

**APPLICATION FOR FEDERAL ASSISTANCE
 SF 424 (R&R)**

3. DATE RECEIVED BY STATE	State Application Identifier
<input type="text"/>	<input type="text"/>

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

4. a. Federal Identifier
b. Agency Routing Identifier

2. DATE SUBMITTED
Applicant Identifier

5. APPLICANT INFORMATION * Organizational DUNS:
 * Legal Name:
 Department: Division:
 * Street1:
 Street2:
 * City: County / Parish:
 * State: Province:
 * Country: * ZIP / Postal Code:

Person to be contacted on matters involving this application
 Prefix: * First Name: Middle Name:
 * Last Name: Suffix:
 * Phone Number: Fax Number:
 Email:

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

7. * TYPE OF APPLICANT:
 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:

10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER:
 TITLE:

11. * DESCRIPTIVE TITLE OF APPLICANT'S PROJECT:

12. PROPOSED PROJECT:
 * Start Date * Ending Date

*** 13. CONGRESSIONAL DISTRICT OF APPLICANT**

14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION
 Prefix: * First Name: Middle Name:
 * Last Name: Suffix:
 Position/Title:
 * Organization Name:
 Department: Division:
 * Street1:
 Street2:
 * City: County / Parish:
 * State: Province:
 * Country: * ZIP / Postal Code:
 * Phone Number: Fax Number:
 * Email:

<p>15. ESTIMATED PROJECT FUNDING</p> <p>a. Total Federal Funds Requested <input style="width:150px;" type="text" value="130,358.00"/></p> <p>b. Total Non-Federal Funds <input style="width:150px;" type="text" value="0.00"/></p> <p>c. Total Federal & Non-Federal Funds <input style="width:150px;" type="text" value="130,358.00"/></p> <p>d. Estimated Program Income <input style="width:150px;" type="text" value="0.00"/></p>	<p>16. * IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?</p> <p>a. YES <input type="checkbox"/> THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON: DATE: <input style="width:100px;" type="text"/></p> <p>b. NO <input checked="" type="checkbox"/> PROGRAM IS NOT COVERED BY E.O. 12372; OR <input type="checkbox"/> PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW</p>
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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

19. Authorized Representative

Prefix: * First Name: Middle Name:

* Last Name: Suffix:

* Position/Title:

* Organization:

Department: Division:

* Street1:

Street2:

* City: County / Parish:

* State: Province:

* Country: * ZIP / Postal Code:

* Phone Number: Fax Number:

* Email:

*** Signature of Authorized Representative**

Tony G Waldrop

*** Date Signed**

04/01/2010

20. Pre-application

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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:

DUNS Number:

* Street1:

Street2:

* City: County:

* State:

Province:

* Country:

* ZIP / Postal Code: * Project/ Performance Site Congressional District:

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

Organization Name:

DUNS Number:

* Street1:

Street2:

* City: County:

* State:

Province:

* Country:

* ZIP / Postal Code: * Project/ Performance Site Congressional District:

Additional Location(s)

RESEARCH & RELATED Other Project Information

1. * Are Human Subjects Involved? Yes No

1.a If YES to Human Subjects

Is the Project Exempt from Federal regulations? Yes No

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

If no, is the IRB review Pending? Yes No

IRB Approval Date:

Human Subject Assurance Number:

2. * Are Vertebrate Animals Used? Yes No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending? Yes No

IACUC Approval Date:

Animal Welfare Assurance Number

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

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

4.b. If yes, please explain:

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

4.d. If yes, please explain:

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

5.a. If yes, please explain:

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

6.a. If yes, identify countries:

6.b. Optional Explanation:

7. * Project Summary/Abstract

8. * Project Narrative

9. Bibliography & References Cited

10. Facilities & Other Resources

11. Equipment

12. Other Attachments

PROJECT SUMMARY/ABSTRACT

Individuals are at greatest risk for developing an alcohol use disorder (AUD) during late adolescence (Kandel and Logan, 1984; Brown et al., 2008), possibly due to the relative impulsiveness of late adolescents/young adults. Kandel and Logan (1984) have suggested that the decline in heavy alcohol use that typically occurs in the mid-twenties may reflect a maturational or developmental process, as the development of frontal structures implicated in self-regulation and impulse control is complete in humans around the early-to-mid twenties (Giedd, 2004; Hooper et al., 2004; Rubia et al., 2006; Eshel et al., 2007). Although there is general acceptance of the idea that frontal circuits are still maturing in late adolescents no work to date has specifically investigated changes in the function of frontal circuits engaged during *Now* versus *Later* decision making, a quantifiable measure of impulsiveness. The proposed studies will compare late adolescents (ages 18-21) and adults (ages 22-40) using structural and functional MRI approaches to identify differences in the brain areas engaged during *Now* versus *Later* decision-making. In addition, we will determine whether heavy alcohol use is associated with abnormalities in normally observed age-related differences in these neural circuits. Our central hypothesis is that immaturity in frontal circuits and relatively increased signaling in striato-limbic structures promote impulsive decision making in late adolescents. We will test our central hypothesis via the following Specific Aims: **1) Identify functional differences in frontostriatal circuits associated with *Now* versus *Later* decision making differences in late adolescents versus adults. 2) Identify structural differences in frontostriatal circuits associated with *Now* versus *Later* decision making differences in late adolescents versus adults. 3) Determine whether decision-making impulsiveness in heavy drinking adults is positively correlated with signs of structural or functional immaturity in frontal circuits.**

To achieve the goals of this research plan, a previously validated delay-discounting task (Mitchell et al., 2005; Boettiger et al., 2007) will be used to measure *Now/Later* decision making behavior in late adolescents and adults in the context of functional MRI. Within these same scan sessions, we will also acquire structural MRI and diffusion tensor imaging data to determine whether age-dependent differences in gray and white matter within brain structures of interest correlate with age-dependent differences in decision-making. These studies will be conducted in both moderate and heavy drinking populations to determine how alcohol use impacts age-related changes in brain structures engaged in *Now/Later* decision making.

This research stands to significantly improve our understanding of the neural underpinnings of changes in decision-making from late adolescence to adulthood, which may bear on why late adolescents are at an increased risk for developing alcohol use disorders. Greater knowledge of the mechanisms underlying risk for developing alcohol use disorders may allow for the development of better treatments or interventions.

PROJECT NARRATIVE

This research project seeks to understand the neurobiological bases for changes in the tendency to choose smaller, sooner rewards (“*Now*”) over larger, later rewards (“*Later*”) from late adolescence to early adulthood, a tendency that also characterizes individuals with alcohol use disorders. Studying developmental changes in the frontal structures that regulate *Now/Later* decision-making may provide insight into why late adolescents are at increased risk for developing alcohol use disorders, which may in turn aid in the development of new prevention and treatment approaches for this vulnerable age group.

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FACILITIES & OTHER RESOURCES

Environment – Contribution to Success:

The facilities and other resources available to the Sponsor's research team at UNC Chapel Hill include everything needed to successfully undertake and complete the proposed research project. When she set up her office and adjacent laboratory, they were equipped with this specific project in mind. These resources are complemented by the multitude of shared resources detailed below. Close proximity of all resources and consultants minimizes barriers to project execution and communication. The intellectual environment is rich with other extramurally-funded investigators conducting complementary research. For example, within the Psychology Department, Dr. Gina Carelli is conducting research investigating the role of dopamine in regulating response selection in rats. Dr. Carelli is the director of the Behavioral Neuroscience Program, to which the Sponsor belongs, and also serves on the Sponsor's faculty mentoring committee. The Behavioral Neuroscience Program has a long-standing NIDA training grant, which is available to initially support the Sponsor's trainees. The department's Cognitive Program includes several faculty members, including Dr. Joe Hopfinger, conducting neuroimaging research, with whom the Sponsor holds regular joint meetings; Dr. Hopfinger also serves on the Sponsor's mentoring committee. In addition to these departmental intellectual resources, the sponsor is also a member of the Bowles Center for Alcohol Studies, the Graduate Curriculum in Neurobiology, and the Biomedical Research Imaging Center. Through these associations, the PI will have access to numerous colleagues conducting relevant cognitive, neuroimaging, and addiction research as well as to two additional NIH training grants (in the Bowles Center and Neurobiology Curriculum) available for trainee support. Together these facilities provide a scientific environment that is strongly supportive of the proposed research and will therefore aid in its success.

Although the Sponsor is relatively junior, there is extensive evidence of UNC's commitment to her development as an academic researcher. Her 12-month, tenure-track academic appointment includes a total of three person months (25% effort) dedicated to research, with the option to buy out of one course per year allowing for an additional 3 person months (a total of 50% effort) dedicated to research. In addition, she was awarded an KL2 Translational Scholar Award through the UNC Clinical and Translational Science Award (See NC TraCS under "Other Resources"), which provides three years of salary support, allowing 75% effort dedicated to research; she is currently in year 2 of this award. Moreover, in 2009 Dr. Boettiger was selected as the UNC applicant for two highly competitive private grants: the Pew Scholars Program in the Biomedical Sciences, and the Dana Foundation Brain and Immuno-Imaging Grant Program. The start-up package provided to her included laboratory space, equipment and research funds needed to launch her research program. The package was sufficient to yield the preliminary data needed for this NRSA application. In addition, the sponsor, as a core faculty of the UNC Biomedical Research Imaging Center has been provided with unrestricted access to the MRI facilities and generous startup funds dedicated to scanner time, which will be available to fund the proposed studies. Administrative support is provided to the PI by a Behavioral Neuroscience Program Assistant, as well as a Psychology departmental administrative core that provides grants management, accounting, human resources, and instructional support. Important career-development programs are also available to the PI through NCTraCS and workshops offered through the UNC Center for Faculty Excellence on topics such as creating effective teaching portfolios, and grantsmanship. In addition, NC TraCS provides ongoing opportunities for research pilot funding, for which the PI is eligible to apply.

Facilities:

Laboratory: The Sponsor's lab is assigned 350 sq ft of laboratory space in the Psychology Department (Davie Hall). It is subdivided into a general computer workstation area, a behavioral subject testing area, and a wet lab area for biological sample storage and processing; this space is 100% dedicated to the Boettiger Lab's research. This space includes computer workstations to analyze fMRI data, computer-based testing facilities with high-quality graphics and timing routines for testing subjects, wet lab bench space, and all other resources (email, fax, on-line library catalogs) to facilitate research, writing and collaborations. Testing facilities include two separate testing rooms, both equipped with stimulus display, subject response devices, infrared camera monitors, and intercom communication. The wet lab is adjacent to the workstation and testing area and provides all necessary equipment for biological sample storage, handling, and processing, including refrigerator, freezer, flammables storage, vortexer/shaker, waterbath, full set of pipettors, Sorvall 6000G and Thermo Pico Fuge benchtop centrifuges, sink and eyewash. The lab is Biosafety Level-2 certified. An

additional 750 sq ft is available in the adjacent building (Howell Hall), which is also 100% dedicated to the Sponsor's research. This space includes a third private testing facility, which includes a mock MRI scanner equipped with full sound and visual display capabilities. This mock scanner facility is 100% dedicated to the Sponsor's research. The Howell Hall space also includes a private waiting area for subjects and separate office space (150 sq ft). The Boettiger Lab has access to dedicated parking spaces for research participants behind Davie Hall, and a common bus route stops outside of Davie Hall. *These laboratory facilities were specifically designed and equipped to support the program of research that includes the project proposed here.*

Biohazard Facilities The Boettiger is BSL-2 certified by the UNC Office of Environmental Health and Safety. Certification includes approval of a written lab safety plan, annual surprise audit, and annual training for all lab personnel. The facilities meet all necessary safety standards and include adequate materials and procedures for dealing with spills or other accidents. **Note:** *No research with select agents will be conducted.*

As a core faculty member of the Biomedical Research Imaging Center (BRIC), the sponsor and her research team have full access to its neuroimaging facility and its personnel. See *Equipment* section for greater detail on the BRIC facility. The BRIC is a 15 minute walk across campus from the Boettiger Lab, and also has dedicated parking in front of the building for research participants. The BRIC is also on a common bus route, and a campus bus runs frequently between the two locations. Public transit in Chapel Hill is free of charge, thus there are no significant access barriers to participation at either location.

Office: The Sponsor's office is adjacent to her laboratory. The personnel shared office space has hardwired high-speed internet access, as well as access to the internet via the UNC wireless network, and is equipped with four individual desks, four task chairs, two vertical filing cabinets, and 3 2-drawer filing cabinets, color and B/W laser printers (Davie Hall). Additional office space with four individual desks, four task chairs, two filing cabinets, and a color laser printer is available in the Howell Hall space. *These facilities will enable the PI to formulate experiments, analyze results, supervise undergraduate research assistants, and prepare manuscripts for publication.*

Computing: The Sponsor's lab is equipped with two high-end Linux machines, one of which includes a 1T RAID server. These computer workstations are 100% dedicated to processing and analysis of neuroimaging data. Additionally, the Sponsor's Lab is equipped with 4 Windows XP PCs dedicated to behavioral data collection, and analysis, and Windows XP/Vista desktops (8) and laptops (4), which personnel may use for behavioral paradigm development, off-site subject testing, data processing, and writing up study results. The Sponsor's Lab also has 500GB of dedicated space on a Windows fileserver in Davie Hall, which is backed up daily. Lab software includes Matlab, E-Prime, PASW, Microsoft Office, and Adobe Creative Suite. For additional storage and processing of neuroimaging data, the PI has access to large scale Linux file servers located in the BRIC and accessible locally within the neuroimaging facility or over the network from the Sponsor's Lab. Workstations are also provided within the BRIC for neuroimaging data processing. The BRIC file servers are backed up daily to a remote location in Cary, North Carolina.

Clinical: In the case of adverse events, the BRIC facility is equipped with a crash cart and is also located approximately 5 minutes from the UNC Hospital Emergency Room.

Animal: Not applicable.

Other Resources:

- Mammalian Genotyping Core Facility located on the UNC Campus. The sponsor has access by appointment on a fee-for-service basis. This facility routinely provides rapid and economical ABI TaqMan SNP (single nucleotide polymorphism) and small insertion/deletion genotyping. Such genotyping is suitable for a few to tens of SNPs to be typed for hundreds of samples. The core director, Dr. Jason Luo, will also collaborate with investigators, including providing services beyond genotyping that are important for ensuring the quality of genotyping project. Services include rigorous quality management, and several levels of quality control. In our previous experience with this core, they have provided high-quality results within 48 hours of sample submission.
- North Carolina Translational and Clinical Sciences (NC TraCS) Institute, funded in 2008 with an NIH Clinical and Translational Science Award, aims to support translatable research along every point of the research cycle from discovery to application, to dissemination, to practice and policy change, and back to rediscovery. Principal Investigator of the NC TraCS Institute is Dr. Etta Pisano, Vice Dean for

Academic Affairs in the UNC-CH School of Medicine, Kenan Professor of Radiology and Biomedical Engineering, and Director of the Biomedical Research Imaging Center (BRIC). Notably, as BRIC director, Dr. Pisano played a key role in recruiting the Sponsor to UNC. Through a pilot grant program, the NC TraCS Institute *has a total of \$4.3 million available per year to support basic, clinical, and public health scientists* for discovery-to-bedside and bedside-to-practice translational research. As a member of the NC TraCS institute, the PI is eligible for the TraC\$2K and TraC\$10K Pilot Grant programs (\$2,000 and \$10,000, respectively, for one year), and the Large Pilot Program (\$50-100K for one year). *Based on the translational nature of the proposed research, it is highly suitable for support from NC TraCS. As evidence of this, the Sponsor has already been a recipient of two of these grants (\$2k and \$50k).*

- NC TraCS Biostatistics Core is housed on the UNC campus and is directed by Michael Kosorok, PhD, Professor and Chair of the Biostatistics Department in the School of Public Health. The Biostatistics Core provides a variety of collaborative services to current NC TraCS Institute projects, and it extends the reach of the Institute by helping investigators across UNC-CH develop new projects. The Biostatistics Core consults with investigators about appropriate statistical techniques for different research designs, power and sample size calculations, data management strategies, and analysis of existing data. Statistical collaborations with KL2 scholars (including the Sponsor) are provided via the NC TraCS Institute's Education, Training, and Career Development Core with involvement from Biostatistics Core faculty, who have a broad range of expertise in analysis of clinical trials, observational studies, imaging, genetics, and outcomes research, and can provide general consultation about all phases of research design and analysis.
- NC TraCS Clinical and Translational Research Center (CTRC) (11,000 sq ft) is located on the third floor of UNC Memorial Hospital. The CTRC is available to assist in any clinical needs of the proposed project. For example, the PI has received training through the CTRC to collect blood via venipuncture or finger prick, which could be useful in the proposed studies. The CTRC has two outpatient facilities, which offer waiting rooms, outpatient examination rooms, interview rooms, a centralized nursing station, and a room used for the measurement of height, weight, and vital signs. A phlebotomy room is fully equipped for blood sample processing. Coverage is 24 hours a day, seven days a week for the Memorial Hospital location.

