OMB Number: 4040-0001
Expiration Date: 06/30/2011

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	State Application Identifier

1. * TYPE OF SUBMISSION
☐ Pre-application ☒ Application ☐ Changed/Corrected Application

2. DATE SUBMITTED | **Applicant Identifier**

4. a. Federal Identifier

b. Agency Routing Identifier

5. APPLICANT INFORMATION

*** Organizational DUNS:** 004413456

* Legal Name: Vanderbilt University

Department: Division of Sponsored Research

Division: College of Arts and Science

* Street1: Station B # 357749

Street2: 2301 Vanderbilt Place

* City: Nashville

County / Parish: Davidson

* State: TN: Tennessee

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 37235-7749

Person to be contacted on matters involving this application

Prefix:

* First Name: Holland

Middle Name:

* Last Name: Carley

Suffix:

* Phone Number: 615-322-2450

Fax Number: 615-322-3827

Email: sponsored_research@vanderbilt.edu

6. * EMPLOYER IDENTIFICATION *(EIN) or (TIN):* 1620476822A2

7. * TYPE OF APPLICANT: O: Private Institution of Higher Education

Other (Specify):

Small Business Organization Type ☐ Women Owned ☐ Socially and Economically Disadvantaged

8. * TYPE OF APPLICATION:
☒ New ☐ Resubmission
☐ Renewal ☐ Continuation ☐ Revision

If Revision, mark appropriate box(es).
☐ A. Increase Award ☐ B. Decrease Award ☐ C. Increase Duration ☐ D. Decrease Duration
☐ E. Other (specify):

* Is this application being submitted to other agencies? Yes ☐ No ☒ What other Agencies?

9. * NAME OF FEDERAL AGENCY: National Institutes of Health

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:

TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:
Imaging the human reward system across the adult life span

12. PROPOSED PROJECT:
* Start Date: 12/01/2010
* Ending Date: 11/30/2013

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT:** TN-005

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix:

* First Name: Gregory

Middle Name: Russell

* Last Name: Samanez Larkin

Suffix:

Position/Title: Postdoctoral Fellow

* Organization Name: Vanderbilt University

Department: Psychology

Division: College of Arts and Science

* Street1: 111 21st Avenue South

Street2: 301 Wilson Hall, PMB 407817

* City: Nashville

County / Parish: Davidson

* State: TN: Tennessee

Province:

* Country: USA: UNITED STATES

* ZIP / Postal Code: 37240-7817

* Phone Number: 650-799-5715

Fax Number: 615-343-8449

* Email: glarkin@stanford.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested	143,670.00
b. Total Non-Federal Funds	0.00
c. Total Federal & Non-Federal Funds	143,670.00
d. Estimated Program Income	0.00

16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?

a. YES ☐ THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:

DATE:

b. NO ☒ PROGRAM IS NOT COVERED BY E.O. 12372; OR

☐ PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

17. By signing this application, I certify (1) to the statements contained in the list of certifications* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances * and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious. or fraudulent statements or claims may subject me to criminal, civil, or administrative penalities. (U.S. Code, Title 18, Section 1001)

☒ *** I agree**

**** The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.***

18. SFLLL or other Explanatory Documentation

Add Attachment | Delete Attachment | View Attachment

19. Authorized Representative

Prefix: * First Name: John Middle Name: T

* Last Name: Childress Suffix:

* Position/Title: Director

* Organization: Vanderbilt University

Department: Sponsored Research Division:

* Street1: Station B # 357749

Street2: 2301 Vanderbilt Place

* City: Nashville County / Parish: Davidson

* State: TN: Tennessee Province:

* Country: USA: UNITED STATES * ZIP / Postal Code: 37235-7749

* Phone Number: 615-322-3977 Fax Number: 615-322-3827

* Email: sponsored_research@vanderbilt.edu

*** Signature of Authorized Representative**: Holland Carley

*** Date Signed**: 04/05/2010

20. Pre-application Add Attachment | Delete Attachment | View Attachment

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OMB Number: 4040-0010
Expiration Date: 08/31/2011

Project/Performance Site Location(s)

Project/Performance Site Primary Location ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Vanderbilt University
DUNS Number: 0044134560000
* Street1: Station B # 357749
Street2: 2301 Vanderbilt Place
* City: Nashville
County: Davidson
* State: TN: Tennessee
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 37235-7749
* Project/ Performance Site Congressional District: TN-005

Project/Performance Site Location 1 ☐ I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Stanford University
DUNS Number: 0092142140000
* Street1: 450 Serra Mall
Street2: Jordan Hall, Building 420
* City: Stanford
County:
* State: CA: California
Province:
* Country: USA: UNITED STATES
* ZIP / Postal Code: 94305-2130
* Project/ Performance Site Congressional District: CA-014

Additional Location(s) Add Attachment | Delete Attachment | View Attachment

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? ☒ Yes ☐ No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? ☐ Yes ☒ No

If yes, check appropriate exemption number. ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

If no, is the IRB review Pending? ☒ Yes ☐ No

IRB Approval Date:

Human Subject Assurance Number:

2. * Are Vertebrate Animals Used? ☐ Yes ☒ No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? ☐ Yes ☐ No

IACUC Approval Date:

Animal Welfare Assurance Number

3. * Is proprietary/privileged information included in the application? ☐ Yes ☒ No

4.a. * Does this project have an actual or potential impact on the environment? ☐ Yes ☒ No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed? ☐ Yes ☐ No

4.d. If yes, please explain:

5. * Is the research performance site designated, or eligible to be designated, as a historic place? ☐ Yes ☒ No

5.a. If yes, please explain:

6. * Does this project involve activities outside of the United States or partnerships with international collaborators? ☐ Yes ☒ No

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. * Project Summary/Abstract 7_ProjectSummaryAbstract.pdf Add Attachment Delete Attachment View Attachment

8. * Project Narrative 8_ProjectNarrative.pdf Add Attachment Delete Attachment View Attachment

9. Bibliography & References Cited 9_References.pdf Add Attachment Delete Attachment View Attachment

10. Facilities & Other Resources 10_Facilities.pdf Add Attachment Delete Attachment View Attachment

11. Equipment 11_Equipment.pdf Add Attachment Delete Attachment View Attachment

12. Other Attachments Add Attachments Delete Attachments View Attachments ☒

PROJECT SUMMARY / ABSTRACT

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}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}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.

PROJECT NARRATIVE

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.

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FACILITIES AND OTHER RESOURCES

Department of Psychological Sciences

The Affective Neuroscience Laboratory (aka Zald Lab) in the Department of Psychological Sciences, is housed in a modern 100Base T-wired building (Wilson Hall). The laboratory includes approximately 800 square feet of space, with two rooms set up for patient testing, and the other three rooms set up for image processing and statistical analysis. Computer resources in the lab include: 3 Apple MacPro (Dual 2+G processor, 1 G RAM), 1 Dell Precision LINUX workstation (Pentium IV, 933 mHz, 512 MB RAM). 9 Dell PCs (1GHz-3 gHz, RAM 256-512MB), 3 Toshiba Laptop (Pentium IV,IVm, or M, 833Mhz- 2-4G). The Zald Lab also utilizes Vanderbilt's Advanced Computing Center for Research and Education, which contains 776 x86 processors (160 2.4 GHz Opteron processors, 456 2.0 GHz Opteron processors plus 160 1.8 GHz Opteron processors) and 644 PowerPC processors (2.2 GHz IBM JS20 Blades) running a 64-bit Linux OS.

Dr. Zald's office and offices for graduate students and post-doctoral fellows in the Affective Neuroscience Laboratory are also housed in Wilson Hall. The Department of Psychological Sciences houses all post-doctoral fellows in offices within the building, with no more than 2 post-doctoral fellows per office.

Psychological Sciences has a machine shop staffed with two full-time machinists at its disposal. In addition, the Vanderbilt Vision Research Center also provides a full-time computer programmer, graphic designer, and a systems engineer (with expertise in interfacing experimental stimulus presentation devices with MR scanners) that are available to assist with this project. Poster printing is also available onsite.

The department provides additional educational opportunities to the applicant by sponsoring talks from major researchers in the field on a regular basis. These include 3 weekly seminars on clinical, neuroscience and cognitive science topics, in addition to departmental colloquia. There is also a weekly professional seminar connected to the Developmental Psychopathology Training Grant (for which Dr. Zald is a co-PI), which brings in one external speaker per month.

Vanderbilt University Institute of Imaging Science (VUIIS)

The Vanderbilt University Institute of Imaging Science is a University-wide interdisciplinary initiative that unites scientists whose interests span the spectrum of imaging research—from the underlying physics of imaging techniques to the application of imaging tools to address problems such as understanding brain function. VUIIS faculty are active in developing novel methods of imaging to obtain new types of information as well as in applying current methods to study a wide range of biomedical questions. Dr. Zald has successfully conducted research at the VUIIS since its construction and has an existing and productive relationship with the center's staff. He currently serves on the steering committee for the 3T human scanners.

The VUIIS has a core program of research related to developing new imaging technology based on advances in physics, engineering, and computer science. The VUIIS is housed in a recently completed four-floor, state-of-the-art facility adjacent to Medical Center North. The $28 million project ($21 million for construction) provides a 41,000-square-foot facility to integrate current activities in imaging research and provide research space for 24 faculty members and more than 60 graduate students and postdoctoral fellows in biomedical science, engineering, and physics. The VUIIS facility is a brief 8-minute walk from the Department of Psychological Sciences. The VUIIS operates 2 research dedicated 3T MRI scanners, a 9.4T animal scanner, and a 7T scanner (see Equipment section for details). The VUIIS also hosts a regular 7T users meeting for active users of the high field strength research magnet. 7T users regularly present ongoing research and discuss the optimization of scan protocols for both structural and functional human imaging. Weekly fMRI users meetings are also hosted by the VUIIS.

Within VUIIS, there exists a computer imaging laboratory, consisting of 16 SGI and Sun workstations, a Linux cluster and several Macintoshes. This facility is under the full time direction of Mr. Bruce Martin. MATLAB and Mathematica are available for data analysis and simulations. Brain Voyager, SPM99-SPM8, AFNI, and Analyze, as well as several in-house programs are available for fMRI and structural analysis. Sun and SGI workstations are available for pulse programming simulations and coding, separate from those operating spectrometers.

The VUIIS houses a quiet interview room where subjects can be interviewed prior to entering the scanner or for consenting before beginning a study. A soundproof psychological testing or experiment room is located on the ground floor of the VUIIS. This room equipped with a Mac and PC computer can also be used to conduct psychophysical tests and administer questionnaires for collecting individual difference measures.

VUIIS provides a core staff of 18 individuals that are available for the faculty and all trainees for assistance with imaging and educational activities. They include personnel for training and operating the imaging equipment, for supporting animal preparations, for administrative help, and for other technical support.

Vanderbilt PET Center

The PET center is housed in the Vanderbilt University Medical Center, which is an 8-minute walk from the Department of Psychology. The radiochemistry facility has recently been renovated and is housed in the PET Center. The unit is over 1000 square feet and includes a hot laboratory with 2 cells, 4 mini-cells, and 4 fume hoods, and an organic synthesis laboratory with three chemical fume hoods. We are currently in the process of installing a new cyclotron, which is scheduled to be operational in Summer 2010 (see Equipment section for details). Scanning is accomplished on a GE Discovery STE PET/CT scanner (GE, Milwaukee) (see Equipment section for details). Dr. Zald has successfully conducted research at the PET Center for the last 5 years and has an existing and productive relationship with the center's staff.

Vanderbilt Center for Cognitive and Integrative Neuroscience (CCIN)

The CCIN is a collaborative center that seeks to integrate members of the Departments of Neuroscience, Psychological Sciences, Biological Sciences, Electrical Engineering and Computer Science, Biomedical Engineering, and the Vanderbilt Vision Research Center. The CCIN believes that insights about the human mind will come only through the interdisciplinary efforts of brain scientists, psychologists, clinicians and engineers whose efforts will ultimately provide effective prevention and treatment of mental and neurological disorders and the development of new engineering applications such as prosthetic devices and autonomous robots. The CCIN fosters symbiosis and serendipity among groups of investigators across the Vanderbilt University campus with "no less a goal than to push back the last great frontier in modern science". Not only does the center offer many opportunities for fostering collaborations between experts on campus, but it also provides opportunities for building knowledge by hosting a regular seminar series.

Vanderbilt Brain Institute (VBI)

The VBI was founded in 1999 as a transinstitutional entity to oversee and facilitate the extensive neuroscience-related endeavors carried out at Vanderbilt University. As such, the primary mission of the VBI is to promote research, education, and training in the brain-related disciplines at Vanderbilt, with the stated goal of fostering excellence in each if these arenas. In addition to administering the Neuroscience Graduate Program at Vanderbilt, the VBI also plays major roles in shaping neuroscience research activities at Vanderbilt, in facilitating postdoctoral training, and in community outreach. With help from graduate student and post-doctoral trainees, the VBI sponsors the annual Brain Awareness Month activities, which feature a series of public events designed to promote knowledge about the brain and brain-related illness and dysfunction. The VBI hosts a weekly neuroscience seminar on topics ranging from molecular neuroscience to integrative neuroscience.

Psychiatric Neuroimaging Program

Dr. Zald is also a member of the Psychiatric Neuroimaging Program, which is located on the 3rd floor of the Vanderbilt Psychiatric Hospital, a 10-minute walk from the Department of Psychological Sciences. This program provides additional 16 research bays, image analysis software, physiological monitoring, and weekly journal clubs on issues related to clinical neuroimaging. Grand Rounds are offered every week in Psychiatry, with roughly a quarter being related to clinical neuroimaging.

EQUIPMENT

In addition to the common equipment available in the Zald Lab in the Department of Psychological Sciences (see Facilities section for details), the applicant will have access to major equipment available in the Vanderbilt University Institute of Imaging Science (VUIIS) and the Vanderbilt PET Center.

VUIIS 3T and 7T MRI Scanners

The VUIIS (an 8-minute walk from the applicant's future office) houses two Philips Intera Achieva 3T MRI scanners, state-of-the-art systems with superior gradient performance (80 mT/m gradient strength, 200T/m/s slew-rate), 16 independent digital receiver channels and physiological monitoring. Audio/visual presentation hardware and software are available for functional MRI studies. The number and types of RF coils are continually being expanded. Multinuclear spectroscopy (primarily 13C and 31P), with proton decoupling are also available.

The VUIIS houses a Philips Intera Achieva 7T MRI, one of only 13 ultra high field human MR instruments available worldwide. This research system has 32 independent digital receiver channels and physiological monitoring. A 16-channel receive/volume transmit head coil has recently been incorporated, allowing exquisite anatomical, functional and spectroscopic data collection with high SENSE acceleration factors. Multinuclear capabilities are currently under development. The 7T scanner has the same system software, pulse-programming environment, and pulse sequences as current 3T Philips scanners, although not all sequences have been optimized for 7T yet. One goal of the first proposed study is to optimize protocols for use at the 7T.

The 3T/7T suite is fully equipped with a range of audio and video presentation equipment. For video presentation, an inside-the-scanner-room XGA resolution Avotec projector (which projects to a screen placed just behind the subject's head), Epson DLP projector (for projection onto a screen at the front of the scanner) or a pair of XGA-compatible LCD goggles for video stimulus presentation can be used, depending on the experimenter's preference. Headphones for audio stimulus presentation and a microphone for subject feedback are also available, as well as an infrared eye tracker (built in to the LCD goggles). Macintosh and Dell desktop computers are available for stimulus presentation. Software packages available for use include E-Prime, RSVP, Psyscope and MATLAB (with the Psychological Presentation toolbox). Two five-button keypads (one for each hand) interfaced to the computers can be used to collect subject responses if desired (Rowland Institute of Science, Boston, MA). A range of physiological measures such as skin conductance, finger pulse, and respiration can also be simultaneously measured.

