OMB Number: 4040-0001
Expiration Date: 06/30/2016

APPLICATION FOR FEDERAL ASSISTANCE
SF 424 (R&R)

3. DATE RECEIVED BY STATE	**State Application Identifier** TN: Tennessee

1. TYPE OF SUBMISSION*

❍ Pre-application ● Application ❍ Changed/Corrected Application

4.a. Federal Identifier

b. Agency Routing Number

c. Previous Grants.gov Tracking Number

2. DATE SUBMITTED 2015-04-07

Application Identifier 00036288

5. APPLICANT INFORMATION **Organizational DUNS*:** 004413456

Legal Name*: Vanderbilt University
Department: Psychology
Division: College Of Arts & Science
Street1*: 1400 18th Avenue South
Street2:
City*: Nashville
County: Davidson
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 37212-2809

Person to be contacted on matters involving this application
Prefix: First Name*: Donald Middle Name: Clinton Last Name*: Brown Suffix:
Position/Title: Director, Office of Sponsored Programs
Street1*: 1400 18th Avenue
Street2:
City*: Nashville
County: Davidson
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 37212-2809
Phone Number*: 615-875-6070 Fax Number: 615-343-2447 Email: sponsoredprograms@vanderbilt.edu

6. EMPLOYER IDENTIFICATION NUMBER *(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/Unknown

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER
TITLE: Ruth L. Kirschstein National Research Service Award (NRSA) Individual Postdoctoral Fellowship (Parent F32)

11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*
Linking Temporal Differences in d-Amphetamine Subjective Effects to DRD2 and DAT

12. PROPOSED PROJECT
Start Date* 12/01/2015
Ending Date* 11/30/2018

13. CONGRESSIONAL DISTRICTS OF APPLICANT
TN-005

SF 424 (R&R) APPLICATION FOR FEDERAL ASSISTANCE

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION

Prefix: First Name*: Christopher Middle Name: T Last Name*: Smith Suffix:

Position/Title: Postdoctoral Scholar, Research
Organization Name*: Vanderbilt University
Department: Psychology
Division: College Of Arts & Science
Street1*: PMB 407817
Street2:
City*: Nashville
County: Davidson
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 37235-0002
Phone Number*: 615-322-2874 Fax Number: 615-343-8449 Email*: christopher.t.smith@vanderbilt.edu

15. ESTIMATED PROJECT FUNDING

a. Total Federal Funds Requested*	$157,290.00
b. Total Non-Federal Funds*	$0.00
c. Total Federal & Non-Federal Funds*	$157,290.00
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 penalties. (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 File Name:

19. AUTHORIZED REPRESENTATIVE

Prefix: First Name*: Donald Middle Name: Clinton Last Name*: Brown Suffix:

Position/Title*: Director, Office of Sponsored Programs
Organization Name*: Vanderbilt University
Department: Office of Sponsored Programs
Division:
Street1*: 1400 18th Avenue
Street2:
City*: Nashville
County:
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
ZIP / Postal Code*: 37212-2809
Phone Number*: 615-875-6070 Fax Number: 615-343-2447 Email*: sponsoredprograms@vanderbilt.edu

Signature of Authorized Representative*
Brown,Donald Clinton

Date Signed*
04/07/2015

20. PRE-APPLICATION File Name:

21. COVER LETTER ATTACHMENT File Name:M-20_RRSF424_Cover_Letter.pdf

424 R&R and PHS-398 Specific Table Of Contents

OMB Number: 4040-0010
Expiration Date: 06/30/2016

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:	004413456
Street1*:	1400 18th Avenue South
Street2:	
City*:	Nashville
County:	Davidson
State*:	TN: Tennessee
Province:	
Country*:	USA: UNITED STATES
Zip / Postal Code*:	37212-2809
Project/Performance Site Congressional District*:	TN-005

File Name

Additional Location(s)

Funding Opportunity Number: PA-14-149. Received Date: 2015-04-07T14:58:53.000-04:00

OMB Number: 4040-0001
Expiration Date: 06/30/2016

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 00005756

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 - positive or negative - 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 the United States or partnership with international collaborators?* ❍ **Yes** ● **No**

6.a. If yes, identify countries:

6.b. Optional Explanation:

	Filename
7. Project Summary/Abstract*	M-2_Project_Summary.pdf
8. Project Narrative*	M-1_Narrative.pdf
9. Bibliography & References Cited	M-5_Bibliography.pdf
10.Facilities & Other Resources	M-3_Facilities.pdf
11.Equipment	M-4_Equipment.pdf
12. Other Attachments	Additional Educational Information.pdf Consultant letters of support .pdf

Funding Opportunity Number: PA-14-149. Received Date: 2015-04-07T14:58:53.000-04:00

PROJECT SUMMARY/ABSTRACT

While the speed of delivery of drugs of abuse to the brain are thought to underlie their addictive potential, no research has focused on individual differences in speed of psychostimulant-induced high and liking and whether such differences are reflected at the level of the brain, personality, or genetics. Yet, preliminary data from our research group indicates there are dramatic differences in the temporal profile of subjective responses to oral d-amphetamine. The research proposed in this fellowship will use Positron Emission Tomography (PET) to assess multiple aspects of dopamine system function (striatal and extrastriatal D2-like binding potential, dopamine transporter levels, and d-amphetamine-induced dopamine release) and relate these PET measures to differences in positive subjective responses (drug high and liking) to d-amphetamine, with a particular emphasis on the timing of peak positive subjective drug effects. Furthermore, the proposed research will assess how individual differences in dopamine system function and the positive subjective effects of d-amphetamine vary with personality traits and genetic polymorphisms in healthy adults. Specifically, we will investigate the role of commonly studied polymorphisms in dopamine-related genes as well as a signal nucleotide polymorphism in the cadherin 13 gene previously found to be associated with the positive subjective effects of d-amphetamine in a genome wide association study. The goal of this research plan is to better understand individual differences that confer potential risk for psychostimulant addiction including a fast rise in dopamine and increased subjective high/liking after drug intake. The applicant's long-term goals are to identify how differences in dopamine system function relate to addiction risk at the level of behavioral endophenotypes including subjective drug high/liking time to peak, novelty seeking, and impulsivity (including steep temporal discounting). This fellowship will help the applicant develop expertise in measuring variation in the dopamine system (through PET and genetic approaches) and prepare him for a productive career as an independent investigator of dopamine's role in addiction risk, externalizing behaviors, and other traits often associated with drug addiction.

PROJECT NARRATIVE

Differences in the speed of delivery of drugs of abuse as well as the subjective high they produce are believed to relate to their addiction potential. This research fellowship will investigate whether observed differences in the timing of subjective psychostimulant effects are related to measurable differences in the functioning of the neurotransmitter dopamine, personality traits, and genetics. By understanding how these factors affect individual differences in drug responsivity we hope to identify potential biological and behavioral markers of psychostimulant addiction risk.

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FACILITIES AND OTHER RESOURCES

Department of Psychological Sciences

The Affective Neuroscience Lab (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 three rooms set up for image processing and statistical analysis.

Dr. Zald's office and offices for graduate students and post-doctoral fellows in the Zald Lab 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.

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 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.

Computer resources in the lab include: 2 Apple Mac Pros, 4 Apple Imacs, 6 Dell desktop PCs, and 3 Laptop computers. Backup of data is provided by a RAID server maintained by the Department of Psychology with > 4Tb of dedicated space for the Affective Neuroscience lab. The Zald Lab also utilizes Vanderbilt's **Advanced Computing Center for Research and Education** (ACCRE), 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. Each processor has at least 1 GB of memory, a 40 GB disk drive, and dual copper gigabit Ethernet ports. Over one-third of the systems have Myrinet networking. Each node is monitored via Nagios. The cluster has over 1400 processors and the theoretical peak performance is roughly 7 TFLOPS.

Image analysis packages in use by the Zald Lab include SPM, FSL, AFNI, BrainVoyager, MRICro, MRIcron, and several in house programs scripted at Vanderbilt. Furthermore, the lab has a license for PMOD Technologies (Zurich, Switzerland) suite of PET image processing and analysis software allowing for the application of decay correction and kinetic modeling of the PET data collected in the lab.

PET Center This facility is housed in the Vanderbilt University Medical Center, which is an eight-minute walk from the Department of Psychology. 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. Scanning is accomplished on a GE Discovery STE PET scanner (GE, Milwaukee). The scanner has 24BG 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[104], for full specifications).

Our radiochemistry facility is housed in the PET Center. A General Electric PETtrace-10 cyclotron became operational in 2010. This PETtrace-10 is a 16.5 MeV proton negative-ion compact automated cyclotron and radiochemistry system optimized for production of radionuclides for PET imaging. It features a vertical magnet and self-shielding for compact foot-print, multiple beam lines for simultaneous bombardment of multiple targets, and is capable of producing 10 Curies of fluorine-18 and 3 Curies of carbon-11 with high specific activity. The PET Chemistry Research Lab is connected to the cyclotron through lead-shielded lines allowing direct delivery of [^{18}F] fluoride or [^{11}C]carbon dioxide to shielded "hot cells" for production of radiotracers.

The adjacent hot laboratories utilize 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. Three radiochemical hoods are designated for lower-level work with short-lived gamma-emitting radionuclides other than iodine. Additionally, a dedicated radioiodination hood, equipped with activated carbon and HEPA filters, is located in a separate laboratory 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, allowing analysis of ligands prepared for administration as well as plasma analysis for determining plasma input functions.

Vanderbilt University Institute of Imaging Science (VUIIS)

VUIIS 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.

VUIIS has a core program of research related to developing new imaging technology based on advances in physics, engineering, and computer science. VUIIS is housed in a four- floor, state-of-the-art facility adjacent to Medical Center North. The $28 million project was completed in 2007 and provides a 41,000-square-foot facility to integrate current activities in imaging research and provide research space for faculty members and more than 60 graduate students and postdoctoral fellows in biomedical science, engineering, and physics. VUIIS facility is a brief 8-minute walk from the Department of Psychological Sciences. The VUUIS owns and operates two research-dedicated Philips Achieva 3T scanners and one 7T Philips Achieva scanner for research with human subjects. Each 3T scanner offers a high performance gradient set with strengths up to 80 mT/m, and slew-rates up to 200T/m/s. Both 3T scanners are equipped with state of the art 32-channel SENSE head coils that provide superior SNR, and reduced signal dropout in ventral brain regions due to their highly parallel architecture.

The 3T scanners are housed in specially constructed laboratories devoted exclusively to MRI and fMRI research. The scanner suites are 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). A Macintosh G4 computer, a Dell Pentium IV PC are available for stimuli generation. 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). Galvanic Skin Response (GSR) can also be measured with a biopac system, and pulse oximiter, and pneumatic belt are available for cardio-respiratory monitoring. The scanners are supported by 3 full -time radiological technologists.

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 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 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. The Center for Computational Imaging (CCI) within the VUIIS is led by a frequent collaborator of the Zald lab, Bennett Landman, Ph.D., and provides solutions and services aimed to make imaging research more tractable to members of the scientific community. The CCI works with researchers to provide services, training, and guidance for image analysis and informatics. The CCI develops support tools, informatics tools, and infrastructure, to help advance imaging research for the center's user, collaborators, and the medical imaging community.

Vanderbilt Technologies for Advanced Genomics (VANTAGE)

VANTAGE is a genomics core laboratory housed at Vanderbilt University Medical Center, initiated via an ARRA funded NIH grant. The core is capable of DNA extraction and banking and offers a variety of genetic analysis platforms including Sequenom Services for genetic variation analyses, Applied Biosystems TaqMan Real Time PCR genotyping, Sanger and Next Generation Sequencing, and Illumina genotyping. The Zald lab has used VANTAGE for DNA extraction and banking of blood samples from our neuroimaging studies and for analysis of single nucleotide polymorphisms (SNPs) of interest.

Vanderbilt Institute for Clinical and Translational Research (VICTR)
VICTR is a trans-university institute at Vanderbilt (funded via a Clinical and Translational Science Award from NIH) that supports translational research and the University. VICTR's clinical/translational research center (CTRC) provides support for clinical research at the University including EKG and blood panels performed in our dAMPH PET study participants.

Vanderbilt Center for Cognitive and Integrative Neuroscience (CCIN)
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. 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. 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)
VBI was founded in 1999 as a trans-institutional entity to oversee and facilitate the extensive neuroscience-related endeavors carried out at Vanderbilt University. As such, the primary mission of VBI is to promote research, education, and training in the brain-related disciplines at Vanderbilt, with the stated goal of fostering excellence in each of these arenas. In addition to administering the Neuroscience Graduate Program at Vanderbilt, 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, 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. VBI hosts a weekly neuroscience seminar on topics ranging from molecular neuroscience to integrative neuroscience.

Psychiatric Neuroimaging Program
Dr. Zald is a member of the Psychiatric Neuroimaging Program, located on the 3rd floor of the Vanderbilt Psychiatric Hospital, a 10-minute walk from the Department of Psychological Sciences. This program provides an 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.

Vanderbilt Kennedy Center for Human Development
Dr. Zald is also an investigator at the Vanderbilt Kennedy Center. The goal of the center is to support and apply scientific research on developmental disabilities and human development to bring better services and training to the community. Research at the center is interdisciplinary, commonly forming partnerships between researchers and clinicians in behavior, education, genetics and neuroscience in order to make breakthroughs in prevention and treatment. The Kennedy Center provides an opportunity for the applicant to attend and present in interdisciplinary seminars focused on human development.

Vanderbilt Center for Teaching
The Center for Teaching at Vanderbilt provides a variety of resources to allow members of the Vanderbilt community (including postdocs) to practice and improve their teaching skills. Their Certificate in College Teaching offers a yearly seminar in College Teaching consisting of 8 group sessions, a microteaching experience, and the development of a philosophy of teaching statement. These didactic components are enhanced via a College Teaching Practicum where participants learn to enhance their teaching effectiveness by getting feedback on their teaching in a classroom setting (as a guest lecturer or teaching assistant). Further development of participants' philosophy of teaching also takes place during the semester-long Practicum.

Resources available to the applicant through the Vanderbilt Office of Postdoctoral Affairs

The postdoctoral experience at Vanderbilt is enhanced greatly by the **Office of Postdoctoral Affairs** and the **Vanderbilt Postdoctoral Association**. In 2013, Vanderbilt was ranked 13th (3rd among Universities) in the nation in *The Scientist's* annual survey, "Best Places to work for Postdocs".
The Office of Postdoctoral Affairs serves the following roles: 1) Assist in establishing fair wages for postdoctoral fellows, based on experience and educational background, using the NIH stipend levels as a guide; 2) Advise department administrators on policies and procedures in place for postdoctoral research fellows; 3) Support the Postdoctoral Association in their goals of improving the research environment for all postdoctoral fellows; 4) Disseminate and clarify Vanderbilt policies regarding postdoctoral fellows and provide guidance to fellows with grievances; 5) Direct postdoctoral fellows to available Vanderbilt resources, including the Office of International Services, Employee Assistance Program, Human Resources, etc.; 6) Provide a personal orientation session to each new postdoctoral fellow and provide follow-up consultation as needed; 7) Provide health insurance for Postdoctoral Research Fellow Trainees supported by NIH institutional training grants, NIH National Research Service Awards (NRSA) and other postdoctoral fellowship awards that stipulate no employee/employer relationship exist; 8) Organize and distribute information regarding funding, careers, seminars, meetings, and social events; and 9) Sponsor subsidized English language classes for newly arriving international postdoctoral fellows and their families. For more information see (https://medschool.vanderbilt.edu/postdoc/).

The Vanderbilt Postdoctoral Association (PDA) was formed in 1998 and has successfully united postdoctoral research fellows from the basic science as well as clinical departments. The PDA functions as an invaluable channel for its members' needs and ideas to be heard by the leaders of the VUMC community. The PDA was instrumental in the creation of the Individual Development Plan (IDP), a communication tool for postdoctoral fellows and their mentors. Once a fellow and mentor have discussed their expectations and goals for the year, the IDP becomes a functional document that identifies fellows' annual progress, professional development needs and career objectives.
The PDA holds monthly meetings, including regular Topic Meetings, with one particular subject of interest to postdoctoral fellows and trainees featured. PDA leaders and members practice problem solving, policy shaping, seminar planning, and other skills as they participate in PDA events. Postdoctoral Association seminars offer opportunities for fellows to sharpen their presentation skills, as well as occasions to meet invited speakers offering career guidance. The PDA offers networking opportunities through a variety of social events.

Office of Biomedical Research Education & Training (BRET)
BRET Office of Postdoctoral Affairs
The BRET Office assists graduate students and postdoctoral fellows in labs affiliated with Vanderbilt University Medical Center (VUMC) in scientific skills training and professional development beyond the classroom. BRET supports the Vanderbilt ASPIRE (Augmenting Scholar Preparation and Integration with Research-Related Endeavors) program that assists with career development of biomedical sciences graduate students and postdoctoral fellows. ASPIRE hosts PhD Career Connections talks where trainees can learn about PhD-related career paths and a Postdoctoral Café for Career Planning intended for postdoctoral researchers to learn about skills need for a successful research career. These bi-weekly Postdoctoral Café meetings also allow for postdoctoral fellows across VUMC and Vanderbilt University to network and interact with young scientists at a similar stage of their careers to get advice and information on how to succeed as a postdoc and obtain skills needed to advance to the next stage of their careers.

Vanderbilt Editor's Club
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Portions provided by David H. Zald, Ph.D.

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
VUIIS (an 8-minute walk from the applicant's 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 is also available.

VUIIS also houses a Philips Intera Achieva 7T MRI, one of only 30 ultra-high field human MR instruments available worldwide. This research system has 32 independent digital receiver channels and physiological monitoring. In addition to an existing 16-channel coil, a 32-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.

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 EPrime, 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 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. Our new cyclotron is a General Electric PETtrace-10. This is a 16.5 MeV proton negative-ion compact automated cyclotron and radiochemistry system optimized for production of radionuclides for PET imaging. It features a vertical magnet and self-shielding for compact foot-print, multiple beam lines for simultaneous bombardment of multiple targets, and is capable of producing 10 Curies of fluorine-18 and 3 Curies of carbon-11 with high specific activity. The PET Chemistry Research Lab is connected to the cyclotron through lead-shielded lines allowing direct delivery of [18F] fluoride or [11C] carbon dioxide to shielded "hot cells" for production of radiotracers.

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David H. Zald, Ph.D.
Mentor

Vanderbilt Brain Institute

April 2, 2015

Silvio O. Conte Neuroscience Research Center at Vanderbilt University

Center for Scientific Review
National Institutes of Health

Dear Colleagues,

I am writing to note my enthusiasm for joining Christopher Smith's mentoring committee. I have come to know Chris through his participation in a multi-lab Dopamine Group meeting in which he and his mentor David Zald participate. These meetings involve the PIs, fellows and students from multiple labs who study dopamine signaling and where attendees bring either an abstract of a new paper to share or a piece of data from a recent experiment to discuss. These are lively meetings and range in content from studies of dopamine signaling in *C. elegans* to the role of dopamine in higher cognitive function and reward in humans. Chris and David's participation brings an important dimension to these meetings and I am pleased to extend my interactions further through my participation on his advisory committee. I have extensive experience with postdoctoral training and have for the past 12 years directed the Vanderbilt Functional Neurogenomics Training Program funded by a grant from the NIMH. I look forward to working with Chris and assisting to my fullest capacity in his development.

Sincerely,

Randy D. Blakely, Ph.D.
Allan D. Bass Professor of Pharmacology & Psychiatry Director
Silvio O. Conte Center for Neuroscience Research Vanderbilt University School of Medicine
Director, Postdoctoral Program in Functional Neurogenomics

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Ronald L. Cowan, M.D., Ph.D.
Professor of Psychiatry, Radiology, and Psychology
Vice Chair for Education
Director, Residency Training Program
Director, Psychiatric Neuroimaging Program

March 31, 2015

RE: Chris Smith's NRSA Proposal

Dear Chris:

I am writing to let you know that I am happy to collaborate and assist you on your post-doctoral NRSA proposal examining individual variability in dopamine system function as it relates to differences in positive subjective effects (overall and time to peak) after acute oral d-amphetamine. As a researcher and clinician interested in better understanding reward processing as it relates to addiction and drugs of abuse, I find your proposal to be of great importance to the field. Being able to assess dopamine system function at a variety of levels using 18F-Fallypride (for D2/3 receptors) and 18F-FE-PE2I (for DAT) PET and amphetamine-induced dopamine release measured as Fallypride displacement will allow you the ability to more completely understand how differences in dopamine system function relate to variations in self reports of drug high and liking. Looking at differences in the timing of the peak subjective high across your participants is another novel approach you are using. I was impressed by the behavioral data you shared with me looking at this time to peak effect and was happy to offer assistance in the manuscript you currently have under review at Psychopharmacology. I look forward to helping you interpret your PET findings from these data and the data that you plan to collect as part of your NRSA.

As you know, I have over two decades of experience as a researcher and a clinician investigating dopamine effects on brain processes related to reward and affect. I am highly familiar with the Fallypride PET measures you will be obtaining, as I have been collaborating on PET studies with your mentor David Zald for almost a decade. I will be happy to share with you any knowledge and imaging techniques that I have acquired to help you fully utilize the data you will be collecting. As you progress in your training, I look forward to us discussing your results as they could have important implications for clinicians studying addiction populations.

I look forward to working with you and your mentor David Zald on your training and to helping you to develop the skills you need to become a successful independent investigator in the future.

Sincerely,

Ronald L. Cowan, MD, PhD
Professor of Psychiatry, Radiology, and Psychology
Vice Chair for Education
Director, Residency Training Program
Director, Psychiatric Neuroimaging Program

Email: Ronald.L.Cowan@Vanderbilt.Edu
Lab URL: www.cowanlab.com
Psychiatric Neuroimaging Program URL: www.vandypsychimaging.com

THE UNIVERSITY OF CHICAGO MEDICAL CENTER

Department of Psychiatry and Behavioral Neuroscience
5841 S. Maryland Ave.
MC 3077
Chicago, IL 60637-1470

March 27 2015

NIH Grant Review Committee

RE: Chris Smith's NRSA Proposal

Dear Chris:

I am pleased to be a consultant on your post-doctoral NRSA proposal. I enjoyed working with you on the collaborative paper "*Individual Differences in Timing of Peak Positive Subjective Responses to d-Amphetamine: Relationship to Pharmacokinetics, Physiology, and Personality*" (currently under review at *Psychopharmacology*) examining differences in timing of peak d-amphetamine high and liking in data collected at Vanderbilt and the University of Chicago. These behavioral data provide an excellent basis for your current NRSA proposal. I look forward to assisting you in interpreting the dAMPH data as you collect it. As you know, I have years of experience investigating individual differences in d-amphetamine effects from a behavioral, pharmacokinetic, and genetic level. As such, I hope to offer insights and advice in these areas to you and Dr. Zald. It is important to consider the pharmacokinetic determinants of the fast vs slow responses, but I was encouraged to see that pharmacokinetic factors did not fully account for the differences in time to peak d-amphetamine high and liking (DEQ_{H+L}) in your data. So, I think you are on to a potentially novel and important finding regarding individual differences in time to peak high/liking after d-amphetamine.

I recognize that the data Dr. Palmer and I collected on the genetic determinants of responses to amphetamine are highly relevant to your work. We would be pleased to share our data, so that you can examine genetic differences across the Responder groups in our dataset to identify potential variants to examine further in your PET data. We look forward to discussing any interesting genetic differences you find in our data in the months to come.

I am also happy to serve as an initial reviewer for papers you write on your d-amphetamine effects. I have experience as an editor and editorial board member (at *Psychopharmacology*, *Alcoholism: Clinical and Experimental Research*, *PLoS One*, and *Current Addiction Reports*) and as a reviewer, and I can help you in your manuscript preparations. In addition to serving these roles in assisting you in your proposed research, I can also provide guidance throughout your training to help you gain the necessary professional skills for obtaining a faculty position and succeeding in academia.

I look forward to working with you.

Yours sincerely.

Harriet de Wit, PhD
Professor

DEPARTMENT OF HUMAN GENETICS
THE UNIVERSITY OF CHICAGO
920 EAST 58TH STREET
CLSC 507
CHICAGO, IL 60637

April 6, 2015

Dear Chris:

I am writing to confirm that I am pleased to be a consultant on your post-doctoral NRSA proposal. I enjoyed working with you on your recent paper investigating differences in timing of d-amphetamine high and liking using some of our data collected at the University of Chicago. I know you have mentioned to Dr. de Wit and myself that you are interested in using the genetic data from our University of Chicago participants in some future analyses. As I have communicated to you, I am open and willing to share our genetic data with you and look forward to hearing if any interesting effects emerge. Furthermore, I see you have made exploring the role of the *CDH13* SNP identified in the Hart et al 2012 *PLoSOne* paper part of your proposal. I think this is an exciting avenue of research!

As you also know, though, I am a big proponent of taking a more comprehensive approach to studying genetic variation than the candidate gene studies that have been commonly done over the past several years. My background in genome wide association studies and other approaches (SNP enrichment analyses across a variety of traits: dAMPH response and ADHD, for example) will prove useful in our analysis of your subjective high + liking peak group differences. I am very interested in trying to investigate genetic variability in behavioral phenotypes that may confer risk for addiction and other psychiatric disorders. I believe looking at the temporal patterns of dAMPH-induced High and Liking in our University of Chicago dataset may offer additional insights as we study the complex relationships between genetics and behavioral endophenotypes for addiction (such as subjective effect differences). So part of my role will be to try to expand your training beyond just candidate gene studies.

