Form Approved Through 10/31/08 OMB No. 0925-0002

Department of Health and Human Services
Public Health Service

Ruth L. Kirschstein National Research Service Award
Individual Fellowship Application

Follow instructions carefully.
Do not exceed character length restrictions indicated.

LEAVE BLANK—For PHS use only.

Type	Activity	Number
Review Group		Formerly
Meeting Dates		Date Received

1. TITLE OF RESEARCH TRAINING PROPOSAL (Do not exceed 81 characters, including spaces and punctuation.)
Incentive learning and decision making in the aging brain

2. LEVEL OF FELLOWSHIP
Predoctoral

3. RESPONSE TO SPECIFIC REQUEST FOR APPLICATIONS OR PROGRAM ANNOUNCEMENT ☐ NO ☒ YES
(If "Yes," state number and title)
Number: PA-07-002 Title: Individual Predoctoral Kirschstein - NRSA Fellowship F31

4a. NAME OF APPLICANT (Last, First, Middle)
Samanez Larkin, Gregory, Russell

4b. ERA COMMONS USER NAME
SAMANEZLARKIN.GREG

4c. HIGHEST DEGREE(S)
BA | MA

4d. PRESENT MAILING ADDRESS *(Street, City, State, Zip Code)*
PO Box 19779
Stanford, CA 94309

4e. PERMANENT MAILING ADDRESS *(Street, City, State, Zip Code)*
PO Box 19779
Stanford, CA 94309

4f. E-MAIL ADDRESS: glarkin@stanford.edu

TELEPHONES AND FAX *(Area code, number and extension)*

4g. OFFICE	4h. HOME	4i. PERMANENT	4j. FAX NUMBER
650-799-5715	650-799-5715	650-799-5715	650-725-5688

4k. ☒ U.S. CITIZEN OR U.S. NONCITIZEN NATIONAL or ☐ PERMANENT RESIDENT OF U.S.

5. TRAINING UNDER PROPOSED AWARD (See Fields of Training)
Discipline No.: 3720 Subcategory Name: Psychology of Aging

6. PRIOR AND/OR CURRENT NRSA SUPPORT *(Individual or Institutional)*
☒ NO ☐ YES *(If "Yes," refer to item 24, Form Page 5)*

7a. DATES OF PROPOSED AWARD		7b. PROPOSED AWARD DURATION	8. DEGREE SOUGHT DURING PROPOSED AWARD	
From *(MM/DD/YY)*:	Through *(MM/DD/YY)*:	*(in months)*	Degree:	Expected Completion Date:
07/01/08	07/01/10	24	PhD	07/01/10

9. HUMAN SUBJECTS RESEARCH ☐ No ☒ Yes ☐ Indefinite
9b. Human Subjects Assurance No. FWA00000935
9c. Clinical Trial ☒ No ☐ Yes
9d. NIH-defined Phase III Clinical Trial ☒ No ☐ Yes
9a. Research Exempt ☒ No ☐ Yes
If "Yes," Exemption No.

10. VERTEBRATE ANIMALS ☒ No ☐ Yes
10a. If "Yes," IACUC approval Date
10b. Animal Welfare Assurance No.

11. NAME OF SPONSOR (Last, First, Middle Initial)
Knutson, Brian, D

12. SPONSORING INSTITUTION
Name Stanford University
Address Jordan Hall, Bldg 420
450 Serra Mall
Stanford, CA 94305-2130

13a. ENTITY IDENTIFICATION NO.
1941156365A1

13b. DUNS NO.
009214214

14. OFFICIAL SIGNING FOR SPONSORING INSTITUTION
Name Mary Morrison
Title Director, Funds Management
Address Financial Aid Office
355 Galvez Street
Stanford, CA 94305-3021
Tel: 650-725-0876 Fax: 650-725-0540
E-Mail: morrison@stanford.edu

15. APPLICANT CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete, and accurate to the best of my knowledge, and I agree to comply with the terms and conditions of award if an award is issued as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I certify that I have read the Ruth L. Kirschstein National Research Service Award Assurance, that I will abide by the Assurance if an award is made, and that the award will not support residency training.

SIGNATURE OF APPLICANT NAMED IN 4a. *(In ink. "Per" signature not acceptable.)*	DATE

16. SPONSOR AND SPONSORING INSTITUTION CERTIFICATION AND ACCEPTANCE: We, the undersigned, certify that the statements herein are true, complete, and accurate to the best of our knowledge. If this application results in an award, appropriate training, adequate facilities, and supervision will be provided, and we accept the obligation to comply with the Public Health Service terms and conditions of award. We are aware that any false, fictitious, or fraudulent statement or claim may subject us to criminal, civil, or administrative penalties.

SIGNATURE OF SPONSOR NAMED IN 11. (In ink. "Per" signature not acceptable.)	DATE	SIGNATURE OF OFFICIAL NAMED IN 14. (In ink. "Per" signature not acceptable.)	DATE

Kirschstein–NRSA Individual Fellowship Application *(To be completed by applicant – follow PHS 416-1 instructions)*	NAME OF APPLICANT *(Last, first, middle initial)* Samanez Larkin, Gregory, Russell

SPONSOR and Co-Sponsor Information

17. SPONSOR	18. Co-SPONSOR *(When applicable)*
17a. NAME AND DEGREE(S) Brian Knutson, PhD	NAME AND DEGREE(S)
17b. ERA COMMONS USER NAME KNUTSON.BRIAN	ERA COMMONS USER NAME
17c. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT Psychology & Neuroscience	
17d. MAJOR SUBDIVISION Humanities & Sciences	
17e. Address: Jordan Hall, Building 420 450 Serra Mall Stanford, CA 94305-2130 Telephone: 650-724-2965 Fax: 650-725-5688 E-Mail: knutson@stanford.edu	Address: Telephone: Fax: E-Mail:

RESEARCH PROPOSAL

19. DESCRIPTION: See instructions. State the application's broad, long-term objectives and specific aims, making reference to the health relatedness of the project (i.e., relevance to the **mission of the agency**). Describe concisely the research design and methods for achieving these goals. Describe the rationale and techniques you will use to pursue these goals.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to **public** health. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED THE SPACE PROVIDED.**

As the proportion of older adults continues to grow at an unprecedented rate, aging adults may be required to make increasingly more independent health-related and financial decisions. Thus, it is increasingly imperative to better understand the impact of age-related changes in both cognitive and affective processing on decision-making. Both behavioral and neural evidence suggests that younger and older adults differ in the processing of monetary incentives (e.g., older adults show attenuated anticipation of monetary losses), which could have specific consequences for financial decisions (e.g., older adults may be generally less sensitive to the warning signs of potential negative outcomes). Although these affective preferences may be healthy and adaptive for regulating emotional experience and optimizing well-being, they may have harmful effects on financial learning and decision making. The main objective of the proposed research is to examine age differences in incentive learning and incentive-based decision-making using both behavioral measures of performance and functional magnetic resonance imaging. The specific aims of this proposal are to (1) investigate the influence of reinforcement valence on incentive processing across the life span, (2) examine whether older adults show the same valence asymmetry in more cognitively demanding reversal learning, and (3) examine whether older adults differ from younger adults both in rational risky decision-making and risk preference in a more applied investment decision paradigm.

Findings from this line of basic research may have implications for scientists' understanding of how processes underlying decision-making change with age, and might eventually also facilitate identification of markers for suboptimal decisions in older adults. 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.

20. GOALS FOR KIRSCHSTEIN–NRSA FELLOWSHIP TRAINING AND CAREER

A Kirschstein-NRSA Fellowship from the NIH will support and greatly supplement my graduate training on the path to becoming a psychological scientist. My long-term goal is to have a productive career as a researcher and educator in the field of aging.

The proposed project will further solidify my current understanding of age-related changes in motivation and cognition, while also extending my expertise to reinforcement learning and economic decision-making. In the presence of such a rich community of experienced and ambitious investigators here at Stanford University, the drive for translational research programs will foster the development of creative experimental skills that will one day have great impact on the health of aging adults. I have been inspired by Stanford's translational spirit and have made a personal commitment to conduct sound, well-controlled, basic research that has the potential to make a direct societal impact throughout my career.

(see continuation page)

21. ACTIVITIES PLANNED UNDER THIS AWARD: Approximate percentage of proposed award time in activities identified below. *(See instructions.)*

Year	Research	Course Work	Teaching	Clinical
First	70%	0%	30%	0%
Second	100%	0%	0%	0%
Third				
PREDOCTORAL FELLOWSHIPS ONLY				
Fourth				
Fifth				
MD/PhD FELLOWSHIPS ONLY				
Sixth				

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

While completing the proposed research training, I will serve as a graduate teaching assistant for courses on longevity and statistics. In addition, I will attend weekly seminars with peers and faculty in which the latest research and strategies for improving the field will be discussed. I will also attend and present ongoing research at annual conferences in order to stay current and receive extramural feedback.

22. TRAINING SITE(S) (organization, city, state)

Stanford University, Stanford, California

23. HUMAN EMBRYONIC STEM CELLS ☒ No ☐ Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: http://stemcells.nih.gov/registry/index.asp. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line

20. GOALS FOR KIRSCHSTEIN-NRSA FELLOWSHIP TRAINING AND CAREER (continued)

I am driven by one primary underlying goal – to ease the cognitive strain and improve the emotional and economic health in the daily lives of older adults. I am deeply committed to this pursuit and confident that I can be successful. The level of basic research that I am pursuing at Stanford University and as a trainee of the Kirschstein-NRSA Fellowship has innumerable applications to the everyday challenges of older adults. Over the course of graduate training, as I hone my research skills, I hope to build a solid foundation from which to begin a meaningful career in the psychology of aging.

Kirschstein–NRSA Individual Fellowship Application

Table of Contents

NAME OF APPLICANT *(Last, first, middle initial)*

Samanez Larkin, Gregory, Russell

	Page Numbers *(Number pages consecutively at the bottom throughout the application. Do not use suffixes such as 6a, 6b.)*
Section 1 — Applicant	
Face Page	1
Sponsor's Contact Information, Description (Form Page 2)	2
Training & Career Goals, Activities Planned Under This Award, Training Site, Human Embryonic Stem Cells (Form Page 3)	3
Table of Contents (Form Page 4)	5
Biographical Sketch – Applicant/Fellow (*Not to exceed four pages***)**	6
Previous Research Experience (Form Page 5)	10
Research Training Plan	
Introduction to Revised Application (*not to exceed 1 page*)	12
A. Specific Aims	13
B. Background/Significance *(Not to exceed 10 pages)*	13
C. Preliminary Studies/Progress Report	15
D. Research Design and Methods	17
E. Human Subjects *(Required if Item 9 on the Face Page is marked "Yes")*	22
Protection of Human Subjects (Required if Item 9 on the Face Page is marked "Yes")	22
Data and Safety Monitoring Plan (Required if Item 9 on the Face Page is marked "Yes" ***and*** a Phase I, II, or III clinical trial is proposed	n/a
Inclusion of Women and Minorities (Required if Item 9 on the Face Page is marked "Yes" and is Clinical Research)	23
Targeted/Planned Enrollment Table (for new and continuing clinical research studies)	24
Inclusion of Children (Required if Item 9 on the Face Page is marked "Yes")	23
F. Vertebrate Animals *(Required if Item 10 on the Face Page is marked "Yes")*	25
G. Literature Cited	25
H. Resource Sharing	27
I. Respective Contributions	27
J. Selection of Sponsor and Institution	27
K. Responsible Conduct of Research	28
Section 2 — Sponsor's/Co-Sponsor's Information	
Biographical Sketch--Sponsor	29
Research Support Available	33
Previous Trainees	33
Training Plan, Environment, Research Facilities	33
Number of Fellows/Trainees to be Supervised	36
Applicant's Qualifications and Potential	36
Checklist (Completed by Fellow/Applicant & Sponsoring Institution)	38

Section 3 — References *(Minimum of 3)*

(See instructions for submission of references.)

List full name, institution, and department of individuals submitting reference letters.

(1) Laura L. Carstensen, PhD, Stanford University, Psychology; (2) Ian H. Gotlib, PhD, Stanford University, Psychology; (3) Joseph Mikels, PhD, Cornell University, Human Development

Other Items *(list):*

Personal Data Page for Fellowship Applicants

Section 4 — Appendix

(5 collated sets. No *page numbering necessary. Not to exceed 3 publications; 2 for predoctoral candidates.)*

☒ Check if Appendix is included

APPLICANT/FELLOW BIOGRAPHICAL SKETCH

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

NAME OF APPLICANT/FELLOW	POSITION TITLE
Gregory R Samanez Larkin	Graduate Student (PhD)
eRA COMMONS USER NAME SAMANEZLARKIN.GREG	

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
University of Michigan	BA	04/2002	Psychology
Stanford University	MA	01/2008	Psychology
Stanford University	PhD	In progress	Psychology

A. Positions

ACTIVITY/OCCUPATION	BEGINNING DATE (mm/yy)	ENDING DATE (mm/yy)	FIELD	INSTITUTION/COMPANY	SUPERVISOR/ EMPLOYER
Lab Manager / RA	06/02	09/05	Psychology	Stanford University	Laura Carstensen

Academic and Professional Honors

Branstrom Prize for Freshman Scholars (top 10% of class), University of Michigan, 1999
Psi Chi Psychology Honors Society, 2001
University Honors, University of Michigan, 2002
W.B. Pillsbury Award (for most distinguished undergraduate thesis in psychology as a natural science), University of Michigan, 2002
NSF Graduate Research Fellowship, Honorable Mention, 2006
Summer School in Neuroeconomics Fellowship, Stanford University, 2006
Top Ten Scientific Advances of 2007, National Institute on Aging (for: Samanez-Larkin, et al., 2007)

Grants

Co-Investigator, Risk-Taking and Decision-Making Over the Life Span
Center on Advancing Decision Making for Aging Seed Grant ($40,000) 2005-2007

Co-Investigator, Ambiguity Aversion in Younger and Older Adults
Center on Advancing Decision Making for Aging Seed Grant ($40,000) 2006-2008

Co-Investigator, Incentive Learning and Decision-Making in Younger and Older Adults
Center on the Demography and Economics of Health and Aging Seed Grant ($40,000) 2007-2009

Memberships in Professional Societies

Gerontological Society of America
Society for Neuroscience
Cognitive Neuroscience Society
Association for Psychological Science

B. Publications

Fredrickson, B., Tugade, M., Waugh, C. & **Larkin, G.R.** (2003) What good are positive emotions in crises?: A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. Journal of Personality and Social Psychology, 84, 365-376.