EQUIPMENT

In the Sponsor's Lab (Davie Hall): RAID fileserver. Wet lab includes a refrigerator, freezer, waterbath, flammables storage cabinet, Sorvall 6000G and Therm PicoFuge benchtop centrifuges, sink, and eyewash, for storage, processing and handling of saliva samples for DNA extraction. Mock MRI scanner equipped with full sound and visual display capabilities. Wet lab (bench and storage) are Biosafety Level 2, which allows for blood collection and blood sample storage.

In the Psychology Department (Davie Hall): Boettiger Lab personnel have complete access to a μ Quant microplate spectrophotometer, which is used to quantify DNA sample concentrations.

In the BRIC: This Center within the UNC-Chapel Hill School of Medicine has a Siemens Allegra 3.0T head-only MRI scanner and a Siemens Tim Treo 3.0T whole-body MRI scanner, both of which are 100% dedicated to research. Staff of the Center includes a full time physicist, Dr. Weili Lin (Director of the Neuroimaging facility, see *Letter of Support*), three full time Research Associates responsible for fMRI data acquisition and facilities management, and a computing systems administrator. Personnel in Dr. Lin's lab also provide complementary support for MR sequence development and hardware modification. The Center provides limited pilot scanning free of charge, and additional funds for scanning may be available in extenuating circumstances. The BRIC also provides free access to a mock MRI scanner on site, and private rooms and restroom facilities for participant screening, post-scan testing, and pre-scan waiting periods.

Section II--Sponsor and Co-Sponsor Information**a. Research Support Available**

Funding Source	I.D. number	Title	P.I.	Dates	Amount
UNC, Chapel Hill	N/A	Start-up Funds	Boettiger	07/07-06/11	\$367,000
NIH/NCRR	1KL2RR025746	UNC Clinical Translational Science Award-K12 Scholars Program (KL2)	Pisano	07/08-04/11	\$85,000
UNC-CH Junior Faculty Development Award	N/A	Neuropharmacology of Immediate Reward Bias	Boettiger	01/10-12/10	\$7,500
NC TraCS Institute NC TraC\$2K Pilot	2KR60901	Frontal Dopamine and Immediate Reward Selection Bias	Boettiger	09/09-08/10	\$2,000

Pending Support

Funding Source	I.D. number	Title	P.I.	Dates	Amount
NIH/NIDA	R01 DA030381	Neuropharmacology of Immediate Reward Bias in Human Subjects	Boettiger	12/10-11/15	\$1,250,000

b. Sponsor's/Co-Sponsor's Previous Fellows/ TraineesGraduate students: 1 total (1 current)

Christopher T. Smith (BS, Furman University) PhD Student, Neurobiology Curriculum. 2009-present

Post-doctoral fellows: 2 total (2 current)

Mary K. Kelm (PhD, Pharmacology, UNC-Chapel Hill) 2009-present. Dr. Kelm is supported by a T32 fellowship from NIAAA through the Bowles Center for Alcohol Studies.

Vicki W. Chanon (PhD, Cognitive Psychology, UNC-Chapel Hill) 2007-present. Dr. Chanon has an F32 fellowship through NIDA pending; I am the sponsor on this award.

c. Training Plan, Environment, Research Facilities

Training plan: Chris Smith has been working in my laboratory since May 2009. During this time, he has already made significant progress towards his goal of developing expertise in cognitive neuroscience techniques for the purposes of investigating the neurobiology of alcohol use disorders. To help him achieve his career goal, his training will primarily focus on the following areas: research development, oral and written communication skills, and ethical training. Towards the end of the fellowship period his training will also include guidance in the areas of mentoring/teaching. Although Chris' proposed research is not clinical in nature, it does bear on a clinical issue, thus he will also receive some training as to the clinical aspects of addiction.

Research Development: Chris arrived in the lab with no experience in research with human subjects, thus he requires thorough training in all aspects of initiating studies, conducting cognitive behavioral experiments, executing fMRI studies, and analyzing data.

Study Initiation. Chris has contributed to the design of the experiments outlined in this application from their inception. He contributed to the development of the Institutional Review Board (IRB) protocol for the preliminary studies included in the Research Plan, and he will participate in developing the protocols for the proposed experiments. This process will be educational for him in terms of understanding how to properly implement informed consent. He will submit the IRB protocol for the proposed studies shortly after submitting this fellowship application. While IRB protocol development can be somewhat onerous, it is a skill that he will need in order to successfully conduct independent human subjects research.

Cognitive Behavioral Experiments. Since arriving in the lab, Chris has been trained in the administration of the delay discounting task to be used in the proposed studies. He used the task both during his rotation project in the Spring of 2009, and while collecting preliminary data for this proposal (see *Research Plan – Aims 1 and 3 Justification and Feasibility*). Notably, each of these projects has resulted in a first-authored Abstract for Chris. He will present his rotation project data at the Cognitive Neuroscience Society meeting in Montreal in April 2010. He will present his preliminary studies data at the Research Society on Alcoholism meeting in June 2010. In the course of these projects, he became familiar with the program we use to design computerized tasks and to collect behavioral data (E-Prime) and the program we use to analyze the data (MATLAB). These experiences using E-Prime and MATLAB will be useful in the future when Chris may wish to create different cognitive tasks and analyze behavioral data. Although Chris' undergraduate coursework included substantial training in cognitive psychology, he will take (or audit) one or two graduate courses here at UNC that will augment his training in this area. Three particularly relevant courses are a Behavioral Decision Theory course (PSYC 433), a general Cognitive Neuroscience course (PSYC 434), and a Translational Seminar in Cognitive and Clinical Neuroscience (NBIO 727).

fMRI Experiments. I will provide Chris with direct training in all aspects of fMRI research. In addition, I will provide funds for Chris to attend an fMRI short course, as I have for my other lab personnel. These courses are offered at the New Mexico MIND Institute on a quarterly basis. Experts in the software package Statistical Parametric Mapping (SPM8) have also given 3 day workshops at the BRIC, to which Chris would also have access. In addition to me, within my lab Chris will have an additional mentor in his labmate Dr. Vicki Chanon, who has completed two fMRI studies to date. While I have expertise in acquiring the structural MRI (sMRI) data that will be required for Chris' proposed experiments of Aims 2 and 3, and the analytical approach of voxel-based morphometry is similar enough to that which I have used for fMRI studies that I can provide adequate guidance, Chris will require expertise outside of my lab to successfully conduct the DTI studies he has proposed. In this regard we are fortunate that UNC has such a wealth of expertise in this area. Specifically, Chris will have access to the Imaging Core, Image Analysis Core and Biostatistics Core of the BRIC. These cores include substantial expertise in all forms of structural neuroimaging, including DTI, with a particular strength in the area of development. As evidenced by Dr. Weili Lin's letter of support, Chris will have access to ample expertise within the BRIC that will complement my own. In addition to the support and training offered through the BRIC, the UNC Developmental Neuroimaging Core also provides training in the analysis of fMRI, sMRI, and DTI data. The director of this core, Dr. Aysenil Belger, is a fellow member of the Neurobiology Curriculum and a colleague with whom I regularly interact.

Data analysis. To analyze the behavioral studies, we will use Predictive Analytics SoftWare (PASW-formally SPSS). Chris has experience with PASW through analysis of his preliminary studies. He will also take a short course offered by the UNC Odum Institute in his first year of training that will cover all of the capabilities of PASW. My lab uses SPM8 for MRI data analysis, and Chris attended an SPM8 basics course in the BRIC last Spring led by researchers from the Martinos Center for Biomedical Imaging at Harvard University. Course content included preprocessing, statistical modeling, and visualizing neuroimaging data. Chris will spend a considerable amount of time on learning how to analyze fMRI, sMRI, and DTI data. He will receive guidance primarily from me, Dr. Chanon, and the Biomedical Research Imaging Center (BRIC) image analysis core.

Oral and Written Communication Skills: To improve Chris' oral communication skills, in addition to the didactic training provided in the Neurobiology Curriculum, he will also present monthly at our weekly lab meeting. Although this is an informal setting generally including only our research group, I expect presentations in a format suitable for a larger audience. I will encourage Chris to attend Psychology, Bowles Center for Alcohol Studies, and Neuroscience seminars for exposure to different presentation styles and to gain up-to-date information. Chris will present his data at national and international conferences, such as Research Society on Alcoholism, Society for Neuroscience, Cognitive Neuroscience Society, College on Problems of Drug Dependence, and the Organization for Human Brain Mapping. He will attend two of these meetings per year. In addition to improving his oral communication skills by presenting his data, attending these meetings will enable him to establish scientific relationships beyond UNC.

To improve his written communication skills, Chris will prepare manuscripts for publication and abstracts for the meetings he will attend. He has submitted two abstracts based on his work thus far, and I expect that he will continue that during the period of this fellowship. I expect that Chris will complete data collection and analyses during the Summer of 2010 for the two behavioral studies that form the basis of his submitted abstracts. I expect that he will prepare and submit manuscripts for publication for these two studies in the Fall

and Winter, as reflected in the *Research Plan – Timeline*. In addition to the writing skills he has gained through the preparation of this application, he will contribute to future grant preparation in my laboratory. By presenting at lab meetings and conferences, attending seminars, and preparing manuscripts, grants and abstracts, I expect Chris to develop the oral and written communication skills necessary for scientific success.

Ethical Training: Chris has completed the Collaborative Institutional Training Initiative (CITI) training, which includes information on the history and ethical principles of human research, IRB regulations and review processes, informed consent, data records maintenance and management, vulnerable subjects, conflicts of interest, privacy, confidentiality, and HIPAA. To ensure that the MRI studies are conducted as safely as possible, he has completed an online course on bioeffects, safety and patient management for magnetic resonance procedures; this is required annually for all BRIC members. Through the UNC Environment, Health and Safety Department, he has completed lab environment and bloodborne pathogens courses.

As part of the Neurobiology Curriculum, Chris has received didactic training in the ethical conduct of scientific research. This training was designed to meet NIH standards and has been extensively reviewed in association with UNC's Neurobiology T32 training grant. Topic areas include: conflict of interest, data management, publication and peer review, intellectual property, use of animal and human subjects, university guidelines of research, and handling misconduct. He will expand upon this ethics training during the first year of this award when he will take a responsible conduct of research course through NCTraCS (see *Facilities – Other Resources*) to serve as a refresher for the CITI training. Most importantly, an environment has been established in my lab in which trainees are encouraged to engage in continued discussions regarding ethical issues with me as a part of their research training experience. This aspect of training is particularly important as it is recognized that lectures alone cannot cover all potential ethical concerns that can arise in the course of scientific research. This combination of experiences will ensure that Chris is well-versed in ethical issues.

Mentoring/Teaching: Chris will gain mentoring experience during this fellowship by supervising undergraduate volunteers in the lab. This will give him experience in managing individuals in a mentored environment, which will aid him when he moves on to a more independent stage of his career. Because Chris ultimately hopes to attain a faculty appointment that includes a teaching component, he will pursue opportunities to teach during his fellowship. These could involve being a guest lecturer or teaching assistant in Behavioral Neuroscience (Psychology) or Physiology (Biology) courses. He will also be encouraged to present at conferences, which will teach him to organize his ideas and communicate them to a general audience. Chris will have frequent practice with this on a smaller scale when he presents monthly for our lab meeting. In addition, he will participate in workshops offered by the UNC Office of Faculty Excellence on syllabus development, overcoming teaching anxiety, and creating effective assignments and presentations.

Clinical Training: Chris and I both feel that it is important for him to appreciate the clinical side of alcoholism. For this reason, Chris attends a weekly meeting with Dr. J.C. Garbutt and Dr. Alexei Kampov, who have conducted clinical research in the area of alcohol use disorders (AUDs). In these meetings we discuss collaborations ongoing between our groups, including studies of behavioral risk-factors for AUDs in late adolescents, which is particularly pertinent to Chris' proposed studies. These meetings have been invaluable in exposing Chris to the clinical concerns related to his own studies. Chris also attends the Bowles Center for Alcohol Studies lecture series, which includes basic science and clinical talks. Chris will also participate in a Bowles Center outing to the UNC Alcohol and Substance Abuse Program (ASAP) and Triangle Residential Options for Substance Abusers (TROSA). At the ASAP facility, he will learn about common characteristics of substance abusers. TROSA is a highly structured program that provides two years of free residential treatment for substance abusers in a community-oriented environment. During the TROSA tour, Chris will interact with residents to learn about the TROSA program and their struggle with addiction. Because Chris envisions future research projects focused on alcoholism, participation in all these activities will keep him up to date on current research and help him in developing his postdoctoral plans.

In summary, Chris Smith's training will consist of coursework, seminars, colloquia, formal meetings with faculty advisors, as well the research plan he has outlined in the present proposal. In addition to the training he will receive in my laboratory, there is an abundance of opportunities for didactic training in addiction science and functional neuroimaging at UNC Chapel Hill, which will complement Chris' existing expertise in basic neurobiology and cognitive psychology. Chris will take advantage of graduate course offerings within UNC's Behavioral Neuroscience program, including the Research Seminar Series in Experimental Psychology (co-Directed by Dr. Regina Carelli), which is supported by the program's NIDA training grant for "Research on Drug

Abuse”, and is thus focused on that topic. As Director of the addiction-focused Behavioral Neuroscience program, of which I am a member, Dr. Carelli will provide Chris with additional mentorship in this area. Dr. Carelli’s commitment to Chris’ success is evident in her willingness to support Chris’ first year in my lab through the Behavioral Neuroscience Program’s T32 training grant. Dr. Linda Dykstra, the training grant Co-Director is also committed to Chris’ success, as additionally evidenced by her letter of support, and she will also provide critical senior mentorship to Chris. In addition, UNC Chapel Hill hosts a large number of visiting speakers who are expert in the biology and psychology of drug and alcohol addiction through three independent colloquium series sponsored by the Psychology Department, the Graduate Curriculum in Neurobiology, and the Bowles Center for Alcohol Studies. Moreover, there is ample opportunity to gain exposure to clinical aspects of addiction through the treatment wing of the Bowles Center, and the presentation and discussion of clinical findings through the Center’s seminar series. Chris will attend the weekly group meetings of Dr. J.C. Garbutt, Director of Clinical Studies in the Bowles Center. In addition, the Center’s Director, Dr. Fulton Crews, will provide additional mentorship and guidance to Chris in the course of this fellowship, as Dr. Crews is a member of Chris’ Dissertation Committee. Thus, UNC Chapel Hill has a wide range of didactic and interactive seminars for gaining knowledge on issues pertinent to this proposal. In addition to attending these seminars, Chris will be able to interact on a one-to-one basis with a range of faculty based here at Chapel Hill in Psychology, Neurobiology, Psychiatry, Radiology, and the Bowles Center. Given my relative inexperience as a mentor, these senior colleagues will provide valuable additional guidance to Chris, particularly in the areas of grantsmanship and other aspects of professional development. With regard to grantsmanship, I will encourage Chris to use some of the funds that would accompany this NRSA to attend an NIH regional course on grantwriting. Closer to home, this year he attended a one-day UNC course on this topic directed toward early career investigators. The forums and senior colleagues mentioned above will also be instrumental in providing guidance and feedback when Chris is ready to apply for postdoc positions.

