	SUMMARY STATEMENT	
(Privileged Communication))

PROGRAM CONTACT: JONATHAN KING (301) 402-4156 kingjo@nia.nih.gov

Application Number: 1 K99 AG042596-01

Release Date: 04/13/2012

Principal Investigator

SAMANEZ LARKIN, GREGORY R PHD

Applicant Organization: VANDERBILT UNIVERSITY

Review Group: NIA-N Neuroscience of Aging Review Committee

Meeting Date: 03/0	1/2012	RFA/PA:	PA11-197
Council: MAY	/ 2012	PCC:	2BCOGJK
Requested Start: 07/0	1/2012		

Project Title: Neuromodulation of Motivated Cognition and Decision Making Across Adulthood

SRG Action:	Impact/Priority Score: 18				
Human Subjects:	30-Human subjects involved - Certified, no SRG concerns				
Animal Subjects:	10-No live vertebrate animals involved for competing appl.				
Gender:	1A-Both genders, scientifically acceptable				
Minority:	1A-Minorities and non-minorities, scientifically acceptable				
Children: 3A-No children included, scientifically acceptable					
	Clinical Research - not NIH-defined Phase III Trial				
Project	Direct Costs	Estimated			
Year	Requested	Total Cost			
1	79,736	80,871			
2	81,897	83,062			
3	249,000	252,544			
4	249,000	252,544			
5	249,000	252,544			
TOTAL	908,633	921,564			

ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

RESUME AND SUMMARY OF DISCUSSION: This application from Vanderbilt University is submitted on behalf of Gregory Samanez-Larkin, PhD, who is seeking 5 year support under the K99/R00 mechanism. The candidate obtained his Ph.D. degree from Stanford University and is presently a postdoctoral fellow at Vanderbilt. The proposed research is designed to develop theories for the role of the neurotransmitter dopamine (DA) for cognition and motivation with psychological theories of aging. In the K99 phase, the project will include behavioral and fMRI measures of inhibitory control as well as PET measures of receptor availability across the brain in a group of healthy adults. In the R00 phase, the candidate will use PET scans, behavioral tasks and fMRI to assess reward processing and inhibitory control across adulthood (ages 20-80).

This application and particularly this candidate were met with a high degree of enthusiasm by the review committee. The research and career development plans were seen to mesh well with the candidate's interests and background and thus represents an excellent mechanism by which the candidate can develop into an independent investigator. Reviewers noted the outstanding environment in which this training and research will take place. One reviewer felt that it would have been helpful if the candidate had discussed and incorporated stronger bridges between imaging modalities in order for the proposed work to better leverage the "multimodal" approach. Additional attention to potentially confounding influences on blood-oxygen-level-dependent (BOLD) signal was sought. Two reviewers noted the lack of testable hypotheses presented in the comparison of temporal discounting (TD) and stop signal task (SST) imaging results. Concerns were expressed about the treatment of multiple comparisons related to the behavioral measures that are to be correlated with SST and particularly if such measures will be used to explore the imaging data. One reviewer sought greater justification and details regarding the use of advisors assembled for this career development plan, though another reviewer felt that the inclusion of advisors Drs. Jagust and D'Esposito was an added strength to this already impressive mentorship and advisory team. Overall, there was consensus that the application was an innovative and exciting approach to transition this promising candidate toward independence. Balancing the considerable strengths of the application against minor concerns, support was recommended at the requested budget level with outstanding enthusiasm.

TRAINING IN THE RESPONSIBLE CONDUCT OF RESEARCH: The plan for this training is described and is adequate.

DESCRIPTION (provided by applicant): The goal of this Pathway to Independence Award is to expand the base of knowledge, methodological expertise, and theoretical development skills of the candidate as he transitions from a post-doctoral trainee to an independent scientist focused on the decision neuroscience of aging. A wealth of behavioral research on the psychology of aging reveals change over the life span in both cognition and motivation. Many prominent theories of cognitive aging are centered on changes in neuromodulation, focusing specifically on the neurotransmitter dopamine (DA). However, DA is not only implicated in variability in cognitive function, but also plays an important role in motivation. Yet, the relation between age-related changes in DA functioning and motivational factors has received little study. The goal of the initial K99 mentored phase is to begin to examine interactions between motivation and cognition across adulthood, increase the candidate's base of knowledge of the dopamine system, gain experience with computational modeling, and expand the candidate's expertise with multiple imaging measures. To achieve these goals, the candidate will conduct a collaborative multimodal imaging project focused on clarifying the link between DA functioning and self-regulation (R21-DA033611). The project will include behavioral and fMRI measures of inhibitory control as well as PET measures of receptor availability across the brain in a group of healthy adults. All participants will complete two behavioral tasks that capture distinct aspects of motivated cognitive control and engage distinct, albeit overlapping neural networks. The candidate will begin to extend this line of work as well as his previous work on age differences in decision making into

