Applicant: 1  
Sponsors, Collaborators, and Consultants: 3  
Research Training Plan: 5  
Training Potential: 4  
Institutional Environment & Commitment to Training: 1

### **Overall Impact/Merit:**

#### **Strengths**

- Outstanding candidate.
- Excellent match with experienced mentor.
- The training potential is high.

#### **Weaknesses**

- No plans for professional development.
- Research hypotheses not presented.
- Lack of integration between Aim 1 and Aims 2 and 3.

### **1. Fellowship Applicant**

#### **Strengths**

- Excellent academic performance.
- Received a number of honors as an undergraduate and graduate student, including being cited for top ten scientific advances by the National Institute on Aging for a first-author paper.
- Supported by predoctoral NRSA.
- Letters of recommendation were highly supportive. Ratings were all 1s.
- 10 publications with 5 as first author, including Nature Neuroscience and Journal of Neuroscience. One first-author manuscript under review and two manuscripts, including 1 first-author in preparation. One first-author review, 2 book chapters, including one first-author and 17 abstracts.
- Past research experience supports interest in a research career.

#### **Weaknesses**

### **2. Sponsors, Collaborators, and Consultants:**

#### **Strengths**

- The primary sponsor, Dr. David Zald has a strong training record, having trained 7 predoctoral and 6 postdoctoral fellows. Examples provided suggest previous trainees have continued on with successful academic research careers.
- Mentor is a co-PI on a training grant.

- Funding is in place to support candidate's research efforts.
- Training will include learning new skills in fMRI and PET imaging, broadening knowledge base via selected readings, auditing of courses and attendance and participation in seminars and colloquia, honing teaching and mentoring skills by leading workshops and co-mentoring undergraduates, building grant writing skills, and networking via attendance at national meetings.
- The candidate will have biweekly one-on-one meetings with his mentor and will participate in weekly lab meetings.
- The co-mentor Dr. Samuel McClure will provide training in the use of computational models. This will occur via once monthly phone calls and several weeks in the summer will be spent at Stanford.

#### **Weaknesses**

- Additional forms of professional development, such lab and grant management, interviewing and job search skills were not described.
- Very minor weakness in co-mentor who is unfunded and has no postdoctoral training experience.

### **3. Research Training Plan:**

#### **Strengths**

- Studies will optimize techniques to be used for a 7-tesla MRI and will correlate differences in decision-making with dopamine receptor binding using F18-fallypride PET and fMRI.
- Correlations between PET imaging and fMRI will also be made
- Studies are clearly described

#### **Weaknesses**

- No hypothesis was presented.
- Aim 1 is not hypothesis-driven research.
- Aims 2 and 3 use a 3-T MRI rather than the 7-T MRI and thus Aim 1 is not well integrated.
- Potential pitfalls and alternative approaches not discussed.

### **4. Training Potential:**

#### **Strengths**

- The proposed training will allow the candidate to be adept at multiple imaging techniques, which is the exception rather than the rule in this field.

#### **Weaknesses**

### **5. Institutional Environment & Commitment to Training:**

#### **Strengths**

- Rich, collaborative environment that provides expertise in the approaches necessary to complete research program.
- Equipment necessary for completion of proposed studies is available.

#### **Weaknesses**

**Protections for Human Subjects:**

Acceptable Risks and Adequate Protections

- Risks are outlined and protections, including confidentiality, are described.

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

Acceptable

- DSMP in place and independent monitor described.

**Inclusion of Women, Minorities and Children:**

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Children under age 18 excluded and acceptable.

**Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Not Applicable (No Biohazards)

**Training in the Responsible Conduct of Research:**

Unacceptable

Comments on Format (Required):

- No formal course described, but will have informal discussions with mentor

Comments on Subject Matter (Required):

- Topics identified

Comments on Faculty Participation (Required):

- Mentor will participate

Comments on Duration (Required):

- Will occur throughout training

Comments on Frequency (Required):

- Topics will be discussed regularly.

**Applications from Foreign Organizations:**

Not Applicable

**Select Agents:**

Not Applicable (No Select Agents)

**Resource Sharing Plans:**

Not Applicable (No Relevant Resources)

**Budget and Period of Support:**

Recommend as Requested

Recommended budget modifications or possible overlap identified:

**CRITIQUE 2:**

Fellowship Applicant: 1

Sponsors, Collaborators, and Consultants: 2

Research Training Plan: 4

Training Potential: 2

Institutional Environment & Commitment to Training: 1

**Overall Impact/Merit:**

**Strengths**

- Excellent applicant for the requested post-doctoral award (see details below)
- Very rich research training plan to familiarize the applicant with some of the latest PET and MRI techniques so that he can apply them to studies involved with the DA reward system.
- Well established sponsors and collaborators.
- Exciting research area with potential benefit to understanding changes in brain functioning associated with aging.

**Weaknesses**

- Lack of detail and alternative possibilities if some of the methods are unsuccessful.