Within my lab, weekly meetings of all personnel are held to discuss current projects and recent journal articles relevant to our research. We also have a joint lab meeting on a recurring basis with other UNC faculty engaged in neuroimaging research, including Aysenil Belger, Kelly Giovanello, and Joseph Hopfinger, to discuss matters specific to fMRI.

In his first year, I expect that Chris will take a course each semester in order to cultivate expertise in addiction neuroscience and multivariate statistics, which will complement his strong background in neurobiology. He will also attend selected talks and seminars when they are relevant, meet with addiction clinicians at the Bowles Center, and initiate his research plans. In his second year, I expect that he will continue to attend relevant talks, and complete his initial data collection and analysis and write up the preliminary results of his research. I expect his third year to be devoted primarily to the completion of his studies and preparation of results for publication. Each year, I also expect that he will present abstracts at the Society for Neuroscience annual meeting, as well as the annual meeting of either the Cognitive Neuroscience Society, the Organization for Human Brain Mapping, the Research Society on Alcoholism, or the College on Problems of Drug Dependence.

Table 1. Specific Skill Development Activities and Instructors

Skill	Activity	Mentor/Instructor
1. MRI methods; fMRI experimental design and data analysis	1. Training and supervision in fMRI experimental design, including issues of statistical power, signal strength, artifact reduction, novel data acquisition, and analysis techniques 2. Training and supervision in data analysis using software packages including SPM. 3. Training and supervision in data interpretation	Charlotte Boettiger, Ph.D. Weili Lin, Ph.D. Aysenil Belger, M.D., Ph.D.
	Attendance of the BRIC seminar series	BRIC Members
2. Specific issues regarding alcohol use disorders	Directed readings, training and supervision regarding substance abuse issues in research	Charlotte Boettiger, Ph.D. J.C. Garbutt, M.D.

3. Advanced biostatistics	Consultation with BRIC faculty (Biostatistics)	Hongtu Zhu, Ph.D.
4. Advanced training in theoretical issues of the neurobiological bases of addiction	1. Attendance at the Behavioral Neuroscience Seminar at UNC-CH focused on the neural mechanisms of addictive behavior 2. Attendance of the Bowles Center for Alcohol Studies seminar series	Charlotte Boettiger, Ph.D. Regina Carelli, Ph.D. Fulton T. Crews, Ph.D. Linda Dykstra, Ph.D. J.C. Garbutt, M.D.
5. Publication and presentation of research results; writing grants, and training in the responsible conduct of research	Meetings with mentors to discuss progress of project, responsible conduct, appropriate avenues for presentation of preliminary results, publication of final results, and grantsmanship.	Charlotte Boettiger, Ph.D. Regina Carelli, Ph.D. Fulton T. Crews, Ph.D. Linda Dykstra, Ph.D. J.C. Garbutt, M.D.

Environment and research facilities: The combined resources of my own lab, the Psychology Department, the Biomedical Research Imaging Center, and the Bowles Center for Alcohol Studies, and the NC TraCS Institute will be available to Chris to support his research plans. These include:

In my lab: Functional MRI laboratory with computer workstations to analyze data, computer-based testing facilities with high-quality graphics and timing routines for testing subjects, wet lab bench space, and all other resources (email, fax, on-line library catalogs) to facilitate research, writing and collaborations; ample office and lab space. Testing facilities include three separate testing rooms, one equipped with state-of-the art eye-tracking equipment (Tobii 1750), and one equipped with a mock scanner, and a third equipped with physiological monitoring equipment (BioPac Systems Inc.). My wet lab is adjacent to the workstation and testing area and provides all necessary equipment for biological sample storage, handling, and processing, including refrigerator, freezer, flammables storage, vortexer/shaker, waterbath, pipettors, Sorvall 6000G and Thermo Pico Fuge benchtop centrifuges, sink and eyewash. We have excellent access to a pool of research subjects from throughout the Chapel Hill campus and Research Triangle area. During the period of Chris' fellowship, I have dedicated funding for scanner time (included in start-up funds), of which I will commit a sufficient amount for Chris' studies. Any shortfall in the first year could be absorbed by my KL2 research funds of \$25,000 - \$35,000 per year. Additionally, pilot funds from the NC TraCS Institute or the Bowles Center for Alcohol Studies are other likely sources of funds for these studies. In addition, I have applied for R01 funding, which would fully and directly fund Chris' studies.

In the Department of Psychology: The department provides several key resources which support my lab's research mission. Such resources include shared equipment located within Davie Hall and thus easily accessible from our lab. We also have access to the Department's large participant pool, who may participate in our studies for credit, at no cost to the researcher. The department also provides full administrative support for IRB protocol and extramural grant submissions. In addition, we have access to the expertise of numerous senior faculty within the Behavioral Neuroscience program engaged in addiction neuroscience research.

In the Biomedical Research Imaging Center: This Center within the UNC-Chapel Hill School of Medicine has a Siemens Allegra 3.0T MRI scanner and a Siemens Tim Trio 3.0T whole-body MRI scanner that are both 100% dedicated to research. Staff of the Center includes a full time physicist, Dr. Weili Lin (Director of the Neuroimaging facility), three full time Research Associates responsible for fMRI data acquisition and facilities management, an Imaging Analysis Core (Dr. Dinggang Shen, Director) and a computing systems administrator. The BRIC seminar series provides access to a wide range of neuroimaging expertise and a forum for critique of one's work. Dr. Hongtu Zhu, a BRIC faculty member expert in Biostatistics will be a particularly valuable influence in guiding Chris' approaches towards his data. As a BRIC faculty member, my lab is entitled to ample free data storage space on the BRIC servers as well as full access to the entire range of analytical software, including consultation. Moreover, these resources are accessible over a secure network from my laboratory in Davie Hall. Personnel in Dr. Lin's lab also provide complementary support for MR sequence development and hardware modification. The Center provides pilot scanning free of charge for up to three subjects per study, and additional funds for scanning may be available in extenuating circumstances.

In the Bowles Center for Alcohol Studies: The numerous faculty and postdocs within the Bowles Center possess relevant expertise spanning from basic addiction research to clinical treatment of substance abuse. As a faculty member of the Bowles Center, I have routine access to the personnel and resources of the Center.

In the UNC School of Medicine: In addition, to my primary appointment in Psychology, I have a 25% appointment in the BRIC, a part of the school of Medicine. I am also a member of the NC TraCS Institute and the Bowles Center for Alcohol Studies. Through the School of Medicine, several key resources are available to my lab, including the Developmental Neuroimaging Core (Dr. Aysenil Belger, Director).

Relationship of training to applicant's career: The proposed training will equip Chris with the knowledge and skills necessary to address a range of issues in addiction neuroscience, not limited to a single technique and not necessarily limited to the topic of the present proposal. A young scientist with Chris' background in basic neurobiology and psychology, who will gain training in addiction, cognitive neuroscience and neuroimaging will be ideally positioned to make major scientific contributions. The proposed fellowship training is the perfect avenue for Chris to learn to apply cognitive neuroscientific approaches towards studying behaviors linked to alcohol abuse. This new training will lead to his being highly qualified to pursue postdoctoral training at a major research university.

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

I anticipate that there will be 1-3 other trainees in my lab during the period of Chris' fellowship, which would result in a maximum of 4 trainees at any one time in the lab. Currently, in addition to Chris, I supervise two postdoctoral fellows. The NRSA application of the more senior fellow, Dr. Chanon, has been put forward for funding by NIDA. I intend to maintain a mixture of post-docs and graduate students in the lab, as I feel that the students benefit from secondary mentors within the lab, and post-docs benefit from the opportunity to practice mentoring more junior scientists.

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

Chris was enthusiastically recruited by the highly selected BBSP program at UNC, which suggests that he is one of the promising young academic biomedical scientists of his age cohort. My own interactions with him have been entirely consistent with this evaluation. I was impressed with Chris when I interviewed him for the BBSP program and was delighted when he approached me about rotating in my lab during his first year. Despite lacking any practical experience with the type of work we do in my lab, Chris was one of the most productive members of the lab during his brief (2 month) rotation. He learns new skills extremely quickly and, even more impressive, he readily and easily imparts those skills to others. Although Chris currently has no neuroimaging experience, I am completely confident that he will master all of the necessary skills in rapid fashion. I can say without reservation that I have not been disappointed with the decision to accept Chris into my lab as a graduate student.

Chris is a very bright and internally motivated scientist. He is a clear thinker, and he has shown great creativity and initiative in designing his research program. He voraciously pursues the literature in an effort to contextualize his ideas and his results. In addition, he has demonstrated himself to be a consistent, dedicated, and detail-oriented experimentalist. This aptitude for research enabled him to collect sufficient data to submit first-authored abstracts, based on two different studies, to the Cognitive Neuroscience Society and Research Society on Alcoholism (RSA) meetings. I also note that Chris received a student merit travel award to attend the RSA meeting based on his submission. Chris demonstrates a growing aptitude for presenting his ideas in different forums and I am confident that his commitment to this aspect of his career will help to make him an excellent teacher as well as researcher.

In summary, Chris has outstanding intellectual potential and is pursuing a line of inquiry that is highly relevant to NIAAA's mission. He demonstrates a level of maturity and ability that exceeds my expectations for more senior graduate students. Moreover, Chris is fully committed to following a career in research on alcoholism. In this proposal, he will clearly be able to build expertise in new areas by drawing upon my experience in cognitive neuroscience, addiction, and fMRI. Thus, he will be uniquely qualified to address future questions related to the neurobiological bases of alcohol use disorders using numerous research tools. For these reasons, I feel that Chris will develop into a leading alcohol researcher. I am highly supportive of Chris' NRSA proposal and I am delighted to be working with him as his sponsor on this project.



March 24, 2010

To whom it may concern:

I am happy to support the NRSA application of Christopher Smith as a Doctoral Fellow in the lab of Dr. Charlotte Boettiger. The Boettiger lab has full access to the imaging facilities of the Biomedical Research Imaging Center (BRIC) at UNC-Chapel Hill. The BRIC currently has a Siemens Allegra 3.0T head-only MRI scanner and a Siemens Tim Trio 3.0T whole-body MRI scanner that are 100% dedicated to research. In addition to the scanners in our imaging core, Chris will have access to our image analysis core and biostatistics core, which includes extensive expertise in the structural MRI and DTI techniques that will complement the fMRI expertise of Dr. Boettiger.

Sincerely,

A handwritten signature in black ink, appearing to read "Weili Lin". The signature is written in a cursive style and is placed on a light-colored rectangular background.

Weili Lin, PhD

Professor and Vice Chair of Basic Research, Radiology
Professor of Biomedical Engineering and Neurology
Associate Director, Biomedical Research Imaging Center

List of Referees:

Linda A. Dykstra, Ph.D., Department of Psychology, University of North Carolina at Chapel Hill

Judith E. Grisel, Ph.D., Department of Psychology, Furman University

Clyde W. Hodge, Ph.D., Departments of Psychiatry and Pharmacology, University of North Carolina at Chapel Hill

RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator				
Prefix:	<input type="text"/>	* First Name:	<input type="text" value="Christopher"/>	
		Middle Name:	<input type="text" value="Thomas"/>	
* Last Name:	<input type="text" value="Smith"/>	Suffix:	<input type="text"/>	
Position/Title:	<input type="text" value="Graduate Student"/>	Department:	<input type="text" value="Psychology"/>	
Organization Name:	<input type="text" value="The University of North Carolina at Chapel Hill"/>		Division:	<input type="text" value="College of Arts & Sciences"/>
* Street1:	<input type="text" value="Department of Psychology"/>			
Street2:	<input type="text" value="Davie Hall, CB 3270"/>			
* City:	<input type="text" value="Chapel Hill"/>	County/ Parish:	<input type="text" value="Orange"/>	
* State:	<input type="text" value="NC: North Carolina"/>	Province:	<input type="text"/>	
* Country:	<input type="text" value="USA: UNITED STATES"/>	* Zip / Postal Code:	<input type="text" value="27599-3270"/>	
* Phone Number:	<input type="text" value="919-962-8340"/>	Fax Number:	<input type="text"/>	
* E-Mail:	<input type="text" value="cts2014@email.unc.edu"/>			
Credential, e.g., agency login:	<input type="text" value="CTS2014"/>			
* Project Role:	<input type="text" value="PD/PI"/>	Other Project Role Category:	<input type="text"/>	
Degree Type:	<input type="text" value="BS"/>			
Degree Year:	<input type="text" value="2008"/>			
* Attach Biographical Sketch	<input type="text" value="CTSmithBiosketch1001900051.pdf"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	
Attach Current & Pending Support	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	
		<input type="button" value="View Attachment"/>	<input type="button" value="View Attachment"/>	

PROFILE - Senior/Key Person 1				
Prefix:	<input type="text"/>	* First Name:	<input type="text" value="Charlotte"/>	
		Middle Name:	<input type="text" value="A"/>	
* Last Name:	<input type="text" value="Boettiger Cooney"/>	Suffix:	<input type="text"/>	
Position/Title:	<input type="text" value="Asst Prof"/>	Department:	<input type="text" value="Psychology"/>	
Organization Name:	<input type="text" value="The University of North Carolina at Chapel Hill"/>		Division:	<input type="text"/>
* Street1:	<input type="text" value="CB:304 B Davie Hall"/>			
Street2:	<input type="text"/>			
* City:	<input type="text" value="Chapel Hill"/>	County/ Parish:	<input type="text" value="Orange"/>	
* State:	<input type="text" value="NC: North Carolina"/>	Province:	<input type="text"/>	
* Country:	<input type="text" value="USA: UNITED STATES"/>	* Zip / Postal Code:	<input type="text" value="27599-3270"/>	
* Phone Number:	<input type="text" value="(919) 962-2119"/>	Fax Number:	<input type="text" value="(919) 962-2537"/>	
* E-Mail:	<input type="text" value="cab@unc.edu"/>			
Credential, e.g., agency login:	<input type="text"/>			
* Project Role:	<input type="text" value="Other (Specify)"/>	Other Project Role Category:	<input type="text" value="Sponsor"/>	
Degree Type:	<input type="text"/>			
Degree Year:	<input type="text"/>			
* Attach Biographical Sketch	<input type="text" value="Boettiger_biosketch1001899979"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	
Attach Current & Pending Support	<input type="text"/>	<input type="button" value="Add Attachment"/>	<input type="button" value="Delete Attachment"/>	
		<input type="button" value="View Attachment"/>	<input type="button" value="View Attachment"/>	

FELLOWSHIP APPLICANT BIOGRAPHICAL SKETCH**USE ONLY FOR INDIVIDUAL PREDOCTORAL and POSTDOCTORAL FELLOWSHIPS. DO NOT EXCEED FOUR PAGES.**

NAME OF FELLOWSHIP APPLICANT Christopher Thomas Smith	POSITION TITLE Graduate Student, Curriculum in Neurobiology
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.	12/2014	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 alcohol use disorders and particularly the cognitive processes related to problem alcohol use. My academic training and research experience have provided me with a strong background in behavioral neuroscience. Courses in cell and molecular neurobiology and the biological bases of behavior have provided me with a broad understanding of neurobiology from the molecular to behavioral level. While at my undergraduate institution, I worked in a basic behavioral neuroscience lab focused on understanding the relationship of beta-endorphin to depression and anxiety in a mouse model, and how alcohol may act through beta-endorphin to alter behavior. I became familiar with scientific presentation skills by presenting my work in poster form at the Society for Neuroscience 2007 annual meeting. I joined my thesis lab at the University of North Carolina at Chapel Hill in June 2009, and since that time, I have been investigating the neurobiology of decision making processes in human subjects with a special emphasis on decisions between immediate and delayed rewards (“Now” versus “Later”). My work in the lab thus far has resulted in several (4) published abstracts for national meetings, including two first-author abstracts. The proposed research will allow me to gain experience in neuroimaging techniques and provide me with the ability to use the tools of magnetic resonance imaging (MRI) to better understand the neurobiology of *Now/Later* decision making from a developmental prospective and how alcohol use may impact this decision making at a neuroanatomical level. In addition, the proposed training plan will allow me to improve the analytical and scientific communication skills I will need to be a successful independent investigator in the future. My choice of Dr. Charlotte Boettiger as my advisor and the strengths of her lab and the Bowles Center for Alcohol Studies at UNC will provide me with the necessary skills to reach my goal of studying the neurobiology of alcohol use disorders in humans.