a cross-sectional study of age differences in motivated cognition and decision making in this K99 phase. The proposed R00 project will examine relationships between motivated cognitive control and decision making across adulthood (ages 20-80). In addition to a PET scan, subjects will complete behavioral tasks while undergoing fMRI that assess reward processing and inhibitory control. Participants will also complete a full battery of cognitive and motivational individual difference measures, incentive-compatible behavioral economics tasks, as well as a subset of the Health and Retirement Study (HRS) survey. This project will also serve as a foundational study for the development of a longitudinal multi-modal imaging protocol. Together, the mentored and independent phases of this project will provide a framework toward developing a more integrative and comprehensive theory of human aging that incorporates neuroscientific theories of the role of DA function for cognition and motivation with psychological theories of aging. A long-term goal of the candidate's career is to develop a computationally-informed and neurobiologically-specific theory of motivated cognition across adult development and aging. Support through this mechanism will greatly increase the likelihood of the candidate's obtaining an R01 to support a longitudinal multimodal imaging study at an earlier career stage than otherwise possible.

PUBLIC HEALTH RELEVANCE: Relevance The proposal aims to characterize changes in motivation and cognition over the adult life span using behavioral and multimodal neuroimaging techniques. This work will form the basis of a translational research program on age-related change in reward processing and cognitive control, and has the potential to eventually facilitate identification of specific markers for suboptimal decision making in older adults and inform the design of appropriate interventions. The long-term goal of this line of research is to improve the financial and emotional health of older adults by improving decision making at the individual level.

CRITIQUE 1:

Candidate: 1 Career Development Plan/Career Goals Plan to Provide Mentoring: 2 Research Plan: 2 Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1 Environment, Commitment to the Candidate: 1

Overall Impact:

The candidate has assembled an impressive group of mentors and advisors to assist him in gaining expertise in multimodal imaging of the neural bases of decision making and how this changes with aging. The proposed work is innovative and ambitious; the candidate has demonstrated productivity and is in an outstanding environment for achieving the career development and research goals. The main concerns of this reviewer are whether the candidate will obtain sufficient expertise in neuropsychopharmacology and PET imaging through the informal training that he proposes and whether sufficient evidence has been presented to justify the selection of a post-synaptic and methodologically challenging tracer for testing the presented hypotheses. Other more minor concerns are presented below.

1. Candidate:

Strengths

• The candidate obtained his undergraduate degree in Psychology at the University of Michigan, Ann Arbor and his PhD in Psychology at Stanford under Drs. Laura Carstensen and Brian Knutson studying emotion and decision making in aging. This was followed by postdoctoral training at Vanderbilt with Dr. David Zald where he seeks to examine the dopaminergic influences upon emotion and decision making in aging.

- Candidate has been successful in securing funding for his graduate studies as well as his postdoctoral studies.
- Very strong letters of recommendation from leaders in the field.
- Seven first author, peer-reviewed publications. Several in high profile journals

Weaknesses

• None noted.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring: Strengths

- Candidate seeks to add expertise in PET imaging of dopamine receptor availability to supplement his existing expertise in functional imaging and cognitive neuroscience of decision-making in the elderly.
- Career goals are to apply multimodal imaging approaches to the study of decision making in the elderly, which is a relatively unique niche well suited to the candidate.
- Career development activities include mentorship training in PET imaging radioligand development, QC, and kinetic modeling, as well as PET image processing.
- Includes mentorship in novel psychophysical task development and modeling.
- Plan includes approach to gain experience in research professionalism and instruction of junior researchers.

Weaknesses

• Coursework is missing except for audited classes. Learning would benefit from enrollment in classes, and formal didactics might assist the candidate in achieving some of the development goals in PET imaging, radiochemistry, and neuropsychopharmacology, as it seems unlikely that informal instruction in these complex topics will achieve a deep level of understanding.

