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SUMMARY STATEMENT
(Privileged Communication)

Release Date: 06/30/2010

Application Number: 1 F31 AA020132-01

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Review Group: AA-4
Neuroscience Review Subcommittee

Meeting Date: 06/07/2010
Council: OCT 2010
Requested Start:

PCC: AN J

Project Title: Now versus Later Decision-Making: Effects of Frontal Development and Alcohol Use

Requested: 4 years 1 month

Sponsor: Boettiger Cooney, Charlotte A
Department: Psychology
Organization: UNIVERSITY OF NORTH CAROLINA CHAPEL HILL
City, State: CHAPEL HILL NORTH CAROLINA

SRG Action: ++
Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

++NOTE TO APPLICANT: As part of the initial peer review of scientific merit, members of the Scientific Review Group (SRG) were asked to identify those applications with the highest scientific merit, generally the top half of applications that they customarily review. Reviewers' comments, scores for individual review criteria (if applicable), and preliminary overall impact/priority scores were submitted prior to the SRG meeting. At the meeting, the more meritorious applications were discussed and given a final impact/priority score. All other applications, including this application, were not discussed and did not receive an overall impact/priority score. The reviewers' comments (largely unedited by NIH staff) and criterion scores (if applicable) for this application are provided below.

1F31AA020132-01 Smith, Christopher

DESCRIPTION (provided by applicant): 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.

PUBLIC HEALTH RELEVANCE: 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.

CRITIQUE 1:

Fellowship Applicant: 3

Sponsors, Collaborators, and Consultants: 3

Research Training Plan: 6

Training Potential: 4

Institutional Environment & Commitment to Training: 3

Overall Impact/Merit:

Strengths

- This 4-year F31 application proposes functional, structural, and diffusion MRI acquisition in 80 individuals (n=40 age 18-21 and n=40 age 22-40; 16 from each group with high AUDIT scores suggesting heavy drinking), with a focus on now versus later decision making.
- The proposed work has public health relevance as it may provide information on when in early adulthood a shift in present-focused versus future-focused decision-making occurs, and the degree to which frontal maturation can explain this.

Weaknesses

- The ultimate clinical application of this line of research toward preventing or treating alcohol-related problems is not discussed.
- There are concerns with regard to the underspecified training, hypotheses, and data collection of the structural and diffusion imaging data.

1. Fellowship Applicant

Strengths

- The applicant is Mr. Christopher Smith, a 2nd year graduate student in psychology (emphasis in neurobiology) at the University of North Carolina at Chapel Hill, in the lab of Dr. Charlotte Boettiger.
- Reference letters are provided by Drs. Linda Dykstra, Judith Grisel, and Clyde Hodge, which describe him as an “outstanding student,” “bright,” and “genuinely driven.” His application was supported enthusiastically.
- His prior training was in cell and molecular biology and mouse models of depression and anxiety. He now expresses a strong interest in alcohol research and human decision-making.
- He has already presented 5 posters.

Weaknesses

- He does not yet have a publication, although just received his B.S. in 2008.

2. Sponsors, Collaborators, and Consultants:

Strengths

- The Sponsor is Dr. Charlotte Boettiger, Assistant Professor at UNC-Chapel Hill in the Bowles Center for Alcohol Studies, and an expert in fMRI studies of delayed discounting, impulsivity, and decision-making with applications to addiction. She leads several pilot projects, and is PI on a junior faculty development award on Neuropharmacology of Immediate Reward Bias. It is not clear what funding is available to support the proposed imaging sessions.
- While Dr. Boettiger is a relatively new faculty person without a track record yet in mentorship, she also mentors two postdoctoral fellows.
- The Sponsor’s letter details a comprehensive training plan that will provide the applicant with tools for conducting fMRI studies, as well as for presenting results, ethical conduct of research, mentoring undergraduates, and exposure to clinical features of alcohol use disorders.
- Although Dr. Boettiger is the only named Sponsor and primary mentor, other individuals in his graduate training program at the Bowles Center will be involved in his training (including Drs. Crews, Dykstra, Garbutt, Lin, Belger, Carelli, and Zhu) to ensure training in imaging, AUD, statistics, and data presentation.

Weaknesses

- One concern is that Dr. Boettiger is relatively junior, and the application could potentially benefit from a named co-sponsor to ensure that all training needs are addressed, such as Dr. Lin, to solidify the sMRI and DTI training for the applicant.