Furthermore, the ability to use the variety of PET measures of dopamine system function you outline in your proposal should allow you to obtain more information regarding the functional consequence (if any) of commonly studied dopamine genetic polymorphisms including Taq1A, DRD2 C957T, DRD2 -141 C Ins/Del, COMT Val^{158}Met, DAT1 3' UTR VNTR, among others. I believe your ability to investigate the effects of these common polymorphisms on a variety of DA signaling measures will begin to shed light on what role their various alleles may play in DA system function. Your work has the potential to highlight which DA signaling genes play a role in D2/3 receptor levels, DAT levels, and dopamine release. This could have great importance to a large number or researchers that must rely on putative measures of dopamine system function obtained from studying genetic variation in human subjects.

I look forward to working with you to address the many challenges that come with genetics research on relatively small (in genetics terms) samples and think many important findings will come out of the work you are doing.

Most Sincerely,

Abraham A Palmer

Abraham A. Palmer, Ph.D.
Associate Professor
Department of Human Genetics
Department of Psychiatry and Behavioral Neuroscience
University of Chicago
920 E 58th St. CLSC-507D
Chicago, IL 60637
aap@uchicago.edu
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http://pgtg.uchicago.edu

OMB Number: 4040-0001
Expiration Date: 06/30/2016

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator

Prefix: First Name*: Christopher Middle Name T Last Name*: Smith Suffix:

Position/Title*: Postdoctoral Scholar, Research
Organization Name*: Vanderbilt University
Department: Psychology
Division: College Of Arts & Science
Street1*: PMB 407817
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City*: Nashville
County: Davidson
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 37235-0002

Phone Number*: 615-322-2874 Fax Number: 615-343-8449 E-Mail*: christopher.t.smith@vanderbilt.edu

Credential, e.g., agency login: CTS2014

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

Degree Type: Doctor of Philosophy Degree Year: 2014

	File Name
Attach Biographical Sketch*:	ID-0121695_BN-1_BIOSKETCH.pdf
Attach Current & Pending Support:	

Tracking Number: GRANT11882033 Funding Opportunity Number: PA-14-149 . Received Date: 2015-04-07T14:58:53.000-04:00

PROFILE - Senior/Key Person

Prefix: First Name*: David Middle Name H Last Name*: Zald Suffix:

Position/Title*: Professor
Organization Name*: Vanderbilt University
Department: Psychology
Division: College Of Arts & Science
Street1*: 301 David K. Wilson Hall
Street2:
City*: Nashville
County: Davidson
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 37235-0002

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: Doctor of Philosophy Degree Year: 1997

File Name
Attach Biographical Sketch*: ID-0034854_BN-1_BIOSKETCH.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Harriet Middle Name Last Name*: de Wit Suffix:

Position/Title*: Professor
Organization Name*: University of Chicago
Department:
Division: Unknown
Street1*: Biological Sciences Division
Street2: 5841 South Maryland Avenue
City*: Chicago
County:
State*: IL: Illinois
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 60637

Phone Number*: 773-702-1537 Fax Number: E-Mail*: hdew@uchicago.edu

Credential, e.g., agency login: HDEWIT

Project Role*: Other (Specify) Other Project Role Category: Consultant

Degree Type: Doctor of Philosophy Degree Year: 1981

File Name
Attach Biographical Sketch*: ID-25305_BN-1_BIOSKETCH.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Abraham Middle Name A Last Name*: Palmer Suffix:

Position/Title*: Associate Professor
Organization Name*: University of Chicago
Department:
Division: Unknown
Street1*: Biological Sciences Division, Human Genetics
Street2: 920 E 58th St.
City*: Chicago
County:
State*: IL: Illinois
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 60637

Phone Number*: 773-834-2897 Fax Number: E-Mail*: aap@uchicago.edu

Credential, e.g., agency login: PALMERAB

Project Role*: Other (Specify) Other Project Role Category: Consultant

Degree Type: Doctor of Philosophy Degree Year: 1999

File Name
Attach Biographical Sketch*: ID-25304_BN-1_BIOSKETCH.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Ronald Middle Name L Last Name*: Cowan Suffix:

Position/Title*: Professor
Organization Name*: Vanderbilt University
Department: Psychiatry/Adult Psychiatry
Division: School of Medicine
Street1*: VPH3057K
Street2:
City*: Nashville
County: Davidson
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 37235-0002

Phone Number*: 615-322-2303 Fax Number: 615-936-3563 E-Mail*: ronald.l.cowan@Vanderbilt.Edu

Credential, e.g., agency login: COWANRL

Project Role*: Other (Specify) Other Project Role Category: Consultant

Degree Type: Medical Doctor, Doctor of Philosophy Degree Year: 1994

File Name
Attach Biographical Sketch*: ID-0048511_BN-1_BIOSKETCH.pdf
Attach Current & Pending Support:

PROFILE - Senior/Key Person

Prefix: First Name*: Randy Middle Name D Last Name*: Blakely Suffix:

Position/Title*: Professor
Organization Name*: Vanderbilt University
Department: Pharmacology
Division: School of Medicine
Street1*: campus zip 8548
Street2:
City*: Nashville
County: Davidson
State*: TN: Tennessee
Province:
Country*: USA: UNITED STATES
Zip / Postal Code*: 37235-0002

Phone Number*: 615-936-1700 Fax Number: 615-936-1702 E-Mail*: randy.blakely@Vanderbilt.Edu

Credential, e.g., agency login: BLAKELRD

Project Role*: Other (Specify) Other Project Role Category: Consultant

Degree Type: Doctor of Philosophy Degree Year: 1987

	File Name
Attach Biographical Sketch*:	ID-0009190_BN-1_BIOSKETCH.pdf
Attach Current & Pending Support:	

FELLOWSHIP APPLICANT BIOGRAPHICAL SKETCH

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

NAME OF FELLOWSHIP APPLICANT	POSITION TITLE
Christopher Thomas Smith	Postdoctoral Research Fellow Vanderbilt University Psychology Department
eRA COMMONS USER NAME (credential, e.g., agency login) CTS2014	

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
Furman University	B.S.	05/2008	Neuroscience
University of North Carolina, Chapel Hill	Ph.D.	05/2014	Neurobiology

Please refer to the application instructions in order to complete sections A, B, C, and D of the Biographical Sketch.

A. Personal Statement

My long-term research interests involve understanding the neurobiology of aberrant reward, impulse control, and decision making processes as they relate to drug abuse. My doctoral research explored delay discounting (now vs. later reward choice behavior) and its relationship to development and alcohol use behavior. In addition, I have used behavioral genetics to begin to assess the role of dopamine signaling in reward relevant decision making. I have worked with both single nucleotide polymorphism (SNP) and variable number of tandem repeat (VNTR) genetic data to investigate the role of putative frontal (COMT Val158Met SNP) versus striatal (DAT 3′UTR VNTR) dopamine in working memory (Smith, Swift-Scanlan, & Boettiger, 2014) and delay discounting (Smith & Boettiger, 2012) behavior. In addition, I have explored epigenetic effects at the *COMT* gene (Swift-Scanlan et al., 2014). Furthermore, during my graduate training, I was able to work with positron emission (PET) data to investigate the role dopamine synthesis at the level of the putamen and midbrain play in delay discounting behavior, findings that are currently under review at *Journal of Neurophysiology*. These doctoral research experiences have led to my interest to pursue studying the role of dopamine signaling in reward processes using PET and genetic methods.

As a postdoctoral fellow, I plan to learn to utilize [^{18}F]-Fallypride and [^{18}F]-FE-PE2I PET data as a means to interrogate dopamine D2 receptor and DAT levels in the human brain, respectively. Combining these measures of dopamine signaling at baseline and after acute amphetamine (which increases dopamine levels in the brain) along with differences in dopamine signaling related genes, I hope to gain a better understanding of the dopamine system's role in motivated behavior. In particular, I plan to look at individual differences in positive subjective responses to acute d-amphetamine (dAMPH) challenge to better understand if differences in our Fallypride and/or PE2I signal or genetic differences explains individual differences in risk for addiction. We have exciting behavioral data (currently in revision for *Psychopharmacology*) that suggests that there is a great deal of variability in the presence and timing of peak subjective high and liking after dAMPH and that novelty seeking personality explains some of the individual differences we observe. The logical next steps in this line of research, which the current NRSA proposal will pursue, are whether the individual differences in dAMPH responsivity and novelty seeking personality relate to differences in dopamine system function as measured with PET. Furthermore, I am interested in asking whether genetic variation relates to any of our measures as finding SNPs or VNTRs associated with the behavioral and neurochemical differences we observe presents more tractable variables to be studied by others in the future. Exploring a recently identified SNP in *CDH13* associated with variability in subjective dAMPH response will be the starting point in our genetic analyses, though other common DA gene variants and novel SNPs will be investigated. By combining brain (PET) and biological (genetic) data with behavior and personality differences in this proposal, I plan to gain a more complete understanding of dopamine's role in subjective responses to dAMPH. In the future, I plan to take similar experimental approaches to study dopamine's role in a variety of processes found to be abnormal in addiction, including reward responsivity, reinforcement learning, and delay discounting.

B. Positions and Honors

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
America Counts, America Reads Tutor	11/06	05/08	Academic tutoring	Stone Academy of Communication Arts	Connie Buto
Summer Research Fellow	06/07	09/07	Behavioral Neuroscience	Furman University	Dr. Judith E. Grisel
Instructional Assistant	01/11	05/11	Psychology	UNC Chapel Hill	Dr. David Penn
Postdoctoral Research Fellow	08/14	present	Psychology	Vanderbilt University	Dr. David H. Zald

Academic and Professional Honors

2007 S.C. NIH-IDeA Networks of Biomedical Research Excellence Summer Research Fellow
2010, -14 Research Society on Alcoholism Student Merit Travel Award
2010, -12, -14 Graduate Mentor Award from UNC-CH Office of Undergraduate Research
2011 Funded trainee for 2011 *Training Course in fMRI* program at the University of Michigan
2012 Graduate Student Award, Cognitive Neuroscience Society 2012 Annual Meeting
2012 Funded trainee for 2012 *Neuroimaging Training Program* at UCLA
2013 UNC-CH HHMI Future Scientists and Clinicians Summer Program Co-Mentor
2013 Chosen to attend the *Multi-Modality Short Course in Neuroimaging* at the Athinoula A. Martinos Center for Biomedical Imaging, Boston, MA
2014 UNC-CH Psychology Club Research Mentor Award

Memberships in professional societies:

Society for Neuroscience (2007-present)
Cognitive Neuroscience Society (2009-present)
Research Society on Alcoholism (2009-present)

Service:

Peer Reviewer: *Neuropsychologia; Hormones and Behavior*

C. Publications

Research Papers

Smith CT, Sierra Y, Oppler SH, Boettiger CA (2014). Ovarian Cycle Effects on Immediate Reward Bias in humans: a role for estradiol. *Journal of Neuroscience*, *34* (16): 5468-5476. PMCID: PMC3988406

Swift-Scanlan T, **Smith CT**, Bardowell SA, Boettiger CA (2014). Comprehensive interrogation of CpG islands in the gene encoding COMT, a key estrogen and catecholamine regulator. *BMC Medical Genomics*, 7:5, PMCID: PMC3910242.

Smith CT, Swift-Scanlan T, Boettiger CA (2014). Genetic polymorphisms regulating dopamine signaling in the frontal cortex interact to affect target detection under high working memory load. *Journal of Cognitive Neuroscience, 26* (2), 395-407. PMCID: PMC3877727

Smith CT, Boettiger CA (2012). Age modulates the effect of COMT genotype on delay discounting behavior. *Psychopharmacology, 222* (4), 609-617. PMCID: PMC3401276

In Revision

***Smith CT**, Weafer J, Cowan RL, Kessler RM, Palmer AA, de Wit H, Zald DH (2015). Individual differences in timing of peak positive subjective responses to d-amphetamine: Relationship to pharmacokinetics, physiology, and personality. *Psychopharmacology.*

*Focused on DEQ_{H+L} group differences in dAMPH responses, some of which appears in this F32 application.

In Review

Smith CT, Wallace DL, Dang LC, Aarts E, Jagust WJ, D'Esposito M, Boettiger CA (2015). Modulation of impulsivity and reward sensitivity in intertemporal choice by striatal and midbrain dopamine in healthy adults. *Journal of Neurophysiology.*

In Preparation

Smith CT, Steel EA, Parrish MH, Kelm MK, Boettiger CA (2015). Intertemporal Choice Behavior in Late Adolescents and Adults: Effects of Age Interact with Alcohol Use and Family History Status. *Psychopharmacology (targeted).*

Boettiger CA, Chanon VW, **Smith CT**, Kelm MK, Parrish M, Kampov-Polevoi AB, Garbutt JC (2015). Changes in attentional bias towards alcohol cues predicts alcoholism treatment outcome: A role for orbitofrontal cortex and endogenous opioids. *Journal of Neuroscience (targeted).*

Representative Abstracts (6 of 19)

Smith CT, Dang L, Cowan RL, Kessler RM, Zald DH (2015). Risky Choices on the Balloon Analog Risk Task are Positively Associated with Individual Differences in Dopamine Reactivity in Left Ventrolateral Prefrontal Cortex (vlPFC) and Right Superior Frontal Gyrus (SFG). Scientific Research Network on Decision Neuroscience and Aging Conference. Miami, FL.

Smith CT, Chanon VW, Kelm MK, Cerciello ER, Parrish MH, Garbutt JC, Kampov-Polevoy AB, Boettiger CA (2014). Attentional bias to alcohol cues changes in tandem with drinking during treatment: Association with brain activity in a putative visual bias circuit. Research Society on Alcoholism 2014 Annual Meeting. Bellevue, WA.

MH Parrish*, **CT Smith**, M Menceloglu, SH Oppler, CA Boettiger (2014). Family history of alcohol use disorder and large-scale intrinsic network connectivity in adulthood. Society for Neuroscience Annual Meeting. Washington, DC.

Oppler SH*, **Smith CT**, Parrish MH, Steel EA, Kelm MK, Boettiger CA (2014). In young adults, reward sensitivity quadratically relates to genetically predicted striatal dopamine. Celebration of Undergraduate Research, University of North Carolina at Chapel Hill. Chapel Hill, NC.

Smith CT, Boettiger CA (2012). n-back performance moderates the positive relationship between trait impulsivity and immediate reward bias in adults: Potentiation by heavy alcohol use. Society for Neuroscience 2012 Annual Meeting. New Orleans, LA.

Le M*, **Smith CT**, Boettiger CA (2011). Cognitive Impulsivity, Working Memory, and Genotype Effects. Celebration of Undergraduate Research, University of North Carolina at Chapel Hill. Chapel Hill, NC.

* *undergraduate mentee presenter*

D. Scholastic Performance

YEAR	SCIENCE COURSE TITLE	GRADE
	FURMAN UNIVERSITY	
2004	Fundamentals of Chemistry I	A
2005	Fundamentals of Chemistry II – Inorganic Chemistry	A
2005	Foundations of Biology	A+
2005	Fundamentals of Chemistry III – Organic Chemistry	A-
2006	Genetics	A-
2006	Spectroscopy and Molecular Structure (Chemistry course)	A+
2006	Experimental and Statistical Methods (Psychology course)	A-
2007	Human Physiology	A-
2007	Introduction to Biopsychology	A-
2007	Biological Chemistry	C+
2007	Current Topics in Neuroscience	A
2008	Behavioral Neuroscience	B
2008	Neurobiology	A
	UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL	
2008	Introduction to Genetic Analysis	P
2008	Introduction to Cell and Molecular Neurobiology (CMNB)	H
2008	CMNB - Cell Signaling	P
2008	CMNB - Electrical Signals	H
2009	CMNB - Synaptic Mechanisms	P
2009	CMNB - Anatomy and Function	P
2009	Biological Bases of Behavior II	H
2009	Developmental Neurobiology	P
2009	Behavioral Pharmacology	P
2010-11	Behavioral Neuroscience Seminar	H
2012	Neurobiology of Frontal Lobes	H

YEAR	OTHER COURSE TITLE	GRADE
	FURMAN UNIVERSITY	
2005	Vectors and Matrices (Math course)	A
2005	General Psychology	A
2006	Statistics (Economics course)	B
2006	Social Psychology	B
2007	Psychometrics and Assessment (Psychology course	A-
2007	Learning (Psychology course)	A-
2008	Memory and Cognition (Psychology course)	A
2008	Brain and Mind (Interdisciplinary studies course)	A-
	UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL	
2008-9	BBSP 1st Year Seminar in Research Ethics and Scientific Communication	H
2009-10	Scientific Communication Seminar	H
2010	Research Ethics Seminar	P*
	VANDERBILT UNIVERSITY	
2014	Scientific Computing for Psychological and Brain Sciences	
2015	Neuromodulation	

UNC Chapel Hill graduate courses are graded H (high pass), P (pass), L (low pass) or F (fail). Passing is B or better. * Course was Pass/Fail.
Vanderbilt courses were audited as a postdoctoral research fellow.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
David H. Zald	Professor of Psychology and Psychiatry
eRA COMMONS USER NAME (credential, e.g., agency login) zalddh	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Michigan, Ann Arbor	B.A.	04/89	Film-Video/Psychology
University of Minnesota, Minneapolis	Ph.D.	05/97	Psychology (Clinical)
Ann Arbor VA Med. Center/University of Michigan Medical Center, Ann Arbor	Internship	1995-1996	Neuropsychology
University of Minnesota Med. Center/Minneapolis VA Med. Center, Minneapolis	Postdoc	1997-2000	Neuroimaging

A. Personal Statement

Dr. Zald is the director of the Affective Neuroscience Laboratory at Vanderbilt University. His research focuses on understanding the neural and neuropharmacological substrates of emotion and cognition, and the manner in which individual differences in the functioning of these systems impacts temperament, personality and psychopathology. His graduate and post-graduate training combined study of neuropsychology, neuropharmacology, personality, and affective neuroscience. Since 1995 he has been conducting 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 mesolimbic dopamine (DA) system. His research program on the DA system utilizes PET measurements of striatal and extrastriatal DA receptor availability, amphetamine induced DA release (an index of DA system reactivity), and more recently, studies of DA transporter levels. The goal of this research program is to determine how individual differences in DA functioning are associated with individual differences in cognitive and personality factors associated with externalizing psychopathology and the risk for drug abuse. Current research has extended this line of inquiry to issues related to aging and decision-making. Dr. Zald's laboratory remains one of the few labs in the world currently integrating neurotransmitter imaging data and fMRI BOLD responses. An additional major line of research explores the neural correlates of major cross-cutting dimensions of psychopathology. This work was one of the first studies funded by the NIMH Research Domain Criteria (RDoC) initiative. Dr. Zald has extensive mentoring experience at the pre-doctoral and post-doctoral level. In addition to his role as a co-PI on a training grant, he has sponsored multiple successful NRSA's, a K99, two K01s, and a K23 award. He has also served as an external consultant on several additional K-awards, and has served on training faculty on three additional training grants. Recent graduate and post-doctoral advisees from Dr. Zald's lab have gone on to tenure-track positions at institutions including Harvard, Yale, Emory, and Vanderbilt. As such, he brings substantial expertise in training to the current proposal.

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 University, Nashville, TN.
2007-2012 Associate Professor, Depts. of Psychology, Psychiatry, & Integrative Neuroscience Program, Vanderbilt Univ. (Director of Undergraduate Studies, Dept. of Psychology 2007-2009)
2011-2014 Section Editor (Motivation and Social Neuroscience), *Neuropsychologia*.
2012-Present Professor, Depts. of Psychology, Psychiatry, & Integrative Neuroscience Program, Vanderbilt Univ., Nashville, TN.
2015 (starting) Director, Undergraduate Interdisciplinary Neuroscience Program, Vanderbilt Univ.

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
2011 Vanderbilt University Chancellor's Award for Research
2013 Fellow - Association for Psychological Science
2014 Vanderbilt Univ., College of Arts and Sciences, Award for Excellence in Graduate Mentoring

C. Selected peer-reviewed publications (out of 102)

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. [PMC20578].
2. **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. [PMC122385].
3. **Zald DH**: The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Rev* 2003;41:88-123. [PMID: 12505650].
4. **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].
5. **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. [PMC2748420].
6. 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]
7. 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;13:419-21. [PMC2916168].
8. Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith C, Kessler RM, **Zald DH**: Dopaminergic network differences in human impulsivity. *Science* 2010;329(5991):532. [PMC2974644].
9. **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*, 51(1):53-62 [PMC2862467].
10. Woodward ND, Cowan RL, Park S, Ansari MS, Baldwin RM, Li R, Doop M, Kessler RM, **Zald, DH**: Amphetamine induced dopamine release in striatal and extrastriatal brain regions correlates with schizotypal personality traits in healthy individual**s.** *American Journal of Psychiatry* 2011;168:418-26. [PMC3770457].
11. Treadway M, **Zald DH**. Reconsidering anhedonia in depression: Lessons from translational neuroscience. *Neurosci & Biobehavioral Rev* 2011; 35: 537-55. [PMC3005986].

12. Eapen M, **Zald DH**, Gatenby J, Ding Z, Gore J. Using high-resolution MR imaging at 7T to evaluate the anatomy of the midbrain dopaminergic system. *American Journal of Neuroradiology* 2011; 32;688-94 [PMC3076524].
13. Wardle MC, Treadway MT, Mayo LM, **Zald, DH**, de Wit H. Amping up effort: Effects of d-Amphetamine on human effort-based decision-Making. *Journal of Neuroscience 2011;* 31:16597-16602. [PMC3234999]
14. Treadway MT, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman A N, Smith C, Kessler RM, **Zald DH**. Dopaminergic mechanisms of individual differences in human effort-based decision-making. *J Neuroscience* 2012; 32: 6170-6. [PMC3391699].
15. Samanez-Larkin GR, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Arrington, CM, Baldwin RM, Smith C, Treadway MT, Kessler RM, **Zald DH**. A thalamocorticostriatal dopamine circuit for psychostimulant-enhanced human cognitive flexibility. *Biological Psychiatry* 2013;74:10966-105. [PMC 3615042].

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

D. Research Support

Ongoing Research Support

R01AG043458 Zald (PI) 2/15/14-1/31/19
NIH/NIA
Dopaminergic neuromodulation of decision making in young and middle-aged adults
The proposal aims to characterize individual and age differences in motivation and decision making in young and late middle-aged adults using multimodal neuroimaging techniques. This work will form the basis of a translational research program on decision making over adult development, and has the potential to eventually facilitate identification of specific markers for suboptimal decision making in adults of all ages to inform the design of appropriate interventions.

R01AG044838 Zald (PI) 9/30/12-8/31/15
NIH/NIA
Dopaminergic modulation of subjective valuation across adulthood
The proposal aims to characterize individual and age differences in motivation, cognition, and decision making over the adult life span using multimodal neuroimaging techniques. This work will form the basis of a translational research program on decision making over adult development and aging, and has the potential to eventually facilitate identification of specific markers for suboptimal decision making in adults of all ages to inform the design of appropriate interventions.

R01MH098098 Zald/Lahey (MPI) 9/12/12-5/31/16
NIH/NIMH
RD0c constructs: Neural substrates, heritability, and relation to psychopathology
The present study, proposes to test key hypotheses of the Research Domains Criteria (RDoC) initiative, which posits that research on the neurobiological bases of psychopathology has been misled because dysfunctional brain circuits do not align one-to-one with disorders, but align with a number of functional constructs that should be the focus of study.
Role: Contact PI

R01MH102272
National Institute of Mental Health Cascio (PI) 8/7/14-5/31/19
Neural networks for attention to internal and external sensory cues in ASD
The study investigates possible mechanisms for under-responsiveness to external stimuli in autism. It tests the hypothesis that higher order neural networks that integrate and compare competing signals for salience in order to allocate attention are disrupted in autism spectrum disorders
Role: Co-Investigator

R21-DA033341-01A1 Cowan (PI) 12/01/13-1/31/15
Neural Mechanisms of Increased Cortical Excitability in human MDMA/Ecstasy users
This study uses rTMS triggered motor responses to determine if MDMA (Ecstasy) users have altered excitability due to impairments in serotonin functioning arising from MDMA toxicity.
Role: Co-investigator

Completed Research Support

R21DA033611 Zald (PI) 12/01/11 -8/31/14
Dopamine Influences on Self-Regulation and Impulsivity
This study examines whether individual differences in dopamine functioning as measured by [18F]fallypride PET are associated with behavioral measures of impulsivity. The study tests the hypothesis that individuals with lower dopamine autoreceptor levels will have less ability to stop under conditions of high reward. The study also examines whether these dopamine measures are predictive of BOLD fMRI responses during stopping and temporal discounting tasks so as to examine which neural circuits mediate the link between dopamine functioning and behavioral differences.