Mikels, J.A., Fredrickson, B.L., **Larkin, G.R.**, Lindberg, C.M., Maglio, S.J. & Reuter-Lorenz, P.A. (2005). Emotional category data on images from the International Affective Picture System. Behavior Research Methods, 37(4), 626-630.

Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A. & Carstensen, L.L. (2005) Divergent trajectories in the aging mind: Changes in working memory for affective versus visual information with age. Psychology & Aging, 20(4), 542-553.

Samanez-Larkin, G.R., Gibbs, S.E.B., Khanna, K., Nielsen, L., Carstensen, L.L., & Knutson, B. (2007) Anticipation of monetary gain but not loss in healthy older adults. Nature Neuroscience, 10(6), 787-791.

Samanez-Larkin, G.R., Hollon, N.G., Carstensen, L.L., & Knutson, B. (2008) Individual differences in insular sensitivity during loss anticipation predict avoidance learning. Psychological Science, 4(19), 320-323.

Samanez-Larkin, G.R., Mikels, J.A., Robertson, E.R., Carstensen, L.L., & Gotlib, I.H. (in preparation) Selective attention to emotion in healthy older adults.

Samanez-Larkin, G.R. & D'Esposito, M. (in preparation) Imaging the aging brain.

Samanez-Larkin, G.R. & Carstensen, L.L. (invited; in preparation) Emotion and motivation in the aging brain. In J. Decety and J. Cacioppo (Eds.) Handbook of Social Neuroscience, Oxford University Press, NY.

Chaired conference symposia:

Larkin, G.R., Mikels, J.A., & Carstensen, L.L. (2006, November) The Affective Neuroscience of Aging. Symposium at the annual meeting of the Gerontological Society of America, Dallas, TX.

Samanez-Larkin, G.R., Sims, T., & Peters, E. (2007, November) The Influence of Age-related Changes in Emotion and Cognition on Decision Making. Symposium at the annual meeting of the Gerontological Society of America, San Francisco, CA.

Conference talks:

Fredrickson, B., Tugade, M., Waugh, C. & **Larkin, G.** (2002, October). What good are positive emotions in crises?: A prospective study of resilience and emotions following the terrorist attacks on the United States on September 11th, 2001. Paper in S. Goodwin (Chair) "Social, Political, and Emotional Reactions to the September 11th Attacks" Symposium at the annual meeting of the Society for Experimental Social Psychology, Columbus, OH.

Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A., & Carstensen, L.L. (2004, November). Divergent trajectories in the aging mind: Cognitive decline relative to affective preservation in working memory. Paper presented at the Annual Scientific Meeting of the Gerontological Society of America, Washington, D.C.

Kwon, Y., **Larkin, G.R.**, Tsai, J.L., & Carstensen, L.L. (2006, November). Memory for emotional pictures among Korean younger and older adults. Paper in H. Fung & D. Isaacowitz (Chairs) "Socioemotional Selectivity Across Cultures" Symposium at the annual meeting of the Gerontological Society of America, Dallas, TX.

Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A., & Carstensen, L.L. (2006, November) Age differences in affective working memory: Prefrontal contributions to the positivity effect in older adults. Paper in G. Larkin, J.

Mikels, & L. Carstensen (Chairs) "The Affective Neuroscience of Aging" Symposium at the annual meeting of the Gerontological Society of America, Dallas, TX.

Larkin, G.R., Gibbs, S., Khanna, K., Carstensen, L.L., & Knutson, B. (2006, November) Incentive processing in the aging brain: Neural responsiveness to anticipated gain and loss. Paper in G. Larkin, J. Mikels, & L. Carstensen (Chairs) "The Affective Neuroscience of Aging" Symposium at the annual meeting of the Gerontological Society of America, Dallas, TX.

Samanez-Larkin, G.R., Yoo, D., & Knutson, B. (2007, November) Incentive-based decision-making in older adults. Paper in G. Samanez-Larkin, T. Sims, & E. Peters (Chairs) "The Influence of Age-related Changes in Emotion and Cognition on Decision Making" Symposium at the annual meeting of the Gerontological Society of America, San Francisco, CA.

Conference posters:

Larkin, G.R., Mikels, J.A., Lindberg, C., Fredrickson, B.L., & Reuter-Lorenz, P.A. (2002, November). Finding categories in dimensions: Behavioral and psychophysiological insights for an integrative account of emotional structure. Poster presented at the NYAS Emotions Inside Out: 130 Years After Darwin's The Expression of the Emotions in Man and Animals conference, New York City, NY.

Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A., & Carstensen, L.L. (2004, July). Preservation of online emotional processing capacity in the aging mind. Poster presented at the annual APA Convention, Honolulu, HI.

Nielsen, H.L., Knutson, B., **Larkin, G.R.**, Carstensen, L.L. (2005, September). Affect dynamics: Tracking trajectories through affective space. Poster presented at the annual Society for Neuroeconomics conference, Kiawah Island, SC.

Mikels, J.A., **Larkin, G.R.**, Reuter-Lorenz, P.A., & Carstensen, L.L. (2006, April) Age differences in affective working memory: Prefrontal contributions to the positivity effect in older adults. Poster presented at the annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.

Larkin, G.R., Gibbs, S.E.B., Nielsen, L., Khanna, K., Carstensen, L.L., & Knutson, B. (2006, April). Neural responsiveness to anticipated gain and loss in younger and older adults. Poster presented at the annual meeting of the Cognitive Neuroscience Society, San Francisco, CA.

Larkin, G.R., Khanna, K., Kuhnen, C., & Knutson, B. (2006, April). Risk taking and financial decision making in younger and older adults. Poster presented at the biennial Cognitive Aging Conference, Atlanta, GA.

Gibbs, S.E.B., **Larkin, G.R.**, Khanna, K., Wimmer, G.E., Carstensen, L.L., & Knutson, B. (2006, June) Neural responsiveness to incentives in younger and older adults. Poster presented at the annual meeting of the Organization for Human Brain Mapping, Florence, Italy.

Larkin, G.R., Robertson, E.R., Mikels, J.A., Maglio, S.J., Carstensen, L.L., & Gotlib, I.H. (2006, November) Selective attention to emotional stimuli in younger and older adults. Poster presented at the annual meeting of the Gerontological Society of America, Dallas, TX.

Samanez-Larkin, G.R., Carstensen, L.L., & Knutson, B. (2007, March) Deactivation of frontal and striatal regions in response to incentive outcomes in younger and older adults. Poster presented at the NYAS Affect to Action conference, New York, NY.

Samanez-Larkin, G.R., Hollon, N.G., Carstensen, L.L., & Knutson, B. (2007, November) Individual differences in insular sensitivity during loss anticipation predict avoidance learning. Poster presented at the annual meeting of the Society for Neuroscience, San Diego, CA.

C. Scholastic Performance

SCIENCE			OTHER		
YEAR	COURSE TITLE	GRADE	YEAR	COURSE TITLE	GRADE
	UNIVERSITY OF MICHIGAN			UNIVERSITY OF MICHIGAN	
1999	Biology	B	1998	Philosophical Problems	A+
1999	Bio Anthropology: Race and Ethnicity	B	1998	Elementary Spanish	A
2000	Cognitive Psychology	B-	1998	English Composition	A
2001	Human Neuropsychology	A	1998	Precalculus	A
2001	Topics in Biopsychology: Emotion	A+	1999	Principles of Economics II	B+
			1999	College Writing	B+
			1999	Short Stories	A-
			1999	Calculus	B
			1999	Philosophy of Literature and Film	A
			1999	Introductory Psychology	A
			1999	Psychopathology	B+
			2000	Developmental Psychology	B
			2000	Sociological Issues	B-
			2000	Visual Art	A-
			2000	Art & Design: Metals	A-
			2000	Organizational Psychology	A-
			2001	Advanced Lab in Organizational Psyc	A
			2001	Intensive 2nd Year Spanish	A
			2001	Community Outreach	A
			2001	Peer Advising	A
			2001	Clinical Psychology	B
			2001	Advanced Psychological Research	A
			2002	Creative Writing	B+
			2002	20th Century Art History	A
			2002	Senior Honors Research	A
	STANFORD UNIVERSITY			STANFORD UNIVERSITY	
2006	Cognitive Neuroscience	A+	2005	Computational Neuroimaging	B+
2006	Math Tools for Neuroscience	A	2005	Statistical Methods for Social Science	A
2006	Undertnding Techniques in Neurosci	S	2006	Developmental Psychology	B+
2006	Neuroecon and Neural Basis of DM	CR	2006	Social Psychology	B+
2007	Affective Neuroscience	A-	2007	Statistical Theory, Models & Methodol	A+
2008	Reinforcement Learning in the Brain	CR	2007	Foundations of Cognition	A
			2007	Personality & Psychopathology	B

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

GRE Scores (08/2003) Analytical 5.0 Quantitative 650 Verbal 500

Kirschstein–NRSA Individual Fellowship Application

Previous Research Experience

(To be completed by applicant – follow PHS 416-1 instructions.)

NAME OF APPLICANT (Last, first, middle initial)

Samanez Larkin, Gregory, Russell

24. PRIOR AND CURRENT KIRSCHSTEIN–NRSA SUPPORT. List type (individual and/or institutional), level (predoctoral or postdoctoral), dates, and grant or award numbers.

n/a

25. APPLICATION(S) FOR CONCURRENT SUPPORT

☒ NO ☐ YES Using format below, list all support (training, research, supplies, travel, etc.) applied for that would run concurrently with the period covered by this application. Include the type, dates, source, and amount.

Type:	Dates:
Source:	Amount:
Type:	Dates:
Source:	Amount:
Type:	Dates:
Source:	Amount:

26a. TITLE(S) OF THESIS/DISSERTATION(S) (Predoctoral and Senior Fellowships omit this section.)

n/a

26b. NAME OF DISSERTATION ADVISOR OR CHIEF OF SERVICE (*If reference report not included, explain why not.*)	TITLE, DEPARTMENT, AND INSTITUTION
n/a	n/a

27. DOCTORAL DISSERTATION AND OTHER RESEARCH EXPERIENCE
(See Instructions -- particularly Predoctoral and Senior Fellowships should follow special instructions for this section. Use continuation pages. Do not exceed two pages.)

2001–2002 Undergraduate Research Assistant
Cognitive and Affective Neuropsychology Lab, University of Michigan (PI: Patricia Reuter-Lorenz)
Affective working memory
Served as a research assistant to a graduate student examining the influence of emotional processing on working memory maintenance. Responsibilities included designing experiments, collecting data, analyzing data, and reporting findings in lab meetings.

2001–2002 Undergraduate Laboratory Manager / Research Assistant
Positive Emotions and Psychophysiology Lab, University of Michigan (PI: Barbara Fredrickson)
Psychophysiological resilience and regulation of emotional experience
Collected psychophysiological data during recovery from laboratory stressors and mood inductions and then followed up participants after the NYC terrorist attack in 2001. The study found that individuals higher in physiological resilience at baseline prior to the attacks recovered more quickly and showed higher levels of positive emotion after the attacks.

(see continuation page)

27. DOCTORAL DISSERTATION AND OTHER RESEARCH EXPERIENCE (continued)

2002 Undergraduate Honors Thesis
University of Michigan (Advisors: Barbara Fredrickson, Patricia Reuter-Lorenz)
Psychophysiological correlates of affective maintenance
Independently conducted psychophysiological study of emotional maintenance of discrete affective stimuli. Found specificity and overlap of physiological profiles for categorical emotions. Served as primary investigator from study design to manuscript preparation.

2002–2005 Post-Baccalaureate Laboratory Manager / Research Assistant
Life-span Development Lab, Stanford University (PI: Laura Carstensen)
Emotional experience across the life span
Served as primary research coordinator for several studies of emotional experience, attention, and memory across the life span. Innovated neuroimaging analysis tools for the lab. Also served as research mentor for several undergraduate students over the course of three years.

2005– Graduate Student
Life-span Development Lab, Stanford University (PI: Laura Carstensen)
Emotional experience and regulation in the aging brain
Currently serving as the lead researcher on a neuroimaging component of a longitudinal study of individual differences in emotional processing across the life span - a collaborative project with Mara Mather at the University of Southern California Davis School of Gerontology. The study seeks to identify why some adults lead satisfying and healthy emotional lives in late adulthood, whereas others do not.

2005– Graduate Student
Symbiotic Project on Affective Neuroscience, Stanford University (PI: Brian Knutson)
Incentive processing in the aging brain
Currently leading several behavioral and neuroimaging projects on incentive processing and aging. Responsibilities include task design, creating imaging protocols, collecting and analyzing fMRI data, manuscript preparation, and supervising undergraduates in the lab. Initial studies have revealed that simple striatal-dependent incentive processing is intact in healthy older adults.

2007– Graduate Student
Decision Neuroscience Lab, Stanford University (PI: Samuel McClure)
Modeling reinforcement learning in old age
Current project attempts to characterize discrete components of age differences in incentive-based learning tasks using computational modeling. Preliminary analyses reveal that older adults have a higher learning rate than younger adults suggesting that they integrate over a shorter history (i.e. more influenced by most recent outcomes).

2007– Collaborator
Cognitive and Affective Neuroscience Lab, Cornell University (PI: Joseph Mikels)
Framing effects across the life span
Current project seeks to examine the influence of age-related changes in motivation on economic framing effects (i.e. risk seeking when facing losses; risk aversion when facing gains). Preliminary analyses suggest that older adults do not differ from younger adults in risk aversion in the gain frame, but do not show as much risk seeking in the loss frame.

2007– Collaborator
Palo Alto Veteran Affairs Medical Center (PI: Allyson Rosen)
Reward processing and learning in head injured patients
Current pilot project seeks to characterize impairments in reward processing and general decision making in patients with head injuries.

Introduction to Revised Application

This proposal is a revision of a previously submitted application (1 F31 AG032804-01). The reviewers of the previous version pointed out several weaknesses and generously offered a number of suggestions for improvement. The following issues have been addressed in this revision:

Funding
The reviewers pointed out that all listed funding would expire in 2009. The proposal now also includes Laura Carstensen's R01 as a funding source to extend funding through the completion of the applicant's degree. Carstensen is a collaborator on all of the proposed projects. Her R01 has in the past jointly funded the trainee's research projects and will continue to provide supplementary funding through the completion of the proposed studies.