Radiochemistry Lab and PET Scanner

Approximately 1,000 sq ft of radiochemistry laboratory space is located in the PET Center in Robinson Research Building (a 10 minute walk from the applicant's future office), equipped for radiochemical operations with ^{18}F, ^{11}C, ^{123}I and other radionuclides. The laboratory has just completed a renovation as part of the Department of Radiology & Radiological Sciences program for enhancing institutional imaging capabilities, which includes separate areas for research and radiopharmaceutical production and new hoods and benchwork. The cyclotron in the PET facility is a CTI/Siemens RDS-112/00 negative-ion cyclotron with targets and ancillary equipment for producing ^{18}F, ^{11}C, ^{13}N and ^{15}O. Two beam lines are dedicated to ^{18}F production, allowing routine production of 3-4 Curies in multiple runs. The hot lab adjacent to the cyclotron is equipped with 2 Von Gahlen hot cells with CRL manipulators and two "dual mini-cells" housing two GE Tracerlabs FX-FN fluorination modules and an FX-C gas phase [^{11}C]methyl iodide/methylation module. Additional automation capabilities are provided by a National Instruments PXI system running Labview software. Three radiochemical hoods are designated for lower level work with 64Cu, 111In, 99mTc, and other short-lived gamma-emitting radionuclides other than iodine. A dedicated radioiodination hood equipped with activated carbon and HEPA filters is located in a separate lab for 123I and 125I manipulations. A Galaxie-networked system of HPLC equipment includes 3 Varian HPLC setups with UV (conventional and photodiode array) and radiometric detectors, including a Bioscan coincidence-mode metabolite detector, 2 Waters HPLC setups, and a Varian gas chromatograph. The pharmacology lab is equipped with 2 Brandell cell harvesters, Sorvall RC-3B and -5B centrifuges, -80°C freezer, microtome, LKB 1282 auto gamma counter, and Bioscan TLC plate reader. A nonradioactive synthetic lab has two synthetic stations, each with new Labconco 5-ft XStream fume hood, rotary evaporator, flash chromatography setup, flammable solvent and acid storage cabinets. NMR, IR, and

mass spectrometry are obtained via Vanderbilt University Institute of Chemical Biology and Department of Chemistry instrumentation labs.

A PET/CT scanner, a GE Discovery STE, is located adjacent to the radiochemistry facility. The scanner has 24 BG crystal rings, 47 4.4 mm axial slices with in plane measures resolution of 4.9 mm radial and 5.8 mm tangential at 1 cm from the center of the field of view (see M. Teräs, et al., 2007, for full specifications). The scanner provides low dose CT for purpose of attenuation correction.

VUIIS Vanderbilt University Institute of Imaging Science

VANDERBILT UNIVERSITY

JOHN C. GORE, PH.D.
Director
Chancellor's University Professor
john.gore@vanderbilt.edu

Gregory Samanez-Larkin
Vanderbilt University
Nashville, TN

March 30th 2010

Re: Samanez-Larkin NRSA proposal

Dear Gregory,

I am writing to confirm I will be pleased to serve as a consultant for your post-doctoral NRSA proposal in which you propose to scan the midbrain and ventral striatum with ultra high field MRI. As you know, my group has been working on functional imaging with our 7T Philips magnet for the past several years, and have made significant progress in this regard. As director of the Vanderbilt Institute of Imaging Science, I am happy to support your effort to take advantage of the technical tools that we have already developed for addressing the methodological challenges of imaging at 7T. We hold several weekly meetings that should be useful for you to attend, including a 7T fMRI working group and a 7T users group meeting, as well as a weekly seminar on neuroimaging applications that you will want to take advantage of during your time at Vanderbilt. I look forward to working with you and your mentor David Zald on the proposed studies.

Sincerely,

John Gore.

John C. Gore, Ph.D.
Chancellor's University Professor
Director, Vanderbilt University Institute of Imaging Science

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March 15, 2010

Gregory Samanez-Larkin
Stanford University / Vanderbilt University

Dear Greg,

I'm writing to let you know that I am happy to collaborate on your NRSA grant application that is proposing to use PET imaging with fMRI. Currently there is a great shortage of researchers with the in-depth training to combine these imaging methods. Thus, the training opportunity is rare and has great potential for impact in the field. It is my opinion that the more researchers who use PET methods, and especially people who combine PET with other modalities like fMRI, the better off we'll be.

Over the past 20 years of conducting PET research, I have refined a number of methodological techniques for successful imaging of older adults, which I will be happy to share with you during your training. Although I understand that you will primarily be working with younger and middle-aged adults throughout the proposed training, many of these methods are relevant for imaging adults of all ages.

Sincerely,

Bill

William Jagust, MD
Professor of Public Health and Neuroscience

LIST OF REFEREES

I have requested recommendation letters from the following qualified individuals:

Brian Knutson, Ph.D. *(Dissertation Advisor)*
Associate Professor, Psychology & Neuroscience
Stanford University
brian.knutson@stanford.edu

Laura L. Carstensen, Ph.D. *(Dissertation Co-Advisor)*
Professor, Psychology
Fairleigh S. Dickinson Jr. Professor, Public Policy
Founding Director, Stanford Center on Longevity
Stanford University
laura.carstensen@stanford.edu

Ian H. Gotlib, Ph.D.
Albert Ray Lang Professor, Psychology
Senior Associate Dean, Social Sciences
Stanford University
ian.gotlib@stanford.edu

SECTION II – SPONSOR AND CO-SPONSOR INFORMATION

a. Research Support Available

NIDA / NIH 5 R01 DA019670
Individual Differences in Extrastriatal DA Release
Award Dates: 01/2006 – 12/2010 [Competing renewal application submitted]
PI: DH Zald
Direct costs: $225,000 per annum
This grant examines the correlates of dopamine functioning as measured with [^{18}F]fallypride in healthy humans.

NIMH / NIH 5 R01 MH074567
The Amygdala: Emotional Modulation of Attention
Award Dates: 07/2007 – 06/2012
PI: DH Zald
Direct costs: $180,000 per annum
This grant examines the functional consequences of amygdala lesions in humans.

Norvo-Nordisk
Insulin Detemir in Obesity Management
Award Dates: 03/2010 – 03/2013
PI: KD Niswender (Co-Investigator: DH Zald)
Direct costs: $1,000,000 per annum
This is a large scale clinical research grant that examines the hypothesis that the weight-loss effects of an insulin detemir are mediated by changes in measured dopamine functioning. Although this grant is focused on an intervention, all subjects receive baseline [^{18}F]fallypride PET scans which can be used for analyses of age effects.

NIBIB/NIH 5 RO1 EB000461
Integrated Imaging of Brain Function at 7 Tesla
Award Dates: 07/2002 – 01/2013
PI: JC Gore
Direct costs: $1,132,894 per annum
This grant supports the development of ultra-high field MRI techniques at Vanderbilt University.

NIMH /NIH 2 T32 MH018921
Development of Psychopathology: From Biopsychosocial Processes to Intervention
Award Dates: 07/2010 – 06/2015
Co-PIs: J Garber, DA Cole, DH Zald
Direct costs: $374,000 per annum
This training grant supports training of graduate students and post-doctoral fellows in translational neuroscience relevant to developmental psychopathology.

b. Sponsor's Previous Fellows/Trainees

Dr. Zald has sponsored 7 pre-doctoral (4 current) and 6 post-doctoral (2 current) individuals. Dr. Zald is additionally a co-mentor for a current K-award.

Representative Five:
David Lishner, Ph.D., Assistant Professor, Department of Psychology, University of Wisconsin, Osh-Kosh
Steven Most, Ph.D., Assistant Professor, Department of Psychology, University of Delaware (co-sponsor)
Stephen D. Smith, Ph.D., Assistant Professor, Department of Psychology, University of Winnipeg
Neil Woodward, Ph.D., Assistant Professor, Department of Psychiatry, Vanderbilt University
Brad Folley, Ph.D., Assistant Professor, Department of Neurology, Vanderbilt University (co-sponsor)

The co-sponsor, Dr. McClure, is currently sponsoring 4 pre-doctoral individuals. McClure is in his third year as an Assistant Professor and has not previously sponsored a postdoctoral fellow.

c. Training Plan, Environment, Research Facilities

The applicant's training will focus primarily on learning new research methods, but will also include broadening his base of knowledge, honing teaching and mentoring skills, building grant writing skills, and networking to further establish his reputation in the field. The overarching goal of the training plan is to ensure that the applicant is extremely competitive when entering the job market in a few years and fully equipped with the necessary tools to independently direct a unique and comprehensive research program.

Expanding Research Toolbox

The primary training activity will focus on increasing the applicant's toolbox to include high-resolution and high-field strength fMRI, radioligand PET imaging, and the integration of structural and functional measures. This training will occur through hands-on experience with each technique. All research activities from study design to data collection and analysis to manuscript preparation will be carried out not only with the advice and counsel of the sponsor, Dr. Zald, and the co-sponsor, Dr. McClure, but also with additional faculty collaborators (Dr. John Gore, Director of the Vanderbilt University Institute for Imaging Science, for high resolution fMRI studies and Dr. Robert Kessler, Director of PET Research at Vanderbilt, for PET imaging studies). Dr. Zald will contribute to all aspects of the applicant's training. The applicant will have individual bi-weekly meetings with Dr. Zald to discuss progress. Additionally, the applicant will regularly attend the weekly hour-long Zald Lab meetings where labmates provide updates and discuss research in progress, manuscripts in progress, funding deadlines and opportunities, scheduling and human subjects issues, and general lab business. Dr. McClure will specifically contribute to the training plan by educating the applicant in the use of computational models and midbrain imaging methods. The applicant will have, at minimum, monthly phone meetings with Dr. McClure. The applicant will also spend several weeks each summer at Stanford working directly with Dr. McClure on data analyses and manuscript preparation. In general, the sponsor and co-sponsor will continually provide feedback and guidance to the trainee throughout the post-doctoral fellowship.

The facilities and equipment available to the applicant at Vanderbilt University are top notch. Samanez-Larkin will have continued access to the Vanderbilt University Institute for Imaging Science, Vanderbilt PET Center, and the Department of Psychological Sciences. The sponsor, Dr. Zald, has successfully published research collected from all of these facilities for many years and has an existing and productive relationship with the staff of each facility.

Increasing Knowledge Base

Another key training activity will focus on increasing the applicant's knowledge base from affective and cognitive neuroscience to the detailed neurocircuitry and function of the dopamine system. The applicant already has a well-developed expertise on the neuroscience of decision-making, so readings will mainly be aimed at broadening this knowledge base to understand processes that may impact this neural circuitry. A more extensive part of the directed readings will focus on the dopamine system. The sponsor, Dr. Zald, and primary PET collaborator, Dr. Kessler, will generate a list of recommended papers, reviews, and texts that will range from the basics of pharmacology and molecular neuroscience to the details of PET neuroreceptor imaging methods and analysis. The primary faculty collaborator on the high-resolution fMRI studies, Dr. Gore, will make recommendations for selected readings on functional neuroimaging at ultra-high field strength and MR protocol development. Although the specialized nature of this directed reading will be much more relevant for the research training planned under this award than traditional coursework, the applicant also plans to audit one course in neuropharmacology and one relevant statistics course during the first and second year of training. More generally, Vanderbilt University provides a wide range of vital colloquia on a diverse range of topics all relevant to the field of cognitive neuroscience. These include colloquia series sponsored by Psychological Sciences and various interdisciplinary centers across campus (see Facilities and Other Resources). The applicant will regularly attend (at least one 1-hour talk per week) and present (at least once each semester) in progress research in these various forums.

Honing Teaching / Mentoring Skills

Throughout training the applicant will have the opportunity to lead specialized workshops on brain imaging methods for graduate students in Psychological Sciences. These hour-long workshops will be led by the applicant 2–3 times per semester. The applicant will also co-mentor undergraduate and full-time research assistants and undergraduate honors students with Dr. Zald. The applicant is committed to providing mentored junior researchers with valuable experience that will adequately prepare them for graduate studies. In addition to providing junior researchers with hands-on training, the applicant will meet with at least one junior researcher at least once each week for an hour.

Building Grant Writing Skills

During training, the applicant will prepare grant applications with Drs. Zald and McClure to add additional older adult groups to the studies. PET grant applications will be written in collaboration with Dr. William Jagust from the University of California Berkeley, who has decades of experience conducting PET imaging studies with older adults. Dr. Jagust has already agreed to provide additional training for the applicant by serving as a consultant on this future study.

Networking / Establishing Scientific Reputation

The applicant will attend and present at the annual meetings of the Society for Neuroeconomics, Gerontological Society of America, and the Society for Neuroscience – or any relevant smaller conferences that occur during the training period.

The training plan described above will assist the trainee in successfully completing the proposed research projects as well as further developing a strong base of training to achieve his primary career goals. This combination of training experiences is ideally suited for the applicant. The primary goal of the fellowship is to broaden the skill set of the applicant. Samanez-Larkin plans to later combine standard whole-brain imaging and high-resolution imaging using fMRI with radioligand PET in more direct studies of the aging of the human dopamine system in his own laboratory. There is a tremendous shortage of researchers in the field who are able to successfully combine PET and fMRI methods. After completion of the post-doctoral fellowship the applicant will enter the job market with a combination of skills (diverse and cutting edge brain imaging techniques, computational modeling experience) unlike any other researcher in the aging field. Thus, the training plan holds tremendous potential for impact throughout the applicant's career. Combining skills and experiences gained through collaboration with other faculty within and outside of the department, mentoring, and grant writing will set the foundation for a productive and successful career in academic research.

d. Number of Fellows/Trainees to be Supervised During the Fellowship

Dr. Zald will supervise no more than 2 other post-doctoral fellows at a time during the span of this grant, and it is expected that there will only be one other post-doctoral fellow during most of the applicant's fellowship. Dr. Zald expects to supervise 3–4 Ph.D. candidates simultaneously during the applicant's fellowship.

The co-sponsor, Dr. McClure, will supervise 4 Ph.D. candidates and at most one other post-doctoral fellow during the applicant's fellowship.

e. Applicant's Qualifications and Potential for a Research Career

I express my highest possible support for Gregory Samanez-Larkin's candidacy for an NRSA post-doctoral training fellowship. I met Greg at the Human Brain Mapping conference about a year ago, where we discussed the possibility of his pursuing a post-doctoral fellowship in my lab. He is currently completing his Ph.D. dissertation at Stanford University under the supervision of Brian Knutson and Laura Carstensen. Although Dr. Knutson and I have never directly collaborated, we have a history of intellectual discussions about reward circuitry that dates back over a decade, and Brian had given me a heads up about Greg's enormous potential. Based on our discussions it rapidly became clear that Greg's interest fit well with work going on in my lab, Greg became excited about the prospects of working in my lab, and I became excited about attracting such a high

quality post-doctoral fellow. Over this past winter, Greg made an extended visit to my lab, and has already proven himself to be invaluable. He provided substantial assistance to our 7T MRI studies of the midbrain. I'm not sure I have ever seen someone able to so quickly step into my lab, develop excellent collaborative relationships and provide significant intellectual and technical contributions to a project.

It is clear from looking over Greg's CV that he shows great promise for a successful career in integrative neuroscience. As a graduate student he has been extremely productive in publishing first-author papers in high impact journals like *Nature Neuroscience*, the *Journal of Neuroscience*, and *Psychological Science*. His success already at this early career stage indicates that he has great potential for impact in the field. His most recent paper was featured on the cover of the *Journal of Neuroscience* and his work has already received international press coverage. His *Nature Neuroscience* paper from 2007 on changes in the responsiveness to losses in aging is particularly seminal, and has already been cited over 40 times in the literature. By combining the diverse expertise of both of his graduate advisors, he has already begun to carve out a unique research program focused on decision making and the cognitive neuroscience of aging. Indeed, I believe that Greg could do well on the job market for an assistant professor position without additional training. However, based on his graduate work he has identified a domain that he would like to gain specific technical expertise in. As there are few individuals doing aging research who take a multimodal imaging approach, the skill set that he aims to gain during his post-doctoral fellowship will uniquely position him to launch a novel research program in aging research when he is done.

Greg clearly thrives in a collaborative environment. I have no doubt that he will take full advantage of the combined mentorship that will be provided both directly by Dr. McClure and me and indirectly by other senior members of our research team at Vanderbilt, particularly Dr. Gore. My career has greatly benefitted from the ability to foster collaborations and I will ensure that Greg has the necessary skills and a realistic picture of what it takes to build and maintain relationships with diverse colleagues through grant writing, data collection, and publishing. The expansion of Greg's skill set through these collaborations will not only help him secure a faculty position but will also set him on the path to becoming a tremendous asset to the field of aging research.

I will note up front, one place where Greg's research agenda differs from my own. Specifically, I by no means consider myself to be an aging researcher. However, my training included a 6-month rotation in geriatric neuropsychology as part of an accredited internship in neuropsychology at the Ann Arbor VA Medical Center's Geriatric Research and Education Center. Thus, I am highly familiar with the literature on the cognitive effects of normal aging and progressive neurological disorders in the elderly. Moreover, given my broad interest in how individual differences in the dopamine system (and limbic regions) contribute to individual differences in behavior, personality and cognition, and given the effects of aging on the dopamine system, the questions about aging fit nicely with my broader research program. It is thus not a far stretch to incorporate Greg's interest in aging into my lab's research program. In order to facilitate this work, I am committed to both providing Greg access to PET data that is arising in various PET projects at Vanderbilt (which includes older participants than my main series of PET studies), and to work with Greg to write an R21 or even an R01 to recruit participants from older populations.