5R21DA031441 Kessler (PI) 05/01/12-04/30/14
[18F]FPEB Studies of the mGluR5 Receptor and Methamphetamine Abuse
This study aims to develop an mGluR5 ligand for clinical studies and to test for alterations in mGluR 5 receptor availability in subjects with a history of methamphetamine use.
Role: Co-Investigator (primary role completed 10/31/13)

Novo Nordisk Grant Niswender (PI) 01/01/10-06/30/14
Novo Nordisk investigator-initiated weight loss study (Clinical Trial Agreement)
The overall goal of this project is to test the hypothesis that an insulin detimer, known to cause weight loss and alter dopamine transporter functioning in animal studies, causes similar weight loss in humans, and whether this weight loss is associated with changes in dopamine functioning as measured with positron emission tomography.
Role: Co-investigator

R01MH074567 Zald (PI**)** 07/15/07-6/30/13
The amygdala: Emotional modulation of attention
This study examines the effects of unilateral amygdalohippocampectomies on the ability of emotional information to guide attention.

5R21-MH092751 Zald (PI) 12/10/10-11/30/13
Anhedonia and the Neural Basis of Effort-Based Decision-Making in Depression
This study utilizes a translational task based on animal models of motivation (the Effort Expenditure for Reward Task) in conjunction with functional MRI to examine the neural correlates of motivational dysfunction in major depressive disorder.

BIOGRAPHICAL SKETCH

NAME de Wit, Harriet	POSITION TITLE Professor
eRA COMMONS USER NAME hdewit	

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
University of Calgary, Canada	BA	1969	Psychology
Concordia University, Montreal, Canada	MA	1976	Experimental Psychology
Concordia University, Montreal, Canada	PhD	1981	Experimental Psychology

A. Personal statement. I am qualified to provide advice and consultation for this F32 application, investigating individual differences in responses to d-amphetamine. For the past 30 years at the University of Chicago I have studied the behavioral, cognitive, and subjective effects of drugs of abuse, including amphetamine, in human volunteers. The main goal of my research has been to identify determinants and consequences of drug use and abuse, by studying responses to drugs in healthy volunteers in controlled laboratory-based studies. My research overlaps with the research proposed in Dr. Smith's application. I study biological (including genetic), psychological and contextual variables that may be risk factors for drug use, and characterize the direct effects of the drugs on mood and behavior. I have also been actively involved in teaching and education, and have supervised or mentored numerous graduate students, post doctoral fellows and junior faculty. I serve on the executive committees of two post doctoral training grants, I currently co-teach a seminar for K applicants, and I serve on a study section that reviews both research and training applications.

B. Positions and Honors

Positions and Employment

1981-1994	Research Associate to Assistant Professor, Psychiatry, U of Chicago.
1994-2006	Associate Professor (with tenure), Psychiatry, Committee on Clinical Pharmacology, and Biological Sciences Collegiate Division.
2006 -	Professor, Department of Psychiatry and Behavioral Neuroscience; Committee on Neurobiology, Committee on Clinical Pharmacology, and Biological Sciences Collegiate Division, University of Chicago

Memberships and Honors

1991- present	Field Editor, Psychopharmacology
1990-93; 1995-1999	Drug Abuse Advisory Committee, Food and Drug Administration
1997-2001	Biochemistry, Physiology and Medicine Initial Review Group, NIAAA
1999	Solvay Award for Outstanding Basic Psychopharmacological Research in Affective Disorders
1999-2003	Board of Directors, Research Society on Alcoholism
2003	Fellow; American College of Neuropsychopharmacology
2010-14	Deputy Editor, Alcoholism: Clinical and Experimental Research
2004-2008	Member, Training and Career Development Initial Review Group, NIDA
2008-2011	Elected Member of Council of the Senate, University of Chicago
2009	Marian W. Fischman Memorial Lectureship Award, College of Problems on Drug Dependence
2010-	Member, NIH Biobehavioral Regulation, Learning and Ethology Study Section
2015-	Chair, Publications Committee, American College of Neuropsychopharmacology

C. Contributions to science

My research has focused on translational studies of the determinants and consequences of drug use, using laboratory-based drug challenge procedures in laboratory animal models (early studies) and in humans (later). As a graduate student I studied drug self-administration in rodents, developing a reinstatement model of

relapse that has now become a standard procedure in animal studies. For the last 3 decades I have studied behavioral responses to drugs of abuse in healthy young adults, with the goal of identifying risk factors for excessive use. The studies assess the mood-altering effects of licit drugs such as alcohol, caffeine and nicotine, prescription drugs such as d-amphetamine and illicit drugs such as Ecstasy.

Individual differences. Individual differences in responses to drugs, including differences related to personality, sex and hormones, genetics, and stress reactivity, are believed to influence future drug use. Individuals vary markedly in their early responses to drugs, in ways that could influence their risk for repeated use. Understanding this variability and its sources will help to identify those at risk for addiction.

de Wit, H., T.J. Phillips (2012) Do initial responses to drugs predict future use or abuse? *Neuroscience and Biobehavioral Reviews* 36,1565-1576 PMC3372699

Kirkpatrick, M.D., C.E. Johanson, H. de Wit (2013) Personality and the acute subjective effects of *d*-amphetamine in humans. *Journal of Psychopharmacology*, 27. PMID:23343596

Wardle, M.C., A. Hart, A.A. Palmer, H. de Wit (2013) Does *COMT* genotype influence the effects of d-amphetamine on executive functioning? *Genes, Brain and Behavior* 12, 13–20. PMC3553317

King, A, H. de Wit, P. McNamara, D.-C. Cao (2011). Stimulant and sedative alcohol responses and relationship to future drinking. *Archives of General Psychiatry*, 68, 389-399. PMID: 21464363

Hart, A.B., H. de Wit, A.A. Palmer (2013). Candidate gene studies of a promising intermediate phenotype: Failure to replicate. *Neuropsychopharmacology*. 38, 802-816. PMC3671998

Hart, A.B., E.R. Gamazon, B. E. Engelhardt, P. Sklar, C. Hultman, Pa. F. Sullivan, B. Neale, S.V. Faraone, Psychiatric Genomics Consortium: ADHD Subgroup, H. de Wit, N. J. Cox, A.A. Palmer (2014) Genetic variation associated with the euphorigenic effects of *d*-amphetamine is also associated with diminished risk for schizophrenia and ADHD. *Proceedings of the National Academy of Sciences*, 111, 5968-73. PMC4000861

Impulsivity. Impulsivity is a multifaceted construct that is closely linked to drug abuse. I have studied the effects of acute doses of psychoactive drugs on impulsive behaviors in healthy volunteers, and also how individual differences in impulsive behaviors predict acute responses to drugs.

Weafer, J., H. de Wit (2013) Inattention, impulsive action, and subjective response to d-amphetamine. *Drug and Alcohol Dependence* 133, 127-33. PMC3786022

Reynolds, B., Ortengren, A., Richards, J. B., & de Wit, H. (2006). Dimensions of impulsive behavior: Personality and behavioral measures. *Personality and Individual Differences*, *40*, 305-315.

de Wit, H. (2009) Impulsivity as a determinant and consequence of drug use: A review of underlying processes. *Addiction Biology*. 14, 22-31. PMC3640851

Weafer, J. and H. de Wit (in press) Sex differences in impulsive action and impulsive choice. *Addictive Behaviors*. PMC4012004 [Available on 2015/11/1]

de Wit, H., J.D. Flory, A. Acheson, M. McCloskey, S.B. Manuck. (2007) IQ and Nonplanning Impulsivity are independently associated with delay discounting in middle-aged adults. *Personality and Individual Differences* 42, 111-121.

Incubation. 'Incubation' in drug abuse research refers to an escalation in conditioned responses to drug cues after extended periods of abstinence from drugs. It was first identified in animal models, and has been extended to nondrug-rewards. Our laboratory first demonstrated that incubation also occurs in humans. We showed that cigarette smokers experience greater cue-induced craving after 3 weeks of abstinence, than after 1 week of abstinence. This incubation effect has important implications for drug users during treatment, who continue to react to drug-related cues over long periods of time.

Bedi, G., K.L. Preston, D.H. Epstein, S.J. Heishman, G.F Marrone, Y. Shaham, H. de Wit (2011) Incubation of cue-induced cigarette craving during abstinence in human smokers. *Biological Psychiatry* 69, 708-11. PMC3027849.

Conditioned drug effects. Conditioned responses to cues previously paired with drugs promote and sustain drug-seeking behavior. However, most research on drug-cue conditioning has been conducted in animal models, and few studies have investigated acquisition of drug-cue associations in humans. We have developed procedures for studying acquisition of both conditioned place preference and conditioned responses

to drug-paired cues in healthy adults. These procedures extend the preclinical work to humans, and set the stage to study ways to reduce cue-induced relapse.

Childs, E., H. de Wit (2013) Contextual conditioning enhances the psychostimulant and incentive properties of *d*-amphetamine in humans. *Addiction Biology*, 18, 985-92. PMID: 22129527 [PubMed - in process]

Childs, E., H. de Wit (2009) Amphetamine-induced place preference in humans. *Biological Psychiatry* 65, 900-4. PMC2693956

Mayo, L., D. Fraser, E. Childs, R. Momenan, D. Hommer, H. de Wit, M. Heilig (2013). Conditioned preference to a methamphetamine-associated contextual cue in humans. *Neuropsychopharmacology*. 38, 921-929. PMC3629404

Napier, T.C., A.A. Herrold, H. de Wit (2013) Using conditioned place preference in the development of relapse prevention medications. *Neuroscience and Biobehavioral Reviews, 37, 2081-6,* PMC3815959

Link to complete reference list: http://www.ncbi.nlm.nih.gov/sites/myncbi/collections/bibliography/41146552/

D. Research Support

R01DA032015 de Wit (PI) 7/15/2011 -- 4/30/2016
Genetic basis of impulsivity in humans
This project examines the associations between genotypic variation and behavioral indices of impulsive behavior in healthy young adults.

R01DA02812 de Wit (PI) 01/01/1981 -- 1/31/2020
Determinants of drug preference in humans
This project investigates behavioral, physiological and psychological factors that influence acute responses to drugs in healthy adults.

R21DA031796 de Wit (PI) 02/15/2012 - 01/31/2015 (NCE)
Memory effects of stimulant drugs in humans.
This project investigates the effects of stimulant drugs on encoding and retrieval of emotional memories in healthy adults.

R01 DA037011-01 de Wit (PI) 8/1/2014-06/30/2019
Acquisition and persistence of drug cue conditioning in humans.
This project investigates the acquisition of conditioned responses to cues, and investigates the nature of the conditioned response using fMRI techniques.

RO1 AA013746-11 King (PI) 02/01/2014-01/31/2019
Alcohol Stimulation and Sedation in Binge Drinkers
This project investigates acute responses to alcohol in heavy drinkers, and the relation of these responses to future alcohol consumption.

R21DA033488-01 Childs (PI) 08/01/2014-07/31/2016
Contextual conditioning with amphetamine in humans: Causes and consequences
This project investigates the acquisition of conditioned preferences for places where stimulant drugs are experienced.

R01AA022961-01 Childs (PI) 07/01/2014-06/31/2018
How do conditioned alcohol associations promote alcohol drinking
This project investigates the effects of conditioned alcohol-related environments on alcohol consumption.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Palmer, Abraham A.	Associate Professor of Human Genetics; Psychiatry and Behavioral Neuroscience
eRA COMMONS USER NAME (credential, e.g., agency login) PALMERAB	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Chicago	B.A.	09/88-08/91	Biology
University of California, San Diego	Ph.D.	09/93-09/99	Biomedical Sciences
Oregon Health & Science University	Postdoctoral	10/99-02/02	Behavioral Genetics
Columbia University	Postdoctoral	03/02-07/04	Genetics

A. Personal Statement

My work focuses on the role of genetic variation in behavior. I am particularly interested in animal models of psychiatric diseases such as fear and anxiety, drug abuse, schizophrenia and epilepsy. A major aspect of my work has been to develop novel populations and statistical tools to perform forward genetic studies aimed at gene discovery. In addition to discovering new genes, I have also worked to put these discoveries in biological context by doing hypothesis driven studies aimed at elucidating the molecular, cellular and systems level mechanisms by which individual genes (e.g. Glo1, Csnk1e, Cacna1c) influence behavior.

Of special relevance to this proposal, I have been involved in identifying genetic variations in human subjects that relate to differences in subjective response to d-amphetamine. Using a genome wide association approach, we have identified a single nucleotide polymorphism in CDH13 (rs3784943) associated with variability in subjective responses to d-amphetamine. This proposal will explore the functional consequences of that *CDH13* SNP using PET in addition to identifying other SNPs associated with timing of peak subjective responses to d-amphetamine or variation in PET measures of DA system function.

I am the director of a NIDA-funded P50 Center of Excellence (www.ratgenes.org) and a NIMH-funded T32 training grant that focuses on psychiatric genetics (pgtg.uchicago.edu). I am the past president of the International Behavioral and Neural Genetics Society and am also an associate editor for that societies' journal: Genes, Brain and Behavior.

B. Positions and Honors

Prior Employment

1989-91 Laboratory Technician with Dr. **Lewis S. Seiden**, University of Chicago
1991-93 Staff Research Assistant with Dr. **William F. Ganong**, University of California San Francisco
1993-99 Graduate Student with Dr. **Morton P. Printz**, University of California San Diego
1999-02 Postdoctoral Fellow with Dr. **Tamara J. Phillips**, Oregon Health & Science University
2002-03 Postdoctoral Fellow with Dr. **T. Conrad Gilliam**, Columbia University
2004-05 Associate Research Scientist, Columbia Genome Center, Columbia University
2005- Assistant Professor of Human Genetics (primary), University of Chicago
2006- Assistant Professor of Psychiatry (Secondary), University of Chicago
2012- Associate Professor of Human Genetics (primary; with tenure), University of Chicago
2014- Associate Professor of Psychiatry and Behavioral Neuroscience (co-primary)

Professional Memberships

American Association for the Advancement of Science (**AAAS**), American College of Neuropsychopharmacology (**ACNP**; Associate Member), American Society of Human Genetics (**ASHG**), Complex Trait Community (**CTC**), International Behavioral and Neural Genetics Society (**IBANGS**), International Society of Psychiatric Genetics (**ISPG**), International Mammalian Genome Society (**IMGS**), Society for Neuroscience (**SFN**).

Other experience

2006- Grant reviewing for NIH/CSR (ad hoc): GHD, ZRG1, ZMH1, GXM; National Science Foundation (**NSF**); The Wellcome trust; French National Research Agency (**ANR**); site visit for NHGRI

2010- Associate Editor, *Genes, Brain & Behavior*
2010 Organizer of complex trait consortium meeting in Chicago, IL, May 7-10, 2010 (www.CTC2010.org)
2010- Co-organizer of "*Short Course on the Genetics of Addiction*", Jackson Labs, Bar Harbor, ME
2012- External Advisory Board for INIAStress (U01AA013641)
2013-15 President-Elect, President, Past-President (consecutive 1-year terms): IBANGS (www.IBANGS.org)
2013- Program Director of NIMH funded pre-and postdoctoral training grant, *"Training in emerging multidisciplinary approaches to mental health and disease"*; (T32MH020065; pgtg.uchicago.edu)
2014 Director, Center for Rat GWAS (NIDA-funded P50 Center of Excellence; www.ratgenes.org)
2014 Associate Editor, *Genetics*

Honors

2000, '01 Research Society on Alcoholism Junior Investigator Award
2003, '05 NARSAD Young Investigator Award
2006 Schweppe Foundation Career Development Award
2006 International Behavioral and Neural Genetics Society Travel Award
2007 IBANGS Junior Faculty Outstanding Young Investigator Award
2009 IBANGS Young Scientist Award

C. Selected Peer-reviewed Publications (selected from 115 total)

1. Heydemann A, Ceco E, Lim JE, Hadhazy M, Ryder P, Moran JL, Beier DR, **Palmer AA**, McNally EM. Latent transforming growth factor binding protein 4 modifies muscular dystrophy, *J Clin Invest*, **2009** 119:3703, PMC2786802
2. Cheng R, Lim JE, Samocha KE, Sokoloff G, Abney M, Skol AD, **Palmer AA**. Genome-wide association studies and the problem of relatedness among advanced intercross lines and other highly recombinant populations. *Genetics*, **2010**, 185:1033; PMC2907190
3. Samocha KE, Lim JE, Cheng R, Sokoloff G, **Palmer AA**. Fine mapping of QTL for prepulse inhibition in LG/J and SM/J mice using F2 and advanced intercross lines. *Genes Brain Behav*, **2010**, 9:759 PMC3749925
4. Philip VW, Sokoloff G, Ackert-Bicknell C, Striz M, Branstetter L, Beckmann MM, Spence JS, Naswa S, Jackson BL, Galloway LD, Barker P, Wymore AM, Hunsicker PR, Durtschi DC, Shaw GS, Shinpock S, Manly KF, Miller DR, Donahue K, Culiat CT, Churchill GA, Lariviere WR, **Palmer AA**, O'Hara B, Voy BH, Chesler EJ. Genetic analysis in the Collaborative Cross breeding population: Heritability, genetic correlation and QTL mapping, *Genome Res,* **2011** 21:1223; PMC3149490
5. Tarantino LM, Reyes TM, **Palmer AA**. Animal models of prenatal protein malnutrition. In: The Origins of Schizophrenia (Brown AS, Patterson PH, Eds.), Columbia University Press, New York, NY, **2011**
6. Winawer MR, Seal SR, Phillips AG, Rabinowitz D, **Palmer AA**. Mapping a Mouse Limbic Seizure Susceptibility Locus on Chromosome 10, *Epilepsia*, **2011**, 52(11):2076, PMC3346290
7. Bryant CD, Parker CC, Zhou L, Olker C, Chandrasekaran RY, Wager TT, Bolivar VJ, Loudon AS, Vitaterna MH, Turek FW, **Palmer AA**. *Csnk1e* is a genetic regulator of sensitivity to psychostimulants and opioids *Neuropsychopharmacology*, **2012**, 37(4):1026, PMC3280656
8. Distler MG, Plant LD, Sokoloff G, Hawk AJ, Aneas I, Wuenschell GE, Termini J, Meredith SC, Nobrega MA, **Palmer AA**. Glyoxalase 1 increases anxiety by reducing $GABA_A$ receptor agonist methylglyoxal. *J Clin Invest,* **2012**, *1*22(6):2306, PMC3366407
9. Distler MG, Opal M, Dulawa, SC, **Palmer AA**. Assessment of behaviors modeling aspects of schizophrenia in Csmd1 mutant mice, **2012**, *PLoS ONE*, 7(12): e51235, PMC3524225
10. Distler MG, Gorfinkle N, Papale LA, Wuenschell GE, Termini J, Escayg A, Winawer, MR, **Palmer AA**. Glyoxalase 1 and its substrate methylglyoxal are novel regulators of seizure susceptibility. *Epilepsia*, **2013**, 54(4):649, PMC3618549
11. Hart AB, de Wit H, **Palmer AA**. Candidate gene studies of intermediate phenotypes: failure to replicate. *Neuropsychopharmacology*, **2013**, 38(5):802-16, PMC3671998

12. Li Y, Cheng R, Spokas KA, **Palmer AA**, Borevitz J. Genetic Variation for Life History Sensitivity to Future Warming in Arabidopsis thaliana. *Genetics,* **2014**, 196(2):569, PMC3914627 (Issue highlight and also included in 2014 Genetics spotlight booklet)

13. Hart AB, Gamazon ER, Engelhardt BE, Skalr P, Hultman C, Sullivan PF, Neale B, Faraone SV, Psychiatric Genomics Consortium: ADHD Subgroup, de Wit H, Cox NJ, **Palmer AA**. Genetic variation associated with the euphorigenic effects of d-amphetamine is also associated with diminished risk for schizophrenia and ADHD. *PNAS*, **2014**, 11(16):5968, PMC4000861

14. Swaggart KA, Demonbreun AR, Vo A, Swanson K, Kim E, Fahrenbach JP, Holley-Cuthrell J, Eskin A, Chen Z, Squire K, Heydemann A, **Palmer AA**, Nelson SF, McNally EM. Annexin A6 modifies muscular dystrophy by mediating sarcolemmal repair, *PNAS*, **2014**, 111(16):6004, PMC4000833

15. Cacioppo JT, Cacioppo S, Dulawa SC, **Palmer AA**. Social neuroscience and its potential contribution to psychiatry, *World Psychiatry,* **2014**, 13(2):131, PMC4102278

D. Research Support

Ongoing research support

P50 DA037844 (PI: **Palmer, Abraham**) 6/15/14-4/30/19
NIH/NIDA; *"Integrated GWAS of complex behavioral and gene expression traits in outbred rats"*
The goal of this grant is to use quantitative genetic techniques to identify genes and alleles that influence a constellation of psychologically complex behavioral phenotypes that are associated with drug abuse.

T32 MH020065 (MPIs: **Palmer, Abraham** & Cox, Nancy) 07/01/13-06/30/18
NIH/NIMH; *"Training in Emerging Multidisciplinary Approaches to Mental Health and Disease"*
The goal of this project is to train pre- and post-doctoral students in the methodology that will be important for the next generation of progress in understanding the genetics of psychiatric health and disease.

R01 DA021336 (PI: **Palmer, Abraham**) 9/15/06-03/31/16
NIH/NIDA; "*Systems genetic analysis of methamphetamine's motivational effects in a mouse AIL"*
The objective of this project is to assess the motivational properties of drugs in mice and investigate their genetic underpinnings using RNASeq and advanced intercross lines.

R01 GM097737 (PI: **Palmer, Abraham**) 04/01/2011-03/31/15
NIH/NIGMS; *"Genome-wide association studies in outbred mice"*
Performign GWAS in an outbred mouse popualtions for many traits, RNASeq to find eQTLs and synthesis.

R21 DA036672 (PI: **Palmer, Abraham**) 03/01/14-02/28/16
NIH/NIDA; *"GWAS for goal versus signed tracking in genetically heterogeneous rats"*
Perform GWAS in Sprague Dawley rats previously phenotypes for the attribution of incentive salience to a cue.

R21 MH020065 (PI: **Palmer, Abraham**) 09/26/13-08/31/15
NIH/NIMH; *"efficient discovery of epistatic modifiers of Cacna1c in mice: extending on GWAS"*
Detect epistatic modifiers of primary loss-of-function mutation in *Cacna1c* using a series of F_1 crosses.

R01 DA032015 (PI: **de Wit, Harriet**) 07/15/11 – 04/30/16
NIH/NIDA; *"The genetic basis of impulsive behavior in humans"*
Identify the underlying factor structure of impulsive behaviors, and to investigate genetic influences.

R21MH104829-01 (PI: **Dulawa**) 08/01/14 – 07/31/16
NIH/NIMH; "*Translating OCD GWAS findings into mice: identifying epistatic modifiers of BTBD3*"
To 1) identify genetic modifiers of BTBD3, and 2) demonstrate that this novel F1 screening approach provides a powerful and efficient means to identify epistatic modifiers of primary mutations.

Completed research support

R01 MH079103 (PI: **Palmer, Abraham**) 06/01/07-05/31/13 (competitive renewal application pending)
NIH/NIMH; *"Finding Genes that Cause QTL for Fear Learning and Anxiety"*

Use consomic, advanced intercross line (AIL), inbred and bioinformatics to mice to map QTL for fear learning.

R01 NS061991 (PI: **Winawer, Melodie**) 07/01/08 – 06/30/13
NIH/NINDS; *"Genetics of Mouse Seizure Susceptibility"*
Identification of genes that control seizure susceptibility in mice using QTL and bioinformatics.

R01 AR056280 (PI: **Blizard, David**) 04/01/09 – 02/28/14
NIH/NIAMS; "*Genetic Variation of Muscle Mass"*
Identify genes responsible for differences in muscle mass found in inbred strains of mice.

P60 DK020595 (PI: **Bell, Graeme**) 12/01/96 – 01/31/13 (internal pilot grant)
NIH/NIDDK; "*Diabetes Research and Training Center"*
Examine the role of Glo1 and its substrate MG in beta-cell function and other possible roles in diabetes

R03 DA027545 (PI: **Palmer, Abraham**) 09/01/09 – 08/31/11
NIH/NIDA; "*Weighted genome-wide association study of amphetamine sensitivity in humans"*
Identify polymorphisms that influence the response to d-amphetamine in healthy young adults.

R21 DA026570 (PI: **de Wit, Harriet**) 09/30/09 – 08/31/11
NIH/NIDA; **"***Is Ectasy an Empathogen? Effects of MDMA on Social and Emotional Processing"*
Investigate empathogenic properties of MDMA in human subjects including genetic basis of sensitivity.