3. Research Plan:

Strengths

 Highly innovative line of work with appropriate rooting in prior studies. Candidate will first examine in younger adults the behavioral correlates of inhibitory control abilities as measured by the rewarded stop signal task, followed by examination of the neural correlates using fMRI and fallypride PET imaging. This will then be extended to older adults as the candidate transitions to the R00 portion of the grant and begins to test the hypothesis that frontal cortical dopaminergic circuits will be more affected by aging than motivational circuits in ventral striatum, amygdala, and midbrain.

Weaknesses

- Behavioral measures to be correlated with SST seem numerous. Steps should be taken to identify primary measures a priori versus exploratory measures to avoid loss of power due to multiple comparisons, and means for correcting for multiple comparisons should be specified.
- The hypothesis that spatially overlapping and distinct patterns of correlations will be seen in imaging for SST and TD is fairly vague and not really a testable hypothesis.
- Greater discussion about the meaning of increased fallypride binding should be provided for each scenario and hypothesis, given that fallypride binding can be confusing. Fallypride is measuring receptor availability and these receptors might be upregulated when dopamine is low and fallypride might be displaced when dopamine is high (suggesting that low fallypride signal suggests elevated dopamine), but low fallypride binding could alternatively suggest poor dopaminergic transmission, since it perhaps reflects a low concentration of receptors with which to transmit signal.

• The length of scan time (3.5 hours) for fallypride is an additional (and possibly expensive) challenge, especially when expecting to scan a very large number of older adults in the R00 phase. The specifics of how one would add dopamine transporter imaging should be included and the relative advantages of each should be presented, since it is not clear why a postsynaptic measure of dopamine is the preferred approach here.

4. Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Outstanding group of mentors to cover the aspects of fMRI in the aging, cognitive task design, and PET imaging.
- Dr. McArdle can provide specific mentorship in addressing the complex statistical issues.

Weaknesses

• None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Enthusiastic support of the candidate and commitment to protect 100% of his time for the K99 grant activities.
- Outstanding imaging center and availability of radiotracer.

Weaknesses

• None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections.

• Adequate.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable. M1A - Minority and Non-minority, Acceptable. C3A - No Children Included, Acceptable.

• Adequate inclusion.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals).

Biohazards:

Not Applicable (No Biohazards).

Training in the Responsible Conduct of Research:

Acceptable.

Comments on Format:

• Appropriate.

Comments on Subject Matter:

• Adequate.

- Comments on Faculty Participation:
 - Adequate.

Comments on Duration:

- Adequate.
- Comments on Frequency:
 - Adequate.

Select Agents:

Not Applicable (No Select Agents).

Resource Sharing Plans:

Not Applicable (No Relevant Resources).

Budget and Period of Support:

Recommend as Requested.

CRITIQUE 2:

Candidate: 1 Career Development Plan/Career Goals/Plan to Provide Mentoring: 1 Research Plan: 2 Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1 Environment, Commitment to the Candidate: 1

Overall Impact:

This Pathway to Independence (K99) application is designed to allow the candidate to transition to an independent career in the neurobiology of aging by focusing on the question on how motivation and cognition are mediated by age-related changes in the dopaminergic (DA) system. The candidate is an exceptionally strong applicant and the identified question is both interesting and important in further our understanding into mechanisms underlying cognitive aging. The general approach proposed is 'multi-modal' imaging—specifically combining PET imaging to map changes in the DA system with fMRI. The candidate, who already has a very strong background and track record in investigating decision making and DA across the life span, highlights that it is the learning and application of 'multi-imaging' that will be the focus on this application. In this regards, it was a bit disappointing that the candidate did not completely elaborate on the strengths and potential limitations of this combined multi-imaging approach. Nevertheless, this is a relatively minor concern about an otherwise extremely strong, well-written, and well-conceived application. The overall impact of this application is therefore very high.

1. Candidate:

Strengths

 The candidate is extremely strong, both in terms of background and accomplishments to date, and in terms of the position in his career trajectory which is perfectly suited for a K99 pathway to independence mechanism. His accomplishments to date are quite extensive, and include an impressive educational background, a publication track record that has already made the candidate a leader in the field of decision making across the life span (with a landmark paper in Nature Neuroscience that was based on his thesis work), and extremely enthusiastic mentor statements. All these factors engender high confidence that the candidate will be able to successfully use the K99 award to transition to independence.