Monetary Stakes in Experimental Tasks
Reviewer 1 questioned whether the relatively small rewards and punishments in the experimental tasks ($0.50, $1.00, $5.00) were sufficient to engage both young and old participants. Although we have observed differences in both behavioral and neural responses to the anticipation of these relatively small punishments, we have observed similar self-reported negativity and neural reactivity to $5.00 loss outcomes in both younger and older adults (Samanez-Larkin, et al. 2007; Nielsen, Knutson, & Carstensen, in press). Thus, although the stakes are relatively small, it appears that adults of all ages scale both the rewards and punishments within these experimental tasks. Further, it would not be possible to greatly increase the magnitude of these rewards and have the tasks remain incentive compatible (a standard that must be met for any of the findings to be considered economically realistic).

Learning Differences
Reviewer 2 pointed out an inconsistency between the caption in Figure 2 and the accompanying text. The inconsistency has been corrected in the revised application. The behavioral differences in the pilot study were not significant, but suggestive of an age difference. These suggestive pilot results are what motivated the design of proposed studies 1 and 2. The goal of study 1 is to collect a much larger sample to examine the robustness of this potential age difference.

1.5 Tesla vs. 3 Tesla Magnet
Reviewer 2 questioned the use of a 1.5 Tesla magnet. The 1.5 T magnet will be used (instead of a higher field strength 3 T) because systematic testing conducted in the Knutson lab has revealed that a more reliable signal can be observed in the basal ganglia using the 1.5 T magnet. With greater signal comes greater noise (at 3 T), and unfortunately, the basal ganglia are disproportionately affected by this increase in noise. As the proposed studies will primarily focus on striatal and prefrontal regions of interest, this lab standard (1.5 T) will be maintained. This explanation has now been added to the research plan.

Training Plan
All reviewers commented that the training plan lacked specificity. The training plan has now been completely rewritten. Instead of generally describing what is available to the trainee as in the previous version, in this revision the plan now describes in detail how the proposed training will significantly enhance the applicant's skill set and prepare him for his future career. Details about the training received from the sponsor, dissertation committee members, and project collaborators are now clearly described in the revised training plan.

Both Brian Knutson and Laura Carstensen will assist the trainee in the theoretical development of this line of proposed studies, which lie at the intersection of psychology, neuroscience, and economics. The trainee will work with both Knutson and Carstensen to begin to develop a comprehensive theory of aging and economic decision-making that will integrate ideas across these fields. All research activities will be carried out not only with the advice and counsel of the sponsor, Brian Knutson, but also with project collaborators. The training provided through these collaborations will far exceed any knowledge that could be gained through formal coursework and will significantly enhance the trainee's experimental skill set.

Research Training Plan

A. Specific Aims

The main objective of the proposed research is to examine age differences in incentive learning and incentive-based decision-making using both behavioral measures of performance and functional magnetic resonance imaging. In Studies 1–3, we aim to investigate the influence of both reinforcement valence and increasing cognitive demand on incentive processing in younger and older adults.

Specific Aim 1: To investigate the influence of age differences in incentive anticipation on incentive learning.
Previous research has suggested that older adults show preserved reward anticipation/prediction but diminished loss anticipation/prediction relative to younger adults, consistent with affective preferences associated with motivational goals in older age. In Study 1, we propose to examine whether this age difference in incentive anticipation has an influence on incentive learning. Older adults may perform as well or better than younger adults in gain learning due to intact neural reward prediction signals, but perform worse than younger adults in avoidance learning due to diminished neural loss prediction signals.

Specific Aim 2: To investigate age differences in incentive-based reversal learning for gains and losses.
Previous research has revealed age-related impairments in incentive-based reversal learning using mixed gambles, but has not specifically investigated valence effects and age. In Study 2, we propose to examine whether older adults will show the same valence asymmetry in reversal learning due to motivational goals and affective preferences or whether older adults will perform uniformly more poorly than younger adults for both gain-seeking and loss avoidance reversal learning due to cognitive impairment and inflexibility.

Specific Aim 3: To investigate age differences in incentive-based risky decision-making.
Recent economic theory has suggested that older adults may show impairments in risky decision-making due to cognitive decline. However, risky decision-making is dependent on both intact affective/reinforcement learning and cognitive control. In Study 3, we propose to examine (1) whether older adults differ from younger adults both in rational risky decision-making and risk preference and (2) whether cognitive or affective individual difference variables mediate these differences.

B. Background and Significance

<u>The aging brain</u>

Over the past several decades, scientists have made rapid progress towards elucidating the effects of aging on cognition. Both behavioral and neuroimaging studies show a strong negative relationship between age and cognitive performance across many types of tasks [1, 2]. Consistent declines have been shown in many aspects of learning and memory. It has been well established that older adults are especially likely to have difficulty with reversal learning and are likely to make perseverative errors. It is hypothesized that specific and selective neural atrophy underlies these declines in cognitive ability. Studies of brain structure and chemistry provide some evidence for age-related decline. These studies have specifically revealed significant structural atrophy of the caudate, insula, and prefrontal cortex, as well as global declines in dopamine receptors in the striatum and the prefrontal cortex [3-6].

However, a growing body of research also suggests that many affective abilities do not decline with age, and in some cases may improve. Accumulating behavioral evidence suggests that older adults perform relatively better on tasks involving the processing of emotional stimuli [7]. Socioemotional selectivity theory postulates that age-related attempts to optimize emotional well being [8] generate increased positive emotional experiences and decreased negative emotional experiences over the life span [9]. Presently, however, very few neuroimaging studies have focused on changes in emotion with age [10, 11]. Currently, the implications of these anatomical and chemical changes for brain function during incentive processing remain relatively unclear.

Incentive processing and learning in the brain

Simple conditioning paradigms have revealed that basic learning and memory are dependent on the firing of dopamine neurons. Schultz and colleagues have shown that dopamine initially fires when rewards are received but that the signal back-propagates over time and soon dopamine fires when a cue is presented that predicts a reward [12]. It has been well-established that this value prediction in the dopamine signal drives learning [13].

However, a growing body of research suggests that the dopamine signal is also associated with affective experience [14]. In other words, conditioning and reinforcement learning in general can be viewed as driven by an affective learning signal – specifically an anticipatory affective signal to either seek rewards or avoid punishments [15]. Knutson and colleagues have demonstrated that mesolimbic dopamine regions increase is activation during incentive anticipation and that this activation is correlated with self-reports of positive affect [16]. Event-related functional magnetic resonance imaging (FMRI) studies in adolescents and younger adults implicate striatal and insular activation in the anticipation of both uncertain gains and losses [17, 18].

However, if both the root of affective feelings and learning and memory are dependent on the same neurochemical, which has shown marked decline with age, how can these affective preferences and the general sparing of emotional processing with age be accounted for? One recent hypothesis is that this age-related valence asymmetry (viewed as intact and healthy emotional processing in many circumstances) only emerges in individuals with at least a moderate level of cognitive control [9]. Consistent with socioemotional selectivity theory, this hypothesis suggests that these affective preferences are goal directed and not simply a result of neural decline. Goal directed, motivated behavior requires some level of cognitive control, and thus dopamine. It follows that this affective preference for the positive will only emerge in older individuals with some level of intact dopamine transmission. However, in more difficult tasks the higher levels of cognitive load may overwhelm task performance, and this affective profile will likely not be expressed – even in the older individuals with relatively modest dopaminergic decline. Although, even in the least cognitively impaired older individuals, the expression of these affective preferences may be healthy and adaptive for regulating emotional experience and optimizing well-being, but may have harmful and serious effects on financial learning and decision-making.

Incentive processing and learning in the aging brain

Very little work has focused on incentive learning and financial decision-making in the aging brain. In fact, only two studies have examined incentive processing in older age [19, 20]. A recent study found that, relative to younger adults, older adults have reduced ventral striatal activation while engaged in an incentive-based reversal learning task [19]. In that study, however, older subjects also perform more poorly on the task so age differences may be due to performance differences. Additionally, gain and loss cues are in the same array of choices and my early graduate research has demonstrated that younger and older adults differ in their anticipation of gains and losses. In a recent study, we identified an age-related asymmetry such that younger and older adults do not differ in their self-reports of positive affect and neural activation during anticipation of monetary gains, but that older adults show a blunted neural response and reduced self-reported negative affect during the anticipation of monetary losses [20, see Appendix]. In our experiment, the simpler design of our task elicited equivalent performances from younger and older adults so we were able to conclude that age differences were not performance based. In fact, our findings are consistent with a prior psychophysiological study which found that older adults show skin conductance responses prior to choosing options associated with gains rather than losses [21]. Together, these findings suggest that activation during anticipation may not be as compromised by age as the neural substrates recruited in the course of reversing reward associations (e.g., ventrolateral prefrontal cortex [22]). One goal of the set of studies proposed in this application (Studies 1 and 2) is to specifically disentangle reward anticipation from reward reversal to fully test this possibility and investigate the implications of this for more complex decision-making (such as financial investment decisions; Study 3).

While older adults do not significantly differ from younger adults during gain anticipation, they do differ during loss anticipation. Specifically, affective data indicate that older adults experience less negative arousal, and neural data indicate that they show less activation of the insula and caudate when exposed to loss cues. An asymmetry between positive and negative emotional experience has been documented in older adults in a number of behavioral studies employing a variety of tasks [23]. Interpreted through the lens of socioemotional selectivity theory, age-related sparing of positive emotional experience may be related to efforts to optimize

emotional experience as one approaches the end of life [8]. One aspect of this optimization may involve reducing negative arousal during anticipation of negative events. However, this reduction in loss anticipation may have disadvantageous consequences for learning. Recent evidence distinguishes brain mechanisms involved in learning about positive and negative incentives [24], and it is possible that older adults' reduced neural and affective responses during loss anticipation result from slower learning of the significance of loss cues.

Even after learning has taken place (or in the absence of learning), incentives still may vary in their impact. Reduced responsiveness to anticipated loss may also engender biases in certain decision-making scenarios. For instance, risk assessment might be altered.

Risky decision-making and aging

Although common stereotypes suggest that older adults are risk averse [25], experimental results are somewhat mixed [26]. While some studies reveal age differences in risky decision-making [19, 27, 28], others find no age differences [21, 27, 29, 30]. Since many decisions (such as choosing a stock in which to invest) involve high level cognitive processing, performance deficits in older adults may result from cognitive decline [31, 32]. However, preferences, goals, and emotions also heavily influence everyday decisions [33, 34]. As mentioned above, a large body of work reveals a steady decline in cognitive processing capacity over the life span, but a robust preservation of emotional processing – particularly for positive material. Thus, both changes in cognitive and affective processing with age may have differential effects on financial risk taking and decision-making.

First, aging is commonly accompanied by declining cognitive capacities, including working memory [35], which might prove important for rapidly updating probability information in risky or changing circumstances [36]. Risk involves choices with potential gains and losses of known probabilities [37]. Second, research increasingly suggests that older adults may preferentially and actively avoid anxiety-provoking stimuli [38]. If risky choices evoke more negative arousal than risk-less choices, this could provoke risk aversion. Unfortunately, risk aversion may have serious consequences for elders who are called upon to make increasingly important, numerous, and repeated decisions involving some degree of novelty. For instance, elders must make unprecedented decisions about investments and healthcare (particularly with respect to Part D of the new prescription drug plan). If older adults are more risk averse, they may not optimize expected value when faced with risky choices, and may be more susceptible to accepting non-optimal defaults when decisions are enforced. Thus, we propose to assess the independent contributions of cognitive and affective mediating variables on risk preference and rational decision-making across the life span.

Findings from this line of basic research may have implications for scientists' understanding of how processes underlying decision-making change with age, and might eventually also facilitate identification of markers for suboptimal decision-making in older adults [27].

C. Preliminary Studies

Study 1: Reduced insular activation during loss anticipation is associated with impairment in loss avoidance learning

In a prior study on incentive anticipation and aging we found an age-related asymmetry such that younger and older adults did not differ in their anticipation of monetary gains, but that older adults showed a blunted neural response during the anticipation of monetary losses [20, see Appendix]. We conducted a follow-up behavioral study with the same subjects to explore the influence of blunted neural loss anticipation on avoidance learning [39, see Appendix].

Eleven younger (age 19-27, 5 female) and twelve older (age 65-81, 6 female) adults participated in the study. Subjects first played a monetary incentive delay task while undergoing FMRI to localize brain regions involved in the anticipation of monetary incentives. Several months later, subjects returned to our laboratory to play a monetary incentive learning task. The task involved making a series of forced choices between two fractal images. One image in each pair was associated with a high probability (60%) of an optimal outcome and the other was associated with a low probability (30%) of an optimal outcome. There were two conditions each with its own pair of images: gain and loss. For gain pairs the optimal fractal would gain money (+$1.00) with a 60% probability and for loss pairs the optimal fractal would avoid a loss (–$0.00) with a 60% probability. Subjects completed two runs consisting of 80 trials (40 trials for each fractal pair: gain, loss) displayed in a

randomized order for each subject. Performance was calculated as the percentage of correct trials in each condition averaged between the two runs. The goal in both tasks was to make as much money as possible and subjects were paid in real cash according to their performance.

To explore the relationship between anticipatory neural activation and subsequent reinforcement learning, a whole brain regression analysis identified regions of the brain that were significantly related to reinforcement learning (correlation between individual voxel beta weights and average number of correct choices in the learning task). The threshold for statistical significance was set using a global family-wise error rate that corrected for gray matter volume in subcortical and prefrontal cortical regions (approximately 500 voxels corrected at $p < 0.05$, yielding a threshold z of 3.89, $p < 0.0001$, uncorrected) and required a minimum cluster of fifteen face-to-face, contiguous voxels. Confirmatory partial correlational analyses (controlling for age) were performed by extracting peak mean anticipatory signal change from 6mm diameter spheres placed in regions identified in the whole brain analysis and adjusted within individuals to ensure that spheres only contained grey matter and did not sample the neighboring cerebrospinal fluid.