Part of the reason I am so enthusiastic about Greg is that he shows a rare combination of superb technical skills in working with computer programs (which is essential for neuroimaging analysis), with an ability to think broadly about topics, and to integrate disparate types of information (for instance the aging literature, with behavioral economics). As such, he not only is able to come up with unique ideas for experiments, but has the skills to implement and test those ideas.

In conclusion, I believe Greg's research program has great potential and direct implications for public health and well being. He has all the right characteristics to be successful, including great intellect, attention to details, curiosity, computer skills, expertise in image analysis, motivation, and drive. I believe that the expertise available in our laboratory, the Department of Radiology and Radiological Sciences, and at the Vanderbilt University Institute of Imaging Science will provide Greg with invaluable opportunities to take his skill set to the next level. I will note that there are few sites in the world where he could acquire skills in both extrastriatal dopamine imaging and ultra-high field MRI. When combined with the impressive skills that he has already acquired, he will emerge from this post-doctoral fellowship with a great trajectory for a truly outstanding and unique research career.

OMB Number: 4040-0001
Expiration Date: 06/30/2011

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: | * First Name: Gregory | Middle Name: Russell
* Last Name: Samanez Larkin | Suffix:
Position/Title: Postdoctoral Fellow | Department: Psychology
Organization Name: Vanderbilt University | Division: College of Arts and Science
* Street1: 111 21st Avenue South
Street2: 301 Wilson Hall, PMB 407817
* City: Nashville | County/ Parish: Davidson
* State: TN: Tennessee | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 37240-7817
* Phone Number: 650-799-5715 | Fax Number: 615-343-8449
* E-Mail: glarkin@stanford.edu

Credential, e.g., agency login: SAMANEZLARKIN.GREG

*** Project Role:** PD/PI | **Other Project Role Category:**

Degree Type: PhD
Degree Year: 2010

***Attach Biographical Sketch** KP1_GSL_biosketch.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

PROFILE - Senior/Key Person 1

Prefix: Dr. | * First Name: David | Middle Name: H
* Last Name: Zald | Suffix:
Position/Title: Associate Professor | Department: Psychology
Organization Name: Vanderbilt University | Division:
* Street1: 111 21st Avenue South
Street2: 301 Wilson Hall, PMB 407817
* City: Nashville | County/ Parish:
* State: TN: Tennessee | Province:
* Country: USA: UNITED STATES | * Zip / Postal Code: 37240-7817
* Phone Number: 615-343-6076 | Fax Number: 615-343-8449
* E-Mail: david.zald@vanderbilt.edu

Credential, e.g., agency login: ZALDDH

*** Project Role:** Other (Specify) | **Other Project Role Category:** Sponsor

Degree Type: PhD
Degree Year: 1997

***Attach Biographical Sketch** KP2_DHZ_biosketch.pdf [Add Attachment] [Delete Attachment] [View Attachment]
Attach Current & Pending Support [Add Attachment] [Delete Attachment] [View Attachment]

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Senior/Key Person 2

Prefix: Dr. * First Name: Samuel Middle Name: M

* Last Name: McClure Suffix:

Position/Title: Assistant Professor Department: Psychology

Organization Name: Stanford University Division:

* Street1: 450 Serra Mall

Street2: Jordan Hall Building 420

* City: Stanford County/ Parish:

* State: CA: California Province:

* Country: USA: UNITED STATES * Zip / Postal Code: 94305-2130

* Phone Number: 650-209-4833 Fax Number:

* E-Mail: smcclure@stanford.edu

Credential, e.g., agency login: SMCCLURE

*** Project Role:** Other (Specify) **Other Project Role Category:** Co-Sponsor

Degree Type: PhD

Degree Year: 2003

***Attach Biographical Sketch**	KP3_SMM_biosketch.pdf	Add Attachment	Delete Attachment	View Attachment
Attach Current & Pending Support		Add Attachment	Delete Attachment	View Attachment

Tracking Number:GRANT10572775 Funding Opportunity Number:PA-10-110 Received Date:2010-04-05T11:39:21-04:00

FELLOWSHIP APPLICANT BIOGRAPHICAL SKETCH

USE ONLY FOR INDIVIDUAL PREDOCTORAL and POSTDOCTORAL FELLOWSHIPS. DO NOT EXCEED FOUR PAGES.

NAME OF FELLOWSHIP APPLICANT	POSITION TITLE
Gregory R. Samanez Larkin	Graduate Student
eRA COMMONS USER NAME (credential, e.g., agency login) SAMANEZLARKIN.GREG	

EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Michigan, Ann Arbor, MI	B.A.	1998–2002	Psychology
Stanford University, Stanford, CA	M.A.	2005–2008	Psychology
Stanford University, Stanford, CA	Ph.D.	2005–2010	Psychology

A. PERSONAL STATEMENT

Samanez-Larkin's graduate training under the supervision of Dr. Brian Knutson, a pioneering expert on reward processing in the brain, and Dr. Laura Carstensen, an expert on emotion and aging, has provided a solid base from which to begin a productive and successful career in the cognitive neuroscience of adult development and aging. Samanez-Larkin's dissertation research supported by a pre-doctoral NRSA from the National Institute on Aging focuses on behavioral and neural changes in value-based probabilistic learning and risky decision making over the adult life span using functional magnetic resonance imaging. Samanez-Larkin has a solid base of knowledge about human aging and reward processing and the basic tools necessary for neural image processing. Samanez-Larkin's graduate training provides a strong base from which to significantly expand his skill set to include high-resolution functional neuroimaging and PET imaging during a post-doctoral fellowship. Samanez-Larkin's publication record thus far speaks to his ability to manage and complete projects and produce high profile publications.

B. POSITIONS AND HONORS

Positions and Employment

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
Lab Manager / RA	01/01	05/02	Psychology	University of Michigan	Barbara Fredrickson
Research Assistant	01/01	05/02	Neuropsychology	University of Michigan	Patricia Reuter-Lorenz
Lab Manager / RA	06/02	09/05	Psychology	Stanford University	Laura Carstensen

Academic and Professional Honors

1999 Branstrom Prize for Freshman Scholars (top 10% of class), University of Michigan
2001 Psi Chi Psychology Honors Society
2002 University Honors, University of Michigan
2002 W.B. Pillsbury Thesis Award, University of Michigan
2006 NSF Graduate Research Fellowship, Honorable Mention
2006 Summer School in Neuroeconomics Fellowship, Stanford University
2007 Top Ten Scientific Advances, National Institute on Aging (for: Samanez-Larkin, et al., 2007)
2008 Department of Psychology Teaching Award, Stanford University
2009–2010 Individual Pre-doctoral National Research Service Award, National Institute on Aging

C. PUBLICATIONS

Research Papers

1. Fredrickson, B., Tugade, M., Waugh, C., **Larkin, G.R.** (2003) What good are positive emotions in crises?: A prospective study of resilience and emotions following the terrorist attacks on the United States on

September 11th, 2001. *Journal of Personality and Social Psychology*, 84, 365–376. [PMC2755263]
2. Mikels, J.A., Fredrickson, B.L., **Larkin, G.R.**, Lindberg, C.M., Maglio, S.J., Reuter-Lorenz, P.A. (2005). Emotional category data on images from the International Affective Picture System. *Behavior Research Methods*, 37(4), 626–630. [PMC1808555]
3. Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A., Carstensen, L.L. (2005) Divergent trajectories in the aging mind: Changes in working memory for affective versus visual information with age. *Psychology and Aging*, 20(4), 542–553. [PMC2746384]
4. **Samanez-Larkin, G.R.**, Gibbs, S.E.B., Khanna, K., Nielsen, L., Carstensen, L.L., Knutson, B. (2007) Anticipation of monetary gain but not loss in healthy older adults. *Nature Neuroscience*, 10(6), 787–791. [PMC2268869]
5. **Samanez-Larkin, G.R.**, Hollon, N.G., Carstensen, L.L., Knutson, B. (2008) Individual differences in insular sensitivity during loss anticipation predict avoidance learning. *Psychological Science*, 4(19), 320–323. [PMC2365707]
6. Ersner-Hershfield, H., Garton, M.T., Ballard, K., **Samanez-Larkin, G.R.**, Knutson, K. (2009) Don't stop thinking about tomorrow: Individual differences in future self-continuity account for saving. *Judgment and Decision Making*, 4(4), 280–286. [PMC2747683]
7. Kwon, Y., Scheibe, S., **Samanez-Larkin, G.R.**, Tsai, J.L., Carstensen, L.L. (2009) Replicating the positivity effect in picture memory in Korean younger and older adults: Evidence for cross-cultural universality. *Psychology and Aging*, 24(3), 748–754. [PMC2775417]
8. **Samanez-Larkin, G.R.**, Robertson, E.R., Mikels, J.A., Carstensen, L.L., Gotlib, I.H. (2009) Selective attention to emotion in the aging brain. *Psychology and Aging*, 24(3), 519–529. [PMC2791508]
9. **Samanez-Larkin, G.R.**, Kuhnen, C.M., Yoo, D.J., Knutson, B. (2010) Variability in nucleus accumbens activity mediates age-related suboptimal financial risk taking. *Journal of Neuroscience*, 30(4), 1426–1434. [PMC2821055]
10. **Samanez-Larkin, G.R.**, Wagner, A.D., Knutson, B. (in press) Expected value information improves financial risk taking across the adult life span. *Social Cognitive and Affective Neuroscience.*
11. **Samanez-Larkin, G.R.**, Carstensen, L.L., Gotlib, I.H. (under review) Emotion regulation and attentional interference: Individual differences in expressive suppression and neural interference in the prefrontal cortex. *Emotion*.
12. Knutson, B., **Samanez-Larkin, G.R.**, Kuhnen, C.M. (in prep) Affective systems independently contribute to accumulated assets and debts.
13. **Samanez-Larkin, G.R.**, Sims, T.L., Koopmann-Holm, B., Chim, L, Chan, D.P., Tsai, J.L., Knutson, B. (in prep) Individual differences in ideal affect influence anticipatory reward processing in the ventromedial prefrontal cortex.

Abstracts

1. **Larkin, G.R.**, Mikels, J.A., Lindberg, C., Fredrickson, B.L., Reuter-Lorenz, P.A. (2002, November) Finding categories in dimensions: Behavioral and psychophysiological insights for an integrative account of emotional structure. NYAS Emotions Inside Out conference, New York City, NY.
2. Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A., Carstensen, L.L. (2004, July) Preservation of online emotional processing capacity in the aging mind. Annual APA Convention, Honolulu, HI.
3. Nielsen, H.L., Knutson, B., **Larkin, G.R.**, Carstensen, L.L. (2005, September) Affect dynamics: Tracking trajectories through affective space. Annual Society for Neuroeconomics conference, Kiawah Island, SC.
4. Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A., Carstensen, L.L. (2006, April) Age differences in affective working memory: Prefrontal contributions to the positivity effect in older adults. Annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.
5. **Larkin, G.R.**, Gibbs, S.E., Nielsen, L., Khanna, K., Carstensen, L.L., Knutson, B. (2006, April). Neural responsiveness to anticipated gain and loss in younger and older adults. Annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.
6. **Larkin, G.R.**, Khanna, K., Kuhnen, C., Knutson, B. (2006, April). Risk taking and financial decision making in younger and older adults. Biennial Cognitive Aging Conference, Atlanta, GA.
7. **Larkin, G.R.**, Gibbs, S., Khanna, K., Carstensen, L.L., Knutson, B. (2006, November) Incentive processing in the aging brain: Neural responsiveness to anticipated gain and loss. Annual meeting of the Gerontological Society of America, Dallas, TX.
8. **Larkin, G.R.**, Robertson, E.R., Mikels, J.A., Maglio, S.J., Carstensen, L.L., Gotlib, I.H. (2006, November) Selective attention to emotional stimuli in younger and older adults. Annual meeting of the Gerontological

Society of America, Dallas, TX.
9. **Samanez-Larkin, G.R.**, Carstensen, L.L., Knutson, B. (2007, March) Deactivation of frontal and striatal regions in response to loss outcomes in younger and older adults. NYAS Affect to Action conference, New York, NY.
10. **Samanez-Larkin, G.R.**, Yoo, D., Knutson, B. (2007, November) Incentive-based decision making in older adults. Annual meeting of the Gerontological Society of America, San Francisco, CA.
11. **Samanez-Larkin, G.R.**, Hollon, N.G., Carstensen, L.L., Knutson, B. (2007, November) Individual differences in insular sensitivity during loss anticipation predict avoidance learning. Annual meeting of the Society for Neuroscience, San Diego, CA.
12. **Samanez-Larkin, G.R.**, Kuhnen, C., Knutson, B. (2008, September) Financial decision making across the adult life span. Annual meeting of the Society for Neuroeconomics, Park City, UT.
13. **Samanez-Larkin, G.R.**, Knutson, B. (2008, November) Financial risk taking over the adult life span. Annual meeting of the Society for Neuroscience, Washington, DC.
14. Thamrongrattanarit, A., **Samanez-Larkin, G.R.**, Carstensen, L.L., McClure, S.M. (2009, May) The influence of time perspective on exploration and exploitation. Annual meeting of the Association for Psychological Science, San Francisco, CA.
15. **Samanez-Larkin, G.R.**, Carstensen, L.L., Knutson, B. (2009, September) Seeking rewards and avoiding punishments over the adult life span. Annual meeting of the Society for Neuroeconomics, Evanston, IL.
16. **Samanez-Larkin, G.R.**, Knutson, B. (2009, October) Manipulating decision making in the aging brain. Annual meeting of the Society for Neuroscience, Chicago, IL.
17. **Samanez-Larkin, G.R.** (2009, November) Mechanisms underlying age differences in financial decision making: Evidence from functional neuroimaging and behavioral task manipulations. Annual meeting of the Gerontological Society of America, Atlanta, GA.

Reviews / Book Chapters

1. **Samanez-Larkin, G.R.**, D'Esposito, M. (2008) Group comparisons: Imaging the aging brain. *Social Cognitive and Affective Neuroscience*, 3(3), 290–297. [PMC2563421]
2. Knutson, B., **Samanez-Larkin, G.R.** (in press) Brain, decision, and debt. In R. Brubaker, R.M. Lawless & C. Tabb (Eds.) *A Debtor World: Interdisciplinary Perspectives on an Indebted Global Society*. New York: Oxford University Press.
3. **Samanez-Larkin, G.R.**, Carstensen, L.L. (in press) Socioemotional functioning and the aging brain. In J. Decety & J.T. Cacioppo (Eds.) *The Handbook of Social Neuroscience*. New York: Oxford University Press.

D. SCHOLASTIC PERFORMANCE

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
	U OF MICHIGAN, *UNDERGRAD*			U OF MICHIGAN, *UNDERGRAD*	
1999	Biology	B	1998	Philosophical Problems	A+
2001	Human Neuropsychology	A	1999	Introductory Psychology	A
2001	Topics in Biopsychology: Emotion	A+	2001	Community Outreach	A
			2001	Peer Advising	A
			2001	Advanced Psychological Research	A
			2002	Senior Honors Research	A
	STANFORD UNIVERSITY, *GRAD*			STANFORD UNIVERSITY, *GRAD*	
2006	Cognitive Neuroscience	A+	2005	Statistical Methods for Social Science	A
2006	Math Tools for Neuroscience	A	2005	Computational Neuroimaging	B+
2006	Techniques in Neuroscience	S	2007	Statistical Theory, Models & Methodol	A+
2006	Neuroecon and Neural Basis of DM	CR	2007	Foundations of Cognition	A
2007	Affective Neuroscience	A-	2007	Teaching Practicum	S
2008	Reinforcement Learning in the Brain	CR	2008	Hierarchical Linear Modeling	S

CR Credit (student-elected satisfactory: A, B, or C equivalent)
S No option Satisfactory (A, B, or C equivalent)

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
David H. Zald	Associate Professor
eRA COMMONS USER NAME ZALDDH	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Michigan, Ann Arbor	B.A.	1989	Film-Video / Psychology
University of Minnesota, Minneapolis	Ph.D.	1997	Psychology (clinical)
Ann Arbor VA Medical Center / University of Michigan Medical Center, Ann Arbor	Internship	1995–1996	Neuropsychology
University of Minnesota Medical Center / Minneapolis VA Medical Center, Minneapolis	Post Doc	1997–2000	Neuroimaging

A. PERSONAL STATEMENT

Dr. Zald has the appropriate background, experience, expertise, and track record of collaborative productivity to serve as primary sponsor and provide the applicant with strong training. Since the early 1990s Dr. Zald's research has focused on understanding the neural and neuropharmacological substrates of emotion, and the manner in which individual differences in the functioning of these systems impact individual differences in temperament, personality and psychopathology. Dr. Zald's graduate and post-graduate training combined study of psychopathology, neuropharmacology, neuropsychology, and affective neuroscience. Since 1995 he has been conducting functional neuroimaging studies utilizing a combination of PET and fMRI to explore the functioning of limbic and paralimbic regions, with a particular emphasis on the amygdala, orbitofrontal cortex, and ventral striatal/mesolimbic dopamine system. In collaboration with John Gore of the Vanderbilt University Imaging Institute, he has been developing procedures for high resolution scanning the dopamine midbrain at Vanderbilt's 7T magnet. Dr. Zald has extensive experience mentoring graduate students and post-docs, and is currently co-PI on a training grant.