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

Academic and Professional Honors

South Carolina Governor’s School at the College of Charleston Summer Experience Participant, 2003
 South Carolina Palmetto Fellow, 2004-2008

Furman Scholar, 2004-2008

South Carolina NIH-IDEA Networks of Biomedical Research Excellence Summer Research Fellowship, 2007

B.S. awarded with high honors, Furman University, 2008

Research Society on Alcoholism Student Merit Travel Award, 2010

Memberships in professional societies:

Society for Neuroscience (2007-present)

Cognitive Neuroscience Society (2009-present)

Research Society on Alcoholism (2009-present)

C. Publications

Abstracts:

Smith CT, Cloonan G, Lee A, Grisel JE (2007). Role of β -endorphin in behavioral despair, stress, and anxiety. Society for Neuroscience 2007 Annual Meeting.

Smith CT, Boettiger CA (2010). Ovarian Cycle Effects on Immediate Reward Bias: a Window on PFC Dopamine. Cognitive Neuroscience Society 2010 Annual Meeting.

Smith CT, Freeman-Daniels E, Boettiger CA (2010). Effects of Gender, Age, and Alcohol Use Behavior on Impulsive Decision Making. Research Society on Alcoholism 2010 Annual Meeting.

Chanon VW, **Smith CT**, Kalka LS, Kampov-Polevo AB, Garbutt JC, Boettiger CA (2010). Effects Of Naltrexone On Alcohol Attentional Bias And Delay Discounting: A Pilot Study. Research Society on Alcoholism 2010 Annual Meeting.

Boettiger CA, **Smith CT** (2010). Immediate Reward Bias in Humans: Effects of Alcohol Use, Dopamine, Hormones, Age, and Gender. Clinical and Translational Research and Education Meeting. Washington D.C.

Acknowledgements:

Grisel JE, Bartels JL, Allen SA, Turgeon VL (2008). Influence of β -endorphin on anxious behavior in mice: interaction with EtOH. *Psychopharmacology*, 200, 105-115.

D. Scholastic Performance

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
FURMAN UNIVERSITY			FURMAN UNIVERSITY		
2004	Fundamentals of Chemistry I	A	2005	Vectors and Matrices (Math course)	A
2005	Fundamentals of Chemistry II – Inorganic Chemistry	A	2005	General Psychology	A
2005	Foundations of Biology	A+	2006	Statistics (Economics course)	B
2005	Fundamentals of Chemistry III – Organic Chemistry	A-	2006	Social Psychology	B
2006	Genetics	A-	2007	Psychometrics and Assessment (Psychology course)	A-
2006	Spectroscopy and Molecular Structure (Chemistry course)	A+	2007	Learning (Psychology course)	A-
2006	Experimental and Statistical Methods (Psychology course)	A-	2008	Memory and Cognition (Psychology course)	A
2007	Human Physiology	A-	2008	Brain and Mind (Interdisciplinary studies course)	A-
2007	Introduction to Biopsychology	A-			

YEAR	SCIENCE COURSE TITLE	GRADE	YEAR	OTHER COURSE TITLE	GRADE
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			
2008-9	BBSP 1 st Year Seminar in Research Ethics and Scientific Communication	P			
2009	CMNB - Synaptic Mechanisms	H			
2009	CMNB - Anatomy and Function	P			
2009	Biological Bases of Behavior II	H			
2009	Developmental Neurobiology	P			
2009	Behavioral Pharmacology	P			
2009	Scientific Communication Seminar	H			

UNC Chapel Hill graduate courses are graded H (high pass), P (pass), L (low pass) or F (fail). Passing is C plus or better.

BIOGRAPHICAL SKETCH

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

NAME Boettiger, Charlotte A	POSITION TITLE Assistant Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) cboettiger			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
University of California, Berkeley	A.B.	05/93	Integrative Biology
University of California, San Francisco	Ph.D.	12/00	Neuroscience
University of California, San Francisco	Postdoctoral	06/01	Psychiatry
University of California, Berkeley	Postdoctoral	08/03	Psychology

A. Personal Statement

The goal of the proposed research is to identify structural and functional brain changes from late adolescence to early adulthood that correlate with age-dependent changes in immediate reward bias in humans. Clarifying the neurobiology of immediate reward bias, particularly how it may differ between life stages with differential risk for substance use disorders, will significantly advance our ability to identify new targets and strategies for preventing and treating such disorders. My expertise is well suited to successfully mentor the proposed work. I have a broad background in neuroscience, with specific training and expertise in key research areas for this application. As a postdoctoral fellow at UC Berkeley, I carried out functional neuroimaging (fMRI) investigating the neurobiological underpinnings of a form of executive function. At the Ernest Gallo Clinic and Research Center at the UC San Francisco, I expanded my research to include behavioral pharmacology and neuroimaging studies of decision-making behavior in control and alcoholic populations. As PI on a DOD-funded project, I laid the groundwork for the proposed research by developing an IQ-independent delay discounting task with high test-retest reliability, which is fMRI compatible. In addition, I successfully administered the projects (e.g. staffing, research protections, budget, and progress reports), which were conducted off-site at Berkeley, and produced (to date) four peer-reviewed publications from the project. As a result of these previous experiences, I am aware of the importance of meticulous logistical planning, which is required for successful neuroimaging studies with humans. The current application builds logically on my prior work, and our environment provides additional expertise in structural neuroimaging techniques. In summary, I have demonstrated my capacity for successful and productive research in an area of high relevance to addictive disorders, and my expertise and experience will enable me to mentor the proposed project.

B. Positions and Honors

Positions and Employment

1992-1994	Research Asst., University of California, Berkeley, Molecular and Cell Biology Dept.
2001	Postdoctoral Fellow, University of California, San Francisco, Psychiatry Dept.
2001-2003	Postdoctoral Fellow, University of California, Berkeley, H. Wills Neuroscience Institute
2003-2005	Assistant Research Scientist, Ernest Gallo Clinic & Research Center (EGCRC)
2005-2007	Associate Investigator, EGCRC
2005-2007	Adjunct Assistant Professor, Neurology Dept., University of California, San Francisco
2007-	Assistant Professor, Psychology Dept. & Biomedical Research Imaging Center, University of North Carolina, Chapel Hill (UNC-CH)
2007-	Graduate Faculty Member, Curriculum in Neurobiology, UNC-CH
2008-	Faculty Member, Bowles Center for Alcohol Studies, UNC-CH

Other Experience and Professional Memberships

1994-	Member, American Association for the Advancement of Science
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1996-	Member, Society for Neuroscience
2001-	Member, Cognitive Neuroscience Society
2005-2007	Founding President & Representative, San Francisco Bay Area Chapter of the Society for Neuroscience
2007	Medical Research Council (London), ad hoc reviewer
2008	NIAAA Special Emphasis Panel: Behavioral Mechanisms in the Transition to Habitual Alcohol Seeking and Drinking, ad hoc reviewer
2009	NIAAA Scientific Review Group: Neuroscience Research Review Subcommittee (AA-4), ad hoc reviewer
2009-	Member, Research Society on Alcoholism

Selected Honors and Awards

1992	University of California President's Undergraduate Fellowship
1993	HHMI U.C. Berkeley Undergraduate Biology Fellowship
1995	National Science Foundation Graduate Fellowship Honorable Mention
1995	UCSF Graduate Opportunity Fellowship
1997	Pre-doctoral National Research Service Award (NIH/NIMH)
1998	UCSF Graduate Dean's/Anthony Fellowship in Neuroscience
2001	McDonnell Summer Institute in Cognitive Neuroscience Fellowship
2002	Wheeler Center for the Neurobiology of Addiction Hugh O'Connor Memorial Fellowship
2009	IBM Junior Faculty Development Award, UNC-CH

C. Selected Peer-reviewed Publications

Most relevant

- Boettiger CA**, D'Esposito M. (2005) Frontal Networks for Learning and Executing Arbitrary Stimulus-Response Associations. *Journal of Neuroscience*, 25:2723-2732.
- Mitchell JM, Fields HL, D'Esposito M, **Boettiger CA**. (2005) Impulsive Responding in Alcoholics. *Alcoholism: Clinical and Experimental Research*, 29:2158-2169.
- Mitchell JM, Tavares VC, Fields HL, D'Esposito M, **Boettiger CA**. (2007) Regulation of Impulsivity by Endogenous Opioids in Alcoholics and Healthy Controls. *Neuropsychopharmacology*, 32:439-449
- Boettiger CA**, Mitchell JM, Tavares VC, D'Esposito M, Fields HL. (2007) Immediate reward bias in humans: fronto-parietal networks and a role for the catechol-O-methyltransferase 158(Val/Val) genotype. *Journal of Neuroscience* 27:14383-14391.
- Boettiger CA**, Kelley, EA, Mitchell JM, D'Esposito M, Fields HL. (2009) *Now or Later?* An fMRI study of the effects of endogenous opioid blockade on a decision-making network. *Pharmacology Biochemistry and Behavior* 93:291-299. PMID: PMC2729462.

Additional recent publications of importance to the field (in chronological order)

- Bergey EA, **Boettiger CA**, Resh VH. (1995) Effects of water velocity on the architecture and the epiphytes of *Cladophora glomerata* (chlorophyta). *Journal of Phycology*, 31:264-271.
- Boettiger CA**, Doupe AJ. (1998) Intrinsic and thalamic excitatory inputs onto songbird LMAN neurons differ in their pharmacological and temporal properties. *Journal of Neurophysiology*, 79:2615–2628.
- Boettiger CA**, Doupe AJ. (2001) Developmentally restricted synaptic plasticity in a songbird nucleus required for song learning. *Neuron*, 31:809-818.
- Doupe AJ, Solis MM, **Boettiger CA**, Hessler NA. (2004) Birdsong: Hearing in the Service of Vocal Learning and Production. In: *The Cognitive Neurosciences III*, 3rd Edition. M Gazzaniga, ed. pp 245-258. MIT press.
- Boettiger CA**, D'Esposito M (2006) Addiction. In: *The Praeger Handbook of Learning and the Brain*. S. Feinstein ed. pp 5-9 Greenwood.
- Boettiger CA**. (2008) Endogenous Opioids and Impulsive Responding in Alcoholics and Healthy Controls. *European Neuropsychopharmacology* 18:S194.
- Solis MM, Hessler NA, **Boettiger CA**, Doupe AJ (2008) Song selectivity, singing and synaptic plasticity in songbirds. In: *Topics in Integrative Neuroscience: From Cells to Cognition*. JR Pomerantz, ed. Pp 363-384. Cambridge University Press.

Crews FT, **Boettiger CA**. (2009) Impulsivity, Frontal Lobes and Risk for Addiction. *Pharmacology Biochemistry and Behavior* 93:237-247. PMID: PMC2730661

Chanon VM, **Boettiger CA** (2009) Addiction and Cognitive Control. A. Browne-Miller, ed. In: *Praeger International Collections on Addictions*. Vol. 2: Psychobiological Profiles. Praeger-Greenwood.

Garland E, Gaylord, SA, **Boettiger CA**, Howard MO (2010) Mindfulness training modifies cognitive, affective, and physiological mechanisms implicated in alcohol dependence: Results of a randomized controlled pilot trial. *J Psychoactive Drugs (in press)*.

D. Research Support

Ongoing Research Support

UL1 RR025747 Pisano (PI) 04/01/210 –03/31/11

UNC-CH Clinical Translational Science Award - NC TraC\$2K Pilot Grant: Genotyping of neural correlates of attentional bias toward cigarette cues in active smokers

The goal of this study is to determine specific genetic polymorphisms correlate with brain activity associated with attentional bias towards cigarette cues in smokers.

Role: Pilot Project Mentor (Chanon, PI)

IBM Junior Faculty Development Award, UNC-CH Boettiger (PI) 01/01/10 – 12/31/10

Neuropharmacology of Immediate Reward Bias

The goal of this project is to collect pilot data on the effects of amino acid depletion on immediate reward bias in healthy adults.

UL1 RR025747 Pisano (PI) 10/01/09 – 12/31/10

UNC-CH Clinical Translational Science Award - NC TraC\$50K Pilot Grant: Neurocognitive Predictors of Naltrexone Response

The goal of this study is to determine how well changes in two neurocognitive measures, immediate reward bias and alcohol attentional bias, predict treatment outcomes in a clinical trial of naltrexone for alcoholism.

Role: Pilot Project PI

UL1 RR025747 Pisano (PI) 10/01/09 – 12/31/10

UNC-CH Clinical Translational Science Award - NC TraC\$2K Pilot Grant: Frontal Dopamine and Immediate Reward Selection Bias

The goal of this study is to determine the effect of ovarian cycle on immediate reward bias in humans and how any such effect interacts with genotype at the Val158Met COMT polymorphism.

Role: Pilot Project PI

KL2 RR025746 Pisano (PI) 05/19/08 – 04/30/11

Mentored Translational Scientist Award: to develop a neurocognitive research program with a focus on neurobiological markers of addictive disorders and laboratory predictors of therapeutic response in these diseases.

Role: Funded Scholar

Completed Research Support

DOD W81XWH-06-1-0240 White (PI) 01/01/04 – 12/31/08

Neural Circuit Responses to Alcohol and Naltrexone

The goal of this project was to identify brain activity associated with immediate reward bias in humans and to determine the effects of naltrexone on decision-making behavior and underlying brain activity.

Role: PI on peer-reviewed pilot project

F31 MH011896 Boettiger (PI) 10/01/97 – 09/30/00

Developmental Changes in the Circuit of a Songbird Nucleus

The goal of this project was to identify cellular and synaptic changes associated with sensory learning within the song-learning circuitry of the zebra finch.