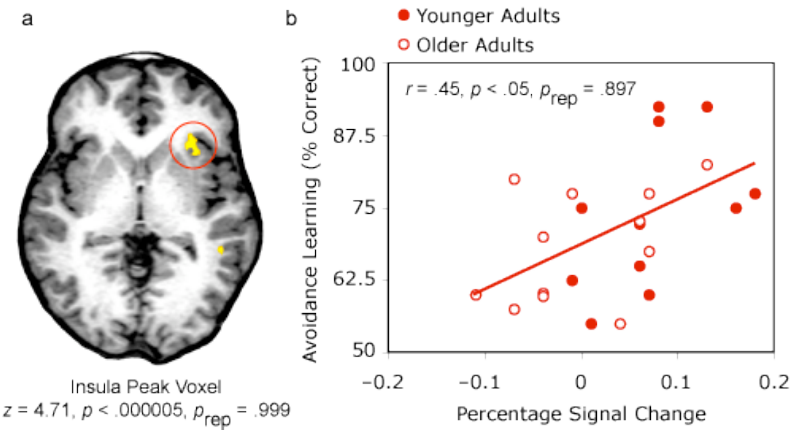

Figure 1. Correlation between insular activation during loss anticipation and loss avoidance learning. Greater neural sensitivity to loss in the anterior insula predicted subsequent loss avoidance learning performance.

The age groups did not significantly differ in overall gain learning, $t(21) = 0.22$, $p = .83$, or loss avoidance learning performance, $t(21) = 1.22$, $p = .24$. However, across all subjects the results of the whole brain analysis revealed a significant relationship between avoidance learning and anticipatory activation in only one region of the brain, the anterior insula (peak voxel Talairach coordinates: 30, 20, 3) $z = 4.746$, $p < 10^{-5}$, effect size: $R^2 = 0.62$ (Fig. 1). This relationship was confirmed in a volume of interest analysis which revealed a significant partial correlation (controlling for age) between raw percent signal change extracted from the anterior insula within individuals and avoidance learning, $r = .45$, $p < .05$. The relationship was specific to anticipatory activation because insular sensitivity to loss outcomes was not significantly related to either gain or loss avoidance learning.

Although the older adults as a group were not statistically impaired in overall avoidance learning, the younger adults did perform slightly better, although not significantly, in the loss avoidance but not gain learning condition. It is possible that our small sample size did not allow for the detection of a behavioral age difference in avoidance learning performance. We also observed non-significant, but suggestive, age differences in learning over time such that older adults were slower to learn which cue was optimal on loss avoidance trials (Fig. 2). Future studies utilizing much larger samples, such as those proposed below will have to examine potential age differences in the acquisition of behavioral loss avoidance more carefully.

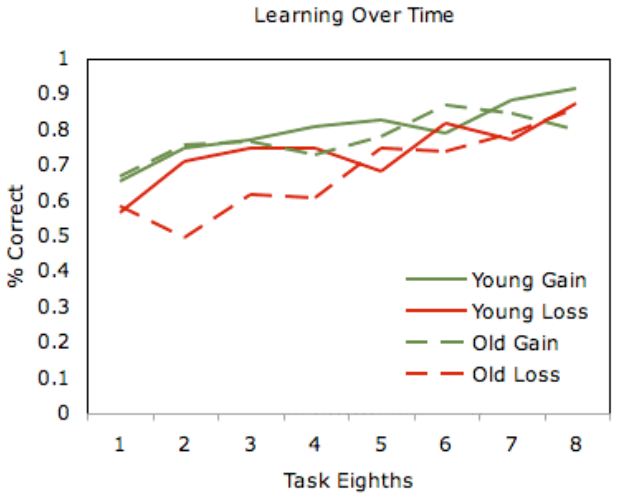

Figure 2. Older adults were non-significantly (but numerically) slower to learn to avoid losses.

D. Research Design and Methods

The proposed research aims to examine age differences in incentive learning and incentive-based decision-making using both behavioral measures of performance and functional magnetic resonance imaging. In Studies 1–3, we aim to investigate the influence of both reinforcement valence and increasing cognitive demand on incentive processing in younger and older adults. In Study 1, we propose to examine whether age differences in incentive anticipation have an influence on incentive learning. In Study 2, we propose to examine whether older adults will show the same valence asymmetry in reversal learning. In Study 3, we propose to examine whether older adults differ from younger adults both in rational risky decision-making and risk preference and whether cognitive or affective individual difference variables mediate these differences.

Hypotheses

1. We expect to observe an age by condition interaction in simple incentive learning: a main effect of age on loss avoidance learning, but no effect of age on gain learning. Behaviorally, older adults may perform as well or better than younger adults in gain learning due to intact reward prediction, but perform worse than younger adults in avoidance learning due to diminished loss prediction. In the neuroimaging analyses we expect to find an intact ventral striatal reward prediction signal, but a diminishing loss prediction signal in the striatum and insula with age. We expect anticipatory activation in these regions to correlate with learning task performance.

2. We expect to observe a similar age by valence interaction in reversal learning, but only for subjects high in cognitive ability (controlling for age). The prediction is that this affective preference will only emerge in older individuals with higher levels of cognitive control. For individuals low in cognitive ability, especially older adults, we will expect to observe uniformly poor performance across both conditions of the reversal learning task due to cognitive impairment and inflexibility. In the neuroimaging analyses for older subjects higher in cognitive ability, we expect to find that an intact ventral striatal reward prediction signal, but a diminishing loss prediction signal in the striatum and insula with age. We expect anticipatory activation in these regions to correlate with learning task performance. We also expect to find a ventrolateral region (in the inferior frontal gyrus) that is more highly activated during reversals. We expect the degree of activity in this region during reversals to correlate with both overall task performance and individual differences in cognitive ability.

3. We expect to observe a main effect of age on overall rational choices in an investment task (the task highest in cognitive demand), which will be mediated by memory for trial outcomes (i.e. history) and cognitive individual difference measures. We expect that the risk preferences of individuals will not be related to age or cognitive ability, but instead to individual differences in trait affect. In the neuroimaging analyses for subjects higher in cognitive ability, we expect to find intact lateral prefrontal or medial temporal regions that covary with increasing load (i.e. history). We expect activation in these regions to correlate with rational performance. We also expect that individual differences in risk preference (independent of age) will correlate with individual differences in anticipatory striatal and insular activation before asset choices.

Common Measures

Sixty individuals will participate in each of the three proposed studies, for a total of 180 subjects in this entire proposal. All individuals in each study will complete the same questionnaire measures and cognitive test battery (described below). Half of the subjects in each study will also complete the proposed experimental tasks while undergoing functional magnetic resonance imaging.

Subjects. Sixty adults ranging in age across the life span (ages 25–85) will participate in each study. A subset of subjects (half: 30/60) from studies 1-3 will also participate in a neuroimaging session. The same experimental tasks that are included in the behavioral sessions will be included in the neuroimaging session. Based on an expected FMRI effect size of ~0.5% signal change in the BOLD contrast, 12 subjects is the

minimum necessary to achieve greater than 80% power at the single voxel level for an alpha of .05 (Desmond and Glover 2002). Because effects of age will be examined using regression analysis with age as a continuous independent variable, the samples of 30 subjects varying in age will be sufficient to detect effects within each study. Further, even if the sample within each study is median split on age to conduct direct group comparisons, the sample size of 15 per group will be sufficient according to the above power analyses.

Subjects will be recruited from the San Francisco Bay Area and then followed up by laboratory personnel for a complete phone interview to determine eligibility. The phone interview will include questions relevant to their safety and their history of physical or mental disorders (specifically stroke and neurological damage, history of heart failure, or prescription medicine shown to interfere with the blood oxygen level dependent signal, e.g., either psychiatric or cardiac). If eligible for neuroimaging, subjects will be given a thorough explanation of the scanning procedures and short practice versions of each of the tasks prior to being scanned.

All subjects will give written informed consent, and the experiment is currently approved by the Institutional Review Board of the Stanford University Medical School. After obtaining informed consent, each subject will play the experimental task either in the laboratory or while undergoing FMRI and will have already completed the packet of demographic and individual difference questionnaires and cognitive test battery described below. Subjects will be paid $20/hour for their participation. Additionally, each experimental task will be incentive compatible such that real money is at stake. Individual winnings on the tasks will be added to the subject's payment. Before beginning the study, subjects will be shown the money that they can earn by performing the task successfully.

Questionnaire measures. A demographics questionnaire will assess the age, marital status, current and previous occupational status, level of income, number of years of education, and ethnicity of the subjects. Several individual difference measures will be included to ensure that age differences in task performance or measures of neural activation are not due to baseline age differences in trait affect or personality. The trait version of the Positive and Negative Affect Schedule (PANAS-T) [40] will be used to assess the extent to which subjects experience each of 22 emotional descriptors on a regular basis. A measure of physical health, the Wahler Physical Symptom Inventory (WPSI) [41], asks subjects to indicate how often they are bothered by each of 42 physical symptoms. The Future Time Perspective (FTP) scale [42] is a 10-item self-report measure that assesses how much time people feel they have left in their lives. A 60-item short form of the Neuroticism-Extroversion/Introversion-Openness-to-Experience Personality Inventory (NEO-SF) [43] asks subjects to indicate their level of endorsement of each of the statements related to commonly-assessed personality traits. The 5-item Subjective Well-being and Satisfaction with Life Scale (SWLS) [44] assesses general overall satisfaction with life.

Cognitive test battery. The Mini-Mental Status Exam (MMSE) [45] will be administered to all subjects as a screen for dementia. Three subtests from the Wechsler Adult Intelligence Scale Third Edition (WAIS-III) [46] with well-validated ranges for older adults will be administered to each subject. The WAIS-III Digit Span test requires that subjects repeat numerical strings forward and backward. It is considered a measure of working memory and correlates well with general intelligence. The WAIS-III Digit Symbol test requires subjects to match symbols with letters as quickly and accurately as possible in a 120-second period. The WAIS-III Vocabulary test requires that subjects provide definitions for words presented in both written and spoken form, and correlates well with verbal intelligence. Two subtests, Verbal and Category Fluency, of the Delis-Kaplan Executive Function System [47] will be administered. The Verbal Fluency (FAS) subtest requires that subjects name as many words as possible beginning with a given letter (first F, then A, then S) in a 60-second period. The similar Category Fluency subtest requires that subjects name as many words as possible that fall into the given category (animals) in a 60-second period. The Trail Making Test (TMT) from the Halstead-Reitan Neuropsychological Test Battery [48] has two parts (A & B) which are both timed until completion. The first part (Trails A) requires that subjects sequentially connect 25 encircled numbers on a standard sheet of paper. The second part (Trails B) requires that subjects connect a series of numbers and letters in an alternating pattern. Trails B is considered to be a good indicator of general frontal lobe cognitive function.

FMRI acquisition and analysis. Imaging of all tasks will be performed using a 1.5 Tesla General Electric (Milwaukee, WI) MRI scanner with a standard quadrature head coil. The 1.5 T magnet will be used (instead of a higher field strength 3 T) because systematic testing conducted in the Knutson lab has revealed that a more reliable signal can be observed in the basal ganglia using the 1.5 T magnet. As the proposed studies will primarily focus on striatal and prefrontal regions of interest, this lab standard will be maintained.

Our acquisition volumes will include twenty-four 4-mm-thick slices (in-plane resolution, 3.75 x 3.75 mm; no gap) extending axially from the midpons to the top of the skull, which provides adequate spatial resolution of subcortical regions of interest (e.g., midbrain, ventral striatum, anterior insula) and omits only the base of the cerebellum or crown of the skull in some subjects. Functional scans of the entire brain will be acquired every 2 s [repetition time (TR), 2 s] with a T2*-sensitive in/out spiral pulse sequence [echo time (TE), 40 ms; flip, 90°] specifically designed to minimize signal dropout at the base of the brain [49]. High-resolution structural scans will be subsequently acquired using a T1-weighted spoiled GRASS sequence (TR, 100 ms; TE, 7 ms; flip, 90°) to facilitate subsequent localization and coregistration of functional data.

Analyses in all three studies will focus on changes in brain activation during anticipation (i.e., after subjects see cues but before they respond), choice (i.e. response), and outcome (i.e., after subjects receive feedback about their gains/losses). All analyses will be conducted using Analysis of Functional Neural Images software [AFNI; 50]. For preprocessing, voxel time series will be concatenated across runs, sinc interpolated to correct for non-simultaneous slice acquisition within each volume, and corrected for three-dimensional motion. Visual inspection of motion correction estimates will be used to confirm that no subject's head moves more than 2.0 mm in any dimension from one volume acquisition to the next. Data will then be bandpass filtered to admit frequencies between 10 and 90 s, and percentage signal change will be calculated for each voxel with respect to the mean activation over the entire experiment.

Preprocessed time series data for each individual will be analyzed with multiple regression [51]. The regression model will consist of a set of orthogonal regressors of interest. Additional covariates will include three orthogonal regressors highlighting the periods of interest (anticipation, choice, and outcome); six regressors describing residual motion; and six regressors modeling baseline, linear, and quadratic trends for each experimental session. Regressors of interest will be convolved with a gamma-variate function which models a prototypical hemodynamic response [52] prior to inclusion in the regression model. Maps of *T*-statistics representing each of the regressors of interest will be transformed into *Z*-scores, slightly spatially smoothed to account for anatomical variability (kernel FWHM = 4 mm), resampled at 2 mm^3, and spatially normalized by warping to Talairach space. Statistical maps will be generated using one-sample t-tests. Thresholds for statistical significance within the predicted volumes of interest will be determined by a local small volume correction (approximately 10 4mm^3 voxels corrected at $P < 0.05$, yielding a threshold Z of 2.81, $P < 0.005$, uncorrected) and will require a minimum cluster of eight face-to-face contiguous 2 mm^3 resampled voxels. Thresholds for statistical significance outside the predicted volumes of interest will be set using a global family-wise error rate that corrects for gray matter volume in subcortical and prefrontal cortical regions (approximately 500 4mm^3 voxels corrected at $P < 0.05$, yielding a threshold Z of 3.88, $P < 0.0001$, uncorrected [16]) and requires a minimum cluster of eight face-to-face contiguous 2 mm^3 resampled voxels.