B. POSITIONS AND HONORS

Positions and Employment

1991–1994 Psychiatric Interviewer, Dept. of Family Studies, Univ. of Minnesota, Minneapolis, MN
1992–1993 Teaching Assistant, Univ. Minnesota Graduate Program in Clinical Psychology, Minnesota, Minneapolis, MN
1994–1996 Instructor, Dept. of Psychology, Univ. Minnesota, Minneapolis, MN (also 1999)
1996–1997 Neuropsychology Intern, VA Medical Center/Univ. of Michigan Hospital, Ann Arbor, MI
1997–2000 Research Physiologist, Cognitive Neuroimaging Unit, VA Medical Center, Minneapolis, MN & Research Fellow, Division of Neuroscience Research in Psychiatry/Pharmacology, Univ. of Minnesota, Minneapolis, MN
2000–2007 Assistant Professor, Dept. of Psychology & Integrative Neuroscience Program, Vanderbilt Univ.
2007–Present Associate Professor, Depts. of Psychology, Psychiatry, & Integrative Neuroscience Program, Vanderbilt University, Nashville, TN (additionally: Director of Undergraduate Studies, Dept. of Psychology 2007-2009)

Honors

1987 University of Michigan Phi Beta Kappa/ University of Michigan James B. Angell Scholar
1988 University of Michigan Senior Class Honors
1989 Hebrew University Faye Grand Memorial Scholarship
1990 University of Minnesota Graduate School Fellowship

1991 University of Minnesota, Dept. of Psychology / NIMH Predoctoral Training Award
1994 University of Minnesota Eva O. Miller Fellowship
1996 American Neuropsychiatric Association Young Investigator Award

C. SELECTED PEER-REVIEWED PUBLICATIONS (OUT OF 57)

1. **Zald DH**, Pardo JV: Olfaction, emotion and the human amygdala: Amygdalar activation during aversive olfactory stimulation. *Proc Natil Acad Sci* 1997;94:4119-4124.
2. **Zald DH**, Lee JR, Fluegel KW, Pardo JV: Aversive gustatory stimulation activates limbic circuits in humans. *Brain* 1998;121:1143-1154.
3. **Zald DH**, Depue RA: Serotonergic functioning inversely correlates with positive and negative affect in healthy males. *Personality and Individual Differences* 2001;30:71-86.
4. **Zald DH**, Matson DL, Pardo JV: Brain activity in the ventromedial prefrontal cortex correlates with individual differences in negative affect. *Proc Natl Acad of Sci* 2002;99:2450-2454.
5. **Zald DH**: The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Rev* 2003;41:88-123.
6. **Zald DH**, Boileau I, El Deredy W, Gunn R, McGlone F, Dichter G & Dagher A: Dopamine transmission in the human striatum during monetary reward tasks. *J Neuroscience* 2004;24:4105-4112. [PMID: 15115805]
7. Riccardi P, Li R. Ansari MS., **Zald D**, Park S, Dawant B, Anderson S, Doop M, Woodward N, Schmidt D, Baldwin R,Kessler R: Amphetamine induced displacement of [^{18}F]Fallypride in striatum and extrastriatal regions. *Neuropsychopharmacology* 2006;31:1016-1026.
8. **Zald DH:** Orbital versus dorsolateral prefrontal cortex: Anatomical insights into content vs. process differentiation models of the prefrontal cortex. *Annals New York Acad. of Sci. 2007*;1121:395-406.
9. Hakyemez HS, Dagher A, Smith SD, **Zald DH**: Striatal dopamine transmission in healthy humans during passive unpredictable monetary reward and novelty. *Neuroimage* 2008;39:2058-65.
10. **Zald DH**, Cowan RL, Riccardi P, Baldwin R, Ansari MS, Li R, Shelby ES, Smith CE, McHugo M, Kessler RM: Midbrain dopamine autoreceptor availability is inversely associated with novelty seeking traits in humans. *J Neuroscience* 2008; 28, 14372-14378. [NIHMS 85634]
11. Woodward ND, **Zald DH**, Ding Z, Riccardi P, Ansari MS, Baldwin R, Cowan RL, Li R, Kessler RM: Cerebral morphology and dopamine D2/D3 receptor distribution in humans: A combined [18F]fallypride and voxel-based morphometry study. *Neuroimage 2009* 46:31-8. [NIHMS99857]
12. Kessler RM, Woodward ND, Riccardi P, Li R, Ansari MS, Anderson S, Dawant B, **Zald D**, Meltzer HY. Dopamine D(2) receptor levels in striatum, thalamus, substantia nigra, limbic regions, and cortex in schizophrenic subjects. *Biological Psychiatry* 2009; 5:1024-31. [PMC2804466]
13. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, **Zald DH**. Worth the 'EEfRT'? The Effort Expenditure for Rewards Task as an objective measure of motivation and anhedonia. *PLOS One* 2009; 4:e6598. [PMC2720457].
14. **Zald DH**, Woodward ND, Cowan RL, Riccardi P, Baldwin R, Ansari MS, Li R, Smith CE, Kessler RM. The interrelationship of dopamine D2-like receptor binding in striatal and extrastriatal brain regions in healthy humans: A Principal component analysis of [18F]fallypride binding. *Neuroimage* 2010 epub [PMC Journal in process]
15. Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Benning SD, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith C, Cole D, Kessler R M, **Zald DH**. Mesolimbic Dopamine Reward System Hypersensitivity in Individuals with Psychopathic Traits. *Nature Neuroscience* 2010 epub [PMC Journal in process]

Books: *The Orbitofrontal Cortex*. Zald, D.H., Rauch, S.L. (eds.) Oxford University Press, Oxford U.K. (2006).

D. RESEARCH SUPPORT

NIDA 1 R01 DA019670 Zald (PI) 2006–2010
Individual Differences in Extrastriatal Dopamine
This study examines whether there are personality and genetic predictors of the subjective and cognitive responses induced by oral d-amphetamine. It also examines the genetic, personality, cognitive and BOLD fMRI correlates of individual differences in striatal and extrastriatal D2/D3 binding, and amphetamine induced

dopamine release. The study combined PET imaging with the [18F]fallypride, with functional MRI of reward tasks.

NIMH 1 R01 MH074567 Zald (PI) 2007–2012
Role of the Amygdala in the Emotional Modulation of Attention
This study examines the ability of emotional stimuli to modulate attention in patients who undergo removal of their left or right amygdala for the treatment of intractable epilepsy. The study provides a formal test of current theories of the lateralization of amygdala functions. The study includes both neuropsychological testing and fMRI of responses to emotional stimuli in patients with amygdala lesions, and age-matched, and medication matched controls.

NIMH 1 R03 MH082210-01A1 Olatunji (PI) 2008–2010
Emotion Induced Attentional Blink in OCD
This study tests the hypothesis that patients with obsessive-compulsive disorder have an impairment in their ability to disengage their attention from emotionally valenced stimuli. The study makes use of the emotional attentional blink paradigm that was initially developed in our laboratory.

Norvo-Nordisk Investigator Initiated Niswender (PI) 2010–2013
Insulin Detemir In Obesity Management
This study investigates the impact of insulin detemir treatment on dopaminergic functioning as measured with PET and fMRI, and the relationship between these central nervous system variables and the weight loss and psychological effects of insulin detemir treatment. The study combines measurement of dopamine transporters, dopamine D2 receptor availability and dopamine release.

Training Support

PENDING
NIMH 2 T32 MH018921-21A1(Garber, Cole, Zald, co-PIs) 7/1/2010–6/30/2015 (pending council)
Development of Psychopathology: From Biopsychosocial Processes to Intervention
This training grant aims to develop researchers to perform translational research on developmental psychopathology that is informed by neurobiological processes. Dr. Zald takes the lead in ensuring that clinical trainees develop appropriate training in biological approaches to understanding psychopathology.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Samuel M. McClure	Assistant Professor
eRA COMMONS USER NAME SMCCLURE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	B.A.	1992–1996	Philosophy and Science
Baylor College of Medicine, Houston, TX	Ph.D.	1996–2003	Neuroscience
Princeton University, Princeton, NJ	Post Doc	2003–2007	Psychology

A. PERSONAL STATEMENT

The goal of this fellowship grant is to provide in-depth training to the applicant in the use of new MRI and PET methods for imaging the human reward system. In support of his role as co-sponsor on this application, Dr. McClure has the appropriate background knowledge, experience with collaborative research, methodological expertise, and publication track record to provide the applicant with strong additional training. Both as a neuroscience graduate student at Baylor and post-doctoral fellow at Princeton University, Dr. McClure's pioneering research on prediction error signaling in the midbrain and striatum, intertemporal choice, and preferences were all greatly enriched through cross-university collaborations. Even at this early career stage, Dr. McClure has many years of experience navigating and maintaining productive remote collaborations. Directly relevant to this proposal, most recently Dr. McClure has begun to collaborate with the sponsor, Dr. Zald, on a series of studies examining the relationship between dopamine function and intertemporal choice using radioligand PET. Additionally, with Dr. Kimberlee D'Ardenne, Dr. McClure has developed a number of optimization techniques for imaging the human midbrain. The focus of Dr. McClure's research also fits in well with the applicant's goals for expanding the focus of his own research program. The majority of Dr. McClure's prior publications and the research currently being conducted in his laboratory at Stanford University focus on studies that examine the integration of reward processing and behavioral control.

B. POSITIONS AND HONORS

Positions and Employment

2003–2007 Post-Doctoral Fellow, Center for the Study of Brain, Mind, & Behavior, Princeton University
2007–current Assistant Professor, Department of Psychology, Stanford University

Honors

2005–2007 Ruth L. Kirchstein NRSA Post-Doctoral Fellowship
2009–2011 John Philip Coghlan Fellow

C. SELECTED PEER-REVIEWED PUBLICATIONS

1. Berns, G.S., **McClure, S.M.**, Pagnoni, G., Montague, P.R. (2001) Predictability modulates human brain response to reward. *Journal of Neuroscience*, 21:2793-2798.
2. Montague, P.R., Berns, G.S., Cohen, J.D., **McClure, S.M.**, Pagnoni, G., Dhamala, M., Wiest, M.C., Karpov, I., King, R.D., Apple, N., Fisher, R.E. (2002) Hyperscanning: Simultaneous fMRI during linked social interactions. *NeuroImage,* 16: 1159-1164.
3. **McClure, S.M.**, Berns, G.S., Montague, P.R. (2003) Temporal Prediction Errors in a Passive Learning Task Activate Human Striatum. *Neuron,* 38: 339-346.
4. **McClure, S.M.**, Daw, N.D., Montague, P.R. (2003) A computational substrate for incentive salience. *Trends in Neurosciences*, 26: 423-428.

5. Montague, P.R., **McClure, S.M.**, Baldwin, P.R., Phillips, P.E.M., Budygin, E.A., Stuber, G.D., Kilpatrick, M.R., Wightman, R.M. (2004) Dynamic gain control of dopamine delivery in freely-moving rats. *Journal of Neuroscience*, 24: 1754-1759.
6. **McClure, S.M.**, Li, J., Tomlin, D., Cypert, K.S., Montague, L.M., Montague, P.R. (2004) Neural correlates of behavioral preference for culturally familiar drinks. *Neuron*, 44: 379-387.
7. **McClure, S.M.**, Laibson, D.I., Loewenstein, G., Cohen, J.D. (2004) Separate neural systems value immediate and delayed rewards. *Science*, 306: 503-507.
8. McClure, K.D., **McClure, S.M.**, Richter, M., McClure, W. (2005) Kinetics of the BOLD response depend on inter-stimulus interval. *NeuroImage*, 27: 817-23.
9. **McClure, S.M.**, Gilzenrat, M.S., Cohen, J.D. (2005) An exploration-exploitation model based on norepinepherine and dopamine activity. *Advances in Neural Information Processing Systems 18*.
10. Li, J., **McClure, S.M.**, King-Casas, B., Montague, P.R. (2006) Policy adjustment in a dynamic economic task. *PLoS ONE* 1: e103. [PMC1762366]
11. Cohen, J.D., **McClure, S.M.**, Yu, A.J. (2007) Should I stay or should I go? Exploration versus exploitation. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 362: 933-942. [PMC2430007]
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17. Seymour, B., **McClure, S.M.** (2008) Anchors, scales, and the relative coding of value in the brain. Current Opinion in Neurobiology 18: 173-178.
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19. Waltz, J.A., Schweitzer, J.B., Gold, J.M., Kurup, P.K., Ross, T.J., Salmeron, B.J., Rose, E.J., **McClure, S.M.**, Stein, E.A. (2008) Patients with schizophrenia show a reduced BOLD response to both unpredictable and predictable primary reinforcers. *Neuropsychopharmacology* 34: 1567-77.
20. Kang, M.J., Hsu, M., Krajbich, I., Loewenstein, G., **McClure, S.M.**, Wang, J., & Camerer, C.F. (2009) The wick in the candle of learning: Epistemic curiosity activates reward circuitry and enhances memory. *Psychological Science* 20: 963-973.

D. RESEARCH SUPPORT

Active

NIA/NIH R01-AG030310 Cohen (PI) 9/2006–8/2011
Neural mechanisms and social influence in delay discounting and impulsive choice
This project investigates the neural mechanisms underlying delay discounting in behavioral and fMRI experiment. I contribute to experiment design, analysis, and the reporting of results.
Role: Consultant

Recently Completed

NIMH/NIH F32-MH072141 McClure (PI) 8/2005–2/2007
Neural mechanisms of reward processing
This project investigated the brain systems involved in delay discounting in psychologically healthy young adults.

PHS Fellowship Supplemental Form

OMB Number: 0925-0002

A. Application Type:

From SF424 (R&R) Cover Page. The response provided on that page, regarding the type of application being submitted, is repeated here for your reference as you provide the responses that are appropriate for this Fellowship application.

☒ New ☐ Resubmission ☐ Renewal ☐ Continuation ☐ Revision

B. Research Training Plan

1. Introduction to Application *(for RESUBMISSION applications only)*		Add Attachment	Delete Attachment	View Attachment
2. * Specific Aims	B2_SpecificAims.pdf	Add Attachment	Delete Attachment	View Attachment
3. * Research Strategy	B3_ResearchStrategy.pdf	Add Attachment	Delete Attachment	View Attachment
4. Inclusion Enrollment Report *(for RENEWAL applications only)*		Add Attachment	Delete Attachment	View Attachment
5. Progress Report Publication List *(for RENEWAL applications only)*		Add Attachment	Delete Attachment	View Attachment

Human Subjects

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the involvement of human subjects, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

Are Human Subjects Involved? ☒ Yes ☐ No

6. * Human Subjects Involvement Indefinite?	☐ Yes	☒ No	
7. Clinical Trial?	☐ Yes	☒ No	
8. Agency-Defined Phase III Clinical Trial?	☐ Yes	☐ No	

9. Protection of Human Subjects	B9_ProtectionHumanSubjects.pdf	Add Attachment	Delete Attachment	View Attachment
10. Inclusion of Women and Minorities	B10_InclusionWomenMinorities.pdf	Add Attachment	Delete Attachment	View Attachment
11. Targeted/Planned Enrollment	B11_TargetedEnrollment.pdf	Add Attachment	Delete Attachment	View Attachment
12. Inclusion of Children	B12_InclusionChildren.pdf	Add Attachment	Delete Attachment	View Attachment

Other Research Training Plan Sections

Please note. The following item is taken from the Research & Related Other Project Information form. The response provided on that page, regarding the use of vertebrate animals, is repeated here for your reference as you provide related responses for this Fellowship application. If you wish to change the answer to the item shown below, please do so on the Research & Related Other Project Information form; you will not be able to edit the response here.