**1. Fellowship Applicant**

**Strengths**

- Extremely strong candidate.
- Letters of recommendation from faculty who know him well and whose labs he has worked in from Stanford have nothing but praise for him: "Among the top 3 graduate students I have worked with in my 25 years as a professor of Psychology...he may be the very best."
- Very productive: Lists 10 publications and three either under review or in press since 2005. He also lists 3 Reviews/Book Chapters and 17 abstracts. He was the lead author in an article published in Nature Neuroscience with his dissertation co-advisors, Dr. Carstensen and Dr. Knutson. This article was selected as one of the top 10 scientific advances of 2007 by the National Institute of Aging.
- He obtained an NRSA pre-doctoral award and remained at Stanford to focus on his research.

**Weaknesses**

**2. Sponsors, Collaborators, and Consultants:**

**Strengths**

- His sponsor Dr. Zald, has been conducting imaging studies since 1995 using a combination of PET and fMRI to explore the functioning of limbic and paralimbic regions. Importantly, related to the applicant's training, Dr. Zald has been developing procedures for high resolution scanning of the dopamine midbrain using Vanderbilt's 7T magnet. The sponsor has extensive experience training graduate students and post-doctoral fellows and is currently co-PI on a training grant from NIMH that is pending a council decision. This grant focuses on translational research related to biological approaches to understanding psychopathology.
- Dr. Zald will supervise no more than 2 other post-doctoral fellows and 3-4 Ph.D. candidates during the applicant's training period.
- The Co-Sponsor. Dr. McClure, will supervise 4 Ph.D. candidates and at most one post-doctoral fellow during the applicant's training period.
- Dr. McClure, a collaborator at Stanford, has begun to collaborate with Dr. Zald on imaging with PET. His research focuses on studies that examine the integration of reward processing and behavioral control, fitting well into the applicant's research goals.
- Other collaborators are also indicated that are experts in imaging technology. Dr. Zald has a number of collaborators because of his integrative neuroscience approach. As is pointed out by the applicant and is well known, this type of work is dependent on a team of investigators with different expertise.

### **Weaknesses**

- Some concern about how communication will work between co-sponsors at different institutions located at different ends of the country. Dr. Zald is listed as the primary sponsor so this may not be an issue and the applicant will visit Stanford for several weeks during the summer to work with Dr. McClure.

### **3. Research Training Plan:**

#### **Strengths**

- Training will focus on learning new research methods, mainly in imaging, combining innovative fMRI and PET techniques.
- Wants to key off of studies performed for dissertation as well as by other investigators that were limited to standard resolution whole brain fMRI and use more sensitive measures obtainable with high resolution imaging that allow for visualization of very small brain structures (nuclei) of interest to the applicant. High resolution imaging has the potential to dissociate both structurally and functionally individual nuclei in the reward system.
- Combine MRI and PET using cutting edge emerging techniques. No aging papers that combine structural measures with PET measures of DA function across the brain.
- Objective of the research plan is to further develop novel methods for imaging the human reward system across the adult life span using a combination of new techniques in PET and MRI. Unique opportunity for the applicant. Not many institutions have such collaborative research programs.
- Preliminary findings lend support to the feasibility of the proposed research training plan.
- Three studies are outlined: 1) High resolution MR imaging of the human mid brain in order to further optimize techniques for structural and functional measurement of individual nuclei in the adult midbrain using high resolution and ultra high field strength 7 T MRI. 2) Examining the relationship between DA receptor availability and aspects of reward processing and behavioral control in order to combine fallypride PET and functional MRI to characterize associations between DA receptor availability and aspects of reward processing and behavioral control in healthy adults. 3) Morphometric, dopaminergic, and behavioral changes from young adulthood

to middle-age in order to explore age-related change in behavioral, structural, and functional measures collected in Study 2.

- Studies are well thought out and grounded in previous work by the applicant and other investigators.
- The applicant will learn a lot about the proposed methods.

#### **Weaknesses**

- Figures presented in research plan are not well explained.
- No specific approach to the data outlined: statistical analyses, data reduction, etc.
- The methods are highly technical and exploratory. If methods are not reliable or if data do not follow expectations, what alternative approaches are possible? What modifications might be made?

#### **4. Training Potential:**

##### **Strengths**

- Excellent sponsor and co-sponsor: Dr. Zald's work with high resolution imaging coupled with Dr. McClure's expertise in decision neuroscience and computational modeling make for excellent training.
- Vanderbilt is one of a small number of institutions that provides trainees with access to both PET imaging and fMRI facilities. Vanderbilt also houses one of the few research-dedicated 7TMRI scanners.
- Excellent collaborative team.
- Sponsor and co-sponsor committed to training.
- Training will focus mainly on the research methodology, directed readings in a number of relevant areas, course work in neuropharmacology, statistics for example. Statistics courses are planned for all three years. Also grant writing.

##### **Weaknesses**

- Training plan is well structured for a post-doctoral fellow; however although teaching is mentioned, there is no specific plan indicated for teaching activities.

#### **5. Institutional Environment & Commitment to Training:**

##### **Strengths**

- Strong commitment to training.

##### **Weaknesses**

#### **Protections for Human Subjects:**

##### **Unacceptable Risks and/or Inadequate Protections**

- The applicant provides thorough discussion of risks and protection but does not discuss follow up with subjects in the event of an abnormal MRI.