BIOGRAPHICAL SKETCH

NAME Cowan, Ronald L.	POSITION TITLE Professor of Psychiatry, Psychology, and Radiology Director, Psychiatric Neuroimaging Program
eRA COMMONS USER NAME cowanrl	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Christian Brothers College, Memphis, TN	B.S.	1980-1984	Biology
University of Tennessee, Memphis, TN	Ph.D.	1984-1990	Anatomy & Neurobiology
Cornell University Medical College, New York, NY	M.D.	1990-1994	Medicine
Massachusetts General Hospital/Harvard Medical School, Boston MA		1994-1995	Internship in Internal Medicine
McLean Hospital/Harvard Medical School, Belmont MA		1995-1998	Residency in Adult Psychiatry

A. Personal Statement

My research program has focused on the use of neuroimaging approaches to examine the neurobiology of reward system dysfunction in relation to obesity and drug dependence with a particular interest in dopamine and serotonin function. With collaborators, I am investigating the role of dopamine in fundamental human behaviors linked to addiction and behavioral dysregulation (*e.g.,* impulsivity and novelty). Modeled and grounded in our earlier work with addiction, I lead a program of research examining neural systems subserving motivated behavior and its dysregulation. Areas of inquiry include child and adult obesity, MDMA/Ecstasy/Molly effects, cannabis use, and sexual behavior with a focus on monoamine effects and neuroimaging. We have published work examining the role of altered attention salience in obese adults; food cue effects and reward in autism; and the status of dopamine receptors following bariatric surgery. I was the PI on an NICHD-funded grant that examined the neurobiology of feeding behavior in children to examine food cue associated activation, the effect of satiety and hunger on food cue activation, and food composition and palatability on brain activation. I have mentored undergraduate, graduate, and medical students and also mentor several junior faculty regarding fMRI applications in this area. I will work closely with Dr. Smith on all aspects of neuroimaging analysis and data interpretation.

B. Positions and Honors

Positions and Employment

1984-1990 Graduate Teaching Assistant. University of Tennessee, Memphis, TN
1990-1994 Research Associate. Cornell University Medical College, Department of Neurology and Neuroscience; New York, NY. (Sponsor: Dr. Virginia M. Pickel).
1994-1995 Clinical Fellow in Medicine. Harvard Medical School, Boston, MA.
1994-1995 Intern in Medicine. Massachusetts General Hospital, Boston, MA
1995-1998 Clinical Fellow in Psychiatry. Harvard Medical School, Boston, MA
1995-1998 Resident in Psychiatry. McLean Hospital, Belmont, MA
1996-1999 Consultant. Vinfen Corporation, Cambridge, MA
1998-11/02 Instructor in Psychiatry. Harvard Medical School, Boston, MA.
1998-11/02 Assistant Psychiatrist. McLean Hospital, Belmont, MA.
1998-11/02 Assistant Physiologist, Brain Imaging Center. McLean Hospital, Belmont, MA.
1999-1/00 Medical Director, After Hours Program, May Behavioral Health/Bayridge Hospital
10/01-11/02 Director, Laboratory of Human Neurophysiology. Brain Imaging Center, McLean Hospital, Belmont
05/00-3/05 Medical Director, Depression Section, Veritas Medicine (veritasmedicine.com) Cambridge, MA.
11/02-10/03 Research Associate, Psychiatry, Harvard Medical School, Boston MA.

11/02-10/03	Research Associate, Brain Imaging Center, McLean Hospital, Belmont, MA
11/02-	Assistant Professor of Psychiatry, Vanderbilt University Medical Center, Nashville, TN.
11/02-	Assistant Professor of Radiology & Radiological Sciences, Vanderbilt University Medical Center.
11/02-	Attending Psychiatrist, Vanderbilt University Hospital, Nashville, TN
01/03-	Faculty, Vanderbilt University Institute for Imaging Sciences (VUIIS)
02/03-	Investigator, Vanderbilt Center for Integrative and Cognitive Neuroscience (CICN)
05/04-	Member, Vanderbilt Kennedy Center for Research on Human Development
08/05-03/07	Program Director, Vanderbilt Brain Awareness Month
05/06-	Director, Psychiatric Neuroimaging Program, Vanderbilt University Medical Center
03/07-	Faculty, Vanderbilt Addiction Center
07/09-	Faculty, Vanderbilt Institute for Obesity and Metabolism (VIOM)
12/09-	Assistant Professor of Psychology (Secondary), Vanderbilt University, Nashville TN
01/11-	Associate Professor of Psychiatry, Vanderbilt University School of Medicine, Nashville, TN.
10/11-	Associate Professor of Psychology (Primary), Vanderbilt University, Nashville, TN
10/11-	Associate Professor of Radiology (Secondary), Vanderbilt University School of Medicine, Nashville, TN.
07/14-	Vice Chair for Education, Department of Psychiatry, Vanderbilt University School of Medicine, Nashville TN.
07/14-	Director, Residency Training. Department of Psychiatry, Vanderbilt University School of Medicine, Nashville TN.
07/14-	Professor of Psychiatry, Vanderbilt University Medical School of Medicine, Nashville, TN.
09/14-	Professor of Psychology (Secondary), Vanderbilt University, Nashville, TN.
10/14-	Professor of Radiology & Radiological Sciences (Secondary), Vanderbilt University Medical Center, Nashville, TN.

Honors

1986-1988	Neuroscience Center of Excellence Predoctoral Fellow
1989-1990	Snider Scholar, Cornell University Medical College
1988-1990	NIMH Predoctoral Fellow (NRSA)
1992-1994	Bigelow Scholar, Cornell University Medical College
1991-1994	Astor Scholar, Cornell University Medical College
1993	NIH Summer Research Fellow
1993-1994	Rock Sleyster Memorial Scholar
1994	Oskar Diethelm Prize for Excellence in Psychiatry
1996-1998	APA/Glaxo Wellcome Fellow
1996-1998	Council for Research, American Psychiatric Association
1998-1999	Ethel Dupont-Warren Fellow, Harvard University
1998-1999	Livingston Award, Harvard University
1999-	Drug Abuse Research Scholars Program in Psychiatry (NIDA/APA Career Award)
2004, 2007	Future Leaders in Psychiatry

C. Selected Peer-reviewed publications (selected from 52 peer-reviewed publications)

1. Castellanos EH, Charboneau E, Dietrich MS, Park S, Bradley BP, Mogg K, Cowan RL. Obese adults have visual attention bias for food cue images: evidence for altered reward system function. Int J Obes (Lond). 2009 Sep;33(9):1063-73. PMID: 19621020
2. Cascio, CJ, Foss-Feig, JH, Heacock, JL, Newsom, CR, Cowan, RL, Benningfield, MM, Rogers, BP, Cao, A. Response of neural reward regions to food cues in autism spectrum disorders. Journal of Neurodevelopmental Disorders, J Neurodev Disord. 2012; 4(1): 9. Published online 2012 May 17. PMCID: PMC3436657
3. Dunn JP, Cowan RL, Volkow ND, Feurer ID, Li R, Williams DB, Kessler RM, Abumrad NN. Decreased dopamine type 2 receptor availability after bariatric surgery: preliminary findings. Brain Res. 2010 Sep 2;1350:123-30. Epub 2010 Mar 31. PMCID: PMC2926260

4. Savage SW, Zald DH, Cowan RL, Volkow ND, Marks-Shulman PA, Kessler RM, Abumrad NN, Dunn JP. Regulation of novelty seeking by midbrain dopamine D2/D3 signaling and ghrelin is altered in obesity. Accepted January 9, 2014, Obesity. PMCID in progress.
5. Benningfield MM, Blackford JU, Ellsworth ME, Samanez-Larkin GR, Martin PR, Cowan RL, Zald DH. Responses to reward anticipation and delay discounting behavior in healthy youth. Accepted October 30, 2013, Developmental Cognitive Neuroscience. PMCID in progress.
6. Charboneau EJ, Dietrich MS, Park S, Cao A, Watkins TJ, Martin PR, Buchowski MS, Blackford JU, Benningfield M, Cowan RL. Cannabis cue-induced brain activation correlates with drug craving in limbic and visual salience regions*. Accepted June 17, 2013, Psychiatry Research: Neuroimaging. PMCID in progress.*
7. Zald DH, Cowan RL, Riccardi P, Baldwin R, Sib Ansari M, Li R, Shelby ES, Smith CE, McHugo M, & Kessler RM. Midbrain dopamine receptor availability is inversely associated with novelty seeking traits in humans. J Neurosci. 2008 Dec 31;28(53):14372-8. PMCID: PMC2748420
8. Cowan RL. Neuroimaging Research in Human MDMA Users: A Review. Psychopharmacology 2007;189(4):539-536. PMID: 16847678
9. Cowan RL, NR Bolo NR, Dietrich M, Haga E, Lukas SE, Renshaw PF. Occipital cortical proton MRS at 4 Tesla in human MDMA polydrug users. Psychiatry Research: Neuroimaging; 2007(155(3):179-188. PMCID: PMC2132656
10. Cowan RL, Wood J, Dietrich M, Frederick B de B, Lukas S E, Renshaw P F. Differential effects of d-amphetamine on photic activation to blue light: a novel BOLD fMRI assay of human central nervous system dopamine function. 2008 SYNAPSE. Jan 31;62(4):268-272. PMID: 18240321
11. Raj V, Liang HC, Woodward ND, Bauernfeind AL, Lee J, Dietrich MS, Park S, Cowan RL. Altered regional brain activation during semantic processing in human MDMA users: a 3 T fMRI BOLD study. J Psychopharmacol. 010 Feb;24(2):187-201. Epub 2009 Mar 20. PMCID: PMC3198867
12. J. Karageorgiou, M. Dietrich, Neil D. Woodward, Evonne J Charboneau, Jennifer U. Blackford, Ronald Salomon, Cowan RL. Prior MDMA (Ecstasy) use is Associated with Increased Basal Ganglia-Thalamocortical Circuit Activation During Motor Task Performance in Humans: An fMRI Study. Neuroimage. 2009 Jul 1;46(3):817-26. Epub 2009 Mar 2. PMCID: PMC2805435
13. Bauernfeind AL, Dietrich MS, Blackford JU, Charboneau EJ, Lillevig JG, Cannistraci CJ, Woodward ND, Cao A, Watkins T, Di Iorio CR, Cascio C, Salomon RM, Cowan RL. Human Ecstasy Use is Associated with Increased Cortical Excitability: An fMRI Study. Neuropsychopharmacology. 2011 May;36(6):1127-41. Epub 2011 Feb 16. PMCID: PMC3079831
14. Salomon RM, Karageorgiou J, Dietrich MS, McLellan JY, Charboneau EJ, Blackford JU, Cowan RL. *In Press.* MDMA (Ecstasy) association with impaired fMRI BOLD thalamic coherence and functional connectivity. *Drug and Alcohol Dependence,* 2012 Jan 1;120(1-3):41-7. Epub 2011 Jul 31 PMCID: PMC3224864
15. Di Iorio CR, Watkins TJ, Dietrich MS, Cao A, Blackford JU, Rogers BP, Ansari MS, Baldwin RM, Li R, Kessler RM, Salomon RM, Benningfield M, Cowan RL. Evidence for chronically altered cortical serotonin function in human female recreational ecstasy (MDMA) polydrug users. Arch Gen Psychiatry. 2012 April; 69(4): 399–409. Published online 2011 December 5. *PMCID: PMC3538835*

D. Research Support

Ongoing Research Support

1R21DA033341 Cowan, RL (PI)

NIDA

Increased Cortical Excitability in MDMA/Ecstasy Users 01/15/2013-12/31/2015 (NCE)

This application proposes to examine the neural basis of altered cortical excitability in human ecstasy users via a multimodal approach. Methods include MRS spectroscopy, Transcranial Magnetic Stimulation, and fMRI.

NIA R21AG045735 MPI: Cowan, RL; Monroe Todd B.

Age-Related Differences in Psychophysical and Neurobiological Response to Pain

07/01/2014-06/30/2016

This application examines perceptual and neurophysiological differences in response to thermal pain.

Completed Research Support

R21DA031441 (Cowan, RL/Kessler, RM) MPI 05/01/12-04/30/2014
NIH/NIDA
[18F]FPEB Studies of the mGluR5 Receptor and Methamphetamine Abuse
This application characterizes a PET ligand for mGluR5 imaging and applies this ligand to studying glutamate receptor function in methamphetamine users.
Role: Contact PI

VUMC 36281 (Niswender) 04/01/2010 – 12/31/2014
Novo Nordisk
Making an "obese" brain (and body) lean: insulin detemir, monoamines, and reward
This investigator-initiated project is a translational parallel to Dr. Niswender's basic science work exploring insulin action in the brain.
Role: Co-investigator

R21DK079402 Cowan RL (PI) 08/20/2008 - 07/31/2012
NIH/NICHD
Neurobiology of Child Obesity: An MRI Study
This exploratory R21 application seeks to examine differences in regional brain activation in obese and normal weight children and adolescents in response to food cues differing in caloric content.
Role: Principal Investigator

R21DA020149 Cowan RL 05/05/07-04/30/11
NIH/NIDA
Genetic factors in human MDMA toxicity: a PET study
This project seeks to examine the influence of common polymorphisms of the serotonin transporter on MDMA-induced neurotoxicity as assayed by 5-HT2A receptor binding assayed using setoperone PET.
Role: Principal Investigator

R21 MH073800 Cowan RL 01/01/06 - 12/31/08
NIH/NIMH
SERT polymorphisms and human cortical 5-HT2A receptors
This project seeks to examine the influence of common polymorphisms of the serotonin transporter on 5-HT2A receptor binding in healthy control subjects assayed using setoperone PET.
Role: Principal Investigator, responsible for all aspects of the project.

R01 DA15137 Cowan RL 08/01/04-01/31/09
NIH/NIDA
MR Analysis of Persistent CNS Damage in Human MDMA Users
This project is designed to conduct a comprehensive neuroimaging study of regional brain changes in human MDMA users.
Role: Principal Investigator

R21 DA033611 Zald, DH 09/30/11 - 09/29/13
NIDA
Dopamine Influences on Self-Regulation and Impulsivity
The purpose of this project is to form the basis of a translational research program on the prediction and prevention of relapse in disorders characterized by impulse control deficits.
Role: Co-investigator

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Randy D. Blakely	Allan D. Bass Professor of Pharmacology & Psychiatry
eRA COMMONS USER NAME BlakelyR	

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Emory University	B.A.	1981	Philosophy
The Johns Hopkins School of Medicine	Ph.D.	1987	Neuroscience
HHMI/Yale University School of Medicine	Postdoc	1987-90	Molecular Neurobiology

A. PERSONAL STATEMENT:

My research focuses on the molecular neurobiology of neurotransmitter signaling at central and peripheral synapses, and the contribution made by membrane transporter proteins to synaptic neurotransmitter homeostasis and brain disorders. Our work utilizes a range of approaches, from molecular modeling and structure-function paradigms to studies with genetically modified transporters *in vivo* to examination of the impact of transporter gene variation in complex human diseases. Our work began as the molecular era of neurotransmitter transporter biology was beginning, efforts we contributed to in the cloning multiple human, rodent and invertebrate neurotransmitter transporters. Our work has uncovered multiple regulatory pathways that function in cells to control the surface expression and transport capacity of neurotransmitter transporter proteins, basic research findings that merged with translational studies of transporter protein contributions to autism, ADHD, OCD, depression, cardiovascular and gastrointestinal disorders. These studies have led to the creation of important animal models that allow for the study of neurotransmitter transporters *in vivo* and how their alterations impact physiology and behavior and the development of novel diagnostic and therapeutic strategies. Having had, like many, personal experience with the devastating impact of brain disorders on the lives of children, adults and families, I am gratified that my group's contributions, often at a very basic level, have the potential to make a lasting contribution to our understanding of these conditions and their treatment. I am also gratified that my efforts have been extended to training a superior crop of junior scientists who I have learned from as much as I have given. I am delighted that I have the opportunity to assist Mr. Smith as he takes these important steps toward his career objective to become an independent investigator.

B. POSITIONS AND HONORS

Positions: Assistant Professor, Dept of Anatomy and Cell Biology, Emory University (1990-1994), Associate Professor, Dept. of Anatomy and Cell Biology, Emory University (1995), Associate Professor, Dept. of Pharmacology, Vanderbilt School of Medicine (1995-1998); Director, Center for Molecular Neuroscience, Vanderbilt School of Medicine (1996-2011), Professor, Dept. of Pharmacology, Vanderbilt School of Medicine (1997-present); Director, NIMH Cellular and Molecular Neuroscience Training Program (2001-2002); Director, Neurogenomics Postdoctoral Training Program (2002-present); Professor of Psychiatry, Vanderbilt School of Medicine (2004-present); Director (Interim), Vanderbilt Brain Institute (2006-2007); Director, Vanderbilt/NIMH Silvio O. Conte Center for Neuroscience Research (2007-present); NIMH Board of Scientific Counselors (2011-2014, Chair 2012-2014).

Honors: National Merit Scholar (1977), John Gordon Stipe Scholar, Emory University (1977-1981), Macy Fellowship for Foreign Study (1981), National Finalist, Rhodes Scholarship (1981), *Phi Beta Kappa* (1981), Rotary Scholar (1981), *Sigma Xi* Research Award (1982*),* Mallinckrodt Young Investigator Award (1991-1994), Herrick Award, Outstanding Young Investigator in Neuroscience (1992), Allan D. Bass Endowed Chair, Dept. of Pharmacology, Vanderbilt School of Medicine (1995-present), Grass Lecturer, University of British Columbia

(1996), NARSAD Established Investigator Award (1996), Grass Lecturer, Univ. Of Mississippi Med. Ctr., (1997), Vice-Chair, Catecholamine Gordon Conference (1999), ACNP Daniel H. Efron Award for Excellence in Basic Research (1999), Chair, Catecholamine Gordon Research Conference (2001), ASPET Ray Fuller Lecturer (2003), Charles R. Park Prize for Research, Vanderbilt University (2003), ASPET Julius Axelrod Symposium Lecturer (2004), NIMH MERIT Award (2004), NARSAD Distinguished Investigator Award (2005), Alzheimer's Association Zenith Award (2005), Inaugural Ray Fuller Lecturer in the Neurosciences, ASPET (2005), Grass Lecturer, Ohio State (2007), LSU Chancellor's Lecturer in Neuroscience (2007), Julius Axelrod Prize, ASPET (2008), ASPET-Astellas Award in Translational Pharmacology (2008), F. Peter Guengerich Award for Postdoctoral Mentoring, Vanderbilt University (2009), Fellow-American Academy for the Advancement of Science (2009), F.C. MacIntosh Endowed Lectureship, McGill University (2011), Robert M. Hearin Distinguished lectureship, University of Mississippi Medical School (2013), Booney Vance Memorial Lecture, Quinlan College of Medicine, East Tennessee State Univ (2013), SFB35 Symposium, Keynote Speaker (2013), Brain In Flux ISN Satellite Meeting, Keynote Speaker (2013), Chancellor's Award for Research, Vanderbilt University (2013), Cozart Heritage Lecture, Meharry Medical College (2014), University of Montana Innovation and Imagination, Keynote Speaker (2014), Founder's Lecturer, American Academy of Child & Adolescent Psychiatry (2014), Delores Shockley Award for Minority Research Mentorship (2015).

C. SELECTED PEER-REVIEWED PUBLICATIONS (From 283 Published or *in press*)

1. Pacholczyk, T., Blakely, R. D., and Amara, S. G. Expression cloning of a cocaine- and antidepressant-sensitive human noradrenaline transporter, **Nature**, 350:350-354, 1991. [PMID: 2008212]
2. Blakely, R.D., Berson, H.E., Fremeau, Jr., R.T., Caron, M.G., Peek, M.M., Prince, H.K., and Bradley, C.C. Cloning and expression of a functional serotonin transporter from rat brain, **Nature**, 354:66-70, 1991. [PMID: 1944572]
3. Ramamoorthy, S., Bauman, A.L., Moore, K.R., Han, H., Yang-Feng, T., Chang, A.S., Ganapathy, V., and Blakely, R.D. Antidepressant- and cocaine-sensitive human serotonin transporter: Molecular cloning, expression, and chromosomal localization, **Proc Natl Acad Sci USA**, 90:2542-2546, 1993. [PMID: 7681602]
4. Ramamoorthy, S. and Blakely, R.D. Phosphorylation and sequestration of serotonin transporters differentially modulated by psychostimulants, **Science**, 285:763-766, 1999. [PMID:10427004]
5. Prasad, H.C., Zhu, C.B., McCauley, J.L., Samuvel, D.J., Ramamoorthy, S., Shelton, R.C., Hewlett, W.A., Sutcliffe, J.S., Blakely, R.D. Human serotonin transporter variants display altered sensitivity to protein kinase G and p38 mitogen activated protein kinase, **Proc Natl Acad Sci USA**, 102:11545-11550, 2005. [PMID: 16055563; PMCID: 1183547]
6. Carvelli, L., McDonald, P.W., Blakely, R.D., De Felice, L. Dopamine transporters depolarize neurons via a channel mechanism, **Proc Natl Acad Sci USA**, 101: 16046-51, 2004. [PMID: 15520385, PMCID: 528740]
7. Carvelli, L., Blakely, R.D., DeFelice, L.J., Dopamine transporter/syntaxin 1A interactions regulate transporter channel activity and dopaminergic synaptic transmission, **Proc Natl Acad Sci USA,** 105:14192-14197, 2008. [PMID: 18768815, PMCID: 2528871]
8. Sakrikar, D., Mazei-Robison, M.S., Mergy, M.A., Richtand, N.A., Han, Q., Hamilton, P.J., Bowton, e., Galli, A., Veenstra-VanderWeele, J., Gill, M., Blakely, R.D., ADHD-derived coding variation in the dopamine transporter disrupts microdomain targeting and trafficking regulation, **J Neurosci** 32: 5385-5397, 2012. [PMID: 22514303; PMCID: 3342037]
9. Thompson, B, Jessen, T., Henry, L., Field, J., Gamble, K., Gresch, P., Carneiro, A., Horton, R., Chisnell, P., McMahon, D., Daws, L., Blakely, R.D., Transgenic elimination of high-affinity antidepressant and cocaine sensitivity in the presynaptic serotonin transporter, **Proc Natl Acad Sci USA**, 108:3785-3790, 2011. [PMID: 21282638; PMCID: 3048100]
10. Bonnin A., Goeden, N., Chen, K., Wilson, M.L., King, J., Shih, J.C., Blakely, R.D., Deneris, E.S., Levitt, P.R., A transient placental source of serotonin for the fetal forebrain, **Nature**, 472:347-350, 2011. [PMID: 21512572; PMCID: 3084180]

11. Veenstra-VanderWeele, J., Muller, C.L., Iwamoto, H., Sauer, J.E., Owens, W.A., Cohen, J., Shah, C.R., Mannangatti, P., Jessen, T., Thompson, B.J., Carneiro, A.M., Crawley, J.N., Bush, E.S., McMahon, D.G., Ramamoorthy, S., Daws, L.C., Sutcliffe, J.S., Blakely, R.D., Autism gene variant causes hyperserotonemia, serotonin receptor hypersensitivity, social impairment and repetitive behavior, **Proc Natl Acad Sci USA**, 109: 5469-5474, 2012. [PMCID 3325657]

12. Moritz, A.E., Foster, J.D., Balachandra, K.G., Mazei-Robison, M.S., Yang, J.-W., Sitte, H.H., Blakely, R.D., Vaughn, R.A., Phosphorylation of dopamine transporter Ser7 modulates cocaine analog binding, **J Biol Chem** 288: 20-32, 2013 [PMCID:3537014]

13. Bowton, E.A., Saunders, C., Reddy, I., Campbell, N. G., Hamilton, P.J., Henry, L.K., Coon, H., Sakrikar, D. J., Veenstra-VanderWeele, J., Blakely, R.D., Sutcliffe, J.G., Matthies, H.J.G., Erreger, K., Galli, A. *SLC6A3* coding variant Ala559Val found in two autism probands alters dopamine transporter function and trafficking, **Translational Psychiatry**, 2014 Oct 14;4:e464. doi: 10.1038/tp.2014.90. [PMID: 25313507]

14. Mergy, M.A., Gowrishankar, R., Gresch, P.J., Wheeler, C.A., Davis, G.L., Jessen, T.N., Wright, J., Stanwood, G.D., Blakely, R.D. The rare DAT variant Val559 perturbs DA neuron function, changes behavior and alters *in vivo* responses to psychostimulants, **Proc Natl Acad Sci USA**, 111:E4779-88, 2014, [PMCID: 4226116]

15. Kovtun, O., Sakrikar, D., Tomlinson, I.D., Chang, J. C., Blakely, R.D., and Rosenthal, S.D. Single quantum dock tracking of dopamine transporter plasma membrane dynamics: A link between trafficking dysregulation and Attention Deficit/Hyperactivity Disorder, **ACS Chem Neurosci**, 2015 *in press.*

E. RESEARCH SUPPORT

Ongoing Research Support:

5 R01 MH094527 (Blakely) 12/01/93-11/30/15
NIH/NIMH
Regulation of Serotonin Transporters: This project explores the ability of cell surface receptors linked to PKC, PKG and p38 MAPK to regulate serotonin transporter proteins through trafficking-dependent and independent mechanisms and through contributions of associated proteins.

1 R01 MH095044 (Blakely) 05/01/12-04/30/17
NIH/NIMH
Presynaptic Regulation of *C.elegans* Dopamine Transporter
This project supports both forward and reverse genetic analyses of presynaptic mechanisms that control dopamine signaling in general and the dopamine transporter in particular using the model system *C. elegans*

5 R01 MH086530 (Blakely) 09/01/14-08/31/19
NIH/NIMH
Knock-In Mouse Model of Dopamine Dysfunction Underlying Traits of ADHD: This project explores the biochemical, physiological and behavioral perturbations in the DAT Val559 mouse model of ADHD.