Are Vertebrate Animals Used? ☐ Yes ☒ No

13. * Vertebrate Animals Use Indefinite?	☐ Yes	☒ No		
14. Vertebrate Animals		Add Attachment	Delete Attachment	View Attachment
15. Select Agent Research	B15_SelectAgentResearch.pdf	Add Attachment	Delete Attachment	View Attachment
16. Resource Sharing Plan	B16_ResourceSharingPlans.pdf	Add Attachment	Delete Attachment	View Attachment
17. * Respective Contributions	B17_RespectiveContributions.pdf	Add Attachment	Delete Attachment	View Attachment
18. * Selection of Sponsor and Institution	B18_SelectionSponsorInst.pdf	Add Attachment	Delete Attachment	View Attachment
19. * Responsible Conduct of Research	B19_ResponsibleConductResearch.pdf	Add Attachment	Delete Attachment	View Attachment

PHS Fellowship Supplemental Form

C. Additional Information

Human Embryonic Stem Cells

1. * Does the proposed project involve human embryonic stem cells? ☐ Yes ☒ No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s), using the registry information provided within the agency instructions. Or, if a specific stem cell line cannot be referenced at this time, please check the box indicating that one from the Registry will be used:

☐ Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s):

Fellowship Applicant

2. Alternate Phone Number: 650-799-5715

3. Degree Sought During Proposed Award:

Degree:	If "other", please indicate degree type:	Expected Completion Date (month/year):	
			Reset Entry

4. * Field of Training for Current Proposal: 2830 Cognitive neuroscience

5. * Current Or Prior Kirschstein-NRSA Support? ☒ Yes ☐ No

If yes, please identify current and prior Kirschstein-NRSA support below:

* Level	* Type	Start Date *(if known)*	End Date *(if known)*	Grant Number *(if known)*	
Predoctoral	Individual	01/01/2008	09/30/2010	F31AG032804	Reset Entry

6. * Applications for Concurrent Support? ☐ Yes ☒ No

If yes, please describe in an attached file: Add Attachment | Delete Attachment | View Attachment

7. * Goals for Fellowship Training and Career: C7_GoalsTrainingCareer.pdf — Add Attachment | Delete Attachment | View Attachment

8. * Activities Planned Under This Award: C8_ActivitiesPlanned.pdf — Add Attachment | Delete Attachment | View Attachment

9. Doctoral Dissertation and Other Research Experience: C9_DocDissOtherResearch.pdf — Add Attachment | Delete Attachment | View Attachment

10. * Citizenship:
- ☒ U.S. Citizen or noncitizen national
- ☐ Permanent Resident of U.S. Pending
- ☐ Permanent Resident of U.S. *(If a permanent resident of the U.S., a notarized statement must be provided by the time of award)*
- ☐ Non-U.S. Citizen with temporary U.S. visa

Tracking Number:GRANT10572775 Funding Opportunity Number:PA-10-110 Received Date:2010-04-05T11:39:21-04:00

PHS Fellowship Supplemental Form

C. Additional Information (continued)

Institution

11. ☐ Change of Sponsoring Institution

Name of Former Institution:

D. Budget

All Fellowship Applicants:

1. * Tuition and Fees:

☒ None Requested ☐ Funds Requested:

Year 1	
Year 2	
Year 3	
Year 4	
Year 5	
Year 6 *(when applicable)*	
Total Funds Requested:	

Senior Fellowship Applicants Only:

2. Present Institutional Base Salary: Amount | Academic Period | Number of Months | Reset Entry

3. Stipends/Salary During First Year of Proposed Fellowship:

a. Federal Stipend Requested: Amount | Number of Months

b. Supplementation from other sources: Amount | Number of Months

Type (sabbatical leave, salary, etc.)

Source

E. Appendix

Add Attachments | Delete Attachments | View Attachments

Tracking Number:GRANT10572775 Funding Opportunity Number:PA-10-110 Received Date:2010-04-05T11:39:21-04:00

SPECIFIC AIMS

The primary goal of the research proposed in this training plan is to develop and refine novel methods for imaging the human reward system across the adult life span by combining emerging techniques in PET and MRI. Conducting this mentored research will provide the applicant with the necessary skills to successfully implement these techniques in more extensive and focused studies of human aging in the future.

Aim 1: Optimize techniques for structural and functional measurement of individual subregions in the adult midbrain using high-resolution and ultra high field strength (7-Tesla) MRI

Recent studies by the applicant have linked age-related deficits in the functioning of striatal regions to impairments in value-based learning and decision making. fMRI data have identified an age-related decline in the representation of prediction errors throughout the striatum and medial prefrontal cortex. Previous animal work has suggested that dopamine (DA) nuclei in the midbrain play a central role in the computation of prediction error and communicate these signals to striatal and cortical regions. Thus, what appear to be striatal deficits may be the result of deeper dysfunction in the midbrain. Recent attempts to image the midbrain in humans with standard imaging techniques have not succeeded in structurally and functionally dissociating contributions from individual midbrain nuclei, which have quite disparate anatomical projections. Thus, the individual contributions of these subregions can be better understood if the distinct functional contributions of these structures can be individually resolved. In Study 1 we will further optimize techniques for structural and functional measurement of individual nuclei in the adult midbrain using high-resolution and ultra high field strength 7T MRI.

Aim 2: Combine [^{18}F]fallypride PET and functional MRI to characterize associations between DA receptor availability and aspects of reward processing and behavioral control in healthy adults

Although a number of emerging studies have linked individual measures of reward sensitivity and cognitive ability and control to individual differences in the DA system using behavioral genetics, very few studies provide direct measures of DA function. Further, prior studies have not attempted to collect (or at least reported collecting) a comprehensive set of individual difference measures of both reward processing and behavioral control to isolate shared or independent contributions from specific subregions of the reward system. This integrative approach has the potential to not only lead to a more refined understanding of the reward system but also has the potential to more precisely pinpoint potential sources of abnormality in the neural processing stream and provide focused targets for future interventions. In Study 2 we will collect a wide range of behavioral and neural measures hypothesized to be both age and DA sensitive to more precisely isolate the individual contributions of DA function using radioligand PET across substructures of the reward system to specific aspects of reward processing and behavioral control.

Aim 3: Integrate both structural (MRI) and functional (radioligand PET, fMRI) brain imaging measures to investigate the influence of age-related changes from young adulthood to middle age

A growing body of research suggests that age-related decline in both basic cognitive abilities and a number of brain regions progresses linearly from young adulthood (20s) to older age (80s). However, it is currently rare for researchers in the aging field to combine structural and functional measures to examine age-related change across a wide range of behaviors. Further, measurement of individual differences in young adulthood and middle age may facilitate eventual identification of markers of abnormal decline and provide targets for early intervention. In Study 3 we will integrate behavioral, structural, and functional measures collected in Study 2 to explore how the relationships between the different neural measures and between the neural and behavioral measures may change with age. We will address whether the age effects are linear for both morphometry (grey matter density and volume) and dopamine binding potential, whether the correlation between these measures changes with age, and whether these measures make shared or independent contributions to performance on cognitive and behavioral measures.

RESEARCH STRATEGY

Significance

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 understand the processes underlying value-based learning and decision making across the adult life span.

A wealth of data indicates that, across the life span, value-based learning and decision making are mediated by a core network of brain regions supporting reward processing. This reward system is composed of an interconnected network of structures in the midbrain, striatum, and prefrontal cortex [1] (Fig. 1A). In the midbrain, the substantia nigra (SN) and ventral tegmental area (VTA) serve as the core source of dopamine (DA) for the striatum and other cortical and subcortical regions. The key structures in the striatum are the nucleus accumbens (NAcc), caudate, and putamen. A variety of regions across the frontal cortex play a role in reward processing including the orbitofrontal cortex (OFC), medial prefrontal cortex (MPFC), and cingulate. Additionally, more lateral frontal regions like the ventrolateral (VLPFC) and dorsolateral (DLPFC) prefrontal cortices play an important role in regulating these reward circuits. Knowledge about the anatomical connections of these regions was largely drawn from early studies in non-human primates [2], but the connectivity of these circuits has recently been replicated in humans using diffusion tensor imaging [3, 4] (Fig. 1B).

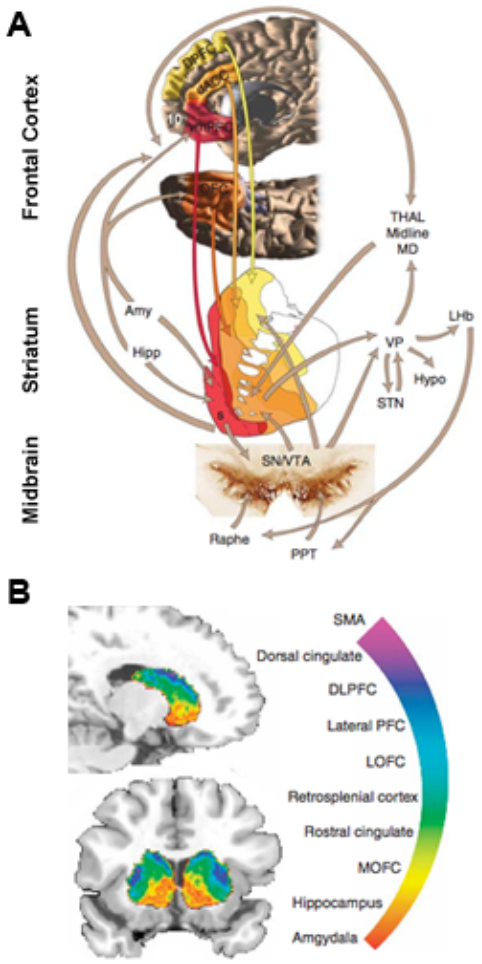

Figure 1. (A) The reward system as illustrated by Haber and Knutson [1]. (B) Connectivity between striatal and extrastriatal regions [3].

In general, very little research has focused on age-related change in this reward network. In fact almost half of the published neuroscience research in this area was collected as part of the applicant's dissertation work. Recent studies by the applicant suggest that although younger and older adults show similar mesolimbic representation of the discrete values of reward outcomes [5, 6], older adults in some situations show deficits in feedback-driven probabilistic reinforcement learning [5, 7, 8]. One particular study [8] (supported by pre-doctoral NRSA F31-AG032804) sought to further clarify the potential mechanism underlying age-related changes in probabilistic reward learning [9, 10]. Using a reinforcement learning model (Rescorla-Wagner) [11-13], we observed age-related declines in behavioral learning rates ($p < .01$) and in the neural representation of prediction errors at feedback throughout the striatum (putamen and NAcc) and MPFC ($p < .005$) (Fig. 2). The study suggests that learning impairments may be due to age-related changes in relative coding, which relies on the comparison of explicit values at feedback to current estimates of expected value for the chosen cue. Previous studies in both human and non-human primates have revealed that this computation relies primarily on communication between dopaminergic nuclei in the midbrain and frontostriatal regions [14-16]. Thus, it is possible that this deficit is due to age-related decline in the DA reward system. What appear to be striatal and cortical deficits may be the result of deeper dysfunction in the midbrain or elsewhere in the reward system. However, the studies collected for the applicant's dissertation were limited to standard resolution whole brain fMRI. Thus, these particular studies cannot directly speak to the possible role of age-related DA changes in relative coding.

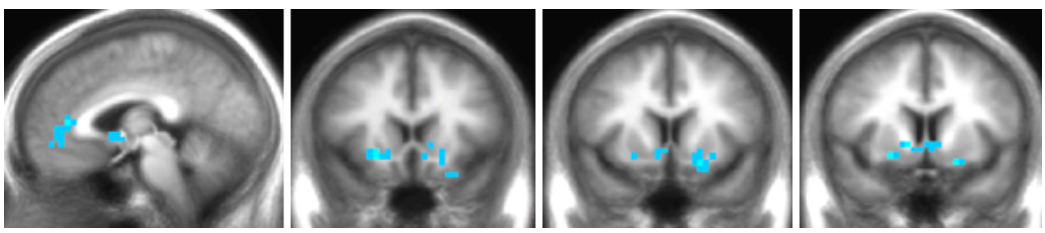

Figure 2. Age-related decline in prediction error signal at feedback in the MPFC and throughout the striatum during probabilistic reward learning ($p < .005$).

In general, commonly used whole brain human imaging techniques are not optimized for focused study of individual nuclei in the reward circuit. Although recent studies in healthy young adults have provided preliminary evidence that BOLD activity in the DA nuclei of the midbrain (SN, VTA) correlates with positive prediction errors and ventral striatal BOLD activity [17] and novelty [18], the imaging protocols used in these studies were not able to structurally or functionally dissociate contributions from the SN and VTA. Likewise, prior studies of age differences have been unable to make specific and separate age-related comparisons of volume in these regions in humans [19]. The SN and VTA have quite disparate dopaminergic projections to dorsal and ventral aspects of the striatum, respectively. Thus, dissociating the individual contributions of the VTA and SN can be better understood if the distinct functional contributions of these structures can be individually resolved. Although a number of theoretical accounts link DA function with age-related cognitive decline [20-22], few studies have attempted to directly measure changes in DA function across the adult life span. Previous PET studies of aging have focused almost exclusively on DA function in striatal regions [23-27] and have only explored relationships between DA and a very limited set of basic cognitive skills [23, 25]. While these studies indicate that D2-like receptor availability declines with age in the striatum, this provides only a partial picture of age related changes in the reward system.

New brain imaging techniques using magnetic resonance imaging (MRI) and positron emission tomography (PET) have the potential to address these limitations when applied to in vivo human neuroimaging across the life span [28]. The majority of fMRI studies are currently being conducted on 1.5T or 3T scanners with protocols limited in sensitivity and signal-to-noise (SNR) ratios. The recent availability of ultra high field strength 7-Tesla (7T) MRI scanners allows for more focused visualization of structures (as small as 700μm) and increased SNR across the brain [29]. The SNR at 7T is approximately 2.33 times higher than the SNR acquired in a similar voxel at 3T. The use of high-resolution protocols (i.e., slice prescriptions that selectively measure a subsection of the brain) at ultra high field strength has the potential to both structurally and functionally dissociate individual nuclei in the reward system. Using radioligand PET, the availability of [^{18}F]fallypride allows for diffuse measurement of DA receptor availability. Unlike other D2/D3 ligands, [^{18}F]fallypride allows stable estimates of D2-like binding in both striatal and extrastriatal (e.g., midbrain, frontal cortical) regions [30-34] (Fig. 3) suitable for individual difference analyses [35, 36]. Combining these emerging MRI and PET techniques allows for previously unavailable in-depth measurement of the human reward system across the life span.

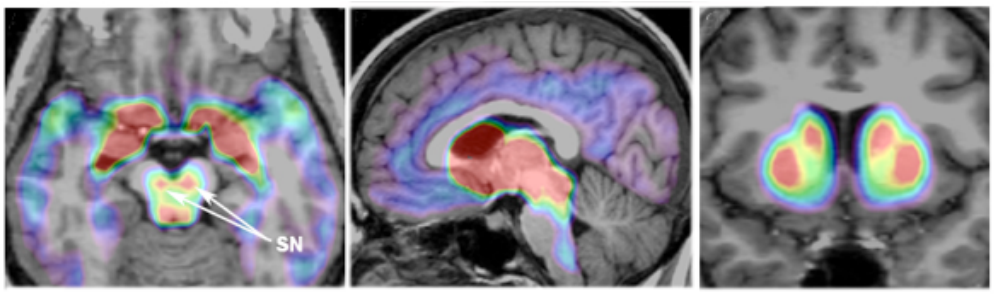

Figure 3. [^{18}F]fallypride binding potential (BP) in the substantia nigra (left), cingulate and OFC (center), and striatum (right). The color scale was adjusted in the striatum for overall higher levels of BP.

When imaging the aging brain it is extremely important to address age differences in morphometry. Aside from common issues that arise with BOLD fMRI as recently summarized in a review by the applicant [37], 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 binding potential could be partially a consequence of changes in grey matter volume or density rather than a specific D2 deficit. Additionally, direct morphometric measures can be used as structural indices of neural decline [38-40]. However, few studies combine structural and receptor imaging measures [41]. There are currently no prior aging papers combining structural measures with PET measures of DA function across the brain.

The combination of high resolution imaging of the midbrain and the use of [^{18}F]fallypride to measure both striatal and extrastriatal receptor availability will significantly expand the existing knowledge of age-related changes across the reward system beyond the striatum alone. Further, assessing relationships between DA function across the brain and a wider variety of psychological processes like reward processing and behavioral control has the potential for tremendous impact in the field. Specifically, combining these techniques has the potential to more precisely pinpoint potential sources of error in the neural processing stream and provide focused targets for future interventions.