Analyses will consist of two types: localization and decomposition. For the localization analysis, one regression analysis will explore contrast coefficient maps across all subjects (regardless of age) and another will examine the effects of age. The goal of the localization analyses will be to verify whether *a priori* regions of interest are activated across age, as well as to identify new regions which might show age differences. For the decomposition analyses, volumes of interest (VOIs) will be anatomically specified in regions of interest identified *a priori* including the midbrain, nucleus accumbens, caudate, anterior insula, mesial prefrontal cortex, and inferior frontal gyrus. Activation time courses will be extracted from functional volumes and averaged from these VOIs by trial type. Peak signal change (at a 4–6 second lag) will then be compared using multiple regression or mixed-model ANOVAs for each VOI. In the event of a significant interaction, values will be compared across incentive and non-incentive conditions with within-subject ANOVAs (corrected for multiple comparisons). No direct tests between younger and older adults for each of the individual trial types will be performed to avoid confounding differences in hemodynamic modulation between age groups as suggested by a recent review of BOLD imaging and aging [53]. Therefore, post-hoc VOI analyses for all tasks will focus on linear effects and age by condition interactions. Correlational analyses (controlling for age) will assess the relationship between individual difference variables (self-reported affect ratings for cues and cognitive ability) and activation in the VOIs.

Methodological issues related to age differences in hemodynamics. Collection of FMRI data in older adults raises many methodological issues, which necessitate careful sampling and measurement. A prevalent concern in cross-sectional FMRI studies of older adults involves potential baseline differences in the shape of the hemodynamic response functions (HRFs) (e.g., due to cardiovascular confounds) [53]. Even assuming good health, the hemodynamic response of older individuals has been shown to be similar but more

variable than that of younger adults in cortical regions [54-57]. A basic perceptual task will also be implemented in the proposed studies to examine age differences in the amplitude of HRFs. The task will consist simply of responding with a button press to flickering checkerboard stimuli that are presented for 2 s, separated by random interstimulus intervals ranging from 2–38 s. Timecourses of activation will be extracted from voxels in primary visual cortex (V1) in individual subjects. A multivariate GLM will examine any effects of age. However, even if differing HRFs were of concern, it should primarily bias localization analyses (for which fit statistics depend on regressors convolved with a canonical HRF) and not statistical tests comparing modulation of raw signal peaks extracted from individuals' volumes of interest between conditions.

Methodological issues related to age differences in structural anatomy. Of additional potential concern, age-related differences in activation may result from increased gray matter atrophy and white matter demyelination in older adults. Specifically, recent reports show that both the insula and caudate undergo substantial atrophy with age [5]. One could infer that structural degeneration in these regions should then uniformly degrade all patterns of activation in the older adults. However, as revealed by prior studies in our laboratory [20], while both caudate and insula are less activated during loss anticipation in older adults, they show no significant differences in either region during gain anticipation. Nevertheless, care will be taken to ensure that data from volumes of interest only includes gray matter for each individual. Volumes of interest will be anatomically defined by manual tracing in each individual subject.

Study 1: Do age differences in incentive anticipation have an influence on incentive learning?

The same subject criteria, questionnaire measures, cognitive test battery, and neuroimaging parameters described in the Common Measures section above will be used in Study 1. For the experimental task, subjects will complete an incentive-based learning task (the MIL task described below).

Monetary Incentive Learning (MIL) task. The design of the monetary incentive learning (MIL) task is inspired by a similar recently published incentive learning paradigm [24]. Across both runs, the entire task will include 40 trials. During each trial, subjects will view a pair of fractal cues (valuation/anticipation), choose a cue (choice), view their highlighted choice on screen, and receive feedback about how much money they won or lost on the trial (outcome). The display duration of the choice frame of the task will be self-paced to accommodate differences in vision and decision reaction time among younger and older subjects. One pair of fractal cues will be used for each condition (gain, loss avoidance). Within gain and loss avoidance pairs one cue will yield a high probability optimal outcome (70% +$1.00, 30% +$0.00; 70% –$0.00, 30% –$1.00) and the other a low probability optimal outcome (30% +$1.00, 70% +$0.00; 30% –$0.00, 70% –$1.00). Each cue within each pair will appear equally often on the left and right side of the screen within runs. The pairing of specific cues with outcomes will be counterbalanced across subjects. The goal of the experiment will be to learn which cue in each pair is higher in expected value (high probability gain acquisition, high probability loss avoidance). Each of two trial types will be presented 20 times per run in an individually randomized order for each subject.

Hits will be calculated as the percentage of correct responses per condition (i.e., the cue associated with a higher expected value). As the goal of this study will be to test for a significant impairment in loss avoidance but not gain acquisition among older adults, hit rate will be analyzed with multiple regression with incentive valence (gain acquisition, loss avoidance) and trial quarter (first 5 trials, second 5 trials, third 5 trials, last 5 trials) as within-subject factors and continuous age (younger, older) as a between-subject factor. Post-hoc analyses will compare hits across all conditions (gain acquisition, loss avoidance) with within-subject t-tests versus chance (50%) (corrected for four comparisons, $P < .013$). Additional post-hoc tests (corrected for multiple comparisons) will assess learning differences across age over time by comparing accuracy within all four quarters (five trials per quarter) across both incentive conditions (gain acquisition, loss avoidance).

Study 2: Will an age-related valence asymmetry emerge in incentive-based reversal learning?

The same subject criteria, questionnaire measures, cognitive test battery, and neuroimaging parameters described in the Common Measures section above will be used in Study 2. For the experimental task, subjects will complete an incentive-based reversal learning task (the MIRL task described below).

Monetary Incentive Reversal Learning (MIRL) task. Similar to the MIL task described in Study 1, in the monetary incentive reversal learning (MIRL) task during each trial, subjects will view a pair of fractal cues

(valuation/anticipation), choose a cue (choice), view their highlighted choice on screen, and receive feedback about how much money they won or lost on the trial (outcome). One pair of fractal cues will be used for each condition (gain acquisition, loss avoidance). Within gain acquisition and loss avoidance pairs the optimal cue will yield a high probability ideal outcome (70% +$1.00, 30% +$0.00; 70% –$0.00, 30% –$1.00) and the other a low probability optimal outcome (30% +$1.00, 70% +$0.00; 30% –$0.00, 70% –$1.00). Each cue within each pair will appear equally often on the left and right side of the screen within runs. The pairing of specific cues with outcomes will be counterbalanced across subjects. However, unlike the MIL task, over the course of the MIRL task the optimal and suboptimal cues will reverse every 6–12 trials. The entire task will include 144 trials organized into four blocks. Two blocks will include gain pairs and two blocks will include loss pairs. Each block will contain 36 trials. Each subject will face eight reversals for each condition (gain, loss). The goal of the study will be to continue selecting the cue in each pair that is currently higher in expected value (high probability gain acquisition, high probability loss avoidance).

Overall performance will be calculated as the percentage of correct responses per condition (i.e., the cue associated with a higher expected value) and age differences will be examined with regressions. As one goal of this study will be to test for an age-related increase in perseverative errors (i.e. impairment in switching after a reversal occurs), the probability of switching to the now optimal stock on each trial over the six trials following a reversal will be analyzed with multiple regression with incentive valence (gain acquisition, loss avoidance) and time (each of the 6 trials post-reversal) as within-subject factors and continuous age as a between-subject factor. Post-hoc tests will utilize change point analysis to compare the number of trials necessary to switch after a reversal within each condition (gain acquisition, loss avoidance) across age.

Study 3: Are age differences in risky decision-making due to age-related changes in affective processing, cognitive decline, or both?

The same subject criteria, questionnaire measures, cognitive test battery, and neuroimaging parameters described in the Common Measures section above will be used in Study 3. For the experimental task, subjects will complete a risky decision-making task (the BIAS task described below).

Behavioral Investment Allocation Strategy (BIAS) task. The BIAS task involves making a series of investments decisions among three assets (one riskless and two risky) across 20 blocks of ten trials each (for a total of 200 trials). During each trial, subjects will view the three assets (two stocks and a bond: anticipation), select which asset they prefer from the set (choice), view their highlighted choice on screen, receive feedback about how much money they won or lost on the trial (individual outcome) and how much they would have won or lost had they chosen the other assets (market outcomes). At the beginning of each block (indicated by a cue), one of the two stocks is randomly assigned to be the “good” stock, while the other is assigned to be the “bad” stock, without the subject’s knowledge. The good stock dominates the bad stock in the sense of first-order stochastic dominance [58]. Specifically, outcomes of the good stock (i.e., +$10 with 50% probability, +$0 with 25% probability, and −$10 with 25% probability) are better than outcomes of the bad stock (i.e., +$10 with 25% probability, +$0 with 25% probability, and −$10 with 50% probability) on average for each trial. The bond pays $1 with 100% probability on each trial. Earnings are drawn independently from these distributions for each trial, and subjects are informed about the distributions before performing the task. The goal of the study is to choose the asset in each set that will maximize monetary earnings.

Behavior is modeled according to the behavior of a risk neutral rational Bayesian actor. The model selects bonds early in the game when uncertainty (risk) is high, but then after tracking the performance of the two risky assets over time eventually switches to the “good” stock and maximizes. In this way, individual trial choices can be characterized as rational stock choices, rational bond choices, irrational stock choices (risk seeking: chose stock but should have chosen bond), irrational bond choices (risk averse: chose bond but should have chosen stock), or confusion mistakes (chose the “bad” stock). Overall performance will be calculated as the percentage of rational choices and age differences will be examined with multiple regression. Additional analyses will explore the influence of age differences in cognitive ability on rational decisions by exploring both correlations between cognitive test scores and rational choices and by exploring decision history as a mediator of age effects. By modifying the “memory” (history input) of the Bayesian rational actor, we can reveal for each subject approximately how many trials in history are taken into account when making an individual decision. This individual history variable can then be explored as a potential mediator of age differences in task performance.

Further analyses will explore the influence of age differences in emotional processing on risk preferences by examining the effects of age on risk seeking or risk aversion mistakes. A previous study using this task in our laboratory has shown that anticipatory emotional neural signals are primarily responsible for these choices [37].

Summary

With drastic changes in age demographics on the horizon, aging adults may be required to make increasingly more independent health-related and financial decisions. Thus, it is increasingly imperative to better understand the impact of age-related changes in both cognitive and affective processing on decision-making. Both behavioral and neural evidence suggests that younger and older adults differ in the processing of monetary incentives (e.g., older adults show attenuated anticipation of monetary losses), which could have specific consequences for financial decisions (e.g., older adults may be generally less sensitive to the warning signs of potential negative outcomes). Although these affective preferences may be healthy and adaptive for regulating emotional experience and optimizing well-being, they may have harmful effects on financial learning and decision-making. The main objective of the proposed research is to examine age differences in incentive learning and incentive-based decision-making using both behavioral measures of performance and functional magnetic resonance imaging. The specific aims of this proposal are to investigate the influence of reinforcement valence on incentive processing across the life span (Study 1), examine whether older adults show the same valence asymmetry in more cognitively demanding reversal learning (Study 2), and examine whether older adults differ from younger adults both in rational risky decision-making and risk preference in a more applied investment decision paradigm (Study 3).

Findings from this line of basic research may have implications for scientists' understanding of how processes underlying decision-making change with age, and might eventually also facilitate identification of markers for suboptimal decisions in older adults. 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.

Projected schedule:

1. Study 1 July 2008 – January 2009
2. Study 2 February 2009 – November 2009
3. Study 3 December 2009 – July 2010

E. Human Subjects Research

This Human Subjects Research meets the definition of 'Clinical Research.'

Protection of Human Subjects

1. Risks to the Subjects

Human subjects involvement and characteristics. Subjects will be 25–85 year-old healthy right-handed individuals with no history of neurological or psychiatric disorders, and no unacceptable risk factors for participation in MRI research, who are native English speakers with normal or corrected-to-normal eyesight. Approximately 120 subjects will be recruited in order to account for data loss due to head motion and artifacts.

Source of materials. Screening interviews will collect data on subjects' neurological and psychiatric history, MR-safety screening, handedness, and native language. In all studies, subjects' behavior (choices in the learning and gambling tasks), responses to various emotion and personality questionnaires, and cognitive test battery results will be recorded. Additionally, all subjects' functional and anatomical brain data will be collected. All subjects will be assigned a code-number, and all dealings with subjects' data will be referred to by code number, not by name. All materials collected will be for research purposes only.

Potential risks. FMRI is not associated with any risks, provided proper screening precautions are observed. Potential risks necessitating exclusion during the screening process include implanted metal and claustrophobia. Potential side effects include slight possibilities of heating from radiofrequency coils and

cables, localized painless muscle twitching due to magnetic field changes during the scan, and dizziness or nausea if scanned at high field strength (>= 3.0 Tesla). Since we intend to conduct this study using a 1.5 Tesla scanner, the risk of dizziness or nausea is minimal. There are no known risks associated with any of the proposed behavioral tasks.

2. Adequacy of protection against risks.

Recruitment and informed consent. Subjects will be recruited from the San Francisco Bay Area community (Stanford students will be excluded) and compensated $20 per hour for participation. Subjects may earn an additional bonus during tasks involving monetary rewards. Subjects will be required to read and sign an informed consent providing detailed information regarding the procedures and general purpose of the study as well as their own rights as subjects, including the right to withdraw at any time from the study.

Protection against risk. Careful screening procedures as described above will be followed to ensure that no individuals participate for whom the magnetic field would be unsafe. Additionally experimenters always perform routine checks for the presence of metal on themselves and on subjects before entering the magnet suite. Subjects are screened for claustrophobia, but additionally are in frequent contact with the experimenter and can communicate their desire to stop at any time throughout the entire study. Stanford University requires that all researchers who deal with human subjects pass a research ethics training program, and MR-researchers an MR safety course. Subjects' data will be considered confidential and identified only with a code-number.

3. Potential benefits of the proposed research to the subjects and others.

There are no anticipated benefits to the subjects. Given the low risk involved, the potential knowledge gained justifies conducting this study. The task dealing with financial decision-making in old age is not designed to offer specific assessment of decision-making competence, but rather to increase basic understanding of age-related changes in psychological and neural processes.

4. Importance of knowledge to be gained.

Deepening the basic understanding of developmental shifts in incentive learning and decision-making in particular will aid in the future development of markers of decisional impairment and may eventually inform policy about financial decision-making in older age. In light of the negligible risks to subjects, this research is justifiable on these grounds.