3. Research Training Plan:

Strengths

- The research plan contains 3 aims. Aim 1 compares OFC activation to now versus later decision-making between adults (ages 22-40) and late adolescents (ages 18-21) using fMRI. This aim has a clear hypothesis, uses a well-characterized task developed by the Sponsor, and is adequately powered with 24 subjects per group.
- Aim 3 relates directly to alcohol involvement, and will compare imaging data in an age group (late adolescent versus adult) x gender x alcohol use group (moderate versus heavy) ANOVA.

Weaknesses

- The goal of Aim 1 is to isolate immature activation patterns, which are presumed to be linked to risk for AUD. This linkage is not always the case as per recent work of Galvan and Casey.
- Aim 2 is very general, proposing that OFC and DPFC will show immature gray and white matter between age groups. The specific variables and regions are not indicated, and the analytic approach is discussed in a vague manner. The data acquisition parameters are not stated, which adds concern for confidence that the applicant will receive adequate direction and training in the structural MRI and DTI aspects of this application.
- Aim 3 is also rather general, proposing differences between heavy drinking and low drinking adults on brain structure and function.
- The specific analysis of the time series data is not apparent, and the distinctions between behavioral and BOLD response data are not always clear in the application.

4. Training Potential:

Strengths

- The applicant has excellent letters of support.
- Potential is excellent for training in fMRI and neural basis of decision-making and future orientation in the lab of Dr. Boettiger.
- Potential is also very good for the applicant to receive exposure to assessment of alcohol use and related constructs and to understanding the neural features linked to addiction through involvement in the Bowles Center for Alcohol Studies.

Weaknesses

- That the applicant will receive sufficient training in structural and diffusion image analysis and neuroanatomy is less clear from the proposed training plan.

5. Institutional Environment & Commitment to Training:

Strengths

- The imaging facilities are excellent, and it appears that the applicant will have access to the one of the two research-dedicated scanners (Allegra and/or Trio).
- The Bowles Center for Alcohol Studies is an outstanding resource for a trainee aspiring to a career in alcohol research.

Weaknesses

- It is less clear how the costs of the imaging sessions will be covered.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Appropriate safety precautions are taken for MRI, and verbal consent will be obtained before screening interviews are conducted.

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Subjects as young as 18 will be included.
- Efforts will be taken to ensure that 50% of participants are female, and that the ethnic composition is representative of the Chapel Hill area.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Responsible Conduct of Research:

Acceptable

- The applicant has completed a core course on this topic, and has additional specialty courses planned.

Budget and Period of Support:

Recommend as Requested

Recommended budget modifications or possible overlap identified:

- 4 years of support are requested.

CRITIQUE 2:

Fellowship Applicant: 2

Sponsors, Collaborators, and Consultants: 3

Research Training Plan: 3

Training Potential: 5

Institutional Environment & Commitment to Training: 1

Overall Impact/Merit:

Strengths

- A highly motivated applicant with a strong behavioral neuroscience background who wishes to transit from animal to human neuroscience alcohol research.
- The sponsor is somewhat junior, but is uniquely positioned to provide the needed training in fMRI and immediate reward bias.
- Senior collaborators and researchers in the larger environment are supportive and will provide additionally needed training in MRI and DTI.
- The use of multiple neuroimaging techniques to assess both functional brain response, integrity of brain structure, and connectivity increase the significance and potential impact of the proposed research on immediate reward bias.

Weaknesses

- Lack of clear rationale for grouping subjects 16-21 versus 22-40 given evidence for continued frontal development beyond 21.
- Lack of consideration of a potential area of innovation by integrating the data from multi-imaging methodologies to explore the interrelation of functional, structural, and connectivity properties of the brain in relation to immediate response bias.
- Lack of formal coursework in the training plan to gain further expertise in human maturation and brain development.

1. Fellowship Applicant

Strengths

- Referee letters from the applicant's current and undergraduate research mentors and professors highlight the candidate's dedication to an independent research career, strong critical thinking skills, ability to communicate clearly in writing, and strong work ethic. The candidate was described as a self-starter, energetic, tenacious, and committed to a research career in an academic environment.
- The applicant received a 2008 undergraduate degree with honors in Neuroscience from Furman University, where he was involved in research on β -endorphin, stress, anxiety and alcohol in transgenic mice. The candidate's undergraduate training provides a strong behavioral neuroscience foundation in alcohol research with animals. This is a particularly useful background for his transition to human neuroscience research in the alcohol field.