Innovation: The present proposal is innovative in its multimodal imaging approach to studying age-related change. Within the cognitive neuroscience of aging community it is common for researchers to focus primarily

on either structural or functional measures. Unfortunately, very few researchers are currently taking advantage of ultra high field strength MR scanners and even fewer researchers are combining PET and MRI techniques. These limitations are primarily because scientists have traditionally been trained in one technique or the other, but not both. Additionally, very few research institutions have existing and active collaborative research programs that combine MRI and PET imaging centers. These are critical barriers to progress in this field. The proposed research training plan provides a rare opportunity for the applicant to learn to combine all of these techniques for more comprehensive study of the human reward system across the adult life span.

Approach

The main objective of this research plan is to further develop novel methods for imaging the human reward system across the adult life span by combining new techniques in PET and MRI. Three studies will focus on training the applicant to use these imaging protocols on subjects in the earlier stages of adult development with the future goal of extending this work into later stages of healthy aging. To facilitate this later transition, the studies here will not only train the applicant to conduct more in-depth studies of core reward systems in the midbrain and striatum (Studies 1–3), but also will expand the conceptual focus of the applicant's research by using experimental tasks that focus on interactions between these subcortical systems (for which there is currently very little age-related research) and prefrontal systems known to decline with age (Studies 2 & 3). The proposed timeline will be from Dec 2010 – Jun 2012 for Study 1, Oct 2011 – Sep 2013 for Study 2, and Jan 2013 – Nov 2013 for Study 3. We provide evidence of the feasibility of these approaches below.

Preliminary Study 1: Developing structural and functional protocols for high resolution midbrain imaging

The sponsor, Dr. David Zald, has recently initiated a collaborative project with Dr. John Gore with the goal of developing both structural and functional protocols for imaging the human midbrain at 7T. The first phase of this project included the initial optimization of the structural scan protocol using a hybrid sequence with a combination of gradient and spin echo (GRASE) sequences in which multiple images are obtained during a single echo [42, 43]. Twelve oblique axial slices were positioned with the base of the slab aligned to the top of the pons allowing for complete coverage of the SN and VTA. This optimized T2-weighted GRASE sequence produces striking images with a high level of contrast for detailed visualization of dopaminergic structures in the midbrain with neuromelanin like the SN (Fig. 4). The applicant has started collaborating on optimizing the functional protocols. A fast field echo sequence (FFE [44]) with 12 oblique axial slices was used for the functional runs. A task that was developed by the applicant's dissertation advisor, the monetary incentive delay task, was programmed by the applicant and has been used for initial testing of this pulse sequence. In this task subjects view cues indicating the potential for rewards of varying magnitude ($0, $1, $5), wait for a variable delay, and, if they respond quickly enough to a target, receive the amount of money cued at the beginning of the trial. Because accuracy is manipulated in the task (via a distribution of target reaction times that dynamically adjust in individual participants), subjects learn to expect that they will successfully hit the target on 66% of trials. Receiving the money cue during feedback produces a positive prediction error. In one pilot subject we have demonstrated our ability to observe positive prediction errors in the SN and VTA (Fig. 4).

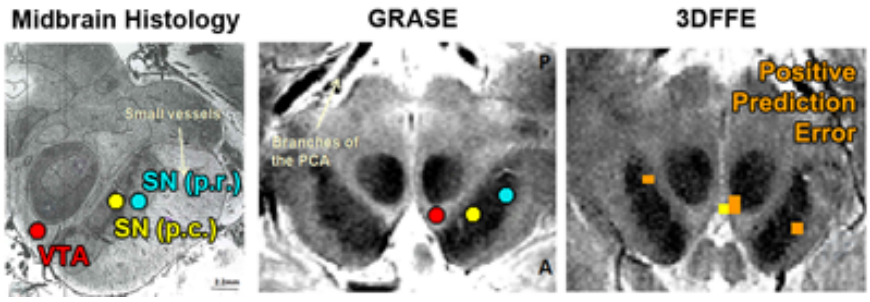

Figure 4. Midbrain histology with VTA and SN (p.r. = pars reticulata; p.c. = pars compacta) labeled (left). VTA and SN in a single subject's GRASE anatomical sequence at 7T (center). Functional activity (collected with an FFE sequence) correlates with positive prediction errors in the VTA and SN ($p < .01$) (right).

Although further optimization is ongoing, these data demonstrate the feasibility of high resolution imaging of the midbrain at 7T.

Preliminary Study 2: Age-related decline in DA binding potential during early stages of adult development

Over the past 5 years, the Zald Lab (supported by NIDA grant R01-DA019670) has collected measures of DA binding potential (BP) using [^{18}F]fallypride PET from a relatively large number of healthy adults. Most of these studies focus on young adults, but a group of 34 subjects with a broader age range of 18-43 were including in one study. This sample is limited to the first half of the adult life span, but the range allows for

examination of age differences in BP. Initial regression analyses reveal suggestive linear age-related declines in the lateral frontal cortex and parts of the striatum and globus pallidus (Fig. 5), consistent with the theory that frontostriatal decline is prominent in healthy aging [45-47]. Previous research suggests age-related declines in both basic cognitive abilities [48] and volume in a number of brain regions [40] are linear from young adulthood (20s) to older age (80s). These preliminary analyses demonstrate the ability to observe linear age effects even at early stages of adult development.

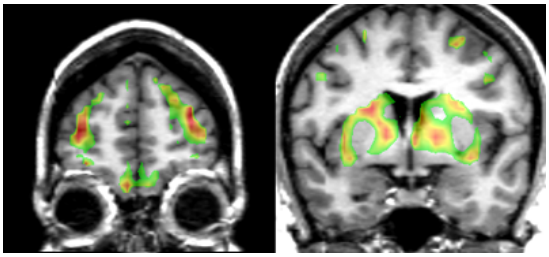

Figure 5. Age-related decline in DA BP from age 18 to 43 (areas in red: $r < -.50$, $p < 0.002$; areas in green: $r < -.34$, $p < 0.05$).

RESEARCH DESIGN AND METHODS

Study 1: High resolution MR imaging of the human midbrain at 7T

The goal of Study 1 is to further optimize techniques for structural and functional measurement of individual nuclei in the adult midbrain using high-resolution and ultra high field strength 7T MRI.

Participants and Behavioral Measures. 20 healthy adult participants (age 18–40) will be recruited to participate in the study. In additional to basic demographic measures all participants will complete a subset of the affective and cognitive individual difference measures described in detail in Study 2.

Modified Monetary Incentive Delay Task. The monetary incentive delay task [49], described above, provides a robust index of both reward anticipation and feedback. On each trial, individuals see a cue indicating the magnitude of the reward at stake on that trial. This is followed by a variable length delay, and a target, which has to be responded to quickly to obtain a reward. It is well demonstrated by Knutson, the applicant, the Zald Lab, and others that activity during anticipation and feedback is modulated by reward magnitude in the striatum and MPFC [6, 35, 49-52]. Because we are focused here on the midbrain, we have modified the task such that rewards in the outcome phase can be more or less than the amount displayed in the cue, allowing for more variable (and unexpected) positive and negative prediction errors. Participants will complete four 6-minute runs of this task.

7T MR Image Acquisition and Analysis. Anatomical images will be collected using a GRASE sequence with twelve oblique axial slices (voxel size: 1.33mm isotropic) positioned with the base of the slab aligned to the top of the pons (Fig. 6). As mentioned above in Preliminary Study 1, this optimized T2-weighted sequence produces images with a high level of contrast for visualization of dopaminergic structures in the midbrain. Functional imaging will be conducted with an FFE sequence (TR = 2000ms) using the same slice prescription as the GRASE. Although analyses will focus on midbrain nuclei, the oblique position of this slice prescription provides adequate coverage of the SN and VTA while also acquiring data in the nucleus accumbens [17]. We also plan to experiment with imaging other regions of the striatum and ventral frontal cortex but are not explicitly proposing to do so here due to technical issues with signal dropout that still need to be resolved.

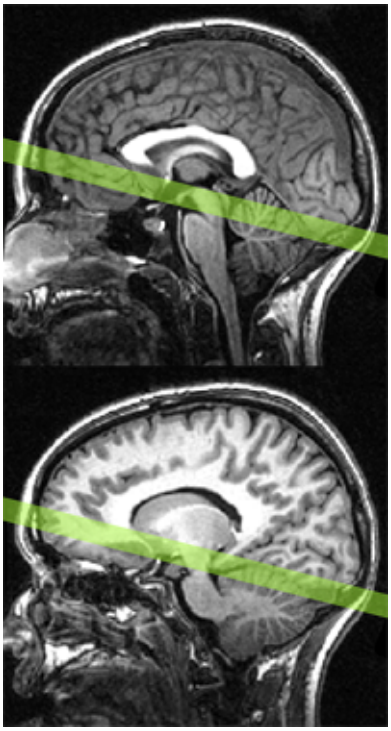

Figure 6. High resolution midbrain slice prescription

All analyses will be conducted using AFNI. Standard preprocessing will include slice timing correction, motion correction, high-pass filtering, and computation of percent signal change. Coregistration of structural and functional images will be performed manually in AFNI. Regions of interest will be hand drawn in individual subjects and group analyses will use these individualized estimates. The co-sponsor, Dr. McClure, and collaborator Dr. Gore (see Appendix for letter of support) will work with the trainee to address a number of barriers to successful imaging of the midbrain including pulsatile artifacts, signal artifacts, geometric distortions, static field inhomogeneities, and noise levels using a combination of array coils and dynamic shimming [53]. We will regress out physiological noise due to heart rate and respiration using RETROICOR. Cardiac and respiratory monitoring will be simultaneously recorded using a photoplethysmograph and pneumatic belt. Regression models will examine the relationship between the representation of prediction error and BOLD signal in the SN and VTA. Based on an expected fMRI effect size of ~0.5% signal change in the BOLD contrast (based on pilot data), 12

subjects is the minimum necessary to achieve greater than 80% power at the single voxel level for an alpha of .05 [54]. Due to the high likelihood of subject exclusion due to motion artifacts when imaging this region, 20 subjects will be recruited to maximize power.

Structurally, we will delineate the VTA and SN and provide volume estimates for each region. After the protocols are optimized through this research training plan, the applicant plans to extend this work and conduct these analyses at later stages of adult development. Functionally, in this study we expect to precisely localize positive prediction errors in the VTA and SN.

It is important to acknowledge here that the BOLD signal in these regions is not a pure measure of DA firing. There are potential contributions to the BOLD signal from acetylcholine and glutamate. In general, we are not claiming that these signals in the SN and VTA are purely dopaminergic. We are merely trying to more accurately measure signals in these core structures of the reward system, in order to be able to specifically measure midbrain activity during reward learning and decision making in aging in the future.

Study 2: Examining the relationship between DA receptor availability and aspects of reward processing and behavioral control

The goal of study 2 is to combine [^{18}F]fallypride PET and functional MRI to characterize associations between DA receptor availability and aspects of reward processing and behavioral control in healthy adults.

Participants. 30 medically and neuropsychiatrically healthy young adult participants (age 18–40) who have been recruited to participate in an ongoing study in the Zald Lab (supported by R01-DA019670) will participate in the study. Following initial screening, subjects will be given an interview of their medical history and the study psychiatrist will administer a physical examination. A complete blood count (CBC), comprehensive metabolic panel (CMP), urine analysis, and an EKG will be performed to ensure that the each subject meets all medical inclusion criteria.

Behavioral Measures. All subjects will complete a cognitive battery including measures of working memory (2-back task), the Stroop task [55], the Wechsler Memory Scale (WMS-III [56]), measures of speed of processing (WAIS-III Digit Symbol Coding and Symbol Search [57]), and two measures of motor speed [58]. All tasks were included based on literature indicating that many of these functions both decline with age [20, 46-48, 59] and are modulated by DA [60, 61].

Subjects will complete 3 experimental tasks while undergoing fMRI. Tasks were selected that range from basic reward processing (modified monetary incentive delay task) to attentional and inhibitory control (flanker go/nogo) to the integration of reward processing and behavioral control (temporal discounting). *Modified Monetary Incentive Delay Task*. The modified monetary incentive delay task described above in Study 1 will also be included in Study 2. Participants will complete two 6-minute runs of this task. *Flanker Go/Nogo*. The Flanker Go/Nogo task [62] assesses both classic Eriksen flanker effects involving the ability to ignore incongruent information [63], and the ability to inhibit prepotent go responses. We selected this task rather than a simple go/nogo task because it provides additional information about anterior cingulate function (an area where D2 BP correlates with impulsivity). On each trial, subjects will be instructed to focus on an array of five stimuli that will include a central target arrow pointing left or right. The target arrow will be flanked by two stimuli (arrows, squares or X's) on either side. Subjects will be instructed to press a button corresponding to the direction of the center arrow. A total of 145 stimuli (no go: 32; neutral: 32; incongruent: 40; congruent: 40) will be randomly presented over two 5-minute runs. We will contrast BOLD signal during no-go versus congruent conditions to examine brain activity related to response inhibition, and during incongruent versus congruent trials to examine activity related to interference monitoring and suppression. *Temporal Discounting*. The temporal discounting paradigm is taken directly from previous work [64] by the co-sponsor, Samuel McClure. On each trial participants choose between an early reward and a late reward. The magnitude of the early reward is 1% to 50% less than the late reward (max = $40). Participants will complete approximately 50 trials, over two 7-minute blocks. Participants are told that at random two of their choices will be selected for payout at the appropriate time (today, 2 weeks, 1 month, 2 months) depending upon their choices. We will contrast BOLD signal during trials in which an immediate choice is available to trials in which only delayed choices are available to identify regions sensitive to immediacy and delay.

MR Image Acquisition and Analysis. All MR imaging will be performed on a Phillips 3T Scanner. In order to provide consistent coverage across the brain, for Study 2 we will use the 3T rather than 7T scanner (because currently the 3T has less distortion in whole brain studies). T1-weighted images will be collected for structural normalization and ROI definition. T2-weighted and T2-Flair scans will be collected to rule out neuropathology. Prior to functional scanning higher order shimming and a field map will be collected to minimize inhomogeneity and allow retrospective distortion correction. Thirty-three 3.5 mm thick (.1 mm skip) axial oblique slices will be

collected (TE=25ms, TR=2000ms, Flip=90, 80 x 80 matrix, SENSE factor 1.6), with slices covering the midbrain through the cingulate. Images will be preprocessed in AFNI. Functional images will be slice-time corrected, motion corrected, corrected for susceptibility-X-movement-related distortions in the EPI images, coregistered to the anatomical images, spatially normalized, resampled into 2mm isotropic voxels, spatially smoothed, and high-pass filtered.

PET Image Acquisition and Analysis. All PET images will be acquired using [^{18}F]fallypride. [^{18}F]fallypride ((S)-N-[(1-allyl-2-pyrrolidinyl)methyl]-5-(3-18F-fluoropropyl)-2,3-dimethoxybenzamide) is a substituted benzamide with very high affinity to D2/D3 receptors [65]. Protocols for PET image acquisition and analysis are derived from a larger ongoing study and have been previously published [36, 66-68]. All PET scans will be acquired on a GE Discovery PET/CT scanner with axial resolution of 4 mm, and in-plane resolution of 4.5–5.5 mm FWHM at the center of the field of view. [^{18}F]fallypride will be produced in the radiochemistry laboratory attached to the PET unit, following synthesis and quality control procedures described in IND 47,245. 3-D emission acquisitions and transmission attenuation correction scans are performed following a 5.0 mCi slow bolus injection of [^{18}F]fallypride (specific activity greater than 3000 Ci/mmol). Serial scans are started simultaneously with the bolus injection of [^{18}F]fallypride and are obtained for approximately 3.5 hours, with two 15-minute breaks for subject comfort. Each subject's serial PET scans will first be corrected for motion and then co-registered to each other and a structural MR image using a mutual information rigid body algorithm [69]. Regional D2/D3 BP (nondisplaceable) will be calculated using the reference region method [70, 71], with cerebellum chosen as the reference region because of its relative lack of D2/D3 receptors [72]. Group-level and individual difference analyses of PET data will be conducted using both region of interest (ROI) and statistical parametric mapping approaches. With an estimate of r = .5 for the average correlation between PET data and measures of reward sensitivity and behavioral control (based on pilot data collected in the Zald Lab), 30 subjects will provide excellent power of .9 for a one-tailed test, and power of .81 for a two-tailed test.