Weaknesses

• None noted.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring: Strengths

• The career development plan nicely outlines how he will work closely with his mentors to learn task development, increase his general knowledge base, and learn equation modeling.

- The candidate nicely articulates his career goals and objective, and how they resonate with his prior accomplishments to date.
- Something quite unique to this application is the manner in which the candidate discusses how he himself will use his knowledge base to mentor graduate students.

Weaknesses

• None noted.

3. Research Plan:

Strengths

- The application has many strengths. In particular the proposed studies nicely build off of his previous accomplishments in investigating reward processing across the life span and current on using PET to investigate the DA system.
- The proposed studies are, generally, well-conceived, in which the first two specific aims will focus on young subjects to clarify: The relationship between inhibitory control abilities as measured with the rewarded stop signal task (SST) and self-report and behavioral measures of motivation and cognition (specific aim 1); and, to characterize the relationship between PET measurements of the DA system and fMRI. With these established, he will them apply the behavioral and neuroimaging tools to investigate an older population of subjects.
- The statistical analyses is sophisticated and appropriate for the questions he is asking
- The preliminary data supports the feasibility of the studies, and suggests he will be able to complete the studies as proposed.

Weaknesses

- One weakness, although relatively minor, is the meager discussion about the utility and potential pitfalls of combining PET and fMRI. This weakness is particularly notable because the candidate highlights this feature as unique to this application and to his career development goals.
- For example, the candidate states, "We hypothesize that both spatially overlapping and distinct patterns of correlations will arise in the PET and fMRI data for the SST and TD measures". Why is this hypothesized? In fact, this does really seem like a hypothesis, but simply a generic statement that PET and fMRI measure different things. Why should they been the same? If different, what does this really mean? This sort of question is not fully discussed, and gives the sense that multi-modal imaging is being performed simply because they can; not, because they will contribute meaningfully to way in which we better understand the questions posed.
- It is not clear how the fMRI findings are going to clarify any question above and beyond what his well validated cognitive tasks have already established (as a measure of frontal lobe function).
- There is a sense that the candidate himself is not completely convinced of the utility of fMRI. For example, he states, "It is important to acknowledge that the BOLD signal here, even in highly localized regions like the ventral striatum, is not a pure measure of DA firing. There are potential contributions to the BOLD signal from other neurotransmitters". Indeed, there is still debate in the field over what exactly the BOLD signal is measuring. It would have been helpful to include a broader discussion on this important topic
- Along the same lines of concern, the candidate does not include any discussion over the
 potential confounds of comparing the BOLD signal between young and old subjects. It is
 suggested that the candidate read the literature on this controversial topic. In particular, very
 elegant work by the lab of Dr. Richard Buxton and others, who clearly show that one differences
 in the BOLD signal are detected between populations (including young versus old) this
 difference might provide misleading information about underlying neural function.

4. Mentor(s), Consultant(s), Collaborator(s): Strengths

• The assembled mentors and consultants are all leaders in the fields of imaging, decision making, and computational analysis. All world class.

Weaknesses

• None noted.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- The environment at Vanderbilt is superb, particularly for the research tools and research questions that the candidate is asking.
- The institutional commitment, as articulated by his chairmen, is extremely strong.

Weaknesses

• None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable.M1A - Minority and Non-minority, Acceptable.C3A - No Children Included, Acceptable.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals).

Biohazards:

Acceptable.

Training in the Responsible Conduct of Research: Acceptable.

Select Agents:

Acceptable

Resource Sharing Plans: Acceptable.

Budget and Period of Support:

Recommend as Requested.

CRITIQUE 3:

Candidate: 1 Career Development Plan/Career Goals/Plan to Provide Mentoring: 1 Research Plan: 3 Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2 Environment, Commitment to the Candidate: 1

Overall Impact:

Dr. Samanez Larkin is a post-doctoral scientist at Vanderbilt University and the K99 application aims to characterize changes in motivation and cognition over the adult life span using behavioral and multimodal neuroimaging techniques. Dr. Samanez Larkin is an exceptionally strong young scientist and appears to be a perfect candidate for a K99 award. The career development plan is strong and the mentoring team, although somewhat large and unwieldy, is likely going to provide excellent mentorship for the candidate. The research plan is generally strong, although Aim 4 seems overly ambitious and perhaps not integral for the success of the candidate.