Weaknesses

- Although this reviewer is not familiar with the grading system at the University of North Carolina (UNC), the candidate had a mixture of Pass and High Pass grades in his graduate work to date. This potential concern was somewhat offset by the apparently large course load he carried during his first year.

2. Sponsors, Collaborators, and Consultants:

Strengths

- The sponsor has substantial expertise in the neurocognitive task and functional imaging methods to be employed by the candidate in his proposed research. She has close collaborative ties with the directors and investigators of the Bowles Alcohol Research Center and the Biomedical Research Imaging Center (BRIC), which will increase their investment in the

candidate's alcohol-related and neuroimaging research training. The quality of her published fMRI research in delay discounting is outstanding.

- The sponsor has sufficient start-up and other research funds to support the candidate's proposed neuroimaging
- Areas of training needed by the candidate that are outside the sponsor's primary areas of imaging expertise (e.g., structural MRI and DTI) will be accomplished via collaborative training and expertise at the BRIC in state-of-the-art MRI and DTI, as confirmed by Dr. Lin, Associate Director of the BRIC in her referee letter.

Weaknesses

- The sponsor is a relatively early career alcohol researcher who has yet to receive substantial independent extramural support, although an R01 has been submitted.
- The sponsor is junior and thus does not have an established track record of mentoring. This concern is largely mitigated by the highly supportive environment of senior researchers, her laboratory environment which includes 2 post-doctoral level trainees, and the thoughtful training plan presented in this application.

3. Research Training Plan:

Strengths

- The candidate completed a preliminary study with the sponsor that demonstrated feasibility of recruitment, competency in the behavioral decision making task, and support for his thesis hypothesis of age-graded differences in immediate reward bias.
- Careful and appropriate screening procedures to rule out potential confounds (although see note at the end of this review regarding where this information should be in the application).
- Plans to use multiple neuroimaging techniques to assess both functional brain response, integrity of brain structure, and connectivity.
- Plans to examine differences between moderate and heavy drinkers, and consideration of alternative ways to define groups based on alcohol consumption histories.

Weaknesses

- Given evidence for continued frontal cortex development in the early to mid-twenties, it was not entirely clear why the age groups comprise 18-21 year olds versus 22-40 year olds.
- There was no attention to the interrelation of brain structure, function, and connectivity in contributing to reward bias, although the data could provide a unique contribution to this question.
- Subsection 3b of the research strategy, Innovation, appeared to be missing.
- Not clear if nondrinkers (Audit < 7) would be included in the moderate alcohol use group, or what the lower level of consumption would be.

4. Training Potential:

Strengths

- The candidate has begun the transition to human neuroscience research and made excellent progress thus far in the sponsor's laboratory. The proposed training will build on the skills he gained in the past year in the delay discounting task, and in the use of E-prime software to design the computer task and collect behavioral data, as demonstrated by the preliminary data presented in the application.

- The candidate has no prior training in functional or structural neuroimaging, so the proposed training will result in his learning many new techniques; the 4 year training plan will provide ample time for him to develop expertise in this area.
- Several referees and the sponsor commented on the candidate's ability to quickly learn and implement new technical skills suggesting that his potential for training in the methods of human neuroimaging is well-conceived and feasible.
- The training proposed in this application is well-aligned with the candidate's future career goals to conduct independent human neuroscience research in alcohol studies.

Weaknesses

- In the timeline, no manuscript preparation was included from the 4th quarter of Year 1 through the 2nd quarter of Year 3. This is an area where the sponsor could have suggested ways for the applicant to consider alternative publication opportunities during the time he is collecting thesis data.
- Lack of formal coursework in the training plan to gain further expertise in human maturation, brain development or other related topics.

5. Institutional Environment & Commitment to Training:

Strengths

- Dr. Lin, Professor and Vice Chair of Basic Research, Radiology and Associate Director, Biomedical Research Imaging Center, confirmed that the BRIC will provide collaborative training and expertise in acquisition and analysis of MRI and DTI data .
- Additional research training opportunities in alcohol, neuroscience, and the responsible conduct of research are provided by the faculty and activities of the Bowles Center for Alcohol Studies, the Developmental Neuroimaging Core of the UNC Medical School, the Behavioral Neuroscience Program and the Department of Psychology.

Weaknesses

- None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

- Appropriate safeguards are in place to exclude individuals who may be at heightened risk from the neuroimaging procedures and to ensure confidentiality of data.

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

Not Applicable (No Clinical Trials)

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

- Men and women will be recruited in approximately equal proportions.
- Ethnic minorities are anticipated to be include in proportion to their representation in the population of Chapel Hill and Durham, NC: 11-42% African-American, 3-12.5% Hispanic, 4.5-7% Asian American, and less than 1% (each) Native American and Pacific Islander.