1 P50 MH078028 (Blakely) 07/01/12-06/30/17
NIH/NIMH
Silvio O. Conte Center for Neuroscience Research: Enduring Impact of Developmental Serotonin Signaling: This Center grant, directed by Dr. Blakely, seeks to elucidate the impact of early life changes in serotonin signaling in the brain and periphery on brain biochemistry, physiology and behavior. The Blakely Project seeks to develop conditional SERT KO and KI mouse models that permit interrogation of the role played by CNS and peripheral serotonin transporters on brain development and function.

Dystonia Foundation (Blakely) 08/01/14-07/31/16
Development of Novel Reagents to Augment Cholinergic Signaling in Dystonia: This project seeks to develop and characterize novel choline transporter antagonists for the treatment of dystonia.

SFARI Award, Simons Foundation (Blakely) 09/01/14-08/31/17
Immune p38 MAPK Activation: Convergent Mechanism Linking ASD Models: This project examines p38 MAPK as a mechanism by which maternal immune activation in a mouse model produces features of autism and whether these features show similarities to genetic insults.

Lundbeck (Blakely) 11/01/13-10/31/14
Dissection of the Role of the Presynaptic Serotonin Transporter in the Chronic Actions of Vortioxetine: This project utilizes transgenic mice bearing a mutation that confers reduced antidepressant binding to SERT proteins to explore the transporter-specificity of chronic vortioxetine action.

Completed Research Support:

5 R37 MH073159-09 (Blakely) 06/01/09-05/31/14
NIH/NIMH (MERIT Award)
Molecular Analysis of Presynaptic Choline Transporters: This project investigates the subcellular distribution, trafficking, and physiology of brain choline transporters using in-vitro biochemical approaches, CHT knockout mice, and transgenic *C. elegans* lines.

5 R01 MH086530 (Sarter) 07/15/10-02/28/15
NIH/NIMH
Choline Transporter Capacity Limits Motivated Behavior on Mice, Rats and Humans: This project examines the physiological and cognitive impact of genetically imposed reduction in the presynaptic choline transporter.

Lundbeck (Blakely) 11/01/13-10/31/14
Dissection of the Role of the Presynaptic Serotonin Transporter in the Acute Actions of Vortioxetine: This project utilizes transgenic mice bearing a mutation that confers reduced antidepressant binding to SERT proteins to explore the transporter-specificity of acute vortioxetine action.

Psychiatric Neuroscience Institute (Blakely) 05/01/13-10/31/14
Role of Raphe p38 MAPK Signaling in Social Defeat: This project uses conditional transgenic mouse models to investigate the role of p38 MAPK signaling in social defeat behavior.

NeuroDetective, Inc (Blakely) 11/18/13-02/17/14
Evaluation of Novel DAT Inhibitors: Kinetics for Uptake Inhibition and Capacity for Dopamine Release: Studies are supported to test novel DAT-targeted drugs *in vitro* for possible therapeutic use in mental illness.

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 attach the sections that are appropriate for this Career Development Award.

● New ❍ Resubmission ❍ Renewal ❍ Continuation ❍ Revision

B. Research Training Plan

1. Introduction to Application (for RESUBMISSION applications only)	
2. Specific Aims*	M-6_PHS_Fellow_SpecificAims.pdf
3. Research Strategy*	M-18_PHS_Fellow_ResearchStrategy.pdf
4. Progress Report Publication List (for RENEWAL applications only)	

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

5. Human Subjects Involvement Indefinite?	❍ Yes ● No
6. Clinical Trial?	❍ Yes ● No
7. Agency-Defined Phase III Clinical Trial?	
8. Protection of Human Subjects	M-14_PHS_Fellow_ProtectionOfHumanSubjects.pdf
9. Inclusion of Women and Minorities	M-15_PHS_Fellow_InclusionOfWomenAndMinorities.pdf
10. Inclusion of Children	M-16_PHS_Fellow_InclusionOfChildren.pdf

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

11. Vertebrate Animals Use Indefinite?	❍ Yes ● No
12. Vertebrate Animals	
13. Select Agent Research	
14. Resource Sharing Plan	M-17_PHS_Fellow_ResourceSharingPlan.pdf
17. Respective Contributions*	M-8_PHS_Fellow_RespectiveContributions.pdf
16. Selection of Sponsor and Institution*	M-9_PHS_Fellow_SelectionSponsorInstitution.pdf
17. Responsible Conduct of Research*	M-10_PHS_Fellow_ResponsibleConductResearch.pdf

PHS Fellowship Supplemental Form

OMB Number: 0925-0002

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:

3. Degree Sought During Proposed Award:

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

4. Field of Training for Current Proposal*: 2810 Behavioral 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	Institutional	07/01/2009	07/15/2011	T32DA007244
Predoctoral	Individual	08/01/2011	05/11/2014	F31AA020132

6. Applications for Concurrent Support?* ❍ Yes ● No

If yes, please describe in an attached file:

7. Goals for Fellowship Training and Career* M-11_PHS_Fellow_Goals_FellowshipTrainingCareer.pdf

8. Activities Planned Under This Award* M-13_PHS_Fellow_ActivitiesPlanned.pdf

9. Doctoral Dissertation and Other Research Experience M-12_PHS_Fellow_DocDissertOtherResExperience.pdf

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

Institution

11. ☐ Change of Sponsoring Institution

Name of Former Institution:*

Funding Opportunity Number: PA-14-149. Received Date: 2015-04-07T14:58:53.000-04:00

PHS Fellowship Supplemental Form

OMB Number: 0925-0002

D. Sponsor(s) and Co-Sponsor(s)

Sponsor(s) and Co-Sponsor(s) Information* M-19_ PHS_Fellow_Sponsor_CoSponsor_Info.pdf

E. 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

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	

F. Appendix

Funding Opportunity Number: PA-14-149. Received Date: 2015-04-07T14:58:53.000-04:00

SPECIFIC AIMS

The degree to which drugs of abuse produce initially positive subjective effects has been linked to their abuse potential[1-3] and may serve as a risk factor for developing addiction[4]. Furthermore, the timing of psychostimulant drug delivery to the brain is thought to impact these positive subjective effects[5-9], with drugs that possess faster onset of effects having a higher potential for abuse – the so-called "rate hypothesis" of drug abuse[10,11].

While psychostimulants produce greater positive subjective (high, liking, euphoria) effects at a group level when administered more rapidly[12-15], no research has focused on individual variability in the timing of subjective responses and how this may relate to variability in the dopamine (DA) system believed to mediate these effects[16-19]. We have preliminary data (see *Research Strategy*) demonstrating large individual differences in the time to onset of subjective responses (drug high and liking; DEQ_{H+L}) to acute oral d-amphetamine (dAMPH): about 15% of participants experience peak effects within 60 minutes of ingestion (Early Peak Responders), whereas about 60% do not experience these peak response until >60 minutes after ingestion (Late Peak Responders). Furthermore, an additional 25% of individuals do not report drug high + liking after dAMPH (Nonresponders). We hypothesize that these individual differences in the presence and onset of effects may correspond with changes in brain DA signaling[16-19]. A deeper understanding of these and other factors (personality, genetics) associated with individual variation in positive subjective responses may help to identify other risk factors associated with dAMPH responsivity and abuse. For example, there is preclinical evidence linking novelty seeking and heightened psychostimulant responsivity[20-22] to variation in DA signaling[23-28].

Here, we propose to investigate the relationship between DA signaling before and after acute dAMPH (measured with Positron Emission Tomography, PET) and positive subjective effects of the drug. The *long-term goal* of this line of research is to ascertain the nature of variability in positive subjective drug effects and DA responses as a means of understanding risk factors for addiction. The *overall objective* of this application is to use PET measures of DA signaling at the level of D2 receptors and DA transporters (DATs) to identify specific sites in the brain that track with faster and more positive subjective responses to acute oral dAMPH. Our *central hypothesis* is that variation in dAMPH-induced DA release, D2 receptor, and/or DAT levels in regions of the mesocorticolimbic system are associated with the presence and onset of positive subjective drug effects. Furthermore, we will test whether novelty seeking or particular variation in the cadherin 13 gene or DA genes relate to our PET measures. ***Specific aims*** are as follows:

Aim 1. Identify the relationship between PET D2 and DAT measures at baseline and dAMPH-induced DA release to speed of positive subjective effects after acute oral dAMPH.

Our *working hypothesis* is that individuals who more rapidly reach peak drug high/liking (DEQ_{H+L} Early Peak Responders) will show enhanced DA signaling and DA release in areas of the mesocorticolimbic DA system (subgenual Anterior Cingulate Cortex (sgACC), VTA/midbrain, striatum, and PFC) relative to individuals with a slower time to peak. As differences in dAMPH absorption could account for observed differences, we will control for dAMPH pharmacokinetic (plasma amphetamine) variation in our analyses. Our *expected outcomes* for Aim 1 are the identification of sites of DA signaling variability associated with fast elevation in drug high and/or liking.

Aim 2. Identify the relationship between personality measures, speed of dAMPH-induced high/liking, and PET measures of DA signaling.

Our *working hypothesis* is that personality traits may be predictive of heightened speed of drug high/liking as well as variations in DA signaling. Specifically, we expect novelty seeking will be inversely related to D2/3 levels in the VTA/midbrain, heightened DA release, and earlier time to peak DEQ_{H+L}. Our *expected outcomes* for Aim 2 are to ascertain whether personality measures can explain individual variability in dAMPH responsivity and if this variability is explained by differences in DA system function at baseline or after dAMPH administration.

Aim 3. Determine whether *CDH13* rs3784943 or common DA signaling genetic polymorphisms relate to variability in PET and subjective timing effect measures of dAMPH responsivity.

Our *working hypothesis* is that a single nucleotide polymorphism (SNP) in the cadherin 13 gene (*CDH13*, rs3784943) related to variation in positive subjective dAMPH response via a genome wide association study (GWAS)[29] (with the broader *CDH13* gene being associated with drug abuse[30-32]) will explain variance in DEQ_{H+L} ratings and dAMPH-induced DA release. Furthermore, common genetic variants (in the Taq1A/*ANKK1*, *DRD2*, *DAT1/SLC6A3* genes) associated with DA signaling will also be examined in addition to more exploratory genetic analyses. Our *expected outcomes* for Aim 3 are to ascertain a functional role for *CDH13* in DA signaling differences associated with dAMPH's subjective effects (DEQ_{H+L} time to peak) as well as if variation in commonly studied DA signaling genes (or other genes we identify) are associated with variability in our DEQ_{H+L} or DA PET measures.

The overall goal of this proposal is to integrate variability at the genetic, personality, and brain level to individual variability in positive subjective responses to dAMPH. This work will lead to a greater understanding of the mechanistic link between addiction risk traits and DA system variability related to individual differences in dAMPH subjective and neurochemical responsivity. The identification of these biological markers of addiction risk may help in the development of future treatment targets.

RESEARCH STRATEGY

Significance

Despite substantial variability in subjective and physiological responses to oral d-amphetamine (dAMPH)[33-38] and a proposed role for rate of psychostimulant delivery in the euphoric[5,6,39] and potentially addictive nature[3,40-43] of these drugs, little work has focused on individual differences in the timing of these effects. In a sample of 49 young adults administered the acute oral dAMPH protocol proposed here (46 (23 male) with usable Fallypride PET data before and after dAMPH), we have reliably identified 3 groups of individuals based on the presence and timing of peak subjective drug "High" and "Liking" effects reported on the Drug Effects Questionnaire (DEQ[44]) after dAMPH (0.43 mg/kg) when compared to placebo (DEQ_{H+L}; **Figure 1**). These effects potentially relate to individual differences in DA signaling. It has been demonstrated that subjective reports of drug liking and high closely follow the level of psychostimulant occupancy of dopamine transporters (DATs) in the striatum[5,6,8]. Psychostimulant uptake by DATs is their primary pharmacological site of action, with the resultant high and euphoria tracking with the increased DA release that accompanies this process[16,17,19,45]. Additional work has demonstrated that similar levels of total striatal DAT occupancy by psychostimulants[7] can produce differences in positive subjective effects based on the timing of delivery of these drugs to the brain[46,47]. It follows, then that differences in the *timing* of such positive subjective effects may also track with the rate of DA release that follows acute psychostimulant administration. By measuring both basal DAT levels (via the PET tracer [^{18}F]-FE-PE2I[48]) and DA tone and release (via the D2/3 DA receptor tracer [^{18}F]-Fallypride[49,50]) after acute dAMPH administration, our proposal aims to clarify the role each of these DA signaling components play in the positive subjective effects of dAMPH. Furthermore, investigating whether differences in these PET measures relate to differences in detection and timing of dAMPH's positive subjective effects will offer unique insight into the role DA plays in speed of psychostimulant response. This work is significant as the speed of a drug's positive subjective effects is associated with its addiction liability[2,3,10,11] and has been proposed as a potential measure of addiction risk[1,4].

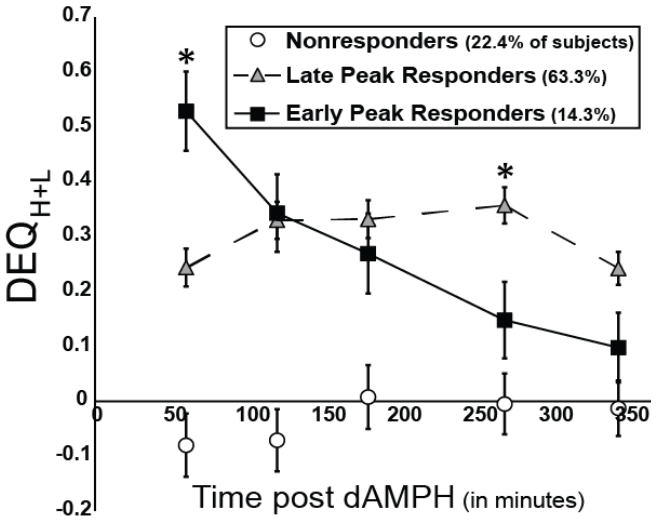

Figure 1: DEQ High + Liking (DEQ_{H+L}) timecourse differences by responder groups. *Responder Groups significantly different, p<0.05

Investigation of other factors (personality and genetics) that are often associated with addiction risk and their relationship to individual differences in speed of dAMPH's subjective effects or our PET measures could also prove informative. For example, a variety of personality factors have been associated with addiction risk in humans, including novelty and sensation seeking[51] and trait impulsivity[52]. Especially pertinent to this proposal is preclinical work demonstrating that rats high in novelty responding are more likely to show increased locomotor responses to acute amphetamine and cocaine[53,54], self-administer more psychostimulants[20,22], and show differences in DA system function and responsivity to psychostimulants[24-26,28] compared to low novelty responders. Thus, individual differences in human responsivity to dAMPH may be reflected by differences in novelty seeking traits in particular, though differences in impulsivity and sensation seeking traits also warrant exploration. As part of this proposal, we will seek to link differences in personality to variation in DA signaling and dAMPH's effects in humans in an effort to draw parallels with preclinical work, which would demonstrate the translational utility of linking such models to study the neurobiological basis of addiction.

Subjective responses to dAMPH and risk for amphetamine dependence are heritable traits[55-57], suggesting a genetic component that mediates these responses. Furthermore, genetic variation in DA signaling genes have been implicated in differences in D2/3 BPnd[58-62], alcohol dependence[63], sensation seeking[64], and individual differences in striatal responsivity to rewards[65,66]. Given the potential relationship between genetic variability in DA signaling and a host of addiction risk factors, studying whether genetic variation explains differences in dAMPH responsivity (overall DEQ_{H+L} scores and timecourse (**Figure 1**) and DA release as measured with Fallypride) may begin to provide a mechanistic link between DA genes and psychostimulant addiction risk.

Innovation

While past work has suggested that PET measures of psychostimulant-DA release in the human striatum correlate with increased positive subjective effects of the administered drugs[6,16,39], this will be the first study, to

our knowledge, to focus on whether psychostimulant-DA release varies with individual differences in the *speed* of these subjective drug effects. There is prior work suggesting that the timing of DAT occupancy and speed of DA release relates to the magnitude of positive subjective effects of psychostimulants[6,67]. Furthermore, a short-acting oral methylphenidate formulation whose DAT occupancy peaked quickly (~1 hr after drug) has been shown to produce a greater positive subjective effect than a longer acting formulation[46]. Thus, measurements of the timing of orally-administered psychostimulant delivery to the brain can dissociate different drug release dynamics' subjective effects but whether such an approach would be able to identify individual differences in timing of subjective effects to a single oral psychostimulant dose is unknown. This study will extend Spencer et al.'s DAT occupancy findings by using [^{18}F]-Fallypride displacement after acute oral dAMPH to probe the role of DA release on the intensity and timing of subjective drug effects (whose dynamics relate more to psychostimulant euphoric effects than overall DAT occupancy[6,68]). Specifically, Fallypride allows for reliable measures of DA release in areas beyond the striatum, including the amygdala, midbrain, and cortical areas (with insula and temporal lobes displaying particularly high levels of DA release). Thus, our approach will extend our knowledge of DA release and subjective effects reported after psychostimulant challenge in the striatum using [^{11}C]-raclopride[16,39] to extrastriatal areas. Furthermore, we will be able to probe for the impact baseline DAT and D2/3 DA receptor levels have on the effects we observe either behaviorally or in DA release. By also searching for personality and genetic differences that relate to subjective dAMPH response variation (**Figure 1**) and DA signaling differences as measured with PET we will be able to better characterize which traits are associated with differences in psychostimulant sensitivity that may confer risk for addiction.

For example, we have observed differences in novelty seeking personality trait between Early and Late Peak Responders (see Aim 2 *Feasibility* and **Figure 4**), a trait previously associated with lower D2/3 (auto)receptor availability in midbrain as measured in our lab with Fallypride[69]. Lower midbrain autoreceptor levels should lead to heighted DA release[70] but whether DA release is heightened in Early Peak Responders and/or high novelty seekers due to low D2/3 in midbrain has yet to be examined. This proposal will be able to test for these relationships between brain measures and behavior in addition to investigating the role of basal DAT levels. This will greatly enhance our understanding of where, neuroanatomically, behavioral/trait components are associated with variation in DA signaling and at what level of DA signaling this occurs. Finally, by studying whether genetic variation explains differences in our PET measures and dAMPH responsivity, we hope to gain a greater understanding of potential DA signaling and other genes' role in addiction risk. Furthermore, the approach of the current proposal will allow us to assess multiple markers of DA system function (D2/3 receptors and DAT levels at baseline, dAMPH-induced DA release) in the same individuals with greater coverage of the brain (via Fallypride's ability to measure striatal and extrastriatal D2/3 levels) than any previous work (which has typically only examined one feature of DA functioning per subject). If genetic variation has effects on these DA measures or differences in subjective effects to dAMPH, we are in a unique position to measure it. Also, while various candidate genes have been implicated in differences in D2/3 BPnd[58-62], no study has attempted to link genetic variants associated with measurable differences in DA system function (via PET) to behavioral measures of addiction risk (heightened early High/Liking as we will measure here) *in the same individuals*. With the assistance of collaborators possessing subjective measures of dAMPH in a large sample of nearly 400 young adults, we will be able to search for genetic variation across the DEQ_{H+L} groups that we have already identified in their data to then probe further in our PET subjects, allowing for a test of replicability of any genetic effects we find related to DEQ_{H+L}. Of note, our collaborators have identified a SNP in *CDH13* associated with variation in dAMPH subjective effects in a GWAS[29]. While several *CDH13* polymorphisms identified to be associated with addiction[30,31] and methamphetamine dependence[32] pass the rigorous criteria of GWAS, no study to date has directly assessed the relationship between *CDH13* polymorphisms and rs3784943 in particular to measured DA variables, though this is a logical mechanism of action given DA's role in heightened euphoric dAMPH effects[16,17]. In our proposal, we aim to test for the relationship between this SNP and our DEQ_{H+L} measure and investigate the functional link between *CDH13* and dAMPH-induced DA release, the biological basis of psychostimulant drugs' subjective effects[16,17,19,39]. Thus, while the genetics aim (Aim 3) of this proposal is more exploratory in nature than Aims 1 and 2, it has the potential of providing information on the mechanistic effects of *CDH13* and commonly studied DA genetic polymorphisms (specifically in the *DRD2*, *ANKK1*, and *DAT1* genes) on PET measures of DA system function in addition to identifying other novel polymorphisms to explore further.

Approach.

Aim 1. Identify the relationship between PET D2 and DAT measures at baseline and dAMPH-induced DA release to speed of positive subjective effects after acute oral dAMPH.

Research Design.

Overview: This study will investigate the relationship between PET DA measures and self-reported subjective responses to dAMPH with a particular focus on differences in timing of peak dAMPH drug High and Liking effects.
Hypothesis. We anticipate that baseline Fallypride BPnd as well as %ΔBPnd will vary as a function of time to peak dAMPH subjective effects in a variety of areas associated with subjective value. Our preliminary data suggest that these differences may be particularly strong in sgACC and SFG (see *Feasibility*). We anticipate that our DAT BPnd measure (PE2I) may differ from our Fallypride findings and identify unique brain areas where baseline DAT levels are associated with differences in dAMPH's subjective effects across our DEQ_{H+L} groups.

General Methods

Subjects will be healthy males and females (ratio: 50:50), *n*=30 per age group (ages 20-30 and 50-60; total *n*=60). Given the large effect sizes we observe for DEQ_{H+L} Groups over time (**Figure 1**; η^2=0.28) and when comparing our two Responder Groups on DEQ_{H+L} at 60 minutes (Cohen's *d*=1.54) and novelty seeking scores (TPQ-NS; **Figure 4**; *d*=1.16), the additional 60 subjects we will recruit here added to current data will result in a minimum of 15 subjects (109*14%) in our smallest DEQ_{H+L} group (Early Peak Responders). This number is sufficient to detect differences in early DEQ_{H+L} and TPQ-NS with 99% and 92% power, respectively. We will collect female's PET data only during the luteal phase of their menstrual cycle. These participants are being recruited as part of a National Institute on Aging grant (R01AG043458) awarded to the Sponsor. While the current proposal does not propose to look at age differences per se, natural declines in DA levels across adulthood[71] should increase variance in our DRD2/3 Fallypride BPnd measure and help identify individual differences in DA function more readily in this dataset (though age will be controlled for in all analyses).

Consent/screening: Subjects will be thoroughly screened for inclusion/exclusion criteria (see *Human Subjects*). This will include a Structured Clinical Interview (SCID-NP) to rule out psychopathology and a physical including EKG administered prior to collection of our PET data.

Questionnaires: To quantify subjective responses to dAMPH or placebo, we will use the Drug Effects Questionnaire (DEQ), which has good psychometric properties[44] and is sensitive to the effect of dAMPH[37,72]. We will administer this questionnaire at multiple timepoints post dAMPH & placebo (30, 60, 90, 120, 180, 270, 345 minutes).

^{18}F-Fallypride: We will collect Fallypride PET data during two separate visits, one a baseline/placebo day and the other the dAMPH day. On each visit, 5 mCi of Fallypride (specific activity > 3000 Ci/mmol) will be administered via a slow bolus injection and 3-D emission data acquired on a GE Discovery STE Scanner.

dAMPH: Oral dAMPH (or placebo) will be delivered based on subjects' weight at a dose of ~0.43 mg/kg (rounded to the nearest 2.5 mg total dose). This administration will occur 3 hours prior to PET scanning to allow for maximum plasma amphetamine levels at time of scanning. Our prior experience with this dose indicates it is well tolerated and produces significant DA release (**Figure 2**).

Plasma amphetamine: Plasma blood samples collected at regular intervals (30, 60, 90, 120, 180, 270 minutes post dAMPH) will be subjected to a selegiline+metabolites assay (NMS Laboratories) to quantify plasma amphetamine levels. These levels will serve as measures of rate of dAMPH absorption across individuals.

^{18}F-FE-PE2I: We will collect PE2I (5 mCi) PET data as a measure of baseline DAT binding during a third (baseline) visit. This probe has excellent kinetic properties and has been successfully used to measure DAT in humans[48] with demonstrated high levels of test-retest reliability[73].

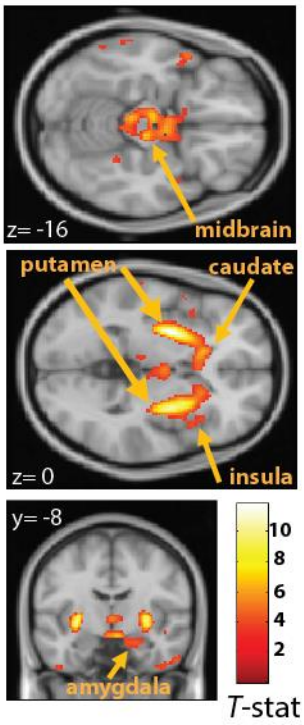

Figure 2: Areas w/ significant DA release (-%ΔBPnd) after dAMPH (FDR p<0.005: T=4.23).

Statistical Analyses. PET data will be realigned, decay corrected, and the simple reference tissue model[74] applied using PMOD software to create binding potential (BPnd) maps for PE2I and Fallypride (Placebo (Plc) and dAMPH days). The two Fallypride sessions' BPnd maps will be coregistered to each other and %ΔBPnd images created:

%ΔBPnd=(dAMPH_BPnd - Plc_BPnd)/Plc_BPnd x 100%, with -%ΔBPnd indicating dAMPH-DA release.