Overall we predict that individual differences in midbrain and striatal BP and BOLD activity will be correlated primarily with measures of reward sensitivity whereas cortical BP and BOLD activity will be correlated primarily with various aspects of behavioral control. For example, we expect midbrain BP to be more strongly correlated with prediction error-related BOLD signal in the modified MID task. We expect striatal BP to be more strongly correlated with measures of processing speed, BOLD measures of reward magnitude in the modified MID task [35], and behavioral and BOLD responses to immediacy in the discounting task. We expect cingulate BP to be more strongly correlated with behavioral and BOLD measures of interference suppression in the flanker/go-nogo, and lateral prefrontal BP to be more strongly correlated with behavioral measures of working memory, behavioral and BOLD measures of response inhibition in the flanker/go-nogo, and willingness to delay rewards in the discounting task. Although Study 2 will focus on relationships between behavioral and neural measures, all of the experimental tasks used here are expected to change with age.

Study 3: Morphometric, dopaminergic, and behavioral changes from young adulthood to middle-age

The goal of Study 3 is to explore age-related change in behavioral, structural, and functional measures collected in Study 2.

Participants and Measures. Data from the 30 healthy adult subjects (ages 18–40) from Study 2 will be used here to explore age effects. Additionally, control subjects from related studies in the Zald lab (supported by other grants but with overlapping measures) may be included for a more uniform and protracted age range with the potential to extend from age 18 to 50.

Analysis Methods. PET and MR data will be collected and analyzed as described in Study 2. We will focus on identifying age effects using integrated approaches recently developed in the Zald Lab to examine relationships between gray matter volume and density across the brain using voxel based morphometry (VBM) and DA BP [73]. The specific VBM techniques used will be slightly modified based on optimization methods (which approximate the accuracy of manual tracing) for accurate measurement across the adult life span [74]. In the planned PET analyses we will manually define regions of interest in the midbrain and striatum and automatically define regions in cortex using methods developed for adults of various ages [75] by consultant William Jagust (see Appendix for letter of support). Consistent with pilot analyses reported in Preliminary Study 2, we expect to observe approximately linear effects of age across the 20s and 30s and hypothesize that a combination of gray matter density and DA function will be a better predictor of basic cognitive ability than gray matter density or volume alone. This study will address whether the age effects are linear for both morphometry (grey matter density and volume) and DA BP, whether the correlation between these measures changes with age, and whether these measures make shared or independent contributions to performance on cognitive and behavioral measures.

PROTECTION OF HUMAN SUBJECTS

1. Risks to the Subjects

a. Human Subjects Involvement, Characteristics & Design

Up to 150 participants will be recruited and screened for this study with the aim of running 30 participants through the PET and 3T fMRI scanning protocol and 20 participants through the high-resolution 7T fMRI protocol. Only subjects who are medically healthy with no significant psychiatric or neurological history and no or minimal history of psychostimulant drug use (not including caffeine) are eligible for this study.

Inclusion criteria: Medically and psychiatrically healthy, estimated IQ greater than 80.

Exclusion criteria: For both MRI and PET studies, 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, metallic body inclusions or other metal implanted in the body, pregnancy, anemia, or hematocrit below 34. Subjects are additionally excluded if they have participated in any research studies in the past year that involve radiation, or if they are exposed to radiation on a routine basis due to their occupation. For PET studies, history of substance abuse, current tobacco use, alcohol intake greater than 8 ounces of whiskey or equivalent per week, any psychotropic medication for the past 6 months (other than occasional use of benzodiazepines for sleep), history of psychiatric illness, significant medical condition, and high blood pressure (Systolic B.P. > 135, Diastolic B.P. > 85).

Recruitment procedures: Healthy participants will be recruited from the Department of Psychology online Research Subject Pool (http://vanderbilt.sona-systems.com). Paid studies are listed on the website, and any individual meeting pre-screening criteria (age, free of self-reported psychiatric problems, imaging contraindicators or history of head trauma) can view the study and contact the research assistant to participate. The Zald lab has been using this mechanism for approximately 6–7 years, and found it to be a highly effective recruitment tool. As of March 1, 2010, there are 1085 registered users interested in participating in paid studies.

b. Sources of Materials

Subjects provide the following specimens and data: self-report of mood, personality, medical, and psychiatric history. For PET studies blood samples for metabolic assessment (CMP), and complete blood count (CBC) are performed both at baseline to determine eligibility and before and after each PET scan. Women provide additional blood samples to ensure they are not pregnant prior to every PET scan. The subjects additionally provide data from 2 PET scans, as well as structural and functional MRI scan data, neuropsychological data, and vital signs. All data is solely collected for research purposes only.

Confidentiality protections: Only members of the Zald lab, and the collaborating faculty at Vanderbilt University and Stanford University (Dr. McClure) have access to participant data, with the following exceptions: blood work processed by the Vanderbilt Clinical Laboratory, are accessible on the Vanderbilt University Medical System computer record system, which can only be accessed by Medical Center personnel with approved access to the system. Paper and pencil data will be stored in a locked file cabinet in Dr. Zald's lab, with duplicate copies of scanning protocol records in Dr. Kessler's office as he is the IND holder for [^{18}F]fallypride. Digital information is stored on password-controlled computers in the Zald laboratory. For ease of access Digital information may additionally be kept on the password protected RedCap (Research Electronic Data Capture) system. REDCap is a secure, web-based application designed exclusively to support data collected for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. The REDCap project (http://project-redcap.org/) was initiated at Vanderbilt University and includes more than 70 active institutional partners. Only members of the Zald lab and the co-investigators will have passwords to the study database.

Wherever possible stored data will only be labeled with an ID number (and not the patient's name or medical record number). Dr. Zald's lab will maintain a password protected spreadsheet that links the subject ID # with name and medical record number, but this will be kept separate from all other relevant data. The Vanderbilt University Institute for Imaging Science maintains a log linking participants' names with their scan ID, but once removed from the VUIIS system, only the Zald lab has access to the original imaging data which is stored only with the subject's ID number.

c. Potential Risks

The possible risks are those associated with the administration of a radiopharmaceutical, the discomfort associated with PET and MRI scanning, and transient psychological discomfort that may arise during medical examination or psychiatric interview.

Administration of radiopharmaceutical: Subjects in Study 2 are exposed to a radiopharmaceutical for up to two PET studies (analyses for the current project only utilize data from one of these studies). For subjects completing two [^{18}F]fallypride studies, the effective dose equivalent is 1180 millirem, which corresponds to the background radiation received in 2.6 years from the environment. Dosing at this level is well within FDA guidelines, and large-scale studies of the long-term risk of radiation exposure (within FDA limits) have shown no increase in cancer rates associated with this amount of exposure. However, because radiation exposure is cumulative, potential subjects who have received radiation exposure as part of other recent research studies, and individuals who work around radiation are excluded.

[^{18}F]fallypride is an investigational drug, and therefore has not received broad clinical testing. However, it has been approved for investigational usage, based on FDA requirements. [^{18}F]fallypride is produced and administered at Vanderbilt using sterile procedures with quality control checks performed to insure purity and sterility. [^{18}F]fallypride is injected at subpharmaceutical doses. Dr. Zald in collaboration with Dr. Robert Kessler, M.D., who holds the IND for [^{18}F]fallypride have now performed over 100 [^{18}F]fallypride PET studies and have seen no laboratory abnormalities from administration of this radiopharmaceutical. Of participants administered [^{18}F]fallypride in the Zald Lab, only one has shown a potential side effect, vomiting - but medical review suggested that this was due to a hypoglycemic response triggered by fasting prior to study, rather than drug administration. An independent safety monitor is assigned to this project in order to review any potential adverse effects. A meeting is held with the independent safety monitor on an annual basis, and following any adverse event that is deemed moderate based on criteria laid out in the IRB protocol.

Discomforts associated with PET and MRI scanning: Discomforts associated with the PET and MRI studies include having to remain motionless for a prolonged period of time (up to 60 minutes), and the loud noise of the MR scanner. Subjects are given pillows to maximize their comfort, and ear plugs to lower the noise of the MR scanner. Some subjects may feel claustrophobic in the MRI scanner, but subjects with known claustrophobia are excluded from participation. There are no known risks of MR scanning at 3T or 7T for healthy individuals. However, these procedures can cause adverse effects in subjects with metal implants. Subjects with aneurysm clips, neural stimulators, possible metal fragments in the eyes, cardiac pacemakers, cochlear implants, artificial cardiac valves, iron based facial tattoos, and body piercings that are not removable are excluded from participation. For the 7T study specifically, the ultra high field strength can increase the chance that subjects experience minor peripheral nerve stimulation or slight dizziness when being moved into or out of the magnet. In pilot testing so far, we haven't had any complaints about dizziness, but have had subjects report occasional but non-painful slight muscle twitching in the back or shoulder.

Psychological Discomfort: Subjects may experience some embarrassment or psychological discomfort when answering interview questions about their psychiatric history, or in the case of women, when asked about pregnancy risk. Such responses are generally minimal, and are further minimized by informing them that the information is completely confidential. Some subjects may experience some mild performance anxiety during cognitive testing. However, this should be no more than is routinely experienced in other venues in which cognitive abilities are assessed. Individuals may also feel hungry because they are not allowed to eat for a period of approximately 5 hours as part of the [^{18}F]fallypride PET protocol.

Discomforts associated with blood draws: Discomforts include a risk of local bruising and discomfort associated with venipuncture for obtaining blood samples and placement of i.v. lines for the PET studies. A small amount of bleeding may occur when an i.v. line is inserted or removed. While there is the possibility of infection associated with venipuncture, this is very unlikely.

2. Adequacy of Protection Against Risks

a. Recruitment and Informed Consent

Participants are recruited through a web-based research scheduling system for paid research volunteers that is maintained by the Department of Psychological Sciences. Subjects are initially given a brief description of the study as part of a list of other paid research studies. They may click on a link to read the details of the study. If interested, they schedule an enrollment interview (or attend a screening session) at which time they are asked to read a complete written informed consent document approved by the Vanderbilt University Institutional Review Board. The procedures and risks, and all inclusion/exclusion criteria are orally reviewed with the participant and the participant is provided with a chance to ask questions before signing the informed consent. The researchers will question each potential participant to make sure that they have an understanding of the risks, especially those related to administration of [^{18}F]fallypride and MRI scanning. Subjects are not enrolled if there is a question regarding their understanding of these risks or their competence to provide informed consent. Only the PI, his research assistants and the primary co-investigators can enroll subjects.

b. Protection Against Risks

Screening for study inclusion/exclusion criteria: For the MRI only protocol (Study 1) subjects will complete MR safety screening forms both over the phone prior to scheduling and at the imaging center prior to entering the scanner. Medical interview/physical, complete blood count (CBC) and metabolite screening (CMP), psychiatric interview, pregnancy test, and physical including vital signs are used to rule out the presence of any medical, neurological or substance use issues that might lead to additional risk from exposure to radiation or MRI scanning for the combined PET and MRI protocols (Study 2). All lab procedures utilize standard sterile techniques.

Safety during MRI procedures: Participants complete a screen of potential contraindications for scanning, which is reviewed by the MRI technician prior to allowing the subject to enter the scanner suite. Subjects are questioned to ensure that they have no metal on their body (or in their body) before entering the scanner. Communication is maintained in case the subject becomes anxious or claustrophobic, and the subject may request to be withdrawn from the magnet. Headphones and earplugs are used to limit the sound of the magnet.

Safety of radiopharmaceutical administration. [^{18}F]Fallypride has been approved by the FDA for use as an investigational new drug (IND 47,245). The IND outlines strict quality control procedures for [^{18}F]fallypride production, and each run is checked for specific activity, purity, pH and sterility. Phase I and Phase 2 studies have been run with [^{18}F]fallypride. The Zald lab has run over 100 studies in humans at Vanderbilt with little evidence of any negative side effects. Radiation dosimetry is carefully monitored to ensure that dosing does not exceed that described in the protocol. An independent safety monitor is assigned to the study and any adverse responses are reviewed with him (see also section 5 below). Subjects are given a CBC and CMP after the [^{18}F]fallypride administration in order to monitor any potential reactions.

Confidentiality: 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. 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. 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.

3. Potential Benefits of the Proposed Research to the Subjects and Others

The benefit to the subject is a physical evaluation (for PET studies), financial compensation, and a picture of their brain. Although evaluations are not being performed for clinical purposes, any abnormalities that are detected will be reported to the patient, and if requested by the subject, their doctor. The primary benefit for others is the expansion of scientific knowledge about the human reward system.

4. Importance of Knowledge to be Gained

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 across the adult life span. This research will expand scientific understanding of processes underlying learning and decision making over the adult life span. The work has the potential to facilitate identification of markers for suboptimal decisions in adults in order to provide appropriate interventions.

5. Data and Safety Monitoring Plan

Investigational New Drug: This study involves an investigational new drug, [^{18}F]fallypride. We have FDA approval for use of [^{18}F]fallypride (IND # 47,245). An amendment to this IND will be submitted in order to increase the sample size, beyond the original proposed amount.

Monitoring: Subjects are followed for 4 hours post [^{18}F]fallypride administration. Monitoring includes a comprehensive metabolic panel, repeated monitoring of blood pressure, brief neurological screen, and a survey of potential side effects before discharge from the study. Subjects are additionally given telephone numbers to reach the study psychiatrist if they should develop any symptoms after being discharged from the study. Potential adverse effects are monitored and recorded for each subject in order to ensure their rapid detection and reporting. An independent safety monitor is assigned to this study. Dr. Richard Shelton, M.D, who is a board certified psychiatrist, currently serves as the independent data safety monitor for this study. Events that are deemed by the study M.D.s (Kessler, Cowan) as more than mild are discussed with the independent safety monitor within 48 hours of their occurrence. Otherwise, safety review of data is conducted annually with the data safety monitor. Adverse events are recorded as follows:

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

2) Moderate – Moderate side effects include events which may affect function and 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, do not respond to treatment, and do not resolve within hours.

Adverse events will be attributed to the study as follows:

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

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

Unrelated: The event occurs more than 96 hours after the end of the study and is more likely due to extraneous factors.

All serious adverse events will be reported to the Human Subjects IRB, NIH, FDA within 10 days by Drs. Zald and Kessler (who is PI on the IND). Annual reports of adverse events are made to the IRB and FDA.

INCLUSION OF WOMEN AND MINORITIES

We anticipate enrolling equal numbers of males and females into this study. Vanderbilt University is located in Nashville, Tennessee, which is an ethnically diverse city, with a significant African American population, and notable Latino/Hispanic population. The university is situated near several diverse neighborhoods. The Zald Lab's past experience in data collection indicates that many of our subjects come from the students or staff at Vanderbilt, based on advertisements, fliers, or word of mouth in the University community, and the demographics of our past studies have reflected the demographics of this population (see below for details).

Inclusion of women: Women are included in this research. However, women who are pregnant, breast feeding a child, or are currently attempting to get pregnant are excluded due to the clear risks to a fetus or newborn associated with radiation exposure. In order to minimize this risk, women participating in the study must take a pregnancy test prior to scanning, unless they have provided documentation of having undergone surgical procedures that have eliminated their child bearing potential.

Inclusion of minorities: There are no inclusion or exclusion criteria related to race or ethnicity. Minorities are encouraged to participate. We note that for reasons that are not entirely clear no Hispanic participants have completed PET scans in the Zald Lab, and few Hispanic/Latino subjects were screened for prior studies. The reason for this is unclear, as over half of the participants come from the Vanderbilt student community, of which 5% are Hispanic or Latino. While we will not specifically attempt to target Hispanic-Latino participants (or any other minority) during recruitment, given any situations where there are participants who qualify for the study, we will give scheduling preference to individuals of a Hispanic or Latino background. African Americans have made up approximately, 9% of the recent study population, and Asian Americans 11%, which is consistent of the demographics of the Vanderbilt and immediately surrounding communities.

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: Imaging the human reward system across the adult life span

Total Planned Enrollment: 50

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	23	23	46
Ethnic Category: Total of All Subjects *	25	25	50
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	3	3	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	19	19	38
Racial Categories: Total of All Subjects *	25	25	50

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

INCLUSION OF CHILDREN

We will not include anyone under the age of 18. The proposed studies focus on adult development. Additionally, children under this age are specifically *excluded* from the PET studies based on regulations prohibiting unnecessary radiation exposure in children.

SELECT AGENT RESEARCH

Not applicable.

RESOURCE SHARING PLANS

Not applicable.

RESPECTIVE CONTRIBUTIONS

This proposal is the product of a number of collaborative discussions between the applicant, the primary sponsor, Dr. David Zald, and the co-sponsor, Dr. Samuel McClure. The applicant developed the first draft of the proposal and subsequently made revisions according to suggestions from the sponsors.