Inclusion of Women and Minorities

There are no known expectations that ethnic/racial group will influence responses to monetary decision cues or tasks. We will consequently plan to recruit subjects reflecting the general ethnic distribution of the San Francisco Bay Area (Asian 25%, Black 10%, Hispanic 20%, White 44%, Santa Clara County, CA, 2002 Census Data) as shown in the targeted enrollment table. We will not select or exclude subjects on the basis of ethnicity. We will explore gender differences in the proposed tasks, and thus will balance all study samples with respect to gender.

Inclusion of Children

We will not include anyone under the age of 25. The proposed studies seek to examine incentive processing as a result of adult aging, and thus children will not be included in the proposed studies.

Name of Applicant *(Last, first, middle):* Samanez Larkin, Gregory, Russell

Targeted/Planned Enrollment Table

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

Study Title: Incentive learning and decision making in the aging brain

Total Planned Enrollment: 180

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	18	18	36
Not Hispanic or Latino	72	72	144
Ethnic Category: Total of All Subjects *	90	90	180
Racial Categories			
American Indian/Alaska Native	0	0	
Asian	20	20	40
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	14	14	28
White	56	56	112
Racial Categories: Total of All Subjects *	90	90	180

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

F. Vertebrate Animals

n/a

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H. Resource Sharing

n/a

I. Respective Contributions

This proposal was written be the applicant. Background information and theory on reward-processing and FMRI approaches were written by the applicant after consulting with the sponsor, Dr. Brian Knutson. Specific hypotheses were developed by the applicant in collaboration with Dr. Knutson.

J. Selection of sponsor and institution

Brian Knutson was selected as the primary sponsor due to his international reputation as an expert in affective neuroscience broadly and specifically for his expertise in incentive processing and incentive-based decision-making. He was the first scientist to examine neural responses to the anticipation of monetary rewards in the human brain using an incentive compatible task. This line of work more recently has lead to the examination of the role of reward circuitry in risky decision-making and consumer choice. He is recognized as a pioneer of the subfield affective neuroscience and is now one of the pioneers of the emerging discipline neuroeconomics.

Laura Carstensen will serve as an additional advisor on the proposed projects due to her international reputation as an expert in the psychology of aging broadly and specifically for her expertise in emotional processing over the human adult life span. She is well known for her work examining age differences in emotional processing using a wide variety of experimental methods and across a wide range of domains from basic attention to complex decision-making. She was recently recognized with a career award from the Gerontological Society of America and a merit award from the National Institute on Aging.

Stanford University is an ideal institution in which to conduct this pre-doctoral training due to its wealth of resources. In addition to my listed advisors, I will benefit greatly from consultation with other faculty such as dissertation committee member Samuel McClure, an expert on reinforcement learning and computational modeling, dissertation committee member Anthony Wagner, a leading cognitive neuroscientist, and dissertation chairperson Alan Garber, a health economist and co-director of Stanford's Roybal center. Additionally, Stanford University is home to one of the most well-equipped and supported neuroimaging facilities in the nation, the Richard M. Lucas Center. Stanford is also home to the academic community provided through the Stanford Center on Longevity, a multidisciplinary center which aims to use "scientific and technological breakthroughs to bring about profound advances in quality of life for people living longer, which benefit people of all ages."

K. Responsible Conduct of Research

Stanford University provides a considerable amount of training in responsible conduct of research. I have participated in and completed the following training components:

(1) Stanford Psychology Department Human Subjects Orientation – Each Autumn the university's human subjects research manager gives a detailed overview of the guidelines set forth by the Stanford IRB to enforce university and federal policy for the protection of human subjects.

(2) Stanford Human Subjects Tutorial – Prior to any interaction with human subjects or human subjects data collected, all students, faculty, and staff must complete an extensive online tutorial. This tutorial covers all topics related to the responsible conduct of research including conflict of interest, adverse report handling, data handling, human subjects policies, the responsibilities of researchers, and the responsibilities of the institute as a whole.

SPONSOR/CO-SPONSOR BIOGRAPHICAL SKETCH

Provide the following information for the sponsor (co-sponsor). **DO NOT EXCEED FOUR PAGES.**

NAME OF SPONSOR (CO-SPONSOR)	POSITION TITLE
Knutson, Brian	Assistant Professor
eRA COMMONS USER NAME	
KNUTSON.BRIAN	

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
Trinity University, San Antonio, TX	B.A.	1989	Psychology
Stanford University, Stanford, CA	Ph.D.	1993	Psychology
UCSF Medical School, San Francisco, CA	Post-Doc	1996	Affective Neuroscience
National Institute of Health, Bethesda, MD	Res. Fellow	1999	Affective Neuroscience

A. Positions and Honors.

Positions

1988-1989 *Research Assistant*, "Strategies of Mental Control," with Dr. Daniel Wegner, Psychology Dept., Trinity University

1993 *Certified Coder*, Facial Action Coding System (FACS), Psychiatry Dept., University of California, San Francisco

1993-1996 *Postdoctoral Fellow*, NIMH Program in Emotion Research, Psychiatry Dept., University of California, San Francisco

1996-1998 *Postdoctoral Fellow*, National Research Council, National Institute on Alcohol Abuse and Alcoholism, National Institute of Health, Bethesda, MD.

1996-2001 *Operator*, GE Signa 1.5 and 3.0 Tesla Magnetic Resonance Scanners, National Institute of Health, Bethesda, MD

1996-2001 *Principal Investigator*, NIH Protocol 98-AA-0056: "Functional neuroanatomy of positive and negative affect in alcoholics and normal controls," National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD.

1996-2001 *Instructor*, Psychology Dept., Johns Hopkins University

1998-2001 *Research Associate*, National Institute on Alcohol Abuse and Alcoholism, National Institute of Health, Bethesda, MD.

2001-present *Assistant Professor*, Psychology and Neuroscience, Stanford University

2002-present *Reviewer*, NIMH B/START Awards, NIMH R24 Awards (RFA-MH-02-004: "Exploratory/developmental grants in social neuroscience;" RFA-MH-00-016: "Basic and translational research in emotion"), NIMH Minority NRSA Awards, NIA T32 Awards, NIA Neuroeconomics of Aging Teleconference & Conference.

Honors

1986-1989 National Merit Scholarship

1986-1989 Trinity University Presidential Scholarship

1989 *Member,* Phi Beta Kappa, Trinity University

1989 Outstanding Psychology Student Award, Trinity University

1989 *Finalist*, Rhodes Scholarship (Kansas)

1989-1993 National Science Foundation Graduate Fellowship

1989-1993 Stanford Graduate Fellowship

1993 American Psychological Association Dissertation Award

1996 New York Academy of Sciences Young Scientist Award

1996 American Psychiatric Association Young Investigator Award

1998-1999 HealthEmotions Research Institute Scholar Awards
2002 Academy of Behavioral Medicine Research Neal E. Miller New Investigator Award
2003 National Alliance for Research on Schizophrenia and Depression Young Investigator Award

B. Selected peer-reviewed publications (in chronological order).

1. **Knutson, B**.,Wolkowitz, O. M., Cole, S. W., Chan, T., Moore, E. A., Johnson, R. C., Terpstra, J., Turner, R. S., & Reus, V. I. (1998). Selective alteration of personality and social behavior by serotonergic intervention. American Journal of Psychiatry, 155, 373-379.
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C. Research Support

Ongoing Research Support

1 R21 AG030778-01, Knutson (PI) 08/15/07 - 06/30/09
NIH/NIA
Title: Anticipation of reward and risk across the lifespan
Goals: To investigate behavioral and neural responses during anticipation of financial reward and risk in young, middle-aged, and old samples.
Role: PI

2006-07-004, Knutson (PI) 01/01/07 - 12/31/08
FINRA Investor Education Fund
Title: Individual differences in financial risk taking across the lifespan
Goals: To investigate the influence of psychological individual difference variables on real world economic decision making.
Role: PI

1 R01 MH076021-01A1, Johnson (PI) 11/01/06 - 06/30/11
NIH/University of Miami
Title: Neural and Cognitive Facets of Reward Responsivity in Bipolar Disorder

Goals: To elucidate how neuronal deficits are translated into cognitive and behavioral processes that trigger manic symptoms in contexts involving research and how this understanding could help identify times when people are at increased risk for manic symptoms and strategies to prevent symptoms.
Role: Co-Investigator

5 R01 MH068879-02, Tsai (PI) 09/30/05 - 08/31/08
NIH
Title: Cultural Variation in Affect Valuation
Goals: To provide empirical support for a theory of affect valuation that integrates theoretical and psychometrically validated models of affect, values and goals in an educationally and cultural diverse sample of American and Chinese college students, investigate the mechanisms underlying cultural differences in affect valuation, and to examine how affect valuation shapes affective experience.
Role: Co-PI

Completed Research Support
1 R03 DA020615-01, Knutson (PI) 09/01/05 - 08/31/07
NIH/NIDA
Title: Affective neuroscience probes of cigarette craving
Goals: The goal of this protocol is to determine whether neural and behavioral responses to cigarette cues are enhanced under conditions of drug availability versus unavailability. A second goal is to determine whether neural and behavioral responses to cigarette cues predict subsequent smoking behavior.
Role: PI

5 R01 MH59259, Gotlib (PI) 04/01/04 - 12/31/06
NIH/NIMH
Title: Information processing biases in depression
Goals: The major goal of this protocol is to study information processing biases in depression.
Role: Co-Investigator, one year

NARSAD Young Investigator Award, Knutson (PI)09/01/03 – 08/31/05
NARSAD
Title: FMRI of reward processing in unipolar depression
Goals: The goal of this protocol is to determine whether neural and behavioral reactivity to rewarding incentives are blunted in outpatients with unipolar depression and whether the degree of compromise predicts responsiveness to psycho- or pharmaco-therapeutic intervention.
Role: PI

1 R03 MH66923-01, Knutson (PI) 09/01/02 – 02/01/05
NIH/NIMH
Title: A neurobehavioral probe of human reward function
Goals: The goal of this protocol is to establish the monetary incentive delay task as a valid and reliable functional magnetic resonance imaging (FMRI) index of individual differences in neural responsiveness to reward. A second goal is to examine the effects of reward probability on brain activation.
Role: PI

OTL Research Incentive Award, Knutson (PI) 07/01/02 – 12/31/04
Office of Technology and Licensing, Stanford University
Title: Visualizing the subcortex
Goals: The goal of this protocol is to optimize FMRI methods for visualizing functional activations in artifact-prone regions of the basal forebrain, ventral striatum, and brainstem.
Role: PI

Section II – Sponsor and Co-Sponsor Information

1. Research Support Available for Proposed Studies

NIH / NIA
1 R21 AG030778-01
Title: Anticipation of reward and risk across the lifespan
PI: Knutson
Award Dates: 08/15/07 - 06/30/09
Amount: $450,000

NIH / NIA
5 R37 AG008816-17
Title: Socioemotional functioning in adulthood and old age
PI: Carstensen
Award Dates: 09/01/05 - 08/31/10
Amount: $2,659,896

FINRA Investor Education Fund
2006-07-004
Title: Individual differences in financial risk taking across the lifespan
PI: Knutson
Award Dates: 01/01/07 - 12/31/08
Amount: $401,514

CDEHA / Stanford University / NIH / NIA
5 P30 AG017253
Title: Incentive learning and decision-making in younger and older adults
Project PI: Garber Seed PIs: Knutson, Samanez-Larkin
Award Dates: 07/01/07 – 01/30/09
Amount: $40,000

2. Sponsor's Previous Fellows/Trainees

R. Alison Adcock, M.D., Ph.D. (postdoctoral fellow). Assistant Professor, Center for Cognitive Neuroscience, Duke University, Durham, NC

Sasha E. B. Gibbs, Ph.D. (postdoctoral fellow). Research Assistant Professor, Helen Wills Neuroscience Institute, University of California at Berkeley, Berkeley, CA

Camelia Kuhnen, Ph.D. (graduate student). Assistant Professor, Department of Finance, Northwestern University, Chicago, IL.

Lisbeth Nielsen Ph.D. (postdoctoral fellow). Extramural Grants Administrator, National Institute of Aging, National Institutes of Health, Bethesda, MD.

Richard Peterson, M.D. (clinical fellow). Clinical Intern, Psychiatric Services, San Mateo County Clinic, San Mateo, CA.

3. Training Plan, Environment, Research Facilities

Progress Monitoring & Evaluation

During the two remaining years of his doctoral program, the trainee will spend the majority of his time on research through the completion of his Ph.D. The trainee and sponsor will meet weekly to discuss the progress of the proposed studies. The trainee will also discuss his dissertation progress formally in a series of quarterly meetings with the dissertation committee (Brian Knutson, Laura Carstensen, Anthony Wagner, Samuel McClure, Alan Garber). The sponsor and committee will continually provide feedback and guidance to the trainee in these meetings.

Theory Development

Both Brian Knutson and Laura Carstensen will assist the trainee in the theoretical development of this line of proposed studies. The proposed studies lie at the intersection of psychology, neuroscience, and economics. Each field offers its own theoretical account of age-related changes in decision-making. Knutson and Carstensen will assist the trainee in integrating theories of age-related neural decline, declines in cognitive ability, changes in motivation associated with perceived time perspective, and age-related increases in investment experience. One goal for the trainee is to work with both Knutson and Carstensen to begin to develop a comprehensive theory of aging and economic decision-making that will integrate all of these perspectives. The trainee will work with these faculty members on a series of book chapters and journal reviews to begin to develop this integrative theory.

Training Through Collaboration

All research activities will be carried out not only with the advice and counsel of the sponsor, Brian Knutson, but also with project collaborators. The trainee will collaborate with Stanford psychologist and neuroscientist, Samuel McClure on proposed studies 1 and 2. McClure is a leading expert on computational models of reinforcement learning. The trainee will consult with McClure on the use of computational models to examine age differences in both behavioral and neuroimaging data. An adeptness with computational models will be essential in the trainee's future career.

The third proposed study on decision-making will be completed as part of a collaboration with Stanford health economist Alan Garber (dissertation chairperson) and Northwestern finance professor Camelia Kuhnen. Garber and Kuhnen will provide specific guidance on the use of Bayesian rational actor models to characterize single trial behavior. Through regular consultation with these collaborators, the applicant will gain essential knowledge of standard economic models and build a stronger econometric base to prepare for a career in the decision sciences.