We will conduct whole-brain and ROI-based comparisons of BPnd and %ΔBPnd images normalized to MNI space across DEQ_{H+L} groups to identify areas displaying group differences in baseline D2/3 and DAT as well as dAMPH-DA release controlling for pharmacokinetic differences (plasma amph levels) as well as other potential factors that can influence DA signaling, namely sex[75-77] and age[71]. We will compare DEQ_{H+L} Responders (Early + Late) to Nonresponders via T-tests conducted in SPM[78,79] to identify dAMPH DEQ_{H+L} responsive regions and further probe these areas by testing whether the PET measures vary between Early and Late Peak Responders

via T-tests. Factorial tests for relationships across all three groups will also be performed in SPM. All analyses will use whole brain correction for multiple comparisons.

Feasibility. Our approach requires that we be able to reliably measure DA release via Fallypride PET. Second, it requires that we are able to use our PET measures (baseline binding potential (BPnd) or release (%ΔBPnd)) to identify individual differences in subjective drug effects and the timing of the peak of these effects. The following preliminary data support the feasibility of the proposed approach. First, the Sponsor and the Vanderbilt PET Center have extensive experience in Fallypride PET imaging[69,80,81] and in dAMPH challenge studies[49,70,82,83]. The trainee, with the help of the Sponsor and another post-doctoral fellow in the lab (Dr. Linh Dang), has successfully measured significant DA release in a host of striatal and extrastriatal regions, including striatum, amygdala, midbrain, insula and temporal cortex (**Figure 2**). We have preliminary data suggesting that individuals who differ on their subjective dAMPH high and liking rating timecourses (DEQ_{H+L} groups, **Figure 1**) differ in Fallypride PET BPnd at baseline. Specifically, we have identified a large cluster (k=586, cluster level $p_{FDR\text{-}corr}$<0.001) in the subgenual anterior cingulate cortex (sgACC; **Figure 3**, yellow) where baseline Fallypride BPnd is higher in DEQ_{H+L} Responders (n=35) versus Nonresponders (n=11) which contains a subcluster (k=62; 25 in cortical gray matter; **Figure 3**, red) where baseline DRD2/3 BPnd is higher in Early (n=8) versus Late Responders (n=27). Importantly, the DEQ_{H+L} group effect on Fallypride BPnd remains significant after controlling for sex, age, early plasma amph levels, and neighboring striatal BPnd ($F_{(2,34)}$= 4.53, p=0.018, η^2=0.17). The sgACC is a key integrator of bodily state and affect[84] that is connected with the ventral striatum[85] and is associated with subjective experiences of pleasure[86]. As such, the sgACC serves as an important component of a system associating internal physiological signals with "reward", as would be expected to occur after psychostimulant use. In fact, psychostimulant administration has been found to increase cerebral blood flow and BOLD signal in this portion of the brain[87,88].

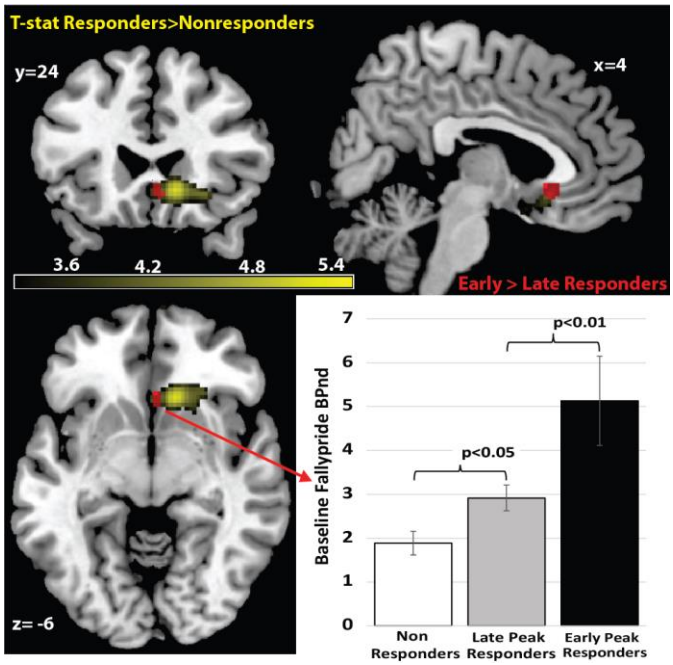

Figure 3: Subgenual ACC (sgACC) baseline BPnd differs in DEQ_{H+L} groups.

In addition to our baseline BPnd measure, we can also use Fallypride to index dAMPH-induced DA release (%ΔBPnd). Of note, in the sgACC cluster differing in baseline BPnd across all groups (**Figure 3**; red cluster), we observe differences in %ΔBPnd with DEQ_{H+L} Responders showing significant DA release (negative %ΔBPnd; T_{34}=-2.34, p=0.025; %ΔBPnd:-6.32±2.70) while this was not the case in the Nonresponders (T_{10}=0.48, p=0.64; %ΔBPnd: 4.00±8.35). Looking at %ΔBPnd in the large, significant Responders>Nonresponders sgACC cluster (yellow in **Figure 3**), we also find significant differences in %ΔBPnd across our DEQ_{H+L} groups ($F_{(2,43)}$=3.81, p=0.03) driven, again, by the Responder groups showing significant DA release (T_{34}=-2.16, p=0.038; %ΔBPnd: -5.54±2.57), which was not seen in Nonresponders (T_{10}=1.50, p=0.16; %ΔBPnd: 10.24±6.85). Thus, our groups differ not only in baseline D2/3 BPnd but also in DA release in the sgACC. While the sgACC demonstrates a scaled BPnd relationship with Early>Late Responders>Nonresponders, we note some areas differ in baseline BPnd for Early Peak Responders only. For example, we identified a superior frontal gyrus (SFG) area (MNI coordinates: 22, 58, -2; k=54) whose activity has been related to subjective pleasantness[89] and outcome (vs decision) valuation[90] in previous meta-analyses. In our data, we find Early Peak Responders have higher BPnd values in this SFG cluster at baseline (0.71±0.04) than either Late Peak (0.52±0.02) or Nonresponders (0.51±0.04; $F_{(2,43)}$=7.45, p=0.001).

Potential Problems & Alternative Strategies. It is possible that the planned DEQ_{H+L} group comparisons of our PET measures will not identify brain regions that survive corrections for multiple comparisons using a whole brain search. ROI-based analyses motivated by prior findings[49] will also be pursued. In addition, we plan to also treat time to peak DEQ_{H+L} ratings as a continuous variable on which to regress PET measures. By recording the exact time when the DEQ components are completed by our participants, we will be able to assign a time in minutes where peak High and/or Liking occurs after dAMPH. Such an approach will serve as a useful confirmation of brain areas' where DA signaling differences relate to differences in time to peak DEQ_{H+L}. We have successfully employed this alternative strategy in preliminary personality differences analyses (see Aim 2 *Feasibility*) despite peak time being sampled at a lower rate than proposed in this application. Furthermore, while we have discussed positive subjective dAMPH effects in terms of our DEQ_{H+L} measure (where DEQ High and Like dAMPH-Plc ratings are

averaged at each timepoint in an effort to increase stability in our measure), it is possible that these two ratings are associated with DA signaling differences in unique areas of the brain. To explore this, we will also regress our PET DA measures on DEQ High and Like independently to search for common and unique DA signaling measures associated with these effects. Finally, we will also search for effects of max High/Liking on our PET measures.

Aim 2. Identify the relationship between personality measures, speed of dAMPH-induced high/liking, and PET measures of DA signaling.

Research Design.

Overview. This aim will test for relationships between the PET and DEQ_{H+L} measures collected in Aim 1 and personality traits often associated with addiction risk.

Questionnaires: Cloninger's Tridimensional Personality Questionnaire – Novelty Seeking (TPQ-NS[91]), Barratt Impulsivity Scale (BIS-11)[92], Zuckerman Sensation Seeking Scale[93], BIS/BAS[94], and the Zuckerman-Kuhlman Personality Questionnaire[95] will be collected at screening/baseline.

See Aim 1 above and the Human Subjects Section for information regarding subjects and screening procedures

Hypothesis. We hypothesize TPQ-NS will explain differences in DEQ_{H+L} time to peak effects as well as differences in some of our PET measures of DA signaling at baseline and after dAMPH challenge. Specifically, we hypothesize that TPQ-NS will relate to D2/3 BPnd in the midbrain as previously demonstrated[69].

Statistical Analyses. We will search for associations between TPQ-NS scores and our PET measures of DA system function by regressing TPQ-NS scores on our Fallypride and PE2I BPnd and %ΔBPnd images (controlling for age, sex, and plasma amph as in Aim 1) using SPM. We will then ask if TPQ-NS scores explain additional variance in subjective responses (DEQ_{H+L} overall or time to peak) to dAMPH above and beyond our PET measures identified in Aim 1. We will use multiple regression initially and progress to structural equation modeling to more accurately determine the relationship between these measures. We will formally conduct mediation tests to ask if TPQ-NS affects DEQ_{H+L} time to peak via its effect on basal DAT and DRD2/3 PET measures or dAMPH-induced DA release. Similar analyses will explore the relationship of other personality traits (impulsivity, sensation seeking) in order to more fully define relations with externalizing/addiction risk traits.

Expected Results & Interpretation. We expect to find that TPQ-NS explains individual variability in DA system function and responsivity to dAMPH. Specifically, we expect DEQ_{H+L} Early Peak Responders (high in TPQ-NS; **Figure 4**) will show reduced midbrain autoreceptor levels (the main D2 receptor in the human midbrain[96]) and thus, heightened DA release in key mesocorticolimbic areas including the ventral striatum and medial PFC (mPFC). We also anticipate that TPQ-NS will explain some of the variability in DEQ_{H+L} ratings via its effects on DA signaling as measured with PET[69] and that common anatomical structures (midbrain, ventral striatum, and mPFC) will show parallel relationships between DEQ_{H+L},TPQ-NS, and dAMPH-induced DA release as suggested in preclinical studies[20,25-27].

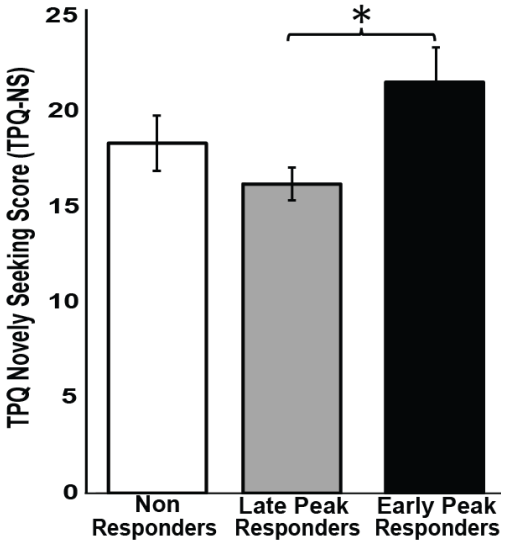

Figure 4: Early Peak Responders have heightened TPQ-NS scores relative to Late Responders.

Feasibility. Previous PET findings from our group have demonstrated an inverse relationship between TPQ-NS and Fallypride DRD2/3 BPnd in the midbrain[69]. Thus, there is a basis to believe that differences in TPQ-NS are associated with differences in DA system function measured by Fallypride PET at baseline. Here, we plan to investigate whether differences in personality traits are associated with differences in DA system function or DA release after dAMPH. We have preliminary data that our DEQ_{H+L} responder groups differ in TPQ-NS scores such that Early Peak Responders have higher Novelty Seeking Scores than Late Peak Responders (*t_{36}=2.95, p=0.005, Cohen's d=1.16; **Figure 4**). Furthermore, we have shown taking dAMPH DEQ_{H+L} time to peak (in minutes) as a continuous variable, that TPQ-NS adds explanatory power in determining this time to peak measure (β=-8.31, p=0.002: +18% of variance) above differences in early pharmacokinetics (plasma amph 60 minutes post dAMPH; explaining 13% of variance alone). Thus, we have strong evidence that high TPQ-NS scores are associated with faster time to peak DEQ_{H+L} after dAMPH above differential absorption factors.

Potential Problems & Alternative Strategies. While we have the strongest *a priori* hypotheses for TPQ-NS, we will also investigate the role of other personality traits in either DA system function or individual differences in positive subjective effects to dAMPH. For example, D2/3 receptor levels obtained with raclopride PET have been associated with Zuckerman Sensation Seeking traits in an inverted-U manner[97] and we have found a trend toward differences in Barratt Impulsivity Scale scores in our DEQ_{H+L} groups ($F_{(2,45)}$=3.06, p=0.057) with Early

Peak Responders displaying slightly higher BIS scores (67.14±10.95) compared to Late Peak Responders (57.17±8.40, t_{35}=2.49, p=0.018). We will test for potential effects of these traits in this proposal.

Aim 3. Determine whether *CDH13* rs3784943 or common DA signaling genetic polymorphisms relate to variability in PET and subjective timing effect measures of dAMPH responsivity.

Research Design.

Overview. As part of their PET visits in Aim 1, we will collect blood samples on all participants of which a fraction will be set aside for genetic analysis.

See Aim 1 above and the Human Subjects Section for information regarding subjects and screening procedures

Genetic Analyses: We will obtain information on SNPs of interest with the assistance of the Vanderbilt Technologies for Advance Genomics (VANTAGE) core (*see Environment*). In addition to this data from VANTAGE, we have developed collaborations with Dr. Wolfgang Sadee at Ohio State University to obtain information on various variable number of tandem repeat (VNTR) polymorphisms in the DAT gene[98] as well as SNPs in DRD2 such as rs1076560 (a polymorphism believed to reflect the balance of pre versus postsynaptic DRD2 short and long isoforms, respectively[99]) not commonly assayed in commercial genotyping.

Hypothesis. We will investigate whether the GG SNP in the cadherin 13 gene (*CDH13,* rs3784943) is associated with enhanced or earlier DEQ_{H+L} peak values and heightened DA release following dAMPH as this SNP has been previously associated with greater positive subjective dAMPH responses[29]. Also, we anticipate genetic variation in commonly studied DA-related genes (Taq1A/*ANKK1*, *DRD2*, *DAT1/SLC6A3*) will be associated with differences in dAMPH subjective responses and/or our PET measures of DA system function.

Statistical Analyses. As we have an *a priori* hypothesis regarding the rs3784943 GG allele, we will test whether this variant is enriched in DEQ_{H+L} Responders (overall or in one of our two Responder groups) via X^2 tests. We will also explore the relationship between this SNP and variation in our DA PET measures via ANOVAs and/or T-tests (GG vs. A carriers) in SPM to identify a potential mechanistic link between its effect on DA signaling and dAMPH subjective response differences observed previously[29]. To identify other genes of interest, we will 1) test for the presence of genetic variation in DEQ_{H+L} groups in a larger (n=381), independent dataset collected at the University of Chicago using X^2 tests and 2) investigate differences in PET DA measures in the identified variants in our Vanderbilt sample. We will test for effects in commonly studied DA related genes (specifically rs1076560[99], rs1800497[61,62], rs6277[58-60], and rs28363170[100]) via this approach in addition to conducting more exploratory analyses to identify novel SNPs enriched in particular DEQ_{H+L} groups.

Feasibility. First, *CDH13* rs3784943 was the only SNP found to relate to variability in oral dAMPH subjective effects via GWAS[29]. Through collaborators Drs. de Wit and Palmer at the University of Chicago, we have identified similar patterns of DEQ_{H+L} ratings and proportions of Early, Late, and Nonresponders in this aforementioned GWAS dataset comparable to our own data (**Figure 1**). In the Chicago data, we found a significant Linear-by-Linear Association (X^2=4.54, p=0.033) between number of rs3784943 G alleles and DEQ_{H+L} group status with Late Peak Responders having a higher proportion of G alleles. This data suggests an ordinal relationship between G alleles and time to peak DEQ_{H+L}, which we will investigate in the current proposal where specific time to peak information will be collected. Via this ongoing collaboration and access to the University of Chicago dataset, we will also be able to probe for the enrichment of particular DA signaling polymorphisms or haplotypes that may differentiate Early, Late, and Nonresponders in this relatively large dataset before testing for the effects of these genes in the smaller PET dataset. This setup allows for the ability to test for replicability of any observed effects and increases confidence in our findings.

Potential Problems & Alternative Strategies. First, we note that the minor allele frequency for rs3784943 is low (0.20). While earlier work[29] and our preliminary X^2 analysis suggests this as a worthy candidate for study, we will also investigate SNPs with higher minor allele frequencies in *CDH13* and DA genes (rs6277 has minor allele frequency of 0.53 in Caucasians[101]). While the value of candidate gene studies has been called into question, such approaches have primarily focused on behavioral or fMRI differences across individuals. We argue that our PET measures of DA system function more accurately capture key components involved in DA signaling, namely DRD2 and DAT (via Fallypride and PE2I BPnd, respectively) and DA release (via Fallypride %ΔBPnd). As such, we believe a candidate gene approach coupled with PET DA measures will yield important insights into the function of common DA genetic polymorphisms. We will also work with our collaborator, Dr. Palmer, to investigate the use of more rigorous approaches to limit false positives in our genetic analyses along the lines of his previously published work[29,102]. Furthermore, we will consider using a multilocus DA score with our data as has been used in previous neuroimaging studies[65,66]. In addition to these approaches, the applicant has a colleague at UNC Chapel Hill (Dr. Theresa Swift-Scanlan) with expertise in epigenetics research, particularly looking at the gene for the DA regulating enzyme catechol-*O*-methyltransferase (COMT[103]). Probing the *DRD2* and *DAT1* genes for epigenetic markers associated with dAMPH differences we observe could thus serve as a first step in investigating more complex gene x environment interactions that may affect psychostimulant responsivity.

PROTECTION OF HUMAN SUBJECTS

1. Risks to the Subjects

a. Human Subjects Involvement, Characteristics & Design

60 total subjects (30 between 20 and 30 years of age; 30 between 50 and 60 years of age) will be recruited to undergo PET, sMRI, behavioral and psychological assessments, and genotyping.

Exclusion criteria: known major systemic disease, a history of psychiatric illness as assessed with the Structured Clinical Interview for DSM-IV (SCID), cognitive or visual impairment, neurological disorders other than headaches, a history of multiple concussions or any closed head injury, a history of substance abuse or use of psychostimulants more than 3 times in the participant's life, current usage of medication known to affect neurological function, a history of claustrophobia, pregnancy, a history of kidney disease, presence of any non-removable metal that may interfere with MRI scanning, high blood pressure (Systolic B.P. > 135, Diastolic B.P. > 85) or an abnormal EKG that suggests any risk under conditions of raised blood pressure, and participation in any study that involves radiation in the past 12 months (or work involving exposure to radiation) to minimize cumulative radiation exposure to the subject.

Recruitment procedures: Participants will be recruited from the Department of Psychology online Research Subject Pool (http://vanderbilt.sona-systems.com). Studies conducted at Vanderbilt can advertise on this website, and volunteers meeting the criteria above can view the study and contact the research assistant. The Zald lab has used this recruitment method successfully for over a decade. As of March 2015, there are more than 5600 registered users on the website. As needed advertisements will also be placed in local Nashville media outlets (which is sometimes necessary to recruit the middle aged population, which is less well represented in the subject pool).

b. Sources of Materials

Subjects provide self-report of personality, medical, and psychiatric history. During screening and after each PET scan, subjects provide blood samples for metabolic assessment (CMP) and complete blood count (CBC). Participants additionally complete a CBC and CMP immediately prior to the [18F]-FE-PE2I scan. Female subjects also provide blood samples for pregnancy testing before each PET scan. Additionally, subjects provide data from 3 PET scans, structural MRI scans, and personality assessments. A single urine drug screen is performed during screening to confirm that the participants are drug free.

All data are for research purposes only.

Confidentiality protections: Participant data, except blood work, are accessible only to members of the Affective Neuroscience lab and collaborating faculty at Vanderbilt University. Blood samples are processed by Vanderbilt Clinical Laboratory and stored on the Vanderbilt University Medical System computer system, which is only accessible to Medical Center personnel with approved access to the system. Paper and pencil data are stored in a locked file cabinet in the Affective Neuroscience lab. Digital information is stored on password-protected computers in the Affective Neuroscience lab and may also be stored on password-protected REDCap (Research Electronic Data Capture). REDCap (projectredcap.org) is a secure, web-based application designed exclusively to collect data for research studies. REDCap was initiated at Vanderbilt University and is now utilized by more than 70 institutional partners. REDCap provides an interface for data collection, a system for tracking data manipulation, and seamless data integration with popular statistical programs such SPSS, SAS, Stata, and R. Only members of the Affective Neuroscience lab and collaborating faculty have the passwords for accessing digital information. Data will be de-identified, and information linking subject study ID number to subject names and medical record number will be stored in a password protected file and kept separate from other participant data. The Vanderbilt University Institute for Imaging Science maintains a temporary log of participants' names and their scan ID. Once this information is removed from the system, imaging data is only identified by subject study ID number. Because of the need for confidentiality regarding questions related to drug use and the urine drug screen, a certificate of confidentiality will be in place to ensure protection from a release of information request relating to drug use.

c. Potential Risks

Potential risks are associated with the administration of [18F]fallypride, [18F]-FE-PE2I, and amphetamine (d-AMPH), the physical discomfort during PET and MRI scanning, and the psychological discomfort during medical examination or psychiatric interview.

Administration of radiopharmaceutical: Subjects are exposed to a radiopharmaceutical for three PET studies (2 Fallypride; 1 PE2I). The total effective dose is 1600-1650 millirem, which approximately corresponds to the background radiation received in approximately 2.6 years from the environment. This level is well within FDA guidelines, which limits radiation exposure for research to a maximum of 5000 mrem per year. Large-scale studies of the long-term risk of radiation exposure show no increase in cancer rates associated with radiation exposure below FDA limit[105]. To minimize radiation exposure for the subject, volunteers who are regularly exposed to radiation at work or have participated in a study using radiation in the last 12 months will be excluded.

[18F]fallypride has been approved by the FDA for investigational usage. [18F]fallypride is produced and administered at subpharmaceutical doses at Vanderbilt University. Quality control checks ensuring purity and sterility are performed for each dose to be injected. Dr. Zald, in collaboration with colleagues at Vanderbilt, have performed over 200 [18F]fallypride PET studies and have seen no laboratory abnormalities from administration of this radiopharmaceutical. An independent safety monitor will be assigned to this study to review any potential adverse effects. A meeting will be 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.

For [18F]-FE-PE2I will be initially covered as a non-FDA approved radioactive drug used in human subject research by the Vanderbilt IRB's Radioactive Drug Research Committee. We anticipate applying for an FDA IND within the next year. [18F]-FE-PE2I is in use in several centers and no adverse effects have been observed in studies with humans and nonhuman primates[106,107]. In order for injection, the [18F]-FE-PE2I has to meet strict quality control requirements, including, specific activity > 500 mCi/mmol (we consistently produce > 1000 mCi/mmol), Radiochemical purity > 90% (we routinely produce 99% purity), chemical impurity of PE2I acid < NMT 1.87/mL, and pH 4.5- 8.0. Sterility after 2-weeks is checked after every production, and 3 new qualifying runs must demonstrate 2-week sterility before any subject may be injected if there is a demonstration of a failure of sterility after any production.

We note that the tracer-level amounts of [18F]fallypride and [18F]-FE-PE2I to be used in our PET scans are sub-pharmaceutical doses, with no observed effects on physiological or mental functions. Because they are delivered at sub-pharmaceutical levels, they have been well tolerated in human participants.

Administration of Amphetamine (d-AMPH): Numerous studies of oral d-AMPH in normal volunteers have been reported. Risks and side effects associated with the use of d-AMPH include an increase in blood pressure and psychological effects such as feeling jittery, anxiety, increased alertness, and restlessness. An oral dose of 0.25 mg/kg in normal volunteers produced an increase in systolic blood pressure of 10 mm Hg (i.e. 114 to 124 mm Hg). A 0.5 mg/kg oral dose of d-AMPH produced a mean increase of 28 mm Hg in systolic blood pressure at 2 hours, i.e. a peak systolic blood pressure of 148 which decreased to a 14 mm Hg increase at 4 hours and returned to normal levels by 6 hours. The pulse rate remained unchanged[108,109]. A PET study from The University of Toronto reported that a 30 mg dose of d-AMPH (0.43 mg/kg) produced only a 20 mm Hg increase in systolic blood pressure[110]. Our own past data indicates a mean increase of 27 mm Hg that peaked (148 mm Hg) in 3 hours and decreased substantially by completion of scanning. Based on this data, we anticipate that the 0.43 mg/kg dose of d-AMPH used in this study should produce blood pressure elevations of 25-30 mm Hg on average. Given strict blood pressure restrictions on enrollment, peak blood pressure levels are likely to be in the range of 140-155 mm Hg and no more than 165 for a period of 4 hours. These increases in blood pressure are less than those seen with moderately vigorous exercise where systolic blood pressure has been shown to increase 40-60 mm/Hg – i.e. to 160 – 180 mm Hg. Subjects' judgment and cognitive abilities might temporarily be altered during the several hours over which d-AMPH exerts its effects. There is an ethical concern regarding the administration of psychostimulant drugs to healthy non-drug using normal control subjects. We have relied on guidelines developed by the National Advisory Council on Drug Abuse (NACDA;

appointed by the Secretary of Health and Human Services and Advisory to the National Institute of Drug Abuse). The entire report is available at: http://www.nida.nih.gov/funding/hsguide.html. In addition, we have relied on the “Human Subject Issues in Drug Abuse Research” published by the College on Problems of Drug Dependence which states “There is no evidence that exposure to drugs in a research setting enhances the desire of an individual to use drugs, leads the individual to addiction, worsens the addiction of an individual, or makes an addict more difficult to treat”[111].