SELECTION OF SPONSOR AND INSTITUTION

Over the past several years during my time in graduate school a new subfield, decision neuroscience, has emerged and is thriving. The field attempts to integrate basic neurobiological research with behavioral economics to not only uncover new insights about the functioning of the human brain but also produce results that have direct implications for improving human health and well being throughout the life course. The majority of the research on humans in this field speculates about the role that dopamine plays in learning and decision making. Surprisingly few researchers have the skills and access to the facilities to actually measure dopamine in the human brain. Dr. David Zald at Vanderbilt University is one of these rare researchers who is clearly pushing the boundaries by developing cutting edge and integrative techniques through collaborative research.

One of the primary reasons I decided to pursue a post-doctoral fellowship was to further expand my skill set before setting out on an independent research career in decision neuroscience. Clearly Dr. Zald is an obvious choice as a post-doctoral mentor. Zald is an established and respected researcher in affective neuroscience with a body of well-cited work on amygdala and orbitofrontal function, so we share a similar core of research interests in emotion and reward processing. However, Dr. Zald's clear strength has been in successfully integrating a variety of neuroscience methods. Integrative neuroscience research cannot be done without a team. I will greatly benefit from interaction with key members of this extended team, especially Dr. Kessler, the primary collaborator in the PET Center, and Dr. Gore, the director of the VUIIS. Zald has the breadth of knowledge necessary to communicate with a variety of scientists and has years of experience in successfully establishing collaborations both remotely (with the Montreal Neurological Institute) and locally (at Vanderbilt). He is a star role model for later developing similar integrative projects in own career. In the past year alone his innovative work combining PET and fMRI has produced publications in Nature Neuroscience and the Journal of Neuroscience (with a recent paper in revision at Science). The integration of this work with the high resolution midbrain imaging projects currently under development will allow for an unprecedented investigation of all aspects of the human reward system from deep in the individual midbrain nuclei through the loops of the striatum and cortex.

Dr. Zald has recently initiated a series of collaborative studies with Dr. Samuel McClure at Stanford University, a rising star in decision neuroscience with multiple publications in Science and a number of other top-tier journals. As Dr. McClure is a collaborator on the first two studies proposed in the research plan, he will serve as the co-sponsor. This has created a rare opportunity to work with two of my role models in the field. Dr. McClure was instrumental in a number of the early studies linking mesolimbic activation with prediction error signaling and has since produced high impact papers focusing on the neural systems coordinating intertemporal choice and recently on developing protocols for midbrain imaging at 3T. Additionally, McClure has the rare combination of a strong computational background, clear teaching ability, and endless patience. As a graduate student I enrolled in his reinforcement learning class and was highly appreciative of his natural ability to both clearly describe the concepts behind the models and teach anyone how to use them. I'm looking forward to the opportunity to further develop these skills under his supervision. A basic facility with computational modeling is becoming a necessary skill for a career in decision neuroscience. In addition to continued remote discussions with McClure, I plan to visit Stanford for several weeks each summer to work with the co-sponsor directly.

The rare combination of superb brain imaging facilities is another major reason I was specifically attracted to Vanderbilt University. There are very few active research dedicated 7T MRI scanners currently in use worldwide. The VUIIS houses new research-dedicated Phillips Intera Achieva 3T and 7T MRI scanners, which are state-of-the-art scanners with superior gradient performance and multi-channel head coils. There are currently fewer than 5 research groups in the country actively using [^{18}F]fallypride to measure both striatal and extra-striatal dopamine binding potential in humans. Dr. Zald's ongoing collaboration with radiology will allow for continued accumulation of PET data on healthy adult subjects. The PET Center is equipped with a recently installed GE Discovery Scanner with combined PET and CT capabilities, and a Siemens RDS 112/00 cyclotron for onsite isotope production. Vanderbilt is one of only a small number of institutions in the world to provide trainees with access to both PET imaging and MRI facilities. Collaborating faculty, Drs. Kessler and Gore, hold directorships in the PET and MRI centers, respectively, and are likewise in a position to ensure that I have access to and am fully supported in using these facilities.

In summary, pursuing postdoctoral training under the primary supervision of Dr. David Zald will provide me with the rare opportunity to collaborate with and learn from a diverse set of talented senior researchers and also take full advantage of the world class research facilities available at Vanderbilt University.

RESPONSIBLE CONDUCT OF RESEARCH

The studies completed during training will follow the standards for responsible conduct of research set by the National Institutes of Health and Vanderbilt University. As a graduate student the applicant participated in annual seminars and online courses on research ethics that emphasized the importance of ethical conduct by scientists and procedures for ensuring the welfare of human subjects (e.g., conflict of interest, adverse report handling, data handling, human subjects policies, the responsibilities of researchers, and the responsibilities of the institute as a whole). Throughout the fellowship period the applicant will maintain certification in Human Subject Research and HIPAA compliance (General Privacy Issues and Privacy Issues Relating to Research). Under the guidance of Dr. Zald, lab members meet regularly to discuss topics in responsible experimental design, data processing and presentation, recruitment and protection of research subjects, authorship and collaboration, and research misconduct.

GOALS FOR FELLOWSHIP TRAINING AND CAREER

A post-doctoral fellowship from the National Institute on Aging will support the next stage of directly mentored training on the path to becoming an independent psychological scientist. My long-term goal is to have a productive career as a researcher and educator in the field of human aging. I am driven by one primary underlying goal – to ease the cognitive strain and improve emotional and economic health in the daily lives of aging adults.

The results of studies I have recently completed as a graduate student at Stanford University have implications for age-related changes in dopamine function, however my current training has been limited to standard whole-brain resolution functional magnetic resonance imaging (fMRI). Thus, I am pursuing a post-doctoral fellowship under the primary supervision of Dr. David Zald at Vanderbilt University to expand my skill set dramatically through training in a number of new techniques currently being developed for imaging the human reward system.

The three primary goals I will pursue during the fellowship period will be to (1) extend my current expertise to include high-resolution and ultra-high field-strength fMRI of midbrain nuclei, (2) acquire new expertise in positron emission tomography (PET) radioligand binding methods and analysis techniques, and (3) acquire new expertise in utilizing MRI, fMRI, and PET images for the quantification of age-related structural and functional changes in the key structures of the human reward system.

This rare training opportunity will be invaluable not only when applying for faculty positions in the near future, but also throughout my career in my own research laboratory. After completion of a post-doctoral fellowship, my goal is to combine these new methods to not only more precisely quantify age-related change in the human dopamine system but also to investigate the implications of these changes throughout the adult life span. Building on my graduate training, the additional training I will receive as a post-doctoral fellow will provide me with the unique opportunity to utilize a comprehensive set of methodological tools to answer fundamental research questions about the aging reward system.

ACTIVITIES PLANNED UNDER THIS AWARD

As detailed in the Training Plan in Section II, training will focus primarily on learning new research methods, but will also include broadening the applicant's base of knowledge through directed reading, honing teaching and mentoring skills, and building grant writing skills. To not only appropriately train future students and fellows but also continue innovating novel techniques to image the human brain throughout his career, the applicant needs to develop a broader base of knowledge in neuropharmacology, cellular and molecular neuroscience, and MRI protocol development which will be supported by directed reading and research projects supervised by the sponsor, co-sponsor, and faculty collaborators. The majority of time will be spent obtaining hands-on experience with combining innovative fMRI and PET techniques. The research time allocated below includes study design, data collection, data processing and analysis, mentoring undergraduate and post-baccalaureate researchers, and preparing manuscripts for publication. These training activities are vital to ensuring the future success of the applicant's independent research career and the allocation of time among these activities is appropriate for a post-doctoral fellow in the final stages of mentored training.

ESTIMATED PERCENTAGE TIME BY YEAR

Year 1

75% Research

Study 1 subject recruitment, data collection & analysis, submit conference abstract (55%); Study 2 subject recruitment, begin data collection (15%); mentoring (5%)

15% Directed Reading / Coursework

Directed reading topics: Cellular Neuroscience, Biogenic Amines, Ultra High Field MR Imaging (5%); Graduate-level course in Neuropharmacology (5%); Advanced grad-level statistics course on ANOVA (5%)

5% Grant Writing

Apply for NARSAD Young Investigator Award

5% Meetings / Colloquia

Year 2

80% Research

Study 1 data analysis, manuscript preparation (20%); Study 2 subject recruitment, data collection & analysis, submit conference abstract (50%); Study 3 data analysis (5%); mentoring (5%)

10% Directed Reading / Coursework

Directed reading topics: Molecular Neuroscience, Dopamine, PET Methods (5%); Advanced grad-level statistics course on regression (5%)

5% Grant Writing

NIA R21 on high resolution MR imaging of reward system

5% Meetings / Colloquia

Year 3

90% Research

Study 2 data collection & analysis, manuscript preparation (45%); Study 3 data analysis, submit conference abstract (40%); mentoring (5%)

5% Grant Writing

NIA R01 on reward processing and behavioral control using [^{18}F]fallypride PET imaging

5% Meetings / Colloquia

DOCTORAL DISSERTATION AND OTHER RESEARCH

Doctoral Dissertation Stanford University September 2005 – September 2010
Incentive processing in the aging brain: Individual differences in value-based learning and decision making over the adult life span
Primary Mentor: Brian Knutson, Co-Mentor: Laura Carstensen, Outside Chair: Alan Garber

As a result of global expansion of the proportion of older adults in the population, in coming decades the relative economic impact of the financial decisions of aging adults will be magnified around the world. Thus, it is increasingly imperative to better understand the processes underlying reward processing across the adult life span. Although theoretical accounts link age-related declines in a number of basic cognitive abilities to dopamine function, when I started my dissertation work, surprisingly, no existing studies had explored age differences in reward processing (which also relies on the dopamine system). Thus, my seven dissertation studies explored potential age differences across a range of reward-related tasks from basic anticipatory and consummatory responses to reward cues (Study 1) to probabilistic reward learning (Studies 2–5) to investment decision making (Studies 6–7). The studies focus on both age- and non-age-related individual differences in learning and decision making across the adult life span.

In study 1, we used functional magnetic resonance imaging to determine whether younger and older adults differed in both self-reported and neural responsiveness to anticipated monetary gains and losses. We found evidence for intact striatal and insular activation during gain anticipation and outcome with age, but a relative reduction in activation during loss anticipation. The findings suggest that there is an asymmetry in the anticipation of gains and losses in older adults. Although the relative lack of anxiety about potential loss may contribute to increased well being, this asymmetry may put individuals with blunted loss anticipation at risk for certain types of financial mistakes. Study 1 was published in *Nature Neuroscience* in 2007.

In study 2, we followed up the subjects from Study 1 almost one year later to explore the implications of the anticipatory asymmetry on probabilistic learning. Although younger and older adults did not significantly differ behaviorally, we identified a subgroup of adults of all ages who performed especially poorly in the loss learning task. We found that sensitivity to anticipated losses in the anterior insula predicted subjects' ability to learn to avoid losses in the learning task several months later. The findings suggest that blunted insular sensitivity may disrupt learning to avoid loss across adult age. Study 2 was published in *Psychological Science* in 2008.

In study 3, we examined whether individual differences in probabilistic gain or loss learning across the adult life span were correlated with real world economic behavior. Directly following the results of study 2, we wondered whether the individuals who performed poorly in the loss learning task also sacrificed more money in the real world. Consistent with this hypothesis and establishing the ecological validity of the probabilistic learning task across age, in a larger continuous sample of adults between the ages of 20 and 85 we found that gain learning was correlated with real world accumulation of assets and that loss learning was associated with real world accumulation of debt (validated with credit reports and controlling for a number of other cognitive, affective, and demographic variables). Thus, the study provides evidence that performance of this lab-based learning task has implications for life financial outcomes.

In study 4, we explored age differences in the probabilistic gain learning task. Consistent with study 1, in this sample we found no evidence for an age-related change in the absolute representation of reward outcomes at feedback in the striatum or MPFC. However, we did observe age-related declines in behavioral learning rates and in the neural representation of prediction errors at feedback throughout the striatum and MPFC. The study suggests that learning impairments may be due to age-related changes in relative coding, which relies on the comparison of explicit values at feedback to current estimates of expected value for the chosen cue. This computation is thought to rely primarily on communication between dopaminergic nuclei in the midbrain and frontostriatal regions. Thus, it is possible that the deficit is due to age-related decline deeper in the DA reward system. In study 5, we replicated the behavioral effects, but also found that with additional trials, older adults could learn to reach the same performance criterion as younger adults. This study reveals that although older adults may take longer to learn, they are capable of performing well in this task.

In study 6, we examined age differences in a more applied dynamic financial investment task. We found that older adults made more suboptimal choices than younger adults when choosing risky assets (which were probabilistically associated with various rewards). After reading theoretical neurocomputational work on DA function and aging by Shu-Chen Li and colleagues, I decided to try test the core theoretical ideas by developing a neural measure of signal variability. Consistent with the theory, we found that the age-related performance effect was mediated by the neural measure of variability in the nucleus accumbens. This study

provided the first empirical neural support for the theory, and reveal a novel neural mechanism by which aging may disrupt rational financial choice. Study 6 was published in the *Journal of Neuroscience* in 2010.

In study 7, we sought to determine whether decision aids could improve financial risk taking. We found that presentation of expected value information improved decision making in both younger and older adults, but the addition of a distracting secondary task (hypothesized to disrupt frontal contributions to declarative learning and memory) had little impact on decision quality. Remarkably, provision of expected value information improved the performance of older adults to match that of younger adults at baseline. These findings are consistent with the notion that mesolimbic circuits play a critical role in optimal choice, and imply that providing simplified information about expected value may improve financial decision making across the adult life span. Study 7 was invited for a special issue on aging research in *Social Cognitive and Affective Neuroscience*.

Overall these studies suggest that although younger and older adults show similar mesolimbic representation of the discrete values of rewards during anticipation and outcome, older adults in some situations show mesolimbic deficits in feedback-driven probabilistic reinforcement learning which can influence decision making. Although the studies have begun to fill the previous gap in scientific understanding of age-related change in the human reward system, this area of research is still in its infancy. Further, these dissertation studies were limited to standard resolution whole brain fMRI, and cannot directly speak to the possible role of age-related DA changes in relative coding or neural signal variability and were not optimized to directly measure activity in the midbrain.

The techniques that I will acquire in a post-doctoral fellowship at Vanderbilt can be directly applied to significantly expanding the existing knowledge of age-related changes across the reward system. Further, assessing relationships between DA function across the brain and a wider variety of psychological processes from reward processing to behavioral control has the potential for tremendous impact in the field. Specifically, combining these techniques has the potential to more precisely pinpoint potential sources of error in the neural processing stream and provide focused targets for future interventions.

Additional Graduate Research

Complementing my thesis work, as a graduate student I served as a collaborator with the Knutson, Carstensen, Gotlib, and Tsai labs on a number of projects focused on individual differences in emotional experience. I am a co-author on a longitudinal experience sampling study of emotional experience, a cross-cultural study of emotional memory, and a study on future self continuity and savings behavior. I am the lead author on a few other cross-lab collaborative research projects on emotional processing using neuroimaging. For example, in one collaborative study between the Carstensen and Gotlib labs, we found that older adults show attentional interference effects in both behavioral and neural measures in a traditional non-emotional flanker task, but not on an emotional flanker task. Although older adults typically show relatively high levels of interference and reduced cognitive control during non-emotional tasks, they appear to be able to successfully reduce interference during emotional tasks. Most recently I have served as a collaborator on two projects that seek to characterize investment fraud victims using a variety of psychological and economic individual difference measures. The projects are in collaboration with AARP Washington and the FINRA Investor Education Foundation with the goal of directly informing current fraud prevention training programs conducted by AARP and FINRA.

Additionally, frustrated by reading and reviewing a number of flawed fMRI studies with group comparisons, as a side project during my third year I decided to co-write (with Mark D'Esposito) a whole brain fMRI methods review with a clear and simple list of suggestions for optimizing studies for the Tools of the Trade section in *Social Cognitive and Affective Neuroscience*. I've been very pleased to receive words of thanks from a number of faculty who are just beginning to get into aging research or adding neuroimaging to existing aging projects.

Post-Baccalaureate Research Stanford University June 2002 – August 2005

As laboratory manager, I served as primary research coordinator for several studies of emotional experience, attention, and memory across the adult life span in Laura Carstensen's lab. I also served as research mentor for several undergraduate students over the course of 3 years.

Undergraduate Thesis University of Michigan January 2001 – May 2002

Psychophysiological correlates of affective maintenance

Primary Mentor: Barbara L. Fredrickson, Co-Mentor: Patricia A. Reuter-Lorenz

For my undergrad thesis I independently conducted a psychophysiological study of emotional maintenance of discrete affective stimuli and found specificity and overlap of physiological profiles for categorical emotions.