Role: PI

PHS Fellowship Supplemental Form

A. Application Type:

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

- New
 Resubmission
 Renewal
 Continuation
 Revision

B. Research Training Plan

- | | | | | |
|---|------------------------------------|--------------------------------|-----------------------------------|---------------------------------|
| 1. Introduction to Application
<i>(for RESUBMISSION applications only)</i> | | Add Attachment | Delete Attachment | View Attachment |
| 2. * Specific Aims | SpecificAims1001900039.pdf | Add Attachment | Delete Attachment | View Attachment |
| 3. * Research Strategy | CSmithNRSAResearchStrategy10019000 | Add Attachment | Delete Attachment | View Attachment |
| 4. Inclusion Enrollment Report
<i>(for RENEWAL applications only)</i> | | Add Attachment | Delete Attachment | View Attachment |
| 5. Progress Report Publication List
<i>(for RENEWAL applications only)</i> | | Add Attachment | Delete Attachment | View Attachment |

Human Subjects

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

Are Human Subjects Involved? Yes No

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

- | | | | | |
|---------------------------------------|------------------------------------|--------------------------------|-----------------------------------|---------------------------------|
| 9. Protection of Human Subjects | HumanSubjects1001900053.pdf | Add Attachment | Delete Attachment | View Attachment |
| 10. Inclusion of Women and Minorities | WomMinor1001899982.pdf | Add Attachment | Delete Attachment | View Attachment |
| 11. Targeted/Planned Enrollment | TargetedPlannedEnrollmentTable1001 | Add Attachment | Delete Attachment | View Attachment |
| 12. Inclusion of Children | Children1001899983.pdf | Add Attachment | Delete Attachment | View Attachment |

Other Research Training Plan Sections

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

Are Vertebrate Animals Used? Yes No

13. * Vertebrate Animals Use Indefinite? Yes No

- | | | | | |
|--|------------------------------------|--------------------------------|-----------------------------------|---------------------------------|
| 14. Vertebrate Animals | | Add Attachment | Delete Attachment | View Attachment |
| 15. Select Agent Research | | Add Attachment | Delete Attachment | View Attachment |
| 16. Resource Sharing Plan | | Add Attachment | Delete Attachment | View Attachment |
| 17. * Respective Contributions | respective_contributions1001899984 | Add Attachment | Delete Attachment | View Attachment |
| 18. * Selection of Sponsor and Institution | Selection_of_Sponsor_rev1001899985 | Add Attachment | Delete Attachment | View Attachment |
| 19. * Responsible Conduct of Research | ResponsibleConductofResearch100189 | Add Attachment | Delete Attachment | View Attachment |

PHS Fellowship Supplemental Form

C. Additional Information

Human Embryonic Stem Cells

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

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

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

Cell Line(s):

Fellowship Applicant

2. Alternate Phone Number:

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:

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	06/30/2010	T32DA007244	<input type="button" value="Reset Entry"/>
					<input type="button" value="Reset Entry"/>
					<input type="button" value="Reset Entry"/>
					<input type="button" value="Reset Entry"/>

6. * Applications for Concurrent Support? Yes No

If yes, please describe in an attached file:

7. * Goals for Fellowship Training and Career

8. * Activities Planned Under This Award

9. Doctoral Dissertation and Other Research Experience

10. * Citizenship: U.S. Citizen or noncitizen national

Permanent Resident of U.S. Pending

Permanent Resident of U.S.
(If a permanent resident of the U.S., a notarized statement must be provided by the time of award)

Non-U.S. Citizen with temporary U.S. visa

PHS Fellowship Supplemental Form

C. Additional Information (continued)

Institution

11. Change of Sponsoring Institution

Name of Former Institution:

D. Budget

All Fellowship Applicants:

1. * Tuition and Fees:

None Requested

Funds Requested:

Year 1	6,893.00
Year 2	7,100.00
Year 3	7,313.00
Year 4	7,532.00
Year 5	
Year 6 (when applicable)	
Total Funds Requested:	28,838.00

Senior Fellowship Applicants Only:

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

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

a. Federal Stipend Requested: Amount Number of Months

b. Supplementation from other sources: Amount Number of Months

Type (sabbatical leave, salary, etc.)

Source

E. Appendix

Add Attachments
Delete Attachments
View Attachments

2. SPECIFIC AIMS

Late adolescence (ages 18-21) is the period of greatest risk for developing an alcohol use disorder (AUD) (Kandel and Logan, 1984; Brown et al., 2008), which may reflect the unique neurobiology of this age group. The development of frontal structures implicated in self-regulation is complete around the early-to-mid twenties (Giedd, 2004; Hooper et al., 2004; Rubia et al., 2006; Eshel et al., 2007), which coincides with the decline in heavy alcohol use that typically occurs in the mid-twenties (Kandel and Logan, 1984). While late adolescents are widely regarded as impulsive (Chambers and Potenza, 2003; de Wit, 2009), little work to date has quantified developmental changes in impulsive decision-making from late adolescence to early adulthood. A recent study found a significant decline in the tendency to choose immediate (“*Now*”) over delayed (“*Later*”) rewards from childhood to adulthood (Olson et al., 2007), yet the differences between late adolescents and adults in *Now/Later* decision making remains unknown. We addressed this gap using a delay discounting task optimized for neuroimaging and known to engage the frontal lobes (Boettiger et al., 2007). Our preliminary data (see *Approach*) show that late adolescents choose *Now* over *Later* significantly more often than do adults; this age-related decrease is not observed in heavy drinking males. We now propose to investigate the neurobiological bases of these behavioral differences. The proposed studies will provide a better understanding of the developmental changes that occur in brain areas governing *Now/Later* decision making and will determine whether future prospective studies of the impact of drinking on late-adolescent brain development are warranted.

The long-term goal of this line of research is to ascertain the nature of late adolescent changes in the structure and function of frontal circuits engaged during *Now/Later* decision making and whether alcohol abuse disturbs these changes. The overall objective of this application is to use neuroimaging to compare the brain areas engaged during *Now/Later* decision-making between late adolescents and adults, and to determine whether heavy alcohol use is associated with abnormalities in observed age-related differences in these neural circuits. Our central hypothesis is that immaturity in frontal circuits and relatively increased signaling in subcortical structures promote impulsive decision making in late adolescents. In addition, we hypothesize that the brains of heavy drinking adults will display structural and functional similarities to those of late adolescents, suggesting that heavy drinking is associated with impaired development of frontal brain structures that govern decision making. We will test our central hypothesis by pursuing the following specific aims:

Aim 1. Identify functional differences in frontostriatal circuits associated with *Now* versus *Later* decision making differences in late adolescents versus adults.

Our working hypothesis is that adults (age 22-40) will activate the orbitofrontal cortex (OFC) to a greater degree during *Now/Later* decisions, which is typically associated with *Later* preference (Boettiger et al., 2007), while late adolescents (age 18-21) will show relative hyperactivity in subcortical structures. Our expected outcomes for Aim 1 are to identify functional neural correlates of age-related differences in decision-making behavior. These outcomes are expected to have an important positive impact because they will elucidate possible neural bases of late adolescent impulsiveness that may contribute to the elevated risk for AUDs in this age group.

Aim 2. Identify structural differences in frontostriatal circuits associated with *Now* versus *Later* decision making differences in late adolescents versus adults.

Our working hypothesis is that frontal structures such as the OFC and dorsal prefrontal cortex (dPFC) will show evidence of immaturity in late adolescents relative to adults, both in terms of gray and white matter, and that such differences will positively correlate with impulsiveness in decision-making. Our expected outcomes for Aim 2 are to identify structural neural correlates of adolescent impulsiveness. We expect these outcomes to have positive impact because they will establish structural differences in the adolescent brain that may underlie maladaptive decision-making and thus play a role in the enhanced risk of AUDs at this age.

Aim 3. Determine whether decision-making impulsiveness in heavy drinking adults is positively correlated with signs of structural or functional immaturity in frontal circuits.

Our working hypothesis is that impulsive decision-making in heavy drinking adults is associated with structural and functional immaturity in frontal cortical structures implicated in the tendency to select *Now* over *Later*. Our expected outcomes for Aim 3 are to ascertain the structural and functional neural correlates of impulsive decision making observed in heavy drinking adults. These outcomes are expected to have an important positive impact because they will identify specific neural structures in which insult by heavy alcohol use may lead to quantifiable, maladaptive decision-making that could perpetuate harmful alcohol use.

The findings from this research plan will provide a better understanding of the development of neural structures governing *Now/Later* decision making (Aims 1 and 2). This research will also provide insight into the relationship between alcohol use patterns and the integrity of neural circuits engaged during *Now/Later* decision making, which may provide novel biological insight into the development and/or maintenance of AUDs (Aim 3).

3. RESEARCH STRATEGY

3a. Significance

In adults, a greater tendency to choose immediate over delayed rewards is a risk factor for addictive disorders (Reynolds, 2006). Existing data suggest that discounting of delayed rewards normally decreases from childhood to the early 30's (Green, 1994; Green et al., 1996; Scheres et al., 2006; Olson et al., 2007). Heightened discounting of delayed rewards in late adolescence could contribute to the increased risk for AUDs at this life-stage (Kandel and Logan, 1984; Brown et al., 2008). Little work to date has investigated the developmental trajectory from late adolescence to early adulthood of discounting behavior or its underlying neural substrates. To begin addressing this issue, we tested late adolescents (ages 18-21) and adults (ages 22-40) in an fMRI-compatible delay discounting (“*Now/Later*”) task. Our preliminary data suggest that late adolescents choose smaller, immediate rewards (“*Now*”) significantly more often than do adults (see *Approach*). We now propose to investigate the underlying neural bases of this age-dependent change in decision-making behavior.

Although the underlying neural bases of the age-related behavioral differences that we observed are unknown, evidence points to developmental maturation of the frontal lobes. First, the development of frontal structures remains incomplete until the early-to-mid twenties (Sowell et al., 1999; Casey et al., 2000; Sowell et al., 2001; Giedd, 2004; Gogtay et al., 2004; Lenroot and Giedd, 2006), consistent with our observed decrease in delay discounting around age 22. Second, fMRI data from adults using the same *Now/Later* task found that activity in two frontal structures, the dorsal prefrontal cortex (dPFC) and orbitofrontal cortex (OFC), predicts choice behavior in this task (Boettiger et al., 2007). These data are consistent with models suggesting a role for the dPFC in cognitive control (Miller and Cohen, 2001) and for the OFC in encoding value of choice outcomes (Wallis, 2007). Thus, developmental changes in these areas would be expected to alter choice behavior. Finally, a study of individuals aged 9-23 found that age-related increases in frontal white matter integrity are positively correlated with preference for larger, delayed rewards (Olson et al., 2009). As this latter study included only seven (of 79) individuals ages 22-23, no conclusions can be drawn with regard to white matter changes from late adolescence to early adulthood. However, Olson et al.'s findings do not refute our hypothesis that maturation of frontal structures underlies the decline of *Now* preference in early adulthood.

In addition to the age-related differences in *Now/Later* decision making described above, we found that heavy drinking adult males (AUDIT scores ≥ 8) choose immediate rewards as frequently as do late adolescents (see *Approach*). We speculate that immaturity in frontal function may persist in some heavy drinkers, as either a cause or a consequence of harmful drinking. It is known that frontal circuits are especially prone to insult by heavy alcohol consumption, especially at binge levels (De Bellis et al., 2005; Miguel-Hidalgo et al., 2006; Jacobus et al., 2009; McQueeney et al., 2009). Moreover, decreased metabolic activity has been observed in the PFC and OFC of abstinent alcohol abusers (Volkow et al., 1997; Catafau et al., 1999), suggesting that heavy alcohol use may impair frontal structures crucial for *Now/Later* decision making. This is consistent with the Sponsor's findings of heightened discounting of delayed rewards in abstinent alcoholics associated with differences in dPFC and OFC activation during *Now/Later* decision-making (Boettiger et al., 2007). Thus, the brain regions that predict behavior in our *Now/Later* task and whose maturation into early adulthood may explain the age-dependent decline in discounting of delayed rewards from late adolescence to early adulthood are also structures in which dysfunction is linked to AUDs (Verdejo-Garcia et al., 2007; Clark et al., 2008; Yeh et al., 2009). We expect that our proposed studies will provide new insight into the neurobiology underlying an important form of decision-making and whether heavy alcohol use is associated with abnormal structure and/or function in brain areas underlying this behavior. *This contribution is significant because it will address the unanswered question of when in early adulthood the shift in Now/Later decision making occurs and whether frontal circuit maturation can explain this shift in behavior. Furthermore, a closer investigation of the neural underpinnings of late adolescent vs. adult decision making and the interaction of drinking behavior with age will provide a means to understand at a behavioral neuroscience level why late adolescents are at an increased risk for developing AUDs (Kandel and Logan, 1984; Brown et al., 2008; Squeglia et al., 2009).*

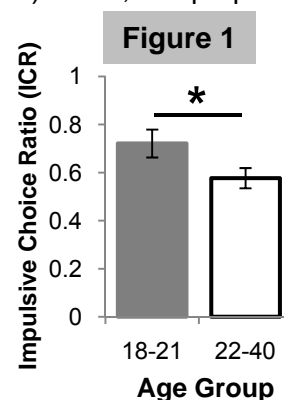
c. Approach.

Aim 1. Identify functional differences in frontostriatal circuits associated with *Now* versus *Later* decision making in late adolescents versus adults.

Introduction. While late adolescents are at increased risk of engaging in maladaptive behaviors, such as problem alcohol use (Crews and Boettiger, 2009; Ernst et al., 2009), we currently lack a complete understanding of the neurobiological bases of such risk. Possible contributors to maladaptive behaviors in late adolescents are differences in decision making processes. The *objective of this aim* is to determine functional brain differences underlying behavioral differences in the tendency to choose immediate (“*Now*”) over delayed (“*Later*”) rewards

observed among late adolescents (age 18-21) relative to adults (age 22-40). To achieve this aim, we will test the *working hypothesis* that adults activate the OFC to a greater degree when making *Now/Later* decisions than do late adolescents, as high OFC activity during *Now/Later* decisions is typically associated with *Later* preference in adults (Boettiger et al., 2007). In contrast, we predict that late adolescents will show greater activity in reward and limbic associated regions (ventral striatum, nucleus accumbens, and amygdala) during *Now/Later* decision-making relative to adults. We will test our working hypothesis by comparing brain activity during *Now/Later* decision-making between late adolescent and adult groups using fMRI. The *rationale* for this aim is that improved understanding of the neural bases of changes in decision making behavior from late adolescence to adulthood may stimulate new strategies to prevent alcohol use disorders (AUDs). Furthermore, identifying brain structures that are differentially engaged during *Now/Later* decisions between late adolescents and adults may identify additional regions of interest (ROI) for investigation in the structural imaging studies of Aim 2. Such findings will be of importance because they will enhance our understanding of how brain maturation from late adolescence to adulthood may contribute to age-dependent changes in decision-making behavior.

Justification and Feasibility. Our approach requires that we be able to reliably measure immediate reward bias, particularly in the context of fMRI. Second, it requires that we are able to adequately collect and analyze fMRI data. The following preliminary data support the feasibility of the proposed approach. First, the Sponsor has developed an fMRI compatible *Now/Later* task that reliably detects differences in the decision-making of adults with versus without a history of alcoholism (Mitchell et al., 2005; Boettiger et al., 2007; Mitchell et al., 2007). A previous fMRI study of this task found that activity in the OFC during decision-making is negatively correlated with the tendency to choose *Now* over *Later* (i.e. with “immediate reward bias”) (Boettiger et al., 2007). This task was also used successfully by the Sponsor in a second fMRI study (Boettiger et al., 2009). Thus, our proposed use of this task during fMRI is feasible. Second, in a preliminary behavioral study, we tested 111 subjects ($n=66$ late adolescents and $n=45$ adults) with this task and, taking immediate reward bias (ICR) as the dependent measure, we performed a factorial ANOVA with factors of age group, gender, and alcohol use (since this can influence ICR (Mitchell et al., 2005; Boettiger et al., 2007; Mitchell et al., 2007)). We found significant main effects of gender ($F_{(1,103)}=4.35$, $p=0.040$) and age ($F_{(1,103)}=4.10$, $p=0.046$) on ICR, with males choosing more impulsively than females. Fig. 1 (right) displays the finding that late adolescents choose immediate rewards significantly more often than do adults. These effects were not explained by SES differences between groups. We suspect that these results reflect immaturity of frontal circuits in late adolescents (Paus et al., 2001; Gogtay et al., 2004; Sowell et al., 2004; Yurgelun-Todd, 2007; Giedd, 2008; Shaw et al., 2008) and expect to find differences in frontal activity underlying *Now/Later* decision-making that correlate with these behavioral differences. Beyond motivating the proposed studies, our preliminary data demonstrate our ability to recruit participants in the proposed age ranges.



Research Design.

Overview: This study will investigate the differences in brain activity underlying *Now/Later* decision-making between late adolescents (age 18-21) and adults (age 22-40).

General Methods

Consent/screening: Subjects will be thoroughly screened for inclusion/exclusion criteria (see *Human Subjects*).

Questionnaires: To identify factors accounting for individual differences, participants will complete standardized questionnaires. These will quantify drug and alcohol use (DDQ, RAPI, DUSI, AUDIT) (Collins et al., 1985; White and Labouvie, 1989; Tarter, 1990; Saunders et al., 1993), family history of alcohol abuse (FTQ) (Mann et al., 1985), affect (Spielberger, 1985; Beck and Steer, 1987; McNair et al., 1992), and personality traits (FTPI, LOC, APS, BIS) (Wallace, 1956; Rotter, 1966; Butcher JN et al., 1990; Barratt, 1994). We will also collect estimates of IQ (SILS) (Zachary, 1991) and socio-economic status (SES) (Hollingshead, 1975).