The training provided through these collaborations will far exceed any knowledge that could be gained through formal coursework and will significantly enhance the trainee's experimental skill set.

Ph.D. Program Requirements

Coursework
The trainee has already completed all required coursework. As described above, the one-on-one training he will receive from project collaborators will far exceed the training potential of standard coursework.

Teaching
Experience in supervised teaching is an integral part of the trainee's program. The trainee has already completed three out of five of these required assistantships. Greg recently volunteered to be a head teaching assistant for an undergraduate statistics course and has previously served as an assistant for courses such as Longevity and Cognition and the Brain. During the first year of NRSA support, Greg will complete his two remaining requirements by teaching courses on statistics and longevity.

Mentoring

Undergraduate Research Assistant Management
The trainee has over the last three years and will continue to supervise several undergraduate research assistants for the duration of the program. In addition to gaining management training, the trainee will also gain the experience of mentoring students preparing to further their academic pursuits in psychology. The trainee will make a commitment to providing undergraduate research assistants with valuable experience that will adequately prepare them for graduate studies. Two current research assistants have decided to complete theses in the lab, and the trainee will serve as their primary supervisor.

University Colloquia and Departmental Meetings

Seminars & Colloquia
Every week, the trainee will attend an area seminar in the Psychology Department, which focuses on the study of emotion. The purpose of the seminar is to share research plans, methods, and feedback in an interactive setting that promotes collaboration within the area.

The trainee will attend the departmental colloquia series, which features speakers from outside institutions. When speakers visit, the trainee will also frequently attend student lunches in which the trainee can engage in a one-on-one discussion with the speaker. He has recently had the opportunity to consult in this setting with John Cacioppo, Michael Gazzaniga, and Randy Gallistel.

Additionally, the trainee will regularly attend and annually present at events sponsored by several research centers at Stanford, including the Stanford Center on Longevity, the Stanford Roybal Center for Advancing Decision Making in Aging, and the Center on the Demography and Economics of Health and Aging. These centers will also serve as a resource to the trainee for feedback and conceptual discussions with faculty and other researchers from a variety of disciplines in addition to Psychology such as Gerontology, Medicine, and Economics.

Research Meetings
Each week, the trainee attends regular lab meetings. The trainee will present quarterly in lab meetings to discuss proposed research ideas, methods, and receive feedback on preliminary results. The trainee attends weekly meetings with the Symbiotic Project on Affective Neuroscience lab and the Life-span Development lab.

Overview of Training Plan

The training plan described above will assist the trainee in successfully completing the proposed research projects as well as further developing a strong base of training to achieve his primary career goals. Combining skills and experiences gained through teaching, mentoring, and collaborating with other faculty within and outside of the department will set the foundation for an outstanding career in academic research.

Research Environment and Facilities

The Stanford environment is ideal for Greg's proposed research, since it is highly supportive, interactive, stimulating, and focused on the neuroscience of incentive processing and decision-making. Greg will have open access to the many resources of the department. Stanford Psychology has a networked computer environment of approximately 100 Apple PCs, 100 Windows PCs, and 25 UNIX workstations. In addition there are two RAID fileservers providing several Terabytes of storage and 10 networked black-and-white and color laser printers. Each student and faculty member is provided with a free account enabling unlimited use of the Department's UNIX system and also accounts on university-wide UNIX systems used for email, simulations, data analysis, program development, data transfer, etc. Space and equipment (i.e., computers, software, button boxes) for behaviorally piloting the proposed studies are available in the sponsor's laboratory.

In addition, the Brain Imaging Analysis Center (BIAC; which the sponsor oversees with two other faculty) is located in the Psychology Department and includes (1) a centralized server and mass storage device; (2) six

work stations; (3) an engineering specialist to design pulse sequences, coils, optimize scanning parameters, and improve reconstruction software; (4) an imaging analysis specialist to advise on the use of software for image analysis and to create software for novel experimental problems; and (5) a systems administrator to configure the hardware and software environment. BIAC resources are available to all Psychology Department researchers and provide state-of-the-art support for experimental design and image analysis.

The Richard M. Lucas Center for Magnetic Resonance Spectroscopy and Imaging opened in July 1992, and has recently undergone expansion with additional office and lab space for two additional magnets. The center is one of the few centers in the world with major centralized resources devoted to research in MR and angiography where both basic and clinical scientists are housed. The center provides office and laboratory facilities for over 7 full-time faculty and their complement of postdoctoral fellows and students. The center supports collaborative and original research using volunteers and patients as well as intact animal models. The Lucas Center has 14,000 square footage of space, entirely dedicated for imaging and spectroscopy research, and is located on the Stanford campus, one block from the School of Medicine and Stanford Hospital, and a 10 minute walk from the Psychology Department. Magnet facilities include a 1.5T GE Signa whole body scanner, a 3.0T GE Signa scanner, and a Bruker (GE) CSI Omega MR system which has a 4.7T 40 cm (horizontal) bore magnet (currently ramped to 2T) with shielded Accustar gradients, for animal and in vitro research. Apple- and PC-based data acquisition systems are available for real-time physiological monitoring, as is a computer controlled pump that can produce physiologically relevant flow waveforms and a flexible, PC-controlled stepper-motor system having 3 axes of motion for phantom development. The center is well-suited for handling the scanning of patients and healthy volunteers safely and comfortably.

General computer facilities in the center, exclusive of an additional 3D imaging laboratory, include 3 SUN 3 workstations, 22 SPARCstations (three with video output capability), two Silicon Graphics Indigo-Elan R4000 workstations, with numerous ancillary X-terminals, tape and optical disk peripherals, and terabytes of magnetic disk storage. In addition, there are numerous Apple and PC computers, which are networked through Ethernet and a Kinetics gateway to the Lucas Center subnet. This switched 10/100 base T subnet, which exclusively services all of the RSL computers and MR scanners, is linked through a router and fiber optic cable to the Medical Center Ethernet backbone and to all the other MR and CT imagers, the Stanford campus network (including the Psychology Department), MRSRL, and to the Internet. The computer and networking systems are maintained and updated by the Lucas Center's Ph.D. systems analyst.

4. Number of Fellows/Trainees to be Supervised

The sponsor will supervise three other Ph.D. candidates and one post-doctoral fellow during the applicant's fellowship.

5. Applicant's Qualifications and Potential

I write to express unqualified support for Gregory Samanez-Larkin's candidacy for an NRSA predoctoral training fellowship. I have known Greg for five years, since the time he began working at Stanford as a research coordinator in Laura Carstensen's laboratory. Relative to the approximately 100 other graduate students I have encountered in my five years at Stanford, Greg falls in the top 5% in his preparedness for a career in Cognitive Neuroscience research.

I first met Greg when he coordinated a project between Carstensen's and our labs. He had already accomplished far more than other graduate applicants, having won an award for his undergraduate thesis at Michigan (which was later published) as well as post-baccalaureate work on the cognitive neuroscience of aging with Carstensen and postdoctoral fellow Joe Mikels. Thus, I was happy to hear that Greg applied for graduate training at Stanford and even more delighted when he accepted our offer. Perhaps because of his practical and rigorous training in the Carstensen lab, Greg immediately dived into research the summer before his graduate training officially began.

For the last three years, Greg has served as the anchor in our laboratory's attempts to extend neural studies of incentive processing (using FMRI) into the domain of aging. For his first year project, Greg investigated neural and behavioral correlates of incentive processing across the life span using a task developed for FMRI in our laboratory. Not only has he obtained a number of NIA seed grants for these investigations, Greg has also been instrumental in obtaining larger grants to fund this research program (i.e., an NIA R21 and a FINRA Investor Education Fund Grant. This work has already culminated in two first authored publications for Greg in top tier journals (i.e,. Nature Neuroscience and Psychological Science). NIA director, Richard Hodes, selected his paper in Nature Neuroscience as one of the top ten scientific advances to emerge from NIA funded laboratories in 2007. To summarize some of these findings, consistent with notions of asymmetric processing of gains and losses with aging, we found that older adults showed preserved affective and neural responses during anticipation of monetary gains but not losses. These findings may have profound implications for the effects of aging on decision-making. However, we are just beginning systematic and programmatic research in this area, and already have extremely promising initial behavioral results to guide studies over the next few years. It is fair to say that largely due to Greg's efforts, this extension of our original research into the realm of aging has not only been possible, but also far more successful than I could have imagined at the outset.

Greg is a model colleague, not only conducting his own research with innovation, persistence, and enthusiasm, but also supporting other laboratory members in experimental design, analysis, and coding. Thus, I wholeheartedly support his application and hope that you will give it your most serious consideration. I am tremendously invested in seeing this young researcher obtain the best training possible to pursue his ideas and a career in research. I believe that the expertise available in our laboratory will provide him with these opportunities. Greg's career goals are to direct research that contributes insight into the neural substrates underlying cognition and decision-making, in areas that have relevance to public health, with an emphasis on aging. Given the fit between his aspirations, our location's resources, and the ongoing mission of the graduate fellowship, I can think of no better candidate than Gregory Samanez-Larkin.

Kirschstein–NRSA Individual Fellowship Application

Checklist

Applicant completes Section 1.

NAME OF APPLICANT *(Last, first, middle initial)*

Samanez Larkin, Gregory, Russell

Section 1 – Applicant

A. TYPE OF APPLICATION

☐ NEW application *(This application is being submitted to the PHS for the first time.)*

☒ REVISION of application number 1 F31 AG032804-01

(This application replaces a prior unfunded version of a new or competing continuation application.)

☐ COMPETING CONTINUATION of award number _____

(This application is to extend a funded award beyond its current award period.)

☐ CHANGE of Sponsoring Institution Name of former Institution:

B. ASSURANCES/CERTIFICATIONS

The following assurances/certifications are made and verified by your signature in Item 15 on the Face Page of the application. • Debarment and Suspension • Delinquent Federal Debt • Drug-Free Workplace *(Applicable only to new or revised applications being submitted to the PHS for the first proposed project period-- Type 1.)* Descriptions of individual certifications are included in Part III, Policies, Assurances, Definitions, and Other Information, of the application instructions. If unable to certify compliance, provide an explanation and place it after this page. Use a Continuation Page.

C. KIRSCHSTEIN–NRSA SENIOR FELLOWSHIP APPLICANTS ONLY

1. PRESENT INSTITUTIONAL BASE SALARY

Amount _____ Academic Period/number of months _____

2. STIPEND/SALARY DURING FIRST YEAR OF PROPOSED FELLOWSHIP

a. Stipend requested from PHS

Amount _____ Number of months _____

b. Supplementation from other sources

Amount _____ Number of months _____ Type (*sabbatical leave, salary, etc.)* _____ Source _____

D. TUITION and FEES

Predoctoral applicants should list estimated combined costs of tuition and fees. Postdoctoral applicants should list the estimated costs for the tuition and fees for courses planned that support the research training experience. For postdoctoral applicants, those courses should be described under Section D. Research Design and Methods of the Research Training Plan. Health insurance for predoctoral and postdoctoral fellowships is now paid as part of the institutional allowance. Senior Fellowship applicants should omit this section.

☐ None Requested

Funds Requested:

Year – 01	Year – 02	Year – 03	Year – 04	Year – 05	Year – 06 (when applicable)
$31,596.00	$31,596.00				

Section II – Sponsoring Institution

ASSURANCES/CERTIFICATIONS *(See instructions.)*

In signing the application Face Page, the authorized organizational representative agrees to comply with the following policies, assurances and/or certifications when applicable. Descriptions of individual assurances/certifications are provided in Part III, Policies, Assurances, Definitions, and Other Information. If unable to certify compliance, where applicable, provide an explanation and place it after this page. •Human Subjects Research •Research Using Human Embryonic Stem Cells •Research on Transplantation of Human Fetal Tissue •Women and Minority Inclusion Policy •Inclusion of Children Policy •Vertebrate Animals• •Debarment and Suspension •Drug-Free Workplace *(applicable to new [Type 1] or revised [Type 1] applications only)* •Non-Delinquency on Federal Debt •Research Misconduct •Civil Rights (Form HHS 441 or HHS 690) •Handicapped Individuals (Form HHS 641 or HHS 690) •Sex Discrimination (Form HHS 639-A or HHS 690) •Age Discrimination (Form HHS 680 or HHS 690) •Recombinant DNA Research, Including Human Gene Transfer Research •Financial Conflict of Interest (except Phase I SBIR/STTR) •Smoke Free Workplace •Prohibited Research •Select Agents and Toxins

Personal Data on Kirschstein–NRSA Individual Fellowship Applicant

Clip this form to the signed original of the application after the checklist. Do not duplicate.

NAME OF APPLICANT *(Last, first, middle initial)*

Samanez Larkin, Gregory, Russell

The Public Health Service has a continuing commitment to monitor the operation of its review and award processes to detect—and deal appropriately with—any instances of real or apparent inequities with respect to age, sex, race, or ethnicity of the proposed applicant.

To provide the PHS with the information it needs for this important task, complete the form below and attach it to the signed original of the application after the Checklist. **Do not attach copies of this form to the duplicated copies of the application.**

Upon receipt of the application by the PHS, this form will be separated from the application. This form will **not** be duplicated, and it will **not** be a part of the review process. Data will be confidential, and will be maintained in Privacy Act record system 09-25-0036, "Grants: IMPAC (Grant/Contract Information)." The PHS requests the last four digits of the Social Security Number for accurate identification, referral, and review of applications and for management of PHS grant programs. Although provision of this portion of the Social Security Number is voluntary, providing this information may improve both the accuracy and speed of processing the application. Please be aware that no individual will be denied any right, benefit, or privilege provided by law because of refusal to disclose this section of the Social Security Number. The PHS requests the last four digits of the Social Security Number under Sections 301(a) and 487 of the PHS Acts as amended (42 U.S.C 241a and U.S.C. 288). All analyses conducted on the date of birth, gender, race and/or ethnic origin data will report aggregate statistical findings only and will not identify individuals. If you decline to provide this information, it will in no way affect consideration of your application. Your cooperation will be appreciated.

DATE OF BIRTH (*MM/DD/YY*)	05/13/1980	SEX/GENDER
SOCIAL SECURITY NUMBER (last 4 digits only)	XXX-XX- 0173	☐ Female ☒ Male

ETHNICITY

1. Do you consider yourself to be Hispanic or Latino? (See definition below.) Select one.

Hispanic or Latino. A person of Mexican, Puerto Rican, Cuban, South or Central American, or other Spanish culture or origin, regardless of race. The term, "Spanish origin," can be used in addition to "Hispanic or Latino."