1. Candidate:

Strengths

- Dr. Samanez Larkin received his PhD from Stanford University in 2010 and he is currently a post-doctoral scientist at Vanderbilt University.
- Dr. Samanez Larkin has 18 publications, 8 as first author, and many of them in top tier, high impact journals.
- Dr. Samanez Larkin holds a F32 grant from NIA to support his post-doctoral studies.
- Overall, Dr. Samanez Larkin is an exceptional young scientist and an ideal candidate for a K99 award.

Weaknesses

• None noted.

2. Career Development Plan/Career Goals & Objectives/Plan to Provide Mentoring: Strengths

- The goal of the career development plan is to obtain training in PET data collection, modeling and analysis, as well as how to combine PET and fMRI data and gain further skills in cognitive/computational modeling.
- The career development goals will be achieved largely through didactic opportunities with members of his mentoring team. Dr. Samanez Larkin also indicates that he will audit several statistics courses that are offered in the very strong Quantitative Psychology program at Vanderbilt.

Weaknesses

• Generally, the career development plans are very strong. However, the extent that the K99 award allows for the development of teaching skills may be problematic.

3. Research Plan:

Strengths

• The research plan consists of four aims across the K99 and R00 phases of the award. Aims 1 and 2 are developmental and will include younger adults. Aims 3 and 4 will include both younger and older adults, using tasks developed in the initial phase of the award.

• Aims 1-3 are generally very strong and follow nicely from the candidate's previous research.

Weaknesses

• Study 4 is not very well developed or described. It appears to be too large for the R00 portion and it may best to leave this to an R01 that the candidate would apply for at a later date. The use of this data as potential for a longitudinal study is not well motivated. The inclusion of the middle-aged group is nice, but probably too much for an initial application like this one.

4. Mentor(s), Consultant(s), Collaborator(s):

Strengths

• Dr. Zald will serve as primary mentor for Dr. Samanez Larkin and he is an outstanding choice for this role. Dr. Zald is currently Dr. Samanez Larkin's post-doctoral mentor and he is an accomplished scientist.

• In addition to Dr. Zald, the mentoring team includes two additional co-mentors and seven consultants, all of whom are exceptionally strong scientists.

Weaknesses

• The size of the mentoring team may pose problems for the successful use of all members. For the investigators who will have direct contact with Dr. Samanez Larkin, the benefits are clear. However, the ability of the consultants to benefit the program of research appears to be somewhat weak.

5. Environment and Institutional Commitment to the Candidate: Strengths

• The environment at Vanderbilt University is excellent and the institution is clearly committed to his success.

Weaknesses

• None noted.

Protections for Human Subjects:

Acceptable Risks and/or Adequate Protections.

• No concerns were identified.

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable.

- M1A Minority and Non-minority, Acceptable.
- C3A No Children Included, Acceptable.
 - The candidate has distributed participants across several racial/ethnic categories. The extent to which the imaging outcomes are affected by persons who are not native English speakers is unclear.

Vertebrate Animals:

Not Applicable (No Vertebrate Animals).

Biohazards:

Acceptable.

• No concerns were identified.

Training in the Responsible Conduct of Research:

Acceptable.

Comments on Format:

• No concerns were identified. Comments on Subject Matter:

- No concerns were identified. Comments on Faculty Participation:
- No concerns were identified.
- Comments on Duration (Required):
- No concerns were identified.
- Comments on Frequency (Required):
 - No concerns were identified.

Select Agents:

Not Applicable (No Select Agents).

Resource Sharing Plans:

Acceptable.

• No concerns were identified.

Budget and Period of Support:

Recommend as Requested.

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE: During the K99 phase 160 participants will be recruited and screened for these studies with the aim of running 36 participants through the PET and 3T fMRI scanning protocol, 24 through a 3T fMRI scanning protocol, and 100 participants through a behavioral protocol only. During the R00 phase 108 participants will be recruited and screened for this study with the aim of running all participants through a behavioral, PET, and 3T fMRI protocol. The details regarding safety, maintenance of confidentiality, and risks associated with the scans are well detailed.

INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE: For the K99 phase, the candidate anticipates enrolling equal numbers of males and females into this study. For the R00 phase, given the unknown location of the candidate's future tenure-track employment the balance of gender may be slightly different.

INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE: There are no inclusion or exclusion criteria related to race or ethnicity. Minorities are encouraged to participate. For reasons that are not entirely clear no Hispanic participants have completed PET scans in the Zald Lab, and few Hispanic/Latino subjects were screened for prior studies. The reason for this is unclear, as over half of the participants come from the Vanderbilt student community, of which 5% are Hispanic or Latino. While the candidate will not specifically attempt to target Hispanic-Latino participants (or any other minority) during recruitment, given any situations where there are participants who qualify for the study, he will give scheduling preference to individuals of a Hispanic or Latino background. African Americans have made up approximately, 9% of the recent study population, and Asian Americans 11%, which is consistent of the demographics of the Vanderbilt and immediately surrounding communities. For the R00 phase, given the unknown location of the candidate's future tenure-track employment the balance of ethnicity may be slightly different.

INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE: The proposed studies focus on individual differences among adults, adult development, and aging. Additionally, children are specifically excluded from the PET studies based on regulations prohibiting unnecessary radiation exposure in children.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-10-080 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-10-080.html.

The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Neuroscience of Aging Review Committee National Institute on Aging Initial Review Group NATIONAL INSTITUTE ON AGING NIA-N March 01, 2012 - March 02, 2012

CHAIRPERSON

ASTHANA, SANJAY, MD PROFESSOR DEPARTMENT OF GERIATRICS & GERONTOLOGY UNIVERSITY OF WISCONSIN SCHOOL OF MEDICINE MADISON, WI 53705

MEMBERS

APOSTOLOVA, LIANA G., MD * ASSOCIATE PROFESSOR DEPARTMENT OF NEUROLOGY MARY S. EASTON CENTER FOR ALZHEIMER'S DISEASE RESEARCH UNIVERSITY OF CALIFORNIA, LOS ANGELES LOS ANGELES, CA 90095

BARTON, BRUCE A., PHD * SENIOR STATISTICIAN DEPARTMENT OF QUANTITATIVE HEALTH SCIENCES UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL SHREWSBURY, MA 01545

BELL, KAREN L., MD * DIRECTOR, ADRC EDUCATION CORE DIRECTOR, ALZHEIMER'S DISEASE CLINICAL TRIALS COLUMBIA UNIVERSITY MEDICAL CENTER TAUB INSTITUTE FOR RESEARCH ON ALZHEIMERS DISEASE NEW YORK, NY 10032

BICKFORD, PAULA C., PHD PROFESSOR DEPARTMENT OF NEUROSURGERY UNIVERSITY OF SOUTH FLORIDA TAMPA. FL 33612

BIMONTE-NELSON, HEATHER A., PHD ASSOCIATE PROFESSOR, HONORS DISCIPLINARY FACULTY PROGRAM DIRECTOR, BEHAVIORAL NEUROSCIENCE DEPARTMENT OF PSYCHOLOGY BEHAVIORAL NEUROSCIENCE DIVISION ARIZONA STATE UNIVERSITY TEMPE, AZ 85287

BREITNER, JOHN , MD * DIRECTOR, CENTRE FOR STUDIES ON PREVENTION OF ALZHEIMER'S DISEASE CANADA RESEARCH CHAIR IN PREVENTION OF DEMENTIA DEPARTMENT OF PSYCHIATRY MCGILL UNIVERSITY MONTREAL, QUEBEC, CANADA BREWER, JAMES B., MD, PHD ASSOCIATE PROFESSOR DEPARTMENTS OF RADIOLOGY AND NEUROSCIENCES UNIVERSITY OF CALIFORNIA, SAN DIEGO SAN DIEGO, CA 92093

BROOKS, WILLIAM M., PHD * PROFESSOR DEPARTMENT OF NEUROLOGY HOGLUND BRAIN IMAGING CENTER UNIVERSITY OF KANSAS MEDICAL CENTER KANSAS CITY, KS 66160

DIAZ-ARRASTIA, RAMON , MD, PHD * PROFESSOR OF NEUROLOGY CENTER FOR NEUROSCIENCE AND REGENERATIVE MEDICINE UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENC ROCKVILLE, MD 20852

FOSTER, NORMAN L., MD PROFESSOR DEPARTMENT OF NEUROLOGY CENTER FOR ALZHEIMER'S CARE, IMAGING AND RESEARCH UNIVERSITY OF UTAH SALT LAKE CITY. UT 84108

JEFFERSON, ANGELA L., PHD ASSOCIATE PROFESSOR DEPARTMENT OF NEUROLOGY VANDERBILT UNIVERSITY MEDICAL CENTER NASHVILLE, TN 37232