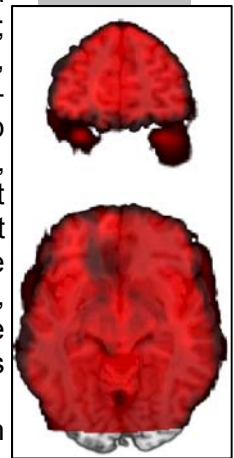
Delay discounting (Now/Later) task: This task is described in detail elsewhere (Mitchell et al., 2005; Boettiger et al., 2007; Mitchell et al., 2007). In brief, participants select between hypothetical reward pairs, each a dollar amount at a point in time; we refer to these two alternatives as “*Now*” and “*Later*”. The *Later* amount and delay time vary across trials, as does the percentage difference between *Now* and *Later*. *Now* is always a lesser amount available “TODAY”. Immediate reward bias is calculated as a ratio of *Now* choices relative to total number of subjective choices made, termed the impulsive choice ratio (ICR).

Subjects will be healthy males and females (ratio: 50:50), $n=24$ per age group (18-21 and 22-40; total $n=48$).

Functional Magnetic Resonance Imaging: Participants will perform the *Now/Later* task within a 3T MR scanner (see *Facilities and Equipment*) while we obtain continuous whole-brain blood-oxygen-level-dependent signal. A high-resolution anatomical image will also be obtained for each subject. Beginning with postdoctoral training,

the Sponsor has acquired considerable experience with this technique, resulting in publications in high level journals. The proposed methods are similar to those used previously by the Sponsor in studies of *Now/Later* decision-making (Boettiger et al., 2007; Boettiger et al., 2009), with minor adjustments to accommodate scanner differences. Here, we briefly review these adjustments. The following parameters will be used to acquire T2*-weighted single shot gradient echo echoplanar images (EPI): TR=2.2 sec, TE=30ms, Flip Angle 80°, FOV=22.4 cm in a 64x64 matrix, 37 interleaved coronal slices (3.5 mm² in plane, 4 mm between plane resolution). These parameters produce whole brain coverage for most participants; when it does not, the occipital pole will be excluded, as our hypotheses do not involve early visual cortex. These parameters were selected to generate adequate coverage for the OFC, dPFC, and anterior temporal lobe (Deichmann et al., 2003; Weiskopf et al., 2006; Du et al., 2007). Fig. 2 (right) depicts mean EPI coverage for one subject using the proposed parameters on the BRIC's Allegra 3T overlaid on a template anatomical image. As shown, coverage appears adequate for the proposed studies.

Figure 2



Hypothesis. Activity in frontal and subcortical structures will vary across age group with adults (22-40) showing greater activity in the OFC and late adolescents (18-21) demonstrating greater activity in subcortical structures such as the amygdala.

Statistical Analyses. With ICR as the dependent measure, we will use a 2X2 mixed model ANOVA to test for a significant age group x gender interaction. An *a priori* power analysis indicates that a sample size of $n=40$ has >90% power to detect a moderately large effect size (0.75). As our preliminary behavioral study has found a moderate (>0.70) effect of age, we anticipate that this study will be adequately powered with 12 subjects per cell for a total $n=48$, even if effect sizes are smaller than expected. Within subjects, we will define ROI *a priori* based on our past studies (Boettiger et al., 2007; Boettiger et al., 2009). Activity differences within these ROI will be assessed via the same type of ANOVA. Additional exploratory mapwise analyses will seek to identify brain areas in which activity during *Now/Later* decisions shows main effects of age or gender, or their interaction.

Expected Results & Interpretation. We expect that during *Now/Later* decision-making, adults will engage the OFC to a greater extent than will late adolescents and that the degree of activation will be negatively correlated with our behavioral measure of immediate reward bias (ICR). Additionally, we expect that late adolescents will show greater activation in subcortical impulse-related structures such as the amygdala and ventral striatum and that the degree of activation in these structures will be positively correlated with ICR.

Time to complete study. See *Timeline*.

Expected Outcomes. This fMRI study will allow us to better understand the role of brain maturation in age-dependent differences in immediate reward bias. In particular, we will be able to identify structures and circuits which function differently in late adolescents versus adults during *Now/Later* decision-making. Such findings will improve our understanding of the neural mechanisms of impulsive decision making and may provide neurobiological insight into why late adolescents tend to be more impulsive than adults.

Potential Problems & Alternative Strategies. It is possible that we will not be able to detect age-related differences in brain activity during *Now/Later* decision-making. Analyzing our participant groups with gender as an independent variable should increase our age effect signal as it is known that the time course of brain development differs between males and females (Lenroot et al., 2007; Lenroot and Giedd, 2010).

Aim 2. Identify structural differences in frontostriatal circuits associated with *Now* versus *Later* decision making differences in late adolescents versus adults.

Introduction. Although we know that frontal structures do not reach adult maturity until the early-to-mid twenties, specific investigation of maturation in gray and white matter in structures engaged during decision-making is needed. This aim will investigate age-dependent changes in brain structures of interest by contrasting gray and white matter densities and volumes between late adolescents and adults. In addition to the ROI defined *a priori* based on previous fMRI studies (see Aim 1), we will also interrogate any novel ROI identified in our Aim 1 analyses as showing significant functional differences between age groups. The *objective of this aim* is to determine if structural differences in the brains of late adolescents can explain differences in their *Now/Later* decision-making relative to adults. To achieve this aim, we will test the *working hypothesis* that frontal structures such as the OFC and prefrontal cortex (PFC) will be less developed in late adolescents than in adults, as measured by both gray matter and white matter density, and that immaturity in these frontal structures will be correlated with greater immediate reward bias. The *rationale* for this aim is to better understand the relationship between age-dependent changes in frontal structures and impulsive decision making. In particular, this aim seeks to determine if frontal immaturity in late adolescents can account for their enhanced immediate reward bias relative to adults.

Justification and Feasibility. Structural data will be obtained during the same scan sessions used to collect fMRI data for Aim 1. We will use voxel based morphometry (VBM) analyses of high-resolution structural MRI (sMRI) data to assess age-related changes in gray matter density, using a strategy similar to that of Sowell et al. (1999). Our study, however, will concentrate on an age group not delineated in the Sowell study: late adolescents (18-21). In addition, we will collect diffusion tensor imaging (DTI) data to investigate changes in white matter density and anisotropy as well as connectivity between structures of interest using an automated fiber tractography technique similar to that of Liston et al., 2006 (Liston et al., 2006). While the Sponsor has limited experience with analysis of structural imaging data, we will take advantage of the great depth of expertise at UNC in this area. For example, the BRIC Director, Dr. Weili Lin has an extensive publication record in the use of basic sMRI and DTI to assess developmental changes in the brain (Lin et al., 2003; Zhai et al., 2003; Lin et al., 2008; Gao et al., 2009b; Gao et al., 2009a; Zhu et al., 2009; Gilmore et al., 2010). As noted in the accompanying letter of support from Dr. Lin, this expertise will be available to enable the success of the proposed research. This expertise includes the analytical tools of Dr. Lin's collaborators in the Neuro Image Research and Analysis Laboratories in the UNC Psychiatry Department (<http://www.ia.unc.edu/dev/>).

Research Design.

Overview: This study will investigate the structural differences in gray and white matter in regions that correlate with *Now/Later* decision-making differences between in late adolescents and adults.

Subjects, questionnaires, and consent and screening practices will be as for Aim 1. It is important to note that the subjects used in this Aim will be the same as those used in Aim 1. During the same scan session in which participants perform the *Now/Later* task during fMRI, we will also collect high resolution anatomical MP-RAGE and DTI scans for analysis of gray and white matter density and volume. In addition to interrogating the ROI identified *a priori* from past studies (see Aim 1), we will also investigate novel ROI identified in Aim 1 exploratory analyses.

Hypothesis. We hypothesize that late adolescents will have less developed frontal structures than adults, as measured by increased gray matter density, reduced white matter density and diffusivity. In addition, we believe that structural immaturity in frontal circuits will be positively correlated with greater immediate reward bias in our delay discounting task.

Statistical Analyses. See Aim 1 *Statistical Analyses* for experimental design and power analysis calculation justifying a sample size of $n=48$ for this Aim. Within subjects, we will define ROI *a priori* based on our past studies (Boettiger et al., 2007; Boettiger et al., 2009). Gray and white matter differences within these ROI will be assessed via a 2X2 mixed model ANOVA with age group and gender as our two factors. Additional exploratory mapwise analyses will seek to identify brain areas in which gray and white matter measures show main effects of age or gender, or their interaction.

Expected Results & Interpretation. We expect that the late adolescent group will display an immature phenotype in frontal structures represented by higher gray matter density and lower white matter density relative to the adult group. Additionally, using fiber tractography of DTI data (Liston et al., 2006), we expect to see less developed frontostriatal circuits in the late adolescent group. Such a finding would suggest that immediate reward bias in late adolescents may stem in part from insufficient connectivity between frontal executive control structures and subcortical, reward-driven structures.

Time to complete study. See *Timeline*.

Expected Outcomes. We expect this study to provide information on the role of age-dependent changes in frontostriatal circuitry (gray and white matter) in regulating *Now/Later* decision making. Understanding the neurobiological basis of late adolescents' progression to a less impulsive decision making style around their early-to-mid twenties will be useful as it will identify key brain structures whose maturation is important in advantageous decision making. Positive results would motivate future longitudinal studies to assess whether, within individuals, observed changes in brain structure and function are associated with behavioral changes.

Potential Problems & Alternative Strategies. While we expect to see differences in gray and white matter measures between our two age groups, it is possible these differences will be small and that effects may be minimized by individual variability. Stratifying our groups by gender (due to the earlier onset of female brain maturation (Lenroot et al., 2007)) should aid in reducing within-group variance and thus improve our ability to detect age effects. If effect sizes are small, we may also increase our statistical power by recruiting additional subjects for structural imaging and behavioral testing beyond those tested in Aim 1. Also, more sophisticated analyses of gray and white matter differences may be necessary to extract differences between groups. For example, we may need to investigate differences in fractional anisotropy and mean diffusivity in our DTI analyses as these variables measure different properties of white matter thought to reflect its organization (Basser, 1995).

Aim 3. Determine whether decision-making impulsiveness in heavy drinking adults is positively correlated with signs of structural or functional immaturity in frontal circuits.

Introduction. Although it is known that abstinent alcoholics choose *Now* more frequently in our task than do control subjects (Mitchell et al., 2005) and our preliminary data suggest that late adolescents are also more likely to choose *Now* over *Later*, investigating the relationship between alcohol use and functional brain immaturity is lacking. The *objective of this aim* is to determine if heavy alcohol use is associated with frontal cortical dysfunction and more impulsive decision making. To achieve this aim, we will test the *working hypothesis* that heavy drinking is associated with structural and functional immaturity in frontal cortical structures engaged during *Now/Later* decision-making, especially in males. The *rationale* for this aim is to assess whether heavy alcohol consumption might impair development of frontal structures, which could contribute to the larger immediate reward bias observed among abstinent alcoholic adults relative to age-matched controls. The findings from this experiment will be useful in determining whether future prospective studies of the impact of drinking behavior on late-adolescent brain development are warranted.

Justification and Feasibility. Previous research suggests that the frontal structures engaged during our delay discounting task (Boettiger et al., 2007) are more sensitive to the neurodegenerative effects of alcohol than any other part of the brain (Corso et al., 1998; De Bellis et al., 2005; Miguel-Hidalgo et al., 2006). Thus, we expect to observe a relationship between immediate reward bias, OFC and PFC function and structure, and degree of alcohol consumption.

Using the Alcohol Use Disorders Identification Test (AUDIT) to group participants into heavy drinkers (AUDIT score ≥ 8) or moderate drinkers (AUDIT < 7), a preliminary behavioral study (see Aim 1, *Justification and Feasibility*) revealed a significant three-way interaction between effects of alcohol use, gender, and age on ICR ($F_{(1,103)}=6.39$, $p=0.013$). This interaction was due to the fact that age and gender effects on decision-making differed between moderate and heavy drinkers. Among moderate drinkers ($n=66$), adults chose less impulsively than did late adolescents ($t_{64}=2.26$, $p<0.05$). In contrast, among heavy drinkers ($n=45$), this age-dependent decline in ICR was only seen in females ($t_{21}=2.79$, $p<0.05$). Among heavy drinking males, we found a trend toward increasing ICR with age ($t_{20}=1.94$, $p=0.067$). Again, these effects were not explained by SES. Thus, heavy alcohol use in adult males is associated with high immediate reward bias in our *Now/Later* task, similar to that observed in late adolescents or abstinent alcoholics. These preliminary data demonstrate that we will be able to recruit the target populations for the proposed studies.

This Aim will involve the same experiments outlined for Aims 1 and 2 with the addition of subclinical heavy drinking populations, which we will compare to moderately drinking participants. We will conduct the experiments of Aim 3 concurrently with Aims 1 and 2, although it will provide results independent of those Aims that may provide insight into neural factors mediating the interaction between alcohol use and age on immediate reward bias.

Research Design.

Overview. This study will investigate functional and structural differences in frontostriatal circuits associated with heightened immediate reward bias in heavy alcohol users.

See Aims 1 and 2 above for General Methods

Subjects: A key difference in the experiments associated with this Aim is that the subject pool will include individuals with AUDIT scores ≥ 8 , which is indicative of a possible drinking problem (Saunders et al., 1993). Subjects meeting DSM-IV criteria for current or past alcohol abuse or dependence will be excluded. The same fMRI, sMRI, and DTI data will be collected from these subjects, and the same analyses will be performed, with the addition of a third factor: alcohol use group. The value of this aim is that we will be able to investigate the impact of problem drinking behavior on immediate reward bias and frontal structures involved in immediate reward bias.

Hypothesis. We hypothesize that heavy drinking adults will display immediate reward bias equivalent to late adolescent control subjects and that this similarity in immediate reward bias will be reflected in equivalent structural and functional immaturity in the frontostriatal circuits of adult problem drinkers and late adolescent controls.

Statistical Analyses. We will use a 2x2x2 ANOVA to test for a significant interaction between age, gender, and alcohol use. An *a priori* power analysis indicates that a sample size of 50 has 85% power ($\alpha=0.05$) to detect a small effect size (0.3). We propose to test $n=64$, which will provide adequate power to detect smaller effects and to accommodate possible data loss due to movement. Thus, we will need to recruit 16 adults and 16 late adolescents (8 females per group) with AUDIT scores ≥ 8 to be combined with control subject data collected in Aims 1 and 2 for a total of 64 subjects. As data collection for all three Aims will be concurrent, the complete data set for Aim 3 may reflect only a subset ($n = 16$ per age group) of the data collected for Aims 1 and 2.

Expected Results & Interpretation. We expect to find interacting effects of age, gender, and alcohol use reflected in frontostriatal activity during *Now/Later* decision-making. Our preliminary behavioral study suggests that we may observe an effect of heavy drinking on our measure of immediate reward bias only in our male subjects. However, that result may reflect differences in drinking habits between male and female participants. Thus in the proposed study we will collect more detailed information on alcohol use, such that we can

characterize what types of drinking behavior (binge drinking, for example) are associated with high immediate reward bias and structural and functional dysfunction in frontostriatal circuits.

Time to complete study. See *Timeline*.

Expected Outcomes. We expect the results from this Aim to provide us with insight into the neural mediators of the relationship between heavy alcohol use and immediate reward bias. Particularly, we hope to identify the role of frontostriatal circuit maturation in immediate reward bias and how alcohol may negatively impact components of these circuits. If we can determine the effect of alcohol use on frontostriatal function and/or structure and the behavioral consequences of this effect on *Now/Later* decision making, we may be able to better understand the increased risk for alcohol use disorders in late adolescents and why these disorders may persist into adulthood (Kandel and Logan, 1984; Brown et al., 2008).

Potential Problems & Alternative Strategies. We expect to see differences between heavy and moderate drinkers in terms of behavior (immediate reward bias) and neurobiology (structural and functional measures of frontostriatal circuits). However, heterogeneity in drinking behavior within groups may make interpreting the relationship between alcohol and our dependent measures difficult. Thus, an extensive battery of drinking measures will be collected from our subjects (see *Human Subjects*) such that we can retroactively place participants into groups of similar alcohol consumption histories for analysis. It may be necessary to follow-up this initial data collection approach with a more targeted recruitment of participants with similar drinking behaviors using a variety of alcohol use measures for subject screening.