##### **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 – Both Children and Adults, Acceptable

- Both males and females will be studied and priority will be given to hispanic subjects if they volunteer. Minorities have participated in previous studies.

**Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Acceptable

- Applicant and his sponsors have FDA approval for the use of fallypride, an investigational new drug. Adequate safety measures have been implemented -- study physician monitors subjects for any adverse effects. Dr. Zald and colleagues have performed over 100 fallypride PET studies and have seen no laboratory abnormalities from administration of this radiopharmaceutical. Also, dose given during the study appears to be low.

**Training in the Responsible Conduct of Research:**

Acceptable

Comments on Format (Required):

- Applicant had formal course work while a graduate student. Will continue discussions in Zald lab and maintain certification in Human Subject Research and HIPPA compliance.

Comments on Subject Matter (Required):

- Subject matter to be discussed includes recruitment and protection, responsible experimental design, authorship and collaboration, etc.

Comments on Faculty Participation (Required):

- Dr. Zald will participate.

Comments on Duration (Required):

- As a graduate student and throughout fellowship.

Comments on Frequency (Required):

- Met as a graduate student but also lab members will meet on a regular basis to discuss issues related to responsible conduct of research.

**Applications from Foreign Organizations:**

Not Applicable

**Select Agents:**

Not Applicable (No Select Agents)

**Resource Sharing Plans:**

Not Applicable (No Relevant Resources)

### **CRITIQUE 3:**

Fellowship Applicant: 2  
Sponsors, Collaborators, and Consultants: 2  
Research Training Plan: 8  
Training Potential: 5  
Institutional Environment & Commitment to Training: 2

### **Overall Impact/Merit:**

#### **Strengths**

- Strong applicant with great letters and publication record
- Excellent facilities and mentors

#### **Weaknesses**

- There are no clear testable hypotheses associated with the aims
- The later aims depend on the outcome of the earlier ones and there is no plan for alternative outcomes

### **1. Fellowship Applicant**

#### **Strengths**

- Strong letters of recommendation
- Good research experience
- Strong publication record

#### **Weaknesses**

- Academic record seems incomplete (only 9 undergrad classes), though what is available is strong

### **2. Sponsors, Collaborators, and Consultants:**

#### **Strengths**

- Well funded lab
- Sponsor has a history of mentorship of graduate students
- Solid collaborators in high field fMRI and PET imaging

#### **Weaknesses**

### **3. Research Training Plan:**

#### **Strengths**

- Interesting integrative focus

- Good preliminary data

#### **Weaknesses**

- The aims are vague and the studies lack clear testable hypotheses. For example, in aim 3, changes in and measures of what?
- The aims are focused on methods rather than the brain, limiting the audience who would be interested in the results as well as future grant opportunities.
- Aim 3 is dependent on the outcome of aim 2.
- There is no plan to deal with alternative outcomes

#### **4. Training Potential:**

##### **Strengths**

- Good opportunity to learn about PET and high field MR

##### **Weaknesses**

- Training plan for expanding the knowledge base is weak, with minimal additional formal coursework

#### **5. Institutional Environment & Commitment to Training:**

##### **Strengths**

- Excellent facilities

##### **Weaknesses**

- Difficult to assess the intellectual environment and opportunity for interaction

#### **Protections for Human Subjects:**

Acceptable Risks and Adequate Protections

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

#### **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:**

Not Applicable (No Biohazards)

#### **Resubmission:**

- Not Applicable

**Renewal:**

- Not Applicable

**Training in the Responsible Conduct of Research:**

Unacceptable

Comments on Format (Required):

- not described

Comments on Subject Matter (Required):

- not described

Comments on Faculty Participation (Required):

- not described

Comments on Duration (Required):

- not described

Comments on Frequency (Required):

- not described

**Applications from Foreign Organizations:**

Not Applicable

**Select Agents:**

Not Applicable (No Select Agents)

**Resource Sharing Plans:**

Not Applicable (No Relevant Resources)

**Budget and Period of Support:**

Recommend as Requested

Recommended budget modifications or possible overlap identified:

**Additional Comments to Applicant (Optional):**

- The proposal would be strengthened if it were reorganized to present aims and specific hypotheses about brain function and behavior rather than focusing on technology.

**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**

**SCIENTIFIC REVIEW OFFICER'S NOTES:** The assigned reviewers found the plans for Training in the Responsible Conduct of Research to be unacceptable.

**COMMITTEE BUDGET RECOMMENDATIONS:** The budget was recommended as requested.

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NOTICE: In 2008 NIH modified its policy regarding the receipt of resubmission (formerly termed amended) applications. Detailed information can be found by accessing the following URL address: <http://grants.nih.gov/grants/policy/amendedapps.htm>

## MEETING ROSTER

**Center for Scientific Review Special Emphasis Panel  
CENTER FOR SCIENTIFIC REVIEW  
Fellowships: Behavioral Neuroscience  
ZRG1 F02A-J (20) L  
June 24, 2010 - June 25, 2010**

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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.