LAKOSKI, JOAN M., PHD * PROFESSOR DEPARTMENT OF PHARMACOLOGY AND CHEMICAL BIOLOGY SCHOOL OF MEDICINE UNIVERSITY OF PITTSBURGH PITTSBURGH, PA 15261

LEE, GLORIA , PHD ASSOCIATE PROFESSOR DEPARTMENT OF INTERNAL MEDICINE UNIVERSITY OF IOWA COLLEGE OF MEDICINE IOWA CITY, IA 52242

MONTINE, THOMAS J., MD, PHD PROFESSOR AND DIRECTOR DEPARTMENT OF PATHOLOGY UNIVERSITY OF WASHINGTON SEATTLE, WA 98104 MURRELL, JILL R., PHD ASSOCIATE PROFESSOR DEPARTMENT OF PATHOLOGY & LABORATORY MEDICINE INDIANA UNIVERSITY SCHOOL OF MEDICINE INDIANAPOLIS, IN 46202

OBISESAN, THOMAS O., MD * DEPARTMENT OF MEDICINE HOWARD UNIVERSITY HOSPITAL WASHINGTON, DC 20060

PARRISH, TODD B., PHD * ASSOCIATE PROFESSOR DEPARTMENT OF RADIOLOGY NORTHWESTERN UNIVERSITY CHICAGO, IL 60611

PATTERSON, DAVID , PHD * PROFESSOR DEPARTMENT OF BIOLOGICAL SCIENCES UNIVERSITY OF DENVER DENVER, CO 80262

SCHNEIDER, JULIE A., MD ASSOCIATE PROFESSOR DEPARTMENT OF PATHOLOGY RUSH ALZHEIMER'S DISEASE CENTER RUSH UNIVERSITY MEDICAL CENTER ARMOUR ACADEMIC CENTER CHICAGO, IL 60612

SILVERMAN, JEREMY M., PHD * PROFESSOR MOUNT SINAI SCHOOL OF MEDICINE DEPARTMENT OF PSYCHIATRY FAMILY STUDIES RESEARCH CENTER NEW YORK, NY 10029

SIMPKINS, JAMES W., PHD PROFESSOR AND CHAIR DEPARTMENT OF PHARMACOLOGY & NEUROSCIENCE UNIVERSITY OF NORTH TEXAS HEALTH SCIENCE CENTER FORT WORTH, TX 76107

SMALL, BRENT J., PHD * PROFESSOR SCHOOL OF AGING STUDIES UNIVERSITY OF SOUTH FLORIDA TAMPA, FL 33620

SMALL, SCOTT A., MD PROFESSOR DEPARTMENT OF NEUROLOGY COLUMBIA UNIVERSITY COLLEGE OF PHYSICIANS AND SURGEONS NEW YORK, NY 10032

SONG, HONGJUN , PHD * ASSOCIATE PROFESSOR DEPARTMENT OF NEUROLOGY THE INSTITUTE FOR CELL ENGINEERING JOHNS HOPKINS UNVERSITY BALTIMORE, MD 21205 WILHELMSEN, KIRK C., MD, PHD PROFESSOR DEPARTMENT OF GENETICS & NEUROLOGY UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL CHAPEL HILL, NC 27517

YAFFE, KRISTINE , MD PROFESSOR DEPARTMENT OF PSYCHIATRY, NEUROLOGY AND EPIDEMIOLOGY UNIVERSITY OF CALIFORNIA, SAN FRANCISCO SAN FRANCISCO, CA 94121

ZANDI, PETER P., PHD * ASSISTANT PROFESSOR DEPARTMENT OF MENTAL HEALTH JOHNS HOPKINS UNIVERSITY BLOOMBERG SCHOOL OF PUBLIC HEALTH BALTIMORE, MD 21205

SCIENTIFIC REVIEW ADMINISTRATOR

CRUCE, WILLIAM, PHD SCIENTIFIC REVIEW BRANCH NATIONAL INSTITUTE ON AGING NATIONAL INSTITUTES OF HEALTH BETHESDA, MD 20814

GRANTS TECHNICAL ASSISTANT

ALFARO, DIANA SCIENTIFIC REVIEW BRANCH NATIONAL INSTITUTE ON AGING NATIONAL INSTITUTES OF HEALTH BETHESDA, MD 20892

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