☐ **Hispanic or Latino**

☒ **Not Hispanic or Latino**

RACE

2. What race do you consider yourself to be? Select one or more of the following.

☐ ***American Indian or Alaska Native.*** A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

☐ ***Asian.*** A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

☐ ***Black or African American.*** A person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black" or African American."

☐ ***Native Hawaiian or Other Pacific Islander.*** A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

☒ ***White.*** A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

☐ Check here if you do not wish to provide some or all of the above information.

Section IV – Appendix

1. Samanez-Larkin, G.R., Gibbs, S.E.B., Khanna, K., Nielsen, L., Carstensen, L.L., & Knutson, B. (2007) Anticipation of monetary gain but not loss in healthy older adults. Nature Neuroscience, 10(6), 787-791.

2. Samanez-Larkin, G.R., Hollon, N.G., Carstensen, L.L., & Knutson, B. (2008) Individual differences in insular sensitivity during loss anticipation predict avoidance learning. Psychological Science, 19(4), 320-323.

nature neuroscience

Anticipation of monetary gain but not loss in healthy older adults

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Although global declines in structure have been documented in the aging human brain, little is known about the functional integrity of the striatum and prefrontal cortex in older adults during incentive processing. We used event-related functional magnetic resonance imaging to determine whether younger and older adults differed in both self-reported and neural responsiveness to anticipated monetary gains and losses. The present study provides evidence for intact striatal and insular activation during gain anticipation with age, but shows a relative reduction in activation during loss anticipation. These findings suggest that there is an asymmetry in the processing of gains and losses in older adults that may have implications for decision-making.

Over the past several decades, scientists have made rapid progress toward determining the effects of aging on cognition. Both behavioral and neuroimaging studies show that there is a strong negative relationship between age and cognitive performance across many types of tasks[1,2]. However, a growing body of research also suggests that many affective abilities do not decline with age, and that in some cases they may improve. Accumulating behavioral evidence suggests that older adults perform relatively better on tasks that involve the processing of emotional stimuli[3]. Socio-emotional selectivity theory postulates that age-related attempts to optimize emotional well-being[4] generate increased positive emotional experiences and/or decreased negative emotional experiences over the life span[5]. To date, however, very few neuroimaging studies have focused on changes in emotion with age[6,7], with only one prior study examining changes in incentive processing over the life span[8].

Studies of brain structure and chemistry provide some evidence for age-related decline. These studies have specifically shown significant structural atrophy of the caudate, insula and prefrontal cortex, as well as global declines in dopamine receptors in the striatum and the prefrontal cortex[9–12]. Currently, the implications of these anatomical and chemical changes for brain function during incentive processing remain unclear.

The monetary incentive delay (MID) task[13] is designed to elicit both affective responses and neural activation in mesolimbic regions during incentive processing. Event-related functional magnetic resonance imaging (fMRI) studies that have used this task in adolescents and younger adults have implicated striatal and insular activation in the anticipation of uncertain gains and losses[14,15]. Because healthy older adults report preserved (or even enhanced) positive affective experience relative to younger adults on a day-to-day basis[16], we predicted that both subjective responses and neural activation in anticipation of rewards would be preserved in a healthy older sample. We compared subjective and neural responses to incentives between healthy younger and older adults.

RESULTS

Self-reported affect

Younger and older adults reported similar subjective responses during anticipation of gains, but differed during anticipation of losses. An analysis of variance (ANOVA) conducted on cue-elicited affect yielded a significant three-way valence (gain, loss) by magnitude ($0.00, $0.50, $5.00) by age (young, old) interaction ($F_{2,21} = 9.142$, $P = 0.001$), indicating that the younger and older adults differed in their ratings of gain and loss cues (**Fig. 1**, **Supplementary Fig. 1** online). Within-group ANOVAs (corrected for four comparisons, $P < 0.013$) revealed significant main effects of magnitude on positive arousal ratings for gain cues ($F_{2,10} = 34.59$, $P < 0.0005$) and negative arousal ratings for loss cues ($F_{2,10} = 39.492$, $P < 0.0005$) in younger adults. Older adults showed a comparable magnitude effect on positive arousal ratings for gain cues ($F_{2,10} = 29.564$, $P < 0.0005$), but a weaker, albeit still significant, magnitude effect on negative arousal for loss cues ($F_{2,10} = 9.825$, $P < 0.013$). Between-group comparisons indicated that younger adults reported greater negative arousal for large loss cues ($5.00) than did older adults ($T_{22} = 5.90$, $P < 0.008$), but ratings for the other cues did not significantly differ (all $P > 0.008$). See **Supplementary Results** online for further analyses of self-reported affect.

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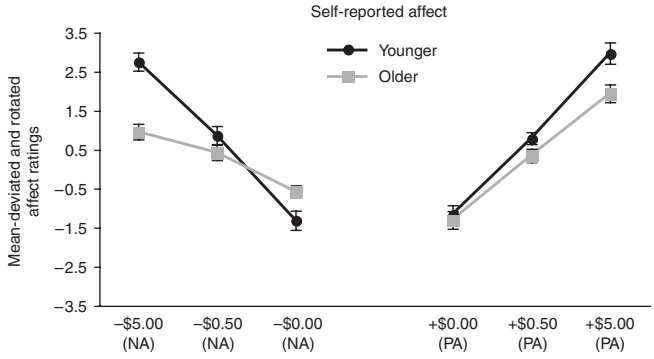

Figure 1 Age by valence by magnitude interaction in post-task cue ratings. Younger adults self-reported monotonically increasing NA for loss cues and PA for gain cues in the anticipatory period. Older adults reported monotonically increasing PA for gain cues, but less significant increases in NA for loss cues. Error bars represent s.e.m.

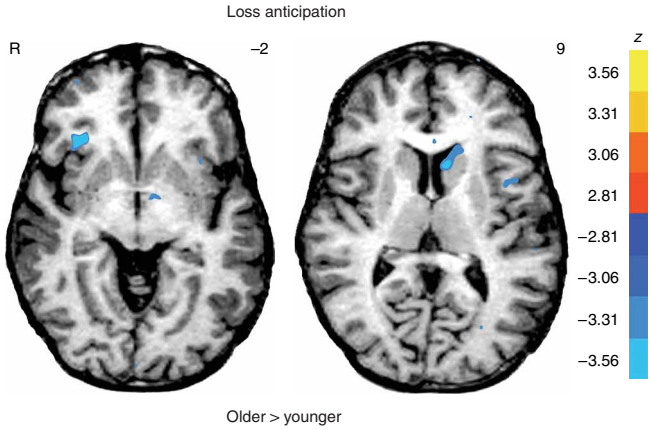

Figure 2 Between-group *t*-tests of loss versus nonloss anticipation contrast maps (older adults > younger adults; SVC, $z > 2.81$; $P < 0.005$ uncorrected). Negative *z*-scores showed less activation for older adults in both the anterior insula and medial caudate. *S* value for each axial image is listed in the upper right ($S = -2$ through anterior insula; $S = 9$ through striatum).

Neural activity

Localization analyses confirmed that during gain anticipation, both younger and older adults showed significant ventral striatal, medial caudatal and anterior insular activation at the global threshold ($P < 0.0001$; **Supplementary Fig. 2** and **Supplementary Table 1** online). During loss anticipation, younger adults showed significant medial caudatal and anterior insular activation at the global threshold ($P < 0.0001$; **Supplementary Fig. 3** online), but showed ventral striatal activation only at the small-volume-corrected threshold ($P < 0.005$). Older adults showed anterior insular activation only at the small-volume-corrected threshold ($P < 0.005$). Between-group *t*-tests revealed no differences during gain anticipation, and also showed that younger adults had greater activation of medial caudate and anterior insula during loss anticipation at the small-volume-corrected threshold ($P < 0.005$; **Fig. 2** and **Supplementary Table 2** online).

Volume of interest (VOI) analyses confirmed that although both younger and older adults activated the ventral striatum, medial caudate (MCAUD) and anterior insula (AINS) during gain anticipation, only younger adults showed significant MCAUD and AINS activation during loss anticipation.

A mixed-model ANOVA of anticipatory activation in the right ventral striatum yielded a significant interaction of valence and magnitude ($F_{2,21} = 3.916$, $P < 0.05$), but a nonsignificant interaction of valence, magnitude and age ($F_{2,21} = 1.50$, $P = 0.25$), suggesting that activation in the ventral striatum was greater for gain than for loss anticipation, and did not differ between younger and older participants (**Supplementary Results**, **Supplementary Discussion** and **Supplementary Figs. 4** and **5** online). Cue-elicited affect was also correlated with activation in the ventral striatum across individuals. Self-reported positive arousal correlated with activation during gain anticipation ($R = 0.42$, $P < 0.05$; **Supplementary Figs. 6** and **7** online), but self-reported negative arousal did not correlate with activation during loss anticipation ($R = 0.21$, $P = 0.16$; **Supplementary Results**).

A mixed-model ANOVA of anticipatory activation in the left MCAUD yielded a significant three-way interaction of valence, magnitude and age ($F_{2,21} = 5.35$, $P < 0.05$; **Fig. 3**). Within-group ANOVAs (corrected for four comparisons, $P < 0.013$) revealed significant linear main effects of magnitude on MCAUD activation for gain ($F_{2,10} = 8.44$, $P < 0.001$) and loss cues ($F_{2,10} = 20.40$, $P < 0.0005$) in younger adults. Older adults, however, showed a significant linear magnitude effect for gain cues ($F_{2,10} = 15.82$, $P < 0.005$), but not loss cues ($F_{2,10} = 1.07$, $P = 0.38$). For full activation time courses see **Supplementary Figure 8** online. Cue-elicited affect was also correlated with activation in the left MCAUD across individuals. Self-reported positive arousal did not correlate with caudatal activation during gain anticipation ($R = -0.01$, $P = 0.47$), but self-reported negative arousal correlated with caudatal activation during loss anticipation ($R = 0.42$, $P < 0.05$; **Supplementary Fig. 6**).

A mixed-model ANOVA of anticipatory activation in the right AINS yielded a significant three-way interaction of valence, magnitude and age ($F_{2,21} = 3.95$, $P < 0.05$) (**Fig. 4**). Within-group ANOVAs (corrected for four comparisons, $P < 0.013$) revealed significant linear main effects of magnitude on AINS activation for gain ($F_{2,10} = 14.549$, $P < 0.005$) and loss cues ($F_{2,10} = 20.571$, $P < 0.005$) in younger adults. Older adults, however, showed a significant linear magnitude effect for gain cues ($F_{2,10} = 71.351$, $P < 0.0005$) but not loss cues ($F_{2,10} = 1.546$, $P = 0.24$). For full activation time courses see **Supplementary Figure 9** online. Cue-elicited affect was also correlated with activation in the right AINS across individuals. Self-reported positive arousal correlated with insular activation during gain anticipation ($R = 0.41$, $P < 0.05$; **Supplementary Fig. 6**), and self-reported negative arousal correlated

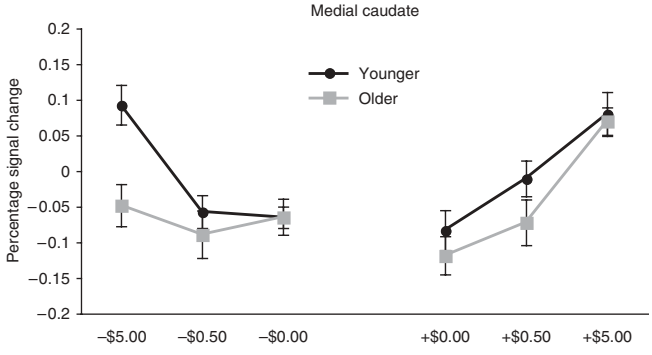

Figure 3 BOLD activation extracted from the medial caudate at anticipation. An age by valence by magnitude interaction shows that younger adults had increasing activation for both gain and loss cues in the anticipatory period, but that older adults had increasing activation for gain, but not loss cues. Error bars represent s.e.m. See **Supplementary Figure 8** for full activation time courses.

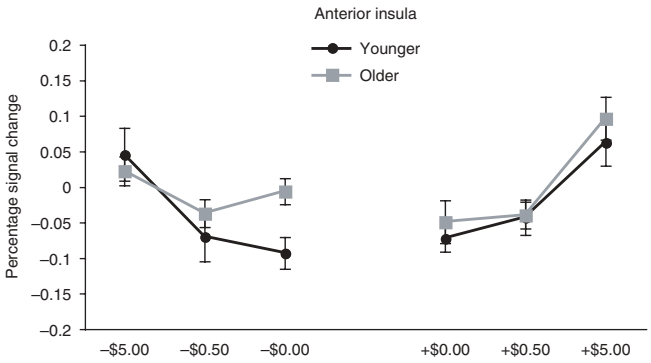

Figure 4 BOLD activation extracted from the anterior insula at anticipation. An age by valence by magnitude interaction shows that younger adults had increasing activation for both gain and loss cues in the anticipatory period, but that older adults had increasing activation for gain but not loss cues. Error bars represent s.e.m. See **Supplementary Figure 9** for full activation time courses.

with insular activation during loss anticipation ($R = 0.38$, $P < 0.05$; **Supplementary Fig. 6**).

For analyses of neural activity during incentive outcomes see **Supplementary Results** and **Supplementary Figures 10**, **11**, and **12** online.

DISCUSSION

Neither self-reported affect nor brain activation data yielded evidence of a difference between younger and older adults during gain anticipation, but both suggested a difference between these groups during loss anticipation. Our neuroimaging findings add at least two significant contributions to our self-report findings. First, little is presently known about mesolimbic function in older adults during basic incentive processing tasks, and functional neuroimaging affords a first glimpse at how activation in these regions may be affected by age. Second, many behavioral studies suggest that healthy older adults report reduced experience of negative emotions. The present findings provide physiological evidence suggesting that these age differences may not purely reflect biases in self-reports, although future research will have to further clarify the relationship between neural activation and self-reported emotion.

The lack of differences between younger and older adults in ventral striatal activation during gain anticipation may seem surprising in light of documented age-related impairments on reward reversal learning tasks. For instance, relative to