Discomforts associated with PET and MRI scanning: Discomforts associated with PET and MRI studies include having to remain still for up to 60 minutes and hearing loud noises from the MR scanner. Subjects are given pillows to maximize comfort and earplugs to lower the impact of MR scanner noise. During scanning, incidental findings could arise, which could cause psychological stress to the participants.

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 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. Participants may also feel hungry because they are not allowed to eat for approximately 5 hours as part of the [18F]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

The study will be advertised on a web-based research scheduling system maintained by the Department of Psychological Sciences at Vanderbilt University. Interested volunteers are asked to contact the Zald lab to schedule an enrollment interview. At the interview, participants are asked to read a complete written informed consent document approved by the Vanderbilt University Institutional Review Board. Procedures and risks will be discussed, and participants will be encouraged to voice any question before signing the informed consent. Researchers will question each potential participant to make sure that they understand the risks, especially those related to administration of [18F]fallypride and d-AMPH and MRI scanning. Subjects will not be enrolled if there is a question regarding their understanding of these risks. Only the PI and research assistants can enroll subjects.

b. Protection Against Risks

Screening for study inclusion/exclusion criteria: 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 will be 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.

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 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 will used to limit the impact of scanner noise.

Incidental findings on MRI: If an incidental finding on MRI occurs, a neuroradiologist at Vanderbilt University Medical Center will be consulted prior to discussing the findings with the participant. If the neuroradiologist

recommends a referral, this information will be provided to the participant. Participants are informed as part of the consent process that scans are strictly being collected for research, but that their scan could be shared with a neuroradiologist on staff in case of an incidental finding.

Safety of radiopharmaceutical administration. [18F]Fallypride has been approved by the FDA for use as an investigational new drug (IND 120035). The IND outlines strict quality control procedures for [18F]fallypride production, and each run is checked for specific activity, purity, pH and sterility. 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 will be assigned to the study to review any adverse response. Subjects are given a CBC and CMP after the [18F]fallypride administration in order to monitor any potential reactions.

As described above [18F]-FE-PE2I will be initially covered as a non-FDA approved radioactive drug used in human subject research by the Vanderbilt IRB's Radioactive Drug Research Committee. We anticipate applying for an FDA IND within the next year. In addition to the quality control procedures described above, all participants will have a blood draw for CBC and CMP before and 60 minutes after administration in order to ensure no alterations in blood chemistry. Participants will have their vital signs measured before and 75 minutes after drug administration, and will also be given a brief neuro-exam before and 75 minutes after administration. A medical doctor will be available throughout the time of the PET scan, and will have the participant remain in the PET suite if there are any concerns about side effects following [18F]-FE-PE2I administration.

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. Data will be 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 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

Benefits to the subject include a physical evaluation (for PET studies), financial compensation, and a picture of their brain. Although not being performed for clinical purposes, a neuroradiologist will review any incidental discovery of abnormalities in brain scans. The primary benefit for others is the expansion of scientific knowledge about the human reward system, which has implications for treating addiction and other reward-related disorders.

4. Importance of Knowledge to be Gained

Addiction is costly to both the individuals and society, and relapses after current treatments are common. To significantly affect the prevalence of addiction and other reward-related disorders, it is imperative to understand the neural mechanisms underlying reward regulation. This research will expand scientific understanding of processes underlying reward-driven behavior and has the potential to facilitate the identification of risk factors and the development of more effective treatments for addiction and other reward-related disorders.

5. Data and Safety Monitoring Plan

This study involves an investigational new drug, [18F]fallypride. We have FDA approval for use of [18F]fallypride (IND # 120035), and the use of [18F]-FE-PE2I, which is a non-FDA approved radioactive drug used in human subject research which is covered by Vanderbilt IRB's Radioactive Drug Research Committee.

Monitoring: Subjects are followed for 4 hours post [18F]fallypride administration and 90 minutes post [18F]-FE-PE2I. Monitoring includes a CMP and CBC, repeated monitoring of blood pressure, brief neurological screen, and a survey of potential side effects before discharge from the study. Any possible adverse events will be reviewed with the study's independent data safety monitor, and any unanticipated adverse events that are

deemed moderate and possibly related to the drug administration will be reported to the Vanderbilt IRB within 10 days of the event.

Subjects are additionally given telephone numbers to reach the study psychiatrist should they 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 will be assigned to this study. Events that are deemed by the study primary M.D. (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 Cowan, the study M.D.. Annual reports of adverse events are made to the IRB and FDA.

INCLUSION OF WOMEN AND MINORITIES

We expect to enroll equal numbers of men and women in this study. Vanderbilt University, located in Nashville, Tennessee, is situated near communities with significant African American and Hispanic/Latino representations. Previous studies in the lab have successfully recruited minorities through advertisements, listserves, and word of mouth in the Vanderbilt community. We will ensure that our subject pool reflects the demographics of Nashville (see targeted enrollment table).

Inclusion of Women: Women will be included this study. However, due to restrictions on unnecessary exposure of radiation to fetus and newborn, women who are pregnant or expecting to get pregnant will be excluded. Prior to scanning, all women in the study will be required to undergo a pregnancy test or provide medical documentation showing that pregnancy is no longer a possibility.

Inclusion of Minorities: African Americans and Asian Americans make up approximately 9% and 11%, respectively, of subjects in recent studies, which is consistent with their populations in Nashville. We expect that our subject pool will also reflect these percentages. We note that for reasons unknown to us no Hispanic participant has completed PET scans in the Zald lab even though 10% of the Nashville area is Hispanic. Although we will not explicitly recruit Hispanics for this study, we will give scheduling preference to individuals of Hispanic or Latino background to encourage participation.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Linking Temporal Differences in d-Amphetamine Subjective Effects to DRD2 and DAT

Domestic/Foreign: Domestic

Comments: No additional information

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	**0**
Asian	2	2	0	0	**4**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	4	4	0	0	**8**
White	23	23	1	1	**48**
More than One Race	0	0	0	0	**0**
Total	**29**	**29**	**1**	**1**	**60**

Study 1 of 1

Funding Opportunity Number: PA-14-149. Received Date: 2015-04-07T14:58:53.000-04:00

INCLUSION OF CHILDREN

This research plan will not include subjects below 20 years of age. Children are excluded from PET studies based on regulations prohibiting unnecessary radiation exposure in children.

Resource Sharing Plan

This study will collect PET, genetic, and behavioral data from healthy subjects aged 20-30 and 50-60. De-identified data will be made available to other investigators upon request. After the primary findings are published and no later than 1 year from the end date of the fellowship, we will make the data and associated documentation available to researchers under a data-sharing agreement that includes commitments to use the data only for research purposes, to not attempt to identify any of the participants, to secure the data using appropriate computer technology, and to destroy or return the data after analyses are completed.

Respective Contributions

This proposal results from discussion between the applicant and Dr. David H. Zald, the primary sponsor. The applicant developed the hypotheses, wrote the proposal, and made revisions with suggestions from Dr. Zald. In addition, collaborators at Vanderbilt (Dr. Ronald Cowan) and the University of Chicago (Drs. Harriet de Wit and Abraham Palmer) reviewed the Specific Aims and Research Strategy sections and provided suggestions on clarifying experimental details and analysis methods.

Selection of Sponsor and Institution

As part of my graduate training, I investigated a potential intermediate phenotype associated with addiction: increased delay discounting behavior (the tendency to choose smaller, sooner rewards over larger, later rewards). As part of my dissertation work, I looked at the role dopamine (DA) signaling differences play on discounting behavior using genetic polymorphisms as putative measures of DA system function. By the end of my graduate training, it was clear to me that to look at variation in human DA signaling I would need to gain experience in Positron Emission Tomography (PET). Furthermore, I wanted to pursue combining PET measures of DA system function with genetic measures to understand whether commonly studied DA genetic polymorphisms are associated with actual DA signaling differences as measured with PET. Finally, I wanted to pursue these questions in a larger context of behavioral and personality measures commonly associated with addiction risk. The obvious choice for me to gain PET experience in a lab with a history of looking at individual differences in DA system function was the Affective Neuroscience Lab at Vanderbilt University. Dr. David H. Zald, the Principal Investigator, has a wealth of experience in PET imaging of the DA system at rest and after d-amphetamine (dAMPH) administration (to measure DA release). In collaboration with colleagues at Vanderbilt, Dr. Zald's lab has collected more ^{18}F-Fallypride PET scans of striatal and extrastriatal DA D2/3 receptor availability than anywhere else in the world. Furthermore, only in this lab is the number of PET scans (>100) large enough to attempt any genetic analyses on the data. By working with Dr. Zald and the large amounts of DA PET data collected (and to be collected) in the lab, I believe I can begin to study individual differences in DA signaling at a variety of levels (DRD2/3 baseline receptor levels; DA release after dAMPH challenge; DAT baseline levels). By combining these measures with personality and genetic data, I hope to gain a more complete understanding of traits that may confer differences in DA system responsivity as well as differences in positive subjective responses to acute dAMPH.

In addition to the topical fit, Dr. Zald's lab was appealing based on his success as both an investigator and a mentor. Dr. Zald is a well-established researcher with a track record of high-quality publications (>100 with over 9700 citations, h-index = 51 according to Google Scholar). His past graduate and postdoctoral trainees have gone on to obtain faculty positions at premier research institutions including Harvard, Yale, and Emory University, and indeed he recently received an award from Vanderbilt for excellence in graduate mentoring. Furthermore, the team that Dr. Zald has assembled here at Vanderbilt and via collaborations will greatly aid in my training. Dr. Linh Dang, a fellow postdoc in the lab, has years of PET imaging experience while collaborators at the University of Chicago, Dr. Harriet de Wit (expert in dAMPH psychopharmacology) and Dr. Abraham Palmer (expert in genetic analyses) have worked closely with the Zald lab in the past and have offered support in helping me complete my current research plan. I also have support from Dr. Ronald Cowan (clinician and researcher at Vanderbilt School of Medicine; a co-author along with Dr. de Wit and Palmer on a recently submitted paper focused on the behavioral effects presented in this proposal) and Dr. Randy Blakely (expert in molecular/transgenic approaches to the study of DAT and DA release in preclinical models). This advisory team of Drs. de Wit, Palmer, Cowan, and Blakely will be instrumental in assisting me with the next steps involving analysis and interpretation of the PET and genetic data collected and to be collected as part of this proposal and aiding me in my postdoctoral training. I will meet with this advisory team at least twice a year via conference call/teleconference to discuss my progress. Members of the team will also be available to assist me with specific areas where they have expertise as data collection and analysis continues. In summary, working with Dr. Zald and the team we have assembled for this Fellowship proposal, I expect to gain training in PET imaging and genetic analyses and a broader understanding of DA signaling, regulation, and its role in a variety of reward related and pathological behaviors. The skills and knowledge I obtain will allow me to pursue my own independent research career focused on studying variation in DA system function as a risk factor for addiction.

The resources at Vanderbilt also contributed to my selection. The radiochemistry core is highly proficient in Fallypride synthesis and has recently added the DAT tracer ^{18}F-FE-PE2I to its stable of routine tracers. The PET unit has substantial experience running research PET studies including over 50 dAMPH challenge scans. Furthermore, the analysis capabilities of Vanderbilt's VANTAGE genetics core provides me with the ability to look at single nucleotide and variable number of tandem repeat polymorphisms in DA genes of interest. The Vanderbilt Institute of Imaging Sciences (VUIIS) provides additional expertise in neuroimaging analysis. Finally, intellectual climate is superb, and includes a rich group of relevant seminar series sponsored by the VUIIS, the Vanderbilt Brain Institute, and the Depts. of Psychology, Psychiatry and Pharmacology.

Responsible Conduct of Research

Studies proposed in this training grant will adhere to all standards for responsible conduct of research set by the National Institutes of Health and Vanderbilt University. Vanderbilt's Human Research Protection Program "requires all Investigators, Key Study Personnel, Students, and Faculty Advisors who are conducting human subjects research to complete human subjects protections training using online courses".

See http://mcapps01.mc.vanderbilt.edu/IRB/policy&procedures.nsf for policies and procedures enforced by Vanderbilt to safeguard the rights and welfare of human subjects and to comply with NIH standards. All personnel involved in the proposed study will undergo training regarding ethical issues such as researchers' responsibilities, subject confidentiality, data handling, conflict of interest, and noncompliance reporting. To maintain compliance vigilance, all personnel annually complete a Collaborative IRB Training Initiative (CITI) responsible conduct of research course, a CITI Refresher Course, or attend an IRB educational session at Vanderbilt University.

During graduate training, the applicant completed a course on research ethics as well as online CITI courses on an annual basis and has a base understanding of standards for responsible conduct of research. Throughout the fellowship period, the applicant will continue to maintain HIPAA and CITI certification and complete the NIH Online Course on human subjects protection as required for obtaining federal research funds. In addition to formal courses and online training, responsible conduct of research will be discussed in weekly lab meetings and practiced under the guidance of Dr. Zald.

Goals for Fellowship Training and Career

My career goal is to become the principal investigator of my own lab at a research university. I plan to couple my knowledge of behavioral genetics and the role of dopamine (DA) in cognition and choice behavior (doctoral work) with neuroimaging techniques uniquely able to measure DA system function (postdoctoral work) to better understand the role of DA in human reward, motivation, and decision making as it relates to drug addiction and externalizing disorders. This proposed research plan will enable me to gain experience in neuroligand positron emission tomography (PET) methods used to measure DA signaling in humans. Specifically, I will gain experience with combining PET data on DA D2/3 and DAT levels with d-amphetamine (dAMPH)-induced DA release to understand individual variability in dAMPH responsivity. By also developing my genetic analysis skills, I plan to study the role genetic variation plays on the PET measures I will be using and work to integrate these data into a more complete understanding of the biological bases of individual differences in factors that confer potential risk for addiction (heightened dAMPH responsivity, novelty seeking traits). These neuroimaging and genetic analysis skills will be transferable and allow me to study the role of DA in a variety of disorders (addiction, ADHD) as an independent investigator. Upon completing this training plan, I will possess a unique set of skills that will allow me to integrate pharmacological and behavioral findings to personality, neuroimaging, and genetic variation. I plan to apply these skills in future work to study a diverse range of behavioral phenotypes associated with addiction (impulsivity, delay discounting, motivation, reward processing) and identify the biological factors associated with them. This work has the potential to identify important biological factors associated with addiction risk as well as potential sites for treatment.

To aid me in achieving my professional and academic goals, I plan to gain experience in PET data analysis, structural equation modeling, and genetic analysis as a postdoc in addition to improving my scientific communication, mentoring and teaching skills. While I have gained experience in PET image processing and analysis during my first 6 months in the Zald lab, my sponsor and I agree that a strong understanding of kinetic modeling of PET data is essential to my training. Thus, with the assistance of Dr. Evan Morris at Yale (expert in PET data processing and analysis) we have selected a series of papers for me to read on the subject (http://tauruspet.med.yale.edu/wiki/index.php/Table_of_Handouts_for_ENAS_915). In addition, I will seek out more formal training either by auditing lectures in one of Dr. Morris's courses at Yale (ENAS 915: Tracer Kinetics & Modeling; ENAS 880: Imaging Drugs in the Brain) or via a workshop such as those organized by INMiND or in conjunction with the biennial BrainPET conference. I also plan to take a course on structural equation modeling (PSY-GS 8873) offered by the Vanderbilt Psychology Department to learn to apply these types of models (including mediation models) to this proposal's data. Finally, I plan to take courses through the Vanderbilt Program in Human Genetics (HGEN courses) and enroll in a Short Course on the Genetics of Addiction offered at The Jackson Laboratory each summer (which features lectures by two of my project's collaborators: Drs. de Wit and Palmer) to develop skills in genetic analysis. To gain experience in scientific communication and hone by presentation skills in preparation for job talks, I will present my postdoctoral work in either of the weekly Neuroscience or Center for Cognitive Neuroscience seminars held in the Vanderbilt Psychology Department at least once per academic year. In addition to inter-department seminar opportunities, I plan to attend at least one major scientific meeting a year (such as Society for Neuroscience (SFN), Cognitive Neuroscience Society (CNS), Organization for Human Brain Mapping (OHBM)) where I will present some of my postdoctoral work, network with colleagues, and seek to build future collaborations. In fact, I have already attended a meeting (the Scientific Research Network on Decision Neuroscience and Aging) to present some of my postdoctoral work and attended a reinforcement learning modeling workshop as part of the conference. Taking advantage of neuroimaging analysis workshops at other conferences is something I plan to pursue when appropriate.

In terms of development other skills, I have a good deal of mentoring experience as a graduate student at UNC. While completing my PhD, I oversaw over 9 students and 3 Senior Honors Projects which culminated in 2014 when one of my mentee's (Scott Oppler) Senior Honors Thesis was award the Dashiell-Thurstone Prize in Psychology for the best thesis. Furthermore, another Honors Thesis student (Michael Parrish) presented some of his work at the Society for Neuroscience meeting in November 2014. The success of my undergraduate mentees gives me a great sense of accomplishment and demonstrates that I have the skills to successfully mentor as research faculty in the future. I am continuing to mentor students (currently 3 undergraduates) at Vanderbilt. To gain teaching skills while at Vanderbilt, I plan to utilize the Vanderbilt Center for Teaching's (CFT) resources, including attending seminars in college teaching and observation of my teaching skills via a semester-long practicum that result in a Certificate in College Teaching. Furthermore, I plan to guest lecture in courses administered by my advisor, David Zald, in the Vanderbilt Department of Psychology, and team-taught classes in the graduate neuroscience program administered by the Vanderbilt Brain Institute. Through the development of my teaching, scientific communication, kinetic modeling, and PET/genetic analysis skills from resources available at Vanderbilt and elsewhere, I plan to leave my postdoctoral fellowship with the tools necessary to succeed in studying DA and addiction as an independent researcher.

Activities Planned Under This Award

This training plan will occur over 3 years. The majority of time will be devoted to data collection, data analysis, and manuscript preparation. Beyond working with data, the applicant will attend graduate-level seminars/classes to learn additional analytical techniques, gain training in grantsmanship, and participate in meetings/colloquia to expand knowledge base.

Timeline:

Project Year	Year 1				Year 2				Year 3			
NIH Quarter	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4	Q 1	Q 2	Q 3	Q 4
Scientific Proposal												
All Aims: Data Collection	■	■	■	■	■	■	■	■				
Aim 1 Data Analysis		■	■	■	■	■	■	■				
Aim 2 Data Analysis					■	■	■	■	■	■		
Aim 3 Data Analysis							■	■	■	■		
Career Development												
Mentoring	■	■	■	■	■	■	■	■	■	■	■	■
Didactic Courses	■	■		■	■	■						
Multidisciplinary Seminars	■	■		■	■	■		■	■	■		■
Workshops and Tutorials			■				■				■	
Professional Conferences		■	■			■	■			■	■	
Manuscript Preparation	■	■	■				■	■	■	■	■	■
Teaching Certificate/Practice					■	■	■	■				
K99/R00 Application					■	■						
Faculty Job Application & Interviews											■	■

Specific Activity Highlights for Each Year of Training Plan:

Year 1: **75% Research** (Data collection & Analysis, 65%; Mentoring students/research assistants, 10%)

20% Coursework / Directed Reading

Directed reading topics (2%): PET/kinetic modeling, psychostimulant psychopharmacology

Courses (18%): Structural Equation Modeling, Vanderbilt (PSY-8873); Human Genetics I & II, Vanderbilt (HGEN-340, -341); PET Kinetic Modeling Course (such as this INMiND course: http://www.uni-muenster.de/imperia/md/content/inmind/training/periodiv/programme/prog_ts10_cop_2015-03.pdf)

3% Grant Writing

Attend grant writing symposia and present grant applications at mock study session for feedback from experienced reviewers at Vanderbilt's Center for Translational Research (VCTR)

2% Meetings / Colloquia

Vanderbilt Department of Psychology's weekly Neuroscience seminar, Vanderbilt Brain Institute's and VUIIS's seminars/colloquia, Grand Rounds talks in Department of Psychiatry (VUMC), monthly Dopamine data meetings with Drs. Randy Blakely and Ariel Deutch's labs

Year 2: **73% Research** (Data collection & Analysis, prepare manuscripts 63%; Mentoring students/RAs, 10%)

11% Coursework

Fundamentals of Genetic Analysis, Vanderbilt (HGEN-385); Short Course on the Genetics of Addiction, The Jackson Laboratory; Advanced Neuroimaging Analysis Course (at Human Brian Mapping Conference)

6% Teaching Experience

Guest lecturing in Psychology and Neuroscience Courses (1%)

Certificate in College Teaching Seminar and Practicum from Vanderbilt Center for Teaching (5%)

8% Grant Writing (Preparation of K99/R00 Pathway to Independence Award)

2% Meetings / Colloquia (as for Year 1)

Year 3: **79% Research** (Analyze data, prepare manuscripts, 69%; Mentoring students/RAs, 10%)

15% Preparation for Job Applications and Interviews

Mock interviews, practice job talks, CV and Career Advice from BRET Career Development Office

6% Meetings / Colloquia / Career Development Workshops

BRET Career Development Events, Seminars, Workshops (4%)

Meetings / Colloquia (as for Year 1; 2%)

Doctoral Dissertation and Other Research Experience

Doctoral Dissertation University of North Carolina at Chapel Hill May 2009 - June 2014

Neurocognitive Investigation of Immediate Reward Selection Bias, A Putative Intermediate Phenotype for Alcohol Use Disorders

Advisor: Charlotte Boettiger Committee: Gabriel Dichter (chair), Regina Carelli, Fulton Crews, Weili Lin

A tendency to choose smaller, sooner *(Now)* over larger, later *(Later)* rewards is heightened in addiction. My dissertation sought to investigate if heightened *Now* choice bias satisfied some of the criteria for an intermediate phenotype for alcohol use disorders. I used behavioral genetic approaches to also investigate the impact of putative frontal dopamine (DA) on *Now* choice bias.

The first key finding from this work was that a single nucleotide polymorphism (rs4680, Val158Met) in the catechol-*O*-methyl transferase (COMT) enzyme that regulates DA levels in the prefrontal cortex interacted with age to affect *Now* choice bias. Specifically, using age (DA levels decline with age) and COMT as putative measures of frontal DA, I demonstrated that *Now*/*Later* choice behavior is related to frontal DA via an inverted-U function with insufficient or excess PFC DA associated with increased tendency to choose *Now* and intermediate levels of frontal DA associated with more *Later* choice selection. Thus individual differences in frontal DA levels may be a critical factor to consider in future attempts to pharmacologically modulate *Now* choice bias.

The second key finding from my dissertation work was that age interacts with problematic alcohol use to affect *Now* choice bias. Specifically, young adults (ages 18-24) show heightened *Now* choice bias relative to adult (ages 26-40) controls. However, heavy drinking adults show no difference in *Now* choice bias relative to young adults and have significantly elevated *Now* bias compared to moderately drinking adults. Thus, problematic alcohol use in young adulthood may “lock-in” high *Now* choice bias in adulthood. Furthermore, I found that moderately drinking adults with a family history of alcohol use disorders (at least one first degree relative with an AUD) had *Now* bias values nearly as high as heavy, problematic drinking adults. This finding suggests that elevated *Now* bias may be an intermediate phenotype associated with increased risk for the development of AUDs in adults. Follow-up neuroimaging studies that were not completed in time for the dissertation will allow us to better understand the effect of normal development and problematic alcohol use on brain circuits critical for *Now/Later* choice behavior.

Finally, as a means to understand if state changes in DA signaling could impact *Now* choice bias, I looked at the effects of naturally fluctuating estradiol levels over the menstrual cycle (which has been associated with increases in DA signaling) on *Now* choice bias. In addition, we sought to test our inverted-U model for frontal DA’s role on *Now* bias by asking whether COMT genotype predicted the effect of elevations in estradiol (and putative DA signaling) on *Now* bias within the same subjects (tested during the follicular phase when estradiol is low and the menstrual phase when estradiol is high; order counterbalanced). We found that increasing estradiol was related to decreases in *Now* bias across all subjects (i.e., they selected the larger, later option at a higher rate; a potentially adaptive behavior (greater future thinking) when females are ovulating). This effect, though, was driven by individuals possessing the low putative PFC DA COMT genotype (Val carriers) who received a boost in putative frontal DA with estradiol that pushed them more toward the optimal intermediate portion of the inverted-U function. In contrast, COMT Met/Met individuals did not see a decline in *Now* bias with increasing estradiol, suggesting they were less responsive to the increasing putative DA levels associated with increasing estradiol. The results from this final experiment indicate that *Now* bias can be modulated by putative changes in DA signaling, presumably at the level of the PFC. This is important as it suggests that future pharmacotherapies that could modulate PFC DA may help to reduce *Now* choice bias, which has implications for addiction, attention-deficit hyperactivity disorder, and other externalizing behaviors where elevated *Now* bias is observed.

Taken together, this dissertation work suggests that *Now* bias may be a useful intermediate phenotype for alcohol use disorders, that age and PFC DA levels may impact the behavior, and that changes in putative PFC DA levels within individuals can modulate this behavior according to a proposed inverted-U function. This work sets the stage for future neuroimaging work investigating structural and functional correlates of *Now/Later* choice bias and how the circuits and structures may be altered with normal development and alcohol use. Additionally, investigations into the parallel effect of DA levels on *Now/Later* bias could be aided with the use of PET indices of DA system function.

Undergraduate Research Furman University May 2007 - May 2008

Neurocognitive Investigation of Immediate Reward Selection Bias, A Putative Intermediate Phenotype for Alcohol Use Disorders

Advisor: Judith Grisel

My research experience began in a basic behavioral neuroscience lab at Furman University during the summer before my senior year of college. I chose to work in the lab of Judith Grisel, where I assisted in the experimental planning, data collection, and data analysis of three interrelated experiments. First, I used *in vivo* microdialysis and HPLC to detect strain differences in baseline dopamine and glutamate levels in the nucleus accumbens of three different strains of mice transgenic for β-endorphin. I also investigated how levels of these transmitters are altered by acute alcohol (EtOH) administration. Second, I used behavioral tests to analyze behavioral despair (a mouse model of depression) and anxiety in these same strains to determine the role of β-endorphin and EtOH in influencing these mice's behavior. Third, I used conditioned place preference experiments to compare the reward value of EtOH in these mouse strains and thus whether β-endorphin affected the mice's propensity to associate EtOH with reward. While in the lab I became proficient in animal husbandry, experimental design, data analysis, and scientific communication techniques. I received funding for this summer research project from the South Carolina NIH-IDeA Networks of Biomedical Research Excellence (INBRE), which provided the opportunity to present my research to a group of fellow students and faculty members. In addition to this experience, I gave a talk in July 2007 entitled "Evaluating the neurocircuitry of β-endorphin mediated reinforcement in the nucleus accumbens using transgenic mice" to a group of faculty and peers at the First Annual Summer Research Conference Between Furman and Davidson Universities. When I completed my research in September 2007, I prepared a poster ("Role of β-endorphin in behavioral despair, stress, and anxiety") to present at the 2007 Annual Meeting of the Society for Neuroscience Faculty for Undergraduate Neuroscience Poster Session. During the 2007-8 academic year, I also presented my findings from this summer research at other conferences including the South Carolina NIH-INBRE 2008 Research Symposium in January 2008 and the Symposium for Young Neuroscientists and Professors of the SouthEast (SYNAPSE) meeting in March 2008. My work in the Grisel lab also received an acknowledgement in a recent paper from the lab: Grisel JE, et al. (2008). Influence of *β*- endorphin on anxious behavior in mice: interaction with EtOH. *Psychopharmacology*, *200*, 105-115. This initial research experience at Furman, which included presenting my findings to the broader scientific community, laid the foundation for my interest in continuing conducting scientific research related to understanding the neurobiology of alcohol addiction and making this the focus of my future academic and career interests.

SECTION II – SPONSOR INFORMATION

I am extremely enthusiastic about serving as Dr. Smith's sponsor for this proposal. As described below I believe that Dr. Smith has enormous potential as a researcher, and believe that the program of training spelled out in this proposal will prepare him for a unique and productive independent research career.

a. Research Support Available

Source	Grant Number	PI	Amount	Date
NIA	R01-AG044838	Zald	$1,632,962	9/30/12 - 6/31/15
Title: Dopaminergic modulation of subjective valuation across adulthood				
NIA	R01-AG1043458	Zald	$2,356,857	2/15/13-1/13/19
Title: Dopaminergic neuromodulation of decision making in young and middle-aged adults				
NIMH	R01-MH098098	Zald	$4,432,184	9/21/12-6/31/16
Title: RDoC constructs: neural substrates, heritability and relation to psychopathology				

There are two active R01 grants that are particularly relevant for this project. The key grant is R01-AG043458 "Dopaminergic Neuromodulation of Decision Making in Young and Middle-Aged Adults", which uses a dual scan PET imaging protocol with [18F]fallypride, on placebo and amphetamine, and measurement of DAT functioning with [18F]-FE-PE2I. R01-AG044838 "Dopaminergic modulation of subjective valuation across adulthood" is also relevant as it aims to characterize individual and age differences in motivation, cognition, and decision making over the adult life span using multimodal neuroimaging techniques that combine PET imaging with [18F]fallypride and fMRI of behavioral tasks. Additional [18F]fallypride PET data is available from 2 prior NIH-funded PET studies on which Dr. Zald was the PI. These include 1R21DA-033611 "Dopamine Influences on Self-Regulation and Impulsivity" and 1 R01-DA019670 –Individual Differences in Extrastriatal Dopamine", both of which were funded by NIDA.

b. Sponsor's Previous Fellows/Trainees

Dr. Zald has previously mentored 8 predoctoral graduate students and 7 postdoctoral scientists. These numbers include two current post-doctoral fellow (not including Dr. Smith) and 4 current graduate students. Dr. Zald has additionally served as primary mentor, or co-mentor for 4 K-awards, at Vanderbilt and as an external mentor for one K-award. Currently, he has one active K-mentee. Sponsored students and K-mentees have included individuals in clinical and cognitive psychology, neurology, neuropsychology, psychiatry and systems neuroscience.

Representative Five: [Dr. Zald's mentorship role in brackets at the end]
Joshua Buckholtz, Ph.D. (2011), Assistant Professor, Department of Psychology, Harvard University [primary doctoral mentor]
Greg Samanez-Larkin, Ph.D., Assistant Professor, Department of Psychology, Yale University [Post-doctoral NRSA & K99 sponsor]
Michael Treadway, Ph.D. (2012), Assistant Professor, Department of Psychology, Emory University [primary doctoral mentor-NRSA sponsor]
Steven Most, Ph.D., Senior Lecturer, School of Psychology, University of New South Wales [Post-doctoral NRSA co-sponsor]
Neil Woodward, Ph.D. (2007), Assistant Professor, Department of Psychiatry, Vanderbilt University [primary doctoral mentor]

c. Training Plan, Environment, Research Facilities

The applicant's training will focus primarily on expanding his range of research skills, broadening his knowledge base and honing his professional skills, including grantsmanship, presentation skills, and mentoring. The over-arching goal of the training plan is to ensure that he is fully equipped with the necessary tools to independently direct a strong research program upon completion of his post-doctoral fellowship. Beyond the necessary skills for research success, we will facilitate building a network of professional contacts that maximizes Dr. Smith's

ability to exchange intellectual ideas and build collaborations with leaders in the field. Similarly, we aim to ensure that Dr. Smith is extremely competitive when he enters the job market in a few years time.

Mentoring Team:
Dr. Zald will serve as the primary mentor for Dr. Smith. The mentorship (advisory committee) team at Vanderbilt has two additional members.
Dr. Ronald Cowan, **MD, Ph.D.** is a board certified psychiatrist with expertise in addiction research. Dr. Cowan is the Director of the Psychiatric Neuroimaging Program and the Vanderbilt Addiction Center. Dr. Cowan has extensive experience as a clinician and researcher investigating the role of dopamine in mood and emotion. In addition to providing additional perspectives on affective neuroscience, Dr. Cowan will advise the applicant on the clinical implications of this study, adapting the applicant's research to clinical populations, and issues related to human subject protections in the context of amphetamine and radiotracer administration.
Dr. Randy Blakely, Ph.D. is an expert on neurotransporter functions including dopamine transporter functions and preclinical models of dopamine functions. Dr. Blakely is the director of the Silvio O. Conte Center for Neuroscience Research and the Vanderbilt Postdoctoral Training Program in Functional Neurogenomics.

There are two external members of the advisory team at the University of Chicago.
Dr. Harriet de Wit, Ph.D. is an internationally recognized authority on behavioral pharmacology of amphetamine. Dr. Zald and de Witt already have an established history of collaboration on the effects of amphetamine on motivation.
Dr. Abraham Palmer, Ph.D. is an associate professor of Human Genetics, and brings expertise in a range of genetic methodology and has been advising us on the potential strengths and limitations of genetic analyses relevant to dopamine functioning and amphetamine responsiveness.

Details of training are described below, but we first outline the primary recurrent meetings with members of the mentoring team. Dr. Zald will hold 3 weekly meetings with Dr. Smith throughout the life of the fellowship. The first is a standing one-on-one meeting to discuss projects, research ideas, papers and professional pragmatics. These meetings range from 15-minute check-ins to hour long detailed discussion of topics. The 2nd is a project-specific meeting held with our research team involved in studies on dopamine. The 3rd is a lab meeting in which we cover a wide range of topics related to affective and clinical neuroscience. In addition to standing meetings, the sponsor keeps an open door policy that allows fellows to have additional brief meetings with the PI on a daily basis as needed. Dr. Smith will also attend a monthly "dopamine" meeting led by Randy Blakely, which covers issues on preclinical studies of dopamine (and is also attended by Dr. Ariel Deutch, Ph.D., who brings added unique expertise on the topic). Finally, every 6 months, the full advisory team will meet (with members from Chicago on Teleconference) to review Dr. Smith's accomplishments, projects and goals.

Expanding Research Toolbox: The primary training activity will focus on expanding research skills, with a particular emphasis on his developing expertise in radioligand PET imaging and neuroimaging analysis techniques. This training will occur through hands-on experience. All research activities, from study design and data collection to data analysis and manuscript preparation, will be carried out with the advice and counsel of the sponsor and additional faculty collaborators/advisors. In order to learn kinetic modeling, Dr. Smith will learn to use PMOD software that allows a range of kinetic modeling (http://www.pmod.com/technologies/index.html). Further work in this area will include guided readings, which Evan Morris, Ph.D., who is an associate professor of diagnostic radiology in the Yale School of Medicine (http://tauruspet.med.yale.edu/staff/edm42/), has helped us prepare based on one of his course at Yale. Chris will also attend an external kinetic modeling workshop or course (the specifics are yet to be determined because dates have yet to be announced from groups that have previously offered such courses, such as that offered this year by INMiND (link: http://www.uni-muenster.de/imperia/md/content/inmind/training/periodiv/programme/prog_ts10_cop_2015-03.pdf). Expanding neuroimaging analysis tools will be accomplished through ongoing talks and working groups in the Vanderbilt University Institute for Imaging Sciences (VUIIS) and the Psychiatric Neuroimaging group in the Dept. of Psychiatry. Dr. Smith will also have access to the VUIIS Center for Computational Imaging resources. Critically, this group includes Dr. Zald's image analysis programmer (Benjamin Yvernault, MSEE) who will provide assistance with developing image processing pipelines, as well as the computational resources in the Advanced Computing Center for Research and Education (ACCRE) at Vanderbilt. The sponsor, Dr. Zald, has successfully published research utilizing each of these facilities and has an existing and productive relationship with the staff

of each facility. We note that Dr. Smith already has significant experience with neuroimaging analysis, so this work is aimed at supplementing his skill set rather than his needing to learn from scratch.

Two additional pieces of his training plan aim to increase his skill set. First, he will take a graduate level course on structural equation modeling (PSY-GS 8873) at Vanderbilt to enhance his analytic skills in executing causal and mediation models in relating different types of neuroimaging data with behavior. In addition, Dr. Smith will take courses through Vanderbilt Program in Human Genetics (http://chgr.mc.vanderbilt.edu/page/courses; HGEN courses; specifically HGEN-340, -341 (Human Genetics) and HGEN-385 (Genetic Analysis)) focused on the analysis and interpretation of genetic data. This training will be instrumental in combining such data with our behavioral and neuroimaging measures.

Increasing Knowledge Base: A key training activity will focus on increasing the applicant's knowledge base. Dr. Smith already has an extensive knowledge of molecular neuroscience with an emphasis on neuropharmacology. On the other hand, we have identified certain domains of cognitive and affective science/neuroscience where additional knowledge would prove helpful. Although Dr. Smith has already published research papers on genetics, one of our goals is to enhance his specific expertise in the genetics of addiction. To enhance his knowledge of this area, he will take a short-course on the Genetics of Addiction offered at The Jackson Laboratory each summer (http://courses.jax.org/2015/addiction.html). To further expand his knowledge of clinical conditions, he will also routinely attend weekly psychiatry grand rounds and the Dept. of Psychology's weekly clinical brown bags, especially when topics relate to externalizing disorders, affective science or psychopharmacology. In addition to directed readings, his knowledge base for neuroscience will be augmented through attendance of weekly neuroscience-cognitive neuroscience colloquia in the Department of Psychology and weekly colloquia in neuroscience sponsored by the Vanderbilt Brain Institute. Additional relevant colloquia on topics related to neuropharmacology are available through the Department of Pharmacology. Dr. Smith will be expected to go to these when relevant (with an average of at least one per week during the academic year). Dr. Smith's participation in the "dopamine club" run by Randy Blakely provides an additional place to expand his knowledge base because of its focus primarily on preclinical models of dopamine functioning. The club's time is split between presentations of data arising from ongoing studies of dopamine, as well as brief coverage of recent journal articles relevant to dopamine functions. A strength of this club is its interdisciplinary nature, as attendees work on models that range from studies of dopamine cells in worms, to rodent behavioral studies to examination of rare gene variants and neuroimaging in humans.

Honing Presentation, Teaching and Mentoring Skills: Throughout training the applicant will be expected to present at least one talk a year in the Department of Psychology and at least two posters or talks at scientific conferences. In each case (and in preparing any external talks), he will be required to first present in laboratory meetings so as to help critique and improve the talks. He will also be expected to present ideas or papers in laboratory meetings, and to provide mini-workshops to the laboratory on methodological developments. Similarly, he will be expected to critique talks provided by other lab members (there are typically 10-15 of these opportunities a year).

The applicant will also mentor undergraduate and full-time research assistants and undergraduate honors students in the Affective Neuroscience Laboratory. This will prepare him for subsequent mentorship responsibilities in his career. We will review issues in mentoring as they come up. The applicant will also attend teaching seminars offered by Vanderbilt's Center for Teaching (http://cft.vanderbilt.edu/), with an expectation that he will earn a Certificate in College Teaching.

Building Grant Writing Skills: During his first year of the fellowship, Dr. Smith will attend at least one in person or online symposia on grant writing. During the 2nd year of training, the applicant will prepare at least one grant application with Dr. Zald with the explicit goal of improving these skills. This proposal will be prepared with enough advance timing to submit it to Vanderbilt mock study section (sponsored by the Vanderbilt University Center for Translational Research), which allows post-doctoral fellows and junior faculty to observe how the submission is discussed and to get direct feedback from experience reviewers. The applicant will also attend grant-writing workshops offered at the Society for Neuroscience meetings.

Summary of Coursework: The applicant will attend multiple classes and seminars on topics relevant to his research and professional development. Courses include: computational modeling of cognition, brain imaging methods, neuropharmacology, statistical methods for genetic and image analysis, and neuropsychological assessment. Seminars include: the clinical brown bag series, the neuroscience brown bag series, the Vanderbilt

Brain Institute seminar series, VUIIS seminar series, and psychiatry and neurology grand rounds. The courses relevant to the applicant's professional development are: seminar and practicum to earn a teaching certificate, preparing STEM faculty for diverse learners, and grant writing seminars.

Timeline for Manuscript Submission: The applicant will be expected to submit, as first author, 2 manuscripts in the first year and 3-4 manuscripts each in the second and third year of his fellowship. We also anticipate that the applicant will also be a coauthor on multiple manuscripts stemming from projects in the lab that he significantly contributes to. As there are already existing datasets relevant to his work in the lab, he will be able to pursue at least some data analyses relatively early in his fellowship before data collection is completed for his primary aims.

Networking / Establishing Scientific Reputation: The applicant will attend and present work at a minimum of two annual meetings per year. These will include at least one presentation at Society for Neuroscience, Cognitive Neuroscience Society, and Organization for Human Brain Mapping during the course of his fellowship, with repeat attendance or attendance at other conferences to be determined based on timing of research and involvement in symposia. Dr. Zald will help facilitate making contact with both leaders in the field and young promising researchers in the field.

Ethics: Dr. Smith has already completed ethics and responsible conduct of research training, but will be expected to renew this training every year. Discussions of topics related to ethics and responsible conduct also occur as part of Dr. Zald's weekly lab meetings. He will also complete the CITI online refresher courses on responsible conduct of research and human subjects research on an annual basis.

Preparing for the Job Market: During the final year of training the applicant will be expected to apply for junior faculty positions at American universities, hospitals or research institutes. The training supported by this fellowship will make the applicant a strong candidate for a faculty position and will ensure his success after securing a job offer. Through mentoring and grant management, the applicant will gain necessary laboratory management experience. The sponsor and collaborators will assist the trainee with the preparation of application materials (e.g., research and teaching statements). The sponsor has served on several search committees for junior faculty and has helped position past mentees to obtain faculty positions at premier research institutes. The applicant will meet with Dr. Zald 6 months before applying for jobs to begin preparing materials and identify candidate positions. The applicant will be expected to present initial drafts of a job talk in the Zald lab meeting and will later practice a final version in area seminars (e.g., Cognitive Neuroscience Area Seminar). There additionally will be routine opportunities for Dr. Smith to attend job talks and practice job talks in both the psychology department and other relevant departments in the medical school. Application materials will also be reviewed by members of his advisory team.

Pragmatics: A final area of training will focus on the pragmatics of running an independent research laboratory. This will include topics related to working with the IRB, budgeting, reporting, management of research staff, as well as broader issues that come up in academia and science. This will be largely dealt with as part of regularly scheduled individual meetings with Dr. Zald, but will also be dealt with as part of weekly lab meetings, and in meetings with departmental administrators and grant managers.

Environment: Several features of the environment make Vanderbilt an ideal institution for Dr. Smith's fellowship. Neuroscience research at Vanderbilt cuts across multiple departments in the College of Arts and Sciences and the Vanderbilt University Medical School. The Vanderbilt Brain Institute (VBI) acts as an umbrella organization that facilitates interdisciplinary research and education in neuroscience. In 2012, the graduate neuroscience program organized and administered by the VBI was named the program of the year by the Society for Neuroscience based on the high caliber of research, education and outreach conducted at Vanderbilt. As Dr. Zald is on the steering committee of the VBI, Dr. Smith will have full access to VBI resources.

Vanderbilt has world-class neuroimaging facilities and support service. Neuroimaging resources are housed within the Vanderbilt University Institute of Imaging Science (VUIIS) which houses MRI facilities including two Phillips 3T Intera-Achieva magnets with state of the art 32 channel coils, as well as a 7T magnet that Dr. Zald and colleagues have used to provide detailed high resolution structural imaging of the substantia nigra. The VUIIS's mission is to deliver advances in neuroimaging, and support the translation of these advances for human imaging studies. The VUIIS provides methodological courses and seminar to facilitate these advances. The

Center for Computational Imaging (CCI) within the VUIIS provides solutions and services aimed to make imaging research more tractable to members of the scientific community. The CCI works with researchers to provide services, training, and guidance for image analysis and informatics. The CCI develops support tools, informatics tools, and infrastructure, to help advance imaging research for the VUIIS's users. For PET imaging, the VUIIS runs a radiochemistry core. Although this radiochemistry core does not produce a wide variety of ligands, it has extensive experience producing the [18F]fallypride needed for this proposal, and indeed the group has produced more runs of [18F]fallypride for human studies than any other center in the world. Dr. Zald has worked closely with the radiochemistry core to make [18F]-FE-PE2I a routine radioligand for research studies. The Department of Radiology currently runs two PET cameras, and the VUIIS has received a large instrument grant to purchase a new research dedicated camera.

The environment is exceptional in terms of cognitive psychology and cognitive neuroscience. Although the Dept. of Psychology is relatively small, it boasts two members of the National Academy of Science. Several members of the faculty have active research programs related to affective science. The clinical area group within the Department of Psychology has strengths in both clinical neuroscience and affective science, providing a rich environment for linking these domains. Collaborations within the Department of Psychiatry's Psychiatric Neuroimaging Program provide a particularly fertile opportunity for translational work, as this group has been able to develop mechanisms for studying psychiatric patient populations, and has a wealth of experience with issues of study design and analysis of studies using clinical groups.

Because of the small footprint of the campus, the Department of Psychology is only a 5-minutes walk from VUIIS and VBI, and is less than 10-minutes to the PET center, Depts. of Neurology and Psychiatry. This helps facilitate both research as well as the ability to develop collaborations across different clinical and basic science departments. The Vanderbilt Institute for Clinical and Translational Research provides a wealth of resources for research with humans, including biostatistical support and funds for pilot studies.

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 fellowship.
Dr. Zald expects to supervise 3 Ph.D. candidates simultaneously during each year of the proposed fellowship.

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

I express my highest possible support for Christopher Smith's candidacy for an NRSA post-doctoral training fellowship. Dr. Smith joined my lab in the fall of 2014. He originally came to my attention based on a superb conference presentation. After hearing his talk, one of my prior post-doctoral fellows concluded that Christopher should be the next post-doctoral fellow to join my lab. Christopher's background and interests are truly a superb fit with my lab. Based on my initial conversations with Christopher, I was impressed enough that I decided to hire him without conducting a formal search for the position. Indeed, I had come to this conclusion before I actually had funding fully available for the position.

Although often presenting himself in a humble light, Christopher shows a range of qualities that indicate his enormous potential. Chief among these is that he possesses a keen eye for seeing patterns in data, and is equally quick to see the significance of those observed patterns. This is reflected in his current proposal, which is built upon his novel observation that there were two distinct temporal patterns of subjective effects to amphetamine among those who are responsive to it. Having made this initial observation he started to dig through existing literatures to figure out what it meant, and after demonstrating something similar in a larger independent dataset, he put together what I believe to be an excellent paper on this finding (currently under review). He did this with remarkable efficiency. Indeed, I have never had a student or post-doctoral fellow write up a high quality paper so quickly after joining the lab. This efficiency comes without any loss of depth or quality in the presented ideas. Overall, Christopher shows well-developed critical reasoning skills, and appreciates the nuances associated with different levels of inference. He understands both the theoretical and methodological context of his studies and where they fit within both the lab and the larger literature. He combines his intellectual prowess with clear dedication and passion for his work. He is an extremely hard worker. If anything, he may have to be told at some point that he should take a day off. Some fellows work hard because of ambition, Christopher works hard out of a shear love of the science.

Christopher arrived at Vanderbilt with a strong knowledge base in issues related to reward, dopamine functions, hormones and genetics, and has rapidly expanded this base while pursuing the human and animal literatures on dopamine, psychostimulants, personality and possible individual differences in temporal dynamics.

He has a well-developed ability to synthesize disparate research literatures. Academia often articulates the value of interdisciplinary training and research, but often fails to facilitate it in students. In this context, it is notable that Christopher has the range of intellectual abilities that allow him to be truly inter-disciplinary in the scope of his questions.

Dr. Smith already has a well-developed sense of how to craft a scientific argument. With 3 published first-authored papers, one second-author paper, and several papers in review or preparation he has already demonstrated an ability to publish in first line journals. His flow of logic in these papers is clear and is consistent with his outstanding ability to articulate ideas and arguments. Part of his ability in this regard may come from the fact that he has a good sense of the areas where he is in command of the literature, as well as knowing where some of the boundaries of his expertise lie. As such, he is an extremely easy person to mentor. He listens carefully to critiques of his ideas or writing, and is quick to use those criticisms to build a strong paper or proposal. He is similarly quick to delve deep into the literature when trying to understand the theoretical or mechanistic bases of a finding. If the reviewers of this proposal provide critiques, one knows that Christopher will take them seriously and turn around with a stronger proposal upon resubmission.

I believe that one of the best signs of a potentially successful researcher is their generativity. By this I refer to the individual's ability to come up with new ideas, be that new experimental paradigms, new insights into how to analyze or look at data, or new theoretical ideas. I am unable to address the first of these types of generativity, but the latter of these two domains he truly excels at. He routinely comes to our meetings with new ideas that he is already finding ways to explore in existing data, and is expressing new ideas regarding the implications of those results. Having seen this, I can say with clarity that this is the exact sort of young scientist that NIH in general, and NIDA in particular, should be funding

Chris is also a quick learner. In the short time since joining my lab, he has quickly picked up new technical skills, such as using the PMOD kinetic modeling software. I anticipate he will be equally quick in mastering any of the additional methods he aims to learn as a fellow.

Christopher already possesses excellent mentoring skills, as revealed by the success of honors students who worked with him at the University of North Carolina. In my own lab, he is already demonstrated these skills. He has several undergraduate students working with him, and in his meetings he provides them with clear and constructive feedback, while also displaying warmth and nurturing. The students working with him clearly feel both challenged and supported, which in my mind is pretty close to the ideal of what a mentor should give their students.

In conclusion, I believe that Christopher has enormous potential as a scientist. His work will have an impact on multiple disciplines, and has clinical relevance for both normal drug use as well as abuse. He has all the right characteristics to be successful, including an already strong knowledge base, outstanding intellect, attention to details, technical skills, passion, drive and critical reasoning. I believe that the expertise available in my laboratory, Vanderbilt, and external advisers at the University of Chicago will provide Dr. Smith with opportunities to take his skill set to the next level. Combined with the impressive skills that he already demonstrates, I am confident that he will emerge from this post-doctoral fellowship with a trajectory for a truly outstanding and unique, independent research career.