- Children under the age of 18 will not be included due to developmental immaturity of the brain regions recruited by the cognitive task that will be administered.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals)

Biohazards:

Not Applicable (No Biohazards)

Responsible Conduct of Research:

Acceptable

- The candidate has completed a year-long formal course in research ethics during his first year of graduate school. He is certified by the UNC Institutional Review Board to conduct research with human subjects. Ongoing formal and hands-on training in the responsible conduct of research is planned throughout the course of the award.

Budget and Period of Support:

Recommend as Requested

Additional Comments to Applicant (Optional):

- A brief description of inclusion and exclusion criteria and subject characteristics should be included in the body of the research strategy, rather than "see Humans Subjects."

CRITIQUE 3:

Fellowship Applicant: 4

Sponsors, Collaborators, and Consultants: 5

Research Training Plan: 2

Training Potential: 1

Institutional Environment & Commitment to Training: 1

Overall Impact/Merit:

Strengths

- Overall this is an applicant and sponsor who show promise with work in a very exciting area of research.

Weaknesses

- I think there is a lot of potential here but it is just not clear if the team and ideas are fully ready for funding at this time.
- I found the research to be somewhat overly ambitious and hard to follow at times which reduced my enthusiasm.

1. Fellowship Applicant

Strengths

- The applicant has a string training background.
- His interests fit well with the current plans.

Weaknesses

- Although strong in training, the applicant's current research productivity is modest.

2. Sponsors, Collaborators, and Consultants:

Strengths

- The sponsor shows some promise as a junior investigator in an area that fits well with the applicant's interests.

Weaknesses

- Although noted by the applicant, the junior status of the PI is a weakness. Currently there is little external funding.
- Although there are other local researchers who are noted as collaborative mentors, and there are opportunities for the applicant to be involved in group settings, some attention to individual meetings would be useful to ensure full access to these supplemental mentors.

3. Research Training Plan:

Strengths

- Clearly the applicant and sponsor have considered a range of experiences and have identified reasonably well explicated plans for those experiences.

Weaknesses

- Some attention to what experiences are possible as a result of funding and not already available would be useful.

4. Training Potential:

Strengths

- The applicant has a strong background for the current work and the potential seems high.

Weaknesses

- none

5. Institutional Environment & Commitment to Training:

Strengths

- This is a strong institution with multiple resources that should provide support.

Weaknesses

- none

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections

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

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

Vertebrate Animals:

Not applicable

Biohazards:

Not applicable

Responsible Conduct of Research:

Acceptable

Budget and Period of Support:

Recommend as Requested

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

MEETING ROSTER

Neuroscience Review Subcommittee National Institute on Alcohol Abuse and Alcoholism Initial Review Group NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM

AA-4 1

June 07, 2010 - June 08, 2010

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

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

NOTIFICATION OF SCIENTIFIC REVIEW ACTION

Release Date: 06/30/2010

Smith, Christopher Thomas
The University of North Carolina at Chapel Hill
Department of Psychology
Davie Hall, CB 3270
Chapel Hill, NC 27599-3270

Our Reference: 1 F31 AA020132-01 AA-4

The scientific merit review of your application is complete. As part of the initial review, reviewers were asked to provide written evaluations of each application and to identify those with the highest scientific merit. These are, customarily, applications that rank in the top half of applications under review. Only these applications are discussed at the meeting and assigned priority scores. Not discussed applications are routinely neither considered at a second level by a national advisory council or board nor considered for funding.

Your application did not receive a score. Although it was not discussed at the meeting, it did receive full written reviews. It is important to note that the not discussing is not a rejection of your application and does not prevent future consideration of a resubmission.

All applicants are strongly advised to read the written critiques carefully to identify project strengths and weaknesses and to consult with the program official listed below to discuss options and to obtain advice. Your summary statement may be found in the Commons (<https://commons.era.nih.gov/commons/>).

PROGRAM CONTACT:

Dr. John Matochik
301-451-7319
jmatochi@mail.nih.gov

If you choose to resubmit, it is important to respond specifically to comments in the summary statement, as outlined in the instructions in the PHS 398 application kit (cf. <http://grants1.nih.gov/grants/funding/phs398/phs398.html> or <http://grant1.nih.gov/grants/funding/424/index.htm>).

Enclosure

cc: Business or institutional official of applicant organization