Timeline:

Project Year	Year 1				Year 2				Year 3				Year 4			
NIH Quarter	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Scientific Proposal																
Aim 1: fMRI controls developmental study																
Data Collection																
Data Analysis																
Aim 2: sMRI & DTI controls developmental study																
Data Collection																
Data Analysis																
Aim 3: fMRI, sMRI, DTI alcohol use study																
Data Collection																
Data Analysis																
Career Development																
Didactic Courses																
Multidisciplinary Seminars																
Workshops and Tutorials																
Professional Conferences																
Manuscript Preparation																
Thesis Preparation & Defense																
Postdoctoral Interviews																
F32 submission																

Future directions

Positive results in these studies would warrant a prospective study where the effects of problem alcohol use on frontostriatal structure and function and *Now/Later* decision making could be monitored within individuals from age 18 to 25. Such a study would be invaluable in understanding how problem alcohol use, especially during late adolescence, can result in neurobiological changes that increase the likelihood that such use could progress into an AUD that persists into adulthood. Thus, the proposed set of studies will provide a more complete understanding of the neurobiological bases of *Now/Later* decision making and how development and alcohol functionally impact these circuits. Such an understanding may eventually lead to improved treatments for those with AUDs.

8. HUMAN SUBJECTS

Human Subjects Involvement and Characteristics.

General inclusionary criteria for all subjects are that they be high school educated and medically healthy subjects aged 18-40. Due to difficulties in interpreting cognitive studies in subjects with English as a second language, only native-English speakers will be asked to participate in these studies. Participants will be selected in an unbiased fashion with respect to race and equal numbers of male and female participants will be recruited. Every effort will be made to insure that the subject population conforms to the NIH policy on Gender and Minority Inclusion in Research Study populations. Subjects will also be excluded if they have any known neurological disease such as dementia, seizures or head trauma; or known psychiatric disease such as depression or psychosis; or known systemic disease such as cancer, cardiovascular or inflammatory disease which could influence cognitive functioning. Subjects will be excluded if they have any type of motor or visual disturbance which precludes them from performing the cognitive tasks. We will also exclude individuals currently using psychoactive drugs (aside from moderate caffeine, alcohol, or nicotine), including prescription medications, and individuals with a history of any substance use disorder.

Neuroimaging Exclusion Criteria Additionally, participants will be excluded from our proposed studies if they have any contraindications to MRI, including electrically, magnetically or mechanically activated implants (such as cardiac pacemakers), intracerebral vascular clips (surgically implanted metal clips in any blood vessels within the brain), other non-removable body metal, tattoos, or if they are pregnant or claustrophobic. Participants will also be excluded from MRI testing if they are left-handed, as previous research has shown that handedness may impact the localization of brain activity. All pregnant women will be excluded from participating.

Screening Procedures People who show initial interest in a study are contacted via phone or e-mail with a questionnaire containing items related to psychiatric and neurological health, medications, use of psychoactive substances, and the presence of contra-indicators for MR research such as metal in the body. Evidence of neurological or psychiatric illness, or current use of psychoactive medications or other chemicals (excluding moderate caffeine, alcohol or nicotine), or meeting DSM-IV criteria for any substance use disorder (based on semi-structured interview) will result in non-inclusion in the study. In addition, the presence of contra-indicators for MR research (such as metal in the body or pregnancy) will result in non-inclusion in the study. After reading and signing an informed consent form, subjects are given a rapid urine test to screen for psychoactive drugs and a breathalyzer test to screen for alcohol use. Results of these screening tests are not written down, but positive results will exclude participants from further participation. Female participants are also provided with a urine early pregnancy test at that time.

Magnetic Resonance Imaging The proposed experiments will take place at the UNC Biomedical Research Imaging Center (BRIC), located at the southern end of the UNC campus. Studies will be performed on a Siemens 3T Trio (full-body) MR scanner. After the on-site screening procedure described above, participants will receive a battery of standardized questionnaires, and receive training in the cognitive task(s) prior to scanning. These procedures take place in private rooms located adjacent to the scanner. Throughout the duration of the MRI session, it is ensured that the participants are well and comfortable. Participant status is assessed after each scan and adjustments are made to ensure participant comfort as necessary.

For all proposed experiments, after testing is complete, the purposes and predictions of the research will be clearly explained to the participants and their questions will be answered.

Sources of Materials.

Research material: We will collect data during the delay discounting task and MRI scans. We will collect demographic information, including gender, age, ethnicity, education, and socio-economic status. Participants will also complete standardized behavioral inventories to quantify personal alcohol and drug use (AUDIT, DDQ, DUSI, RAPI), family history of alcohol use (FTQ), and personality measures that could impact our results (STAI, BDI, LOC, POMS, MMPI, BIS).

Data collection: All data collected will be entered into databases and stored on password protected computers using only alphanumeric subject ID codes as identifiers. Below is a detailed description of how we will collect the data. All data are being collected specifically for the proposed research project.

Neuropsychological/Behavioral Testing Following completion of the screening procedures, participants will receive a battery of standardized neuropsychological inventories to complete. Participants will then receive training in the decision making task. Subjects will then complete the computerized delay discounting task during fMRI.

Magnetic Resonance Imaging Measurement of decision making behavior will take place while participants are scanned at the UNC BRIC. Studies will be performed on a Siemens 3T Trio (full-body) MR scanner. Subjects are verbally read the experimental instructions just prior to scanning. Throughout the duration of the scanning session, it is ensured that the participants are well and comfortable. Participant status is assessed after each scan and adjustments are made to ensure participant comfort as necessary.

Access to individually identifiable private information will be limited to the PI and the Sponsor's research team (all of whom have completed CITI training). All data collected from the computerized tasks will be stored on a computer in the sponsor's lab, with the only identifier attached to the data being subject ID code. All imaging data will be stored in password protected files on secure computers in the sponsor's lab or on the BRIC's secure server; imaging data will include no personal identifiers. Paper copies used to collect questionnaire data and demographic information will be kept in a locked file cabinet in the Sponsor's lab, with subject number as the sole identifier. For each study, a separate file linking the subject ID codes with subject names will be kept on a password protected computer in the Sponsor's lab until completion of the study.

Potential Risks.

Cognitive testing There are no known risks for injury associated with the neuropsychological/behavioral components of these cognitive studies. Other possible risks include frustration, boredom, or fatigue. Moreover, answering detailed questionnaires and participating in computerized cognitive tasks may make subjects anxious or uncomfortable. Based on our previous experience, it is extremely unlikely that participants will find these potential psychological risks extreme enough to end their participation.

MRI studies Potential minor risks and discomforts are associated with MRI acquisition. No known health risks are associated with these types of MRI studies, although the MRI makes loud noises as it acquires data, which could affect a participant's hearing. The only significant risk associated with MRI is the presence of ferromagnetic materials. This is a noninvasive technique involving no catheterizations or injection of exogenous tracers. A great many patients have now undergone magnetic resonance studies without apparent harmful consequences. Radiofrequency power levels and gradient switching times used in these studies are within the FDA approved ranges. Subjects must lie still in the MRI scanner for approximately 90 minutes, which subjects may find uncomfortable. Some people may become claustrophobic while inside the magnet. A relative contraindication to MRI studies is pregnancy, as the risk of MRI to fetuses is unknown.

Questionnaire data collection Answering the questionnaires may make the subjects uncomfortable and could cause emotional distress.

Confidentiality Information collected for the purpose of this research study will be kept confidential as required by law. All copies of testing records and results will be kept in locked filing cabinets, in locked offices, or in password-protected computer files. All information will be accessible only to authorized personnel. Alphanumeric codes will be used on all data sheets and data files in place of names. No participants will be individually identified in any report or publication about this study. No personal identifiers will be associated with any study data. Screening information from participants will be kept in a locked filing cabinet along with their consent forms. The information collected during the initial screening is not retained.

Privacy Telephone interviews will be conducted from the Sponsor's laboratory or office space. All laboratory personnel have undergone the CITI ethics training for conduct of human subjects research. All neuropsychological and behavioral testing will occur in private testing rooms. No mailed or emailed materials or messages will include subject specific data.

There are no known financial or legal risks associated with participating in these studies.

Recruitment and Informed Consent.

All subjects will participate in the informed consent process. Participants will be familiarized with the protocol by the PI or qualified study personnel, including its risks and benefits, and informed consent will be documented according to the regulations governing human subject research at the University of North Carolina, Chapel Hill, which meet the standards of the NIH.

Recruiting Participants will be recruited through local IRB approved flyers and advertisements distributed in the local community. Potential subjects who respond to these advertisements will be contacted initially via telephone or email. If contacted via email, subjects will be called for an initial telephone screening to determine whether the subject meets our inclusion criteria. Secure web-based screening tools may also be employed. Those meeting study criteria based on initial screening, will be scheduled to come to the lab to participate.

Inclusion of Women and Minorities Every attempt will be made to recruit women and minorities, including posting advertisements at the Sonja Haynes Stone Center for Black Culture and History; the Lesbian Gay Bisexual, Transgender Office; the Student Union; the Carolina Women's Center; and the Medical Campus buildings.

Initial Telephone Screening Potential participants are first screened via telephone for eligibility. This process includes a complete explanation of the protocol procedures. At that time, a potential participant can decline to participate.

Obtaining Informed Consent Upon arrival to participate in testing, participants will read and have explained to them the informed consent form. Informed consent is obtained in a comfortable, private room in the BRIC facility. Participants' questions about the protocol will be thoroughly answered prior to obtaining consent, with no time limit to this procedure. Upon consent, the subject is free to withdraw that consent at any time, which will be emphasized to the subject. Consent will be obtained by approved study staff.

Waiver of written consent for telephone pre-screening We have obtained (or will obtain) a waiver of written consent for the initial telephone/web-based screening. This request derives from our need to conduct a health and medical history pre-screen in order to ensure that individuals who respond to our IRB approved recruitment efforts are eligible to participate in our research projects. The health screen is preparatory to our research and its sole purpose is to ensure that participants meet our inclusion/exclusion criteria. A screening procedure that is efficient for both volunteers and the research team is necessary. These studies have strict inclusion/exclusion criteria and the pre-screening efficiently provides information needed to determine eligibility. To require potential study participants to come to our lab for screening that can be done over the telephone or web would place an undue burden on potential participants. Our phone script includes elements of informed consent and explains to potential participants how their privacy will be protected. The potential subject is informed that they may stop the phone conversation at any time. The health and medical information documented during the telephone screen is not disclosed to other investigators. Screens from participants who are excluded are destroyed. Screens from participants who are included are kept in a locked filing cabinet along with their consent forms and other screening information.

Protections Against Risks.

Cognitive testing The computerized tasks will be explained thoroughly and practice sessions will be provided before starting the task to reduce potential anxiety. To address the risk of frustration, boredom or fatigue, subjects will be given brief rests or breaks as needed during testing. Although it is hoped that subjects will complete each task in each session, subjects may choose to stop participating at any time during the cognitive testing.

MRI studies To address the risks posed by contraindications to MRI, detailed routine screening will exclude pregnant individuals and those with non-removable metal in their body, pacemakers, tattoos, or nicotine patches, and all subjects will be carefully checked for metal prior to entering the magnet room. To reduce the incidence of claustrophobia while inside the magnet, people with a history of claustrophobia will be excluded and all subjects will be warned of this possibility. To protect subjects from the loud noises the scanner makes as it acquires data, while still permitting communication between the investigator and subject, subjects are provided with ear plugs and fitted with MR compatible headphones. Efforts will be made to make the subjects as comfortable as possible, and procedures will be explained thoroughly prior to scanning. For example, a temperature and pressure sensitive foam pillow is used to comfortably restrict head motion during scanning, thereby reducing fatigue and motion artifact. The testing and MRI session can be stopped at any

time at the subject's request or due to investigator concerns about subject safety or comfort. Although there has been no demonstrated risk of MRI to fetuses, all women of childbearing age will be informed of possible unknown risks of MRI in pregnancy, and provided with an early response urine pregnancy test to use prior to scanning in order to make an informed decision as to whether to continue their participation.

Questionnaire data collection Although it is hoped that subjects will answer all questions asked, participants may choose not to answer any question and they may terminate participation at any time without penalty, which will reduce any potential emotional distress caused by having to answer a particular question.

Privacy and confidentiality In order to protect subjects' privacy regarding their participation in our studies, participants will not be scheduled in overlapping time slots. No one outside of the research team will have access to participants' data. Participants' data will only be associated with their ID numbers, not personal identifiers. Any paperwork that includes participants' names or other personal information will be stored in a locked file cabinet in the locked lab separate from the data. For each study, the electronic file linking participants' names and subject numbers will be removed from the computer and a hard copy will be archived in the sponsor's locked office when each study is completed.

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

Potential benefits Subjects will not experience any direct benefit from participating in these studies. We anticipate that the results of these studies will improve our understanding of immediate reward bias, which is a behavioral phenotype associated with addictive disorders. Eventually this knowledge could lead to improved treatment options for people with these disorders. Participants may benefit psychologically from knowing that they are participating in medically motivated research.

Risks in relation to benefit While we have taken systematic and comprehensive precautions to reduce the risks involved in these studies, the possibility of an adverse event remains. However, any such adverse events are not expected to exceed what an average individual would experience in the course of daily life. Therefore, the potential benefits anticipated in improved treatment and management of patients with alcohol and other substance use disorders are expected to far outweigh the minimal risks associated with these studies.

Importance of the Knowledge to be Gained.

To date, the cognitive processes and neural mechanisms underlying immediate reward bias are poorly understood, but they likely play a key role in the maintenance of addiction. These studies will provide novel data on the neurobiological mechanisms regulating immediate reward bias, thus bridging this gap in our knowledge. Ultimately, such knowledge may help to identify new therapeutic approaches to treating addictive disorders. Due to the widespread occurrence of addictive disorders, their negative impact on society and the very limited number of treatments currently available, more effectively treating these diseases will substantially benefit society as a whole.

INCLUSION OF WOMEN AND MINORITIES

As noted in the Protection of Human Subjects section (*Informed Consent and Recruiting*), participants will be recruited through IRB approved flyers and advertisements distributed in the local community. Every attempt will be made to recruit women and minorities, including posting advertisements at the Sonja Haynes Stone Center for Black Culture and History; the Lesbian Gay Bisexual, Transgender Office; the Student Union; the Carolina Women's Center; and the Medical Campus buildings.

We anticipate that most subjects will come from Chapel Hill and the adjacent city of Durham. Based on the demographics of these cities (according to the U.S. Census Bureau), we estimate that participants will be: 51-55% female, 11-42% African-American, 3-12.5% Hispanic, 4.5-7% Asian American, and less than 1% (each) Native American and Pacific Islander.

For the proposed studies we will recruit participants without regard to ethnicity. Equal numbers of male and female participants will be recruited for all studies.

Targeted/Planned Enrollment Table

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

Study Title: Now versus Later decision-making: effects of frontal development and alcohol use

Total Planned Enrollment: 80 (48 participants for Aims 1 & 2; 32 additional participants for Aim 3)

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	4	4	8
Not Hispanic or Latino	36	36	72
Ethnic Category: Total of All Subjects *	40	40	80
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	2	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	10	20
White	28	28	56
Racial Categories: Total of All Subjects *	40	40	80

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

Both women and men of all ethnicities are eligible to participate in these studies. Based on the minority composition of the areas surrounding the University of North Carolina at Chapel Hill (averaged U.S. Census Bureau 2008 population estimate information for Durham County and Orange County, <http://quickfacts.census.gov/qfd/index.html>), we estimate that ~25% of the participants will be African American, ~9% will be Hispanic, ~5% will be Asian, and less than 1% combined will be American Indian or Pacific Islander (see the Targeted/Planned Enrollment Table for specific numbers of women and minorities included).

INCLUSION OF CHILDREN

These studies will recruit volunteers between the ages of 18-40, which includes children. Our recruitment area will include a college campus (UNC Chapel Hill), and the mean age for the Chapel Hill-Durham area is 24-30 years of age. Thus, our recruiting materials are expected to reach sufficient numbers of people in the 18-21 age range.

The cognitive processes that we propose to study engage the frontal lobes, an area of the brain that is not fully mature in younger children and adolescents. Thus, we do not intend to recruit children younger than 18 years of age.

Respective Contributions

I have developed this proposed study, including the theory, hypotheses and proposed methods and analysis, in collaboration with my sponsor, Dr. Charlotte Boettiger. I have written this study proposal and have consulted Dr. Boettiger for recommendations and revisions.

Selection of Sponsor and Institution

My undergraduate research experience in the basic behavioral neuroscience lab of Dr. Judith Grisel at Furman University sparked my interest in pursuing graduate study of the neurobiology of reward and substance misuse. My particular interest in alcohol addiction led me to the University of North Carolina at Chapel Hill (UNC), whose Bowles Center for Alcohol Studies (CAS) is one of fourteen National Research Centers funded by NIAAA. I entered graduate school at UNC via the Biological and Biomedical Science Program (BBSP), which allows students to enroll in a wide range of courses and to rotate in 3-4 labs during the first year before choosing a thesis lab and PhD program. The BBSP first-year curriculum includes a course focused on scientific ethics and presentation skills. During this course, I presented a scientific poster on one of my rotations, wrote up my findings from another rotation in journal article format, and gave a talk on my final rotation to the broader biomedical research community at UNC. I felt the experiences offered to me at UNC and in the BBSP program allowed me to find a thesis lab that best fit my research interests and gave me a strong basis in the communication skills needed to become a productive and active member in the scientific community.

The Neurobiology Curriculum at UNC focuses on broad training in all aspects of neurobiology from cellular and molecular neurobiology to cognitive psychology, consists of 70 diverse research faculty, and has demonstrated an excellence in research training as evident by the presence of a NIH training grant. Additionally, as part of the Curriculum, Neuroscience Center and CAS seminars bring in prominent scientists in these fields to discuss their work and demonstrate to students the analytical and creative skills necessary to become successful independent researchers. Due to my interest in the neurobiology of addiction and the strength of the Neurobiology Curriculum at UNC, I focused on rotating in labs affiliated with the Curriculum and CAS during my first year. Although I enjoyed my first few rotations in labs focused on using rodents to investigate the neurobiology of reward and alcohol's depressant effects, I wanted to focus on a different research paradigm for my next rotation. So, I chose to rotate in Dr. Charlotte Boettiger's lab in the Department of Psychology, which investigates the neurobiology of addiction through research with human subjects. This choice was driven by my undergraduate interest in psychology and desire to see how the neurobiology of addiction can be studied from a psychological perspective. In the Boettiger lab, I investigated a cognitive process associated with addiction: discounting of delayed rewards. I also saw the unique benefits of working with human subjects and the value of behavioral and neuroimaging techniques in investigating the underlying biological processes involved in human addiction. I joined the Boettiger lab and Curriculum in Neurobiology in May 2009 and since that time I have been eagerly engaged in further investigation of impulsive decision making (characterized by choosing smaller, immediate rewards over larger, delayed rewards in a delay-discounting task), a cognitive process recognized as a promising intermediate phenotype of addiction. My work focuses primarily on the tendency to select immediate over delayed rewards (i.e. immediate reward bias), including investigation of the neurobiological bases behind this bias. I feel that working in the Boettiger lab has allowed me to combine my interests in biology, psychology, and neuroscience to address a real-world problem that affects millions of Americans – alcohol addiction.

Dr. Boettiger is an excellent advisor and mentor. She allows me to work independently but is always accessible and helpful. I like that Dr. Boettiger is a young faculty member not far removed from graduate school and her postdoctoral training. I feel that she can relate to the problems and difficulties associated with being a graduate student and can provide insight and encouragement when I encounter difficulties. I think that Dr. Boettiger also has a firm grasp of the skills necessary to be a successful independent researcher. Therefore, she has encouraged me to begin establishing myself in the scientific community by writing grants and submitting abstracts to scientific meetings. In addition to Dr. Boettiger's assistance, the two post doctoral fellows in the lab have been helpful in guiding me in my experimental planning, data analysis, and data interpretation. Additionally, the prior success of the lab's postdoctoral fellows in obtaining NRSA support – one as a pre-doctoral student and the other just receiving a postdoctoral fellowship – has encouraged me to seek out funding of my own and suggests to me that the lab's research is deserving of NIH support.

The collaborative nature of the Boettiger lab has provided me an excellent place to grow as a young scientist. I feel that the resources within my Sponsor's lab and elsewhere at UNC will prepare me for a successful career as an independent researcher. The expertise of the Bowles Center for Alcohol Studies and Biomedical Research Imaging Center in particular will allow me to apply neuroimaging techniques to understanding the neurobiological mechanisms of impulsive decision making and the relationship of alcohol use to this behavior.

Responsible Conduct of Research

During my first year in graduate school as part of the BBSP program at UNC, I took a seminar course that included didactic training in research ethics. During the year-long course we focused on diverse ethical topics, including: authorship, proper use of animals and humans in research projects, the importance of the institutional review board, and scientific honesty. This course was designed to satisfy the NIH requirement for training in the responsible conduct of research. In addition to this introductory seminar on scientific ethics, I have completed training necessary to work with human subjects at UNC including being briefed and familiarized with HIPPA and the importance of confidentiality and safe data storage techniques as part of the Collaborative Institutional Training Initiative (CITI) Program of research ethics training. In addition to these previous experiences in the responsible conduct of research, I intend to take an ethics course during the 2010-11 academic year to enhance my knowledge of the various components of ethical research. An example of such a course I am considering taking is Research Management and Ethics in Health Policy (HPAA 711) offered through the UNC School of Public Health. Additionally, I plan to take statistics courses in the future which will emphasize the importance of proper data analysis and interpretation techniques. Through seminars and continuing education received through the Curriculum in Neurobiology and Bowles Center for Alcohol Studies, I will be exposed to proper research practices and have access to faculty and other researchers with which to discuss ethical issues that arise in research. My sponsor also regularly attends these seminars and is available for me to discuss ethical questions regarding research at any time. Thus, I have received and will continue to receive excellent training on ethical integrity in research as a student at UNC.

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 the basic behavioral neuroscience and neurobiology of alcohol use in animal models with the expertise I will obtain in human research and neuroimaging techniques in the course of my thesis work. I envision running a lab that uses a variety of experimental approaches to investigate the neurobiology of alcohol use at a level that is directly applicable to human disease treatment. This proposed research plan will enable me to gain experience in structural magnetic resonance imaging (MRI), functional MRI, and diffusion tensor imaging and provide me with valuable knowledge in these respective areas of neuroimaging. In addition, the proposed research will allow me to work with human subjects extensively and deal with the many unique challenges that accompany this type of research.

While pursuing my thesis research in the Boettiger lab, I plan to continue to mentor undergraduate student researchers and to improve my teaching and mentoring skills. My current undergraduate student has applied for a summer research fellowship through UNC's Office of Undergraduate Research and will be learning about the experiments I am conducting in addition to conducting her own project under my guidance. In addition to mentoring undergraduate students, I plan to gain some experience in teaching while at UNC. There are many opportunities for teaching experience in both the Biology and Psychology departments that are open to graduate students. Additionally, to further my career goals, I will make use of the Center for Faculty Excellence (CFE) at UNC, which offers workshops focused on developing skills that will make graduate students more effective future teachers. The Future Faculty Fellowship Program offered through the CFE prepares graduate students for their first experience as independent instructors and helps them understand the roles and responsibilities they will have as faculty members in higher education. This program is an example of the skills I hope to obtain through the offerings of the CFE at UNC.

As a student in the Curriculum in Neurobiology, I will have many opportunities to present my research and improve my scientific communication skills. The Curriculum sponsors a Tuesday Miniseries that features student presentations in addition to an annual research day where students in the Curriculum present posters focused on their current research. Also, the Behavioral Neuroscience program in the Department of Psychology holds weekly seminars and invites students to present their findings. I am currently preparing to present to this group in April and have plans to continue to share my research in this forum in years to come. Presenting to such diverse groups as cellular and molecular neurobiologists and clinical psychologists will help me to frame my research and findings in ways that are understandable to a broad range of scientists. Such experience in presenting and explaining my research in a broad and general manner will prove useful in preparing journal articles and grants, essential skills for an independent investigator.

In addition to these offerings at UNC, I plan to attend annual meetings of the Research Society on Alcoholism (RSA), Society for Neuroscience, and Cognitive Neuroscience Society (CNS) to present my research and network with other scientists engaged in similar research areas who can offer insight and advice regarding my research projects. I am fortunate to have training grant support from NIDA through the Behavioral Neuroscience program to fund my travel to the CNS and RSA meetings this year to present posters on my current work. I hope that presenting my work at these meetings will allow me to meet faculty members at other institutions who may have an interest in offering me a postdoctoral fellowship opportunity and later a faculty position in the future. Additionally, such faculty members may be interested in forming research collaborations that could be useful in strengthening my current thesis project, perhaps by using animal models to investigate the neurobiology of immediate reward bias in a more invasive manner than is possible in human research.

I think the emphasis on scientific presentations in the Curriculum in Neurobiology, offerings for teaching experience at UNC, and commitment of my sponsor and the university to send me to annual research meetings to present my research and network with other scientists will allow me to reach my goal of becoming an independent principal investigator at a leading research university. In addition, the experience I will receive in neuroimaging data collection and analysis to complete the proposed research will allow me use this powerful technique to understand the neurobiology of decision-making in humans suffering from alcohol use disorders. I will also be able to bring these newly-acquired skills with me as I undertake a postdoctoral fellowship and later set up my own research laboratory as a principal investigator.

Activities Planned Under This Award

Year	Research	Course Work	Teaching	Clinical
First	80%	20%		
Second	90%	10%		
Third	90%		10%	
Fourth	100%			

Briefly explain activities other than research and relate them to the proposed research training.

While I will have completed all of my course requirements for the Curriculum in Neurobiology, during the period of this fellowship, I plan to take a short course or workshop in neuroimaging techniques to gain expertise in MRI data collection and analysis. In addition, I plan to take graduate level biostatistics courses offered through the UNC School of Public Health to increase my knowledge of proper data analysis approaches. In addition, both the Behavioral Neuroscience Program and the Bowles Center for Alcohol Studies at UNC have well-established training programs in place that focus on addiction, and I will take part in course and seminar offerings from both to broaden my knowledge in the area of addiction. I also plan to serve as a teaching assistant in either the Department of Biology or Psychology at UNC to gain some teaching experience before receiving my PhD. All of these experiences should aid me in obtaining the proper training to achieve my goal of becoming an academic research scientist.

Doctoral Dissertation and Other Research Experience

My research experience began in a basic behavioral neuroscience lab at Furman University during the summer before my senior year of college, as part of a requirement for receiving a bachelor's degree in neuroscience. 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 and how levels of these transmitters are altered by acute alcohol (EtOH) administration. Second, I used behavioral tests to analyze behavioral despair (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. As part of receiving funding for this summer research project from the South Carolina NIH-IDeA Networks of Biomedical Research Excellence (INBRE), I was required 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. To continue focusing on understanding the neurobiology of alcohol addiction, I applied for and eventually enrolled in graduate school at the University of North Carolina at Chapel Hill.

My research at the University of North Carolina at Chapel Hill began with rotations in a variety of labs affiliated with the Curriculum in Neurobiology beginning in June 2008 and ending in May 2009. During my first rotation, in Mark Wightman's lab in the Department of Chemistry at UNC, I worked with a post doctoral fellow using fast-scan cyclic voltammetry to investigate changes in dopamine in the nucleus accumbens of rats in response to natural rewards. My experiences in the Wightman lab included performing surgeries to insert the guide for the recording electrode, stimulating electrode, and reference electrode used in the voltammetry procedure, learning the program TarHeel CV used to stimulate and record the electrical signature of dopamine in the rat brain, and conditioning the rats to press for sugar pellets in the operant conditioning chamber used in the later parts of the study. My experience in the Wightman lab was instructive in that I learned about a technique to measure dopamine levels that can complement *in vivo* microdialysis by providing greater temporal resolution.

My second rotation was in the lab of Clyde Hodge in the Departments of Psychiatry and Pharmacology at UNC. Here, I studied the relationship between depression and EtOH in mice through behavioral and immunohistochemical techniques in an effort to understand the cell signaling pathways altered in response to acute i.p. injections of EtOH. While in the Hodge lab, I used an automated Forced Swim Test apparatus from BIOobserve to measure depressant-like behaviors in control mice given i.p. EtOH injections and performed immunohistochemistry on brain tissue from these mice to look for increases in active protein kinases and their downstream targets following EtOH administration. My work in the Hodge lab complimented and extended the behavioral neuroscience work I had done in the Grisel lab at Furman and provided me an example of how behavioral neuroscience research can be coupled with techniques used to investigate cell signaling to try to understand the cellular mechanisms associated with behavior and EtOH's effect on these mechanisms and behavior.

During my third rotation in Charlotte Boettiger's lab in the Department of Psychology at UNC, I studied the effect of dopamine on prefrontal cortex function in a decision-making task by taking advantage of state-related changes in dopamine via estrogen fluctuations in the female menstrual cycle. I also investigated how variations in the catechol-O-methyltransferase (COMT) gene affected performance on a decision making task employed in the lab. While rotating in the Boettiger lab, I learned firsthand about issues important in human research such as Institutional Review Board approval and subject confidentiality. I also became familiar with the programs utilized in the lab to create our experiments (E-Prime) and compile and summarize our data (MatLab). Working in the Boettiger lab showed me the potential of human behavioral neuroscience research and how neuroimaging techniques coupled with behavioral tasks can be used to investigate the neurobiology underlying behaviors (such as immediate reward bias) known to be abnormal in alcohol abusers. Since my academic background at Furman was heavily focused on psychology and biology, I found the type of research taking place in the Boettiger lab to successfully combine these two areas that I had enjoyed learning about. Her lab seemed like the perfect fit for me to conduct my thesis research.

My fourth and final rotation occurred in Patricia Maness's lab in the Department of Biochemistry at UNC. While in the Maness lab, I investigated the role of the L1 cell adhesion molecule and Eph/ephrin signaling in early axonal targeting. I performed growth cone collapse assays using EphrinA-EphA growth cone retraction signaling to see if cortical neurons from L1 null mice collapsed similarly to the cortical neurons of wild-type mice. Additionally, I sought to identify the binding site on L1 for the EphA4 receptor using co-immunoprecipitation experiments. This experience was useful in that it exposed me to cellular and molecular biology techniques with which I was unfamiliar and gave me the knowledge to better understand this type of research when I encounter it in the scientific literature.

Since joining the Boettiger lab in May 2009, I have been continuing to investigate the neurobiological basis of immediate reward bias/impulsive decision making and have had two first-author abstracts accepted to national meetings focused on work I have done during my first full year in the lab. In addition to investigating the role of dopamine on prefrontal cortex function and performance on our delayed-discounting decision making task, I have begun investigating the effect of age and frontal cortical development on our decision making task – the subject of this NRSA research proposal. I plan to investigate structural differences between the frontal cortical areas of late adolescents (ages 18-21) and adults (ages 22-40). In addition, I will be looking at functional differences between how late adolescents and adults' brains function as they complete our decision making task. Finally, I hope to further investigate the role of alcohol on performance on impulsive decision making, which our lab has already begun to study, and how it may interact with frontal development and age to lead to alcohol abuse and dependence. I feel this line of research combines my initial undergraduate interest in psychology, biology, and behavioral neuroscience research while allowing me to learn powerful neuroimaging techniques that will be invaluable to me as I move forward in my academic career. I see myself eventually having my own research lab dedicated to using neuroimaging techniques to study the neurobiology of addiction in humans while possibly conducting complementary, invasive studies in rodents to further delineate the neurobiology of addiction. I hope that my work can eventually lead to a better understanding of the neurobiology of addiction and lead to new and better treatments for individuals suffering from alcohol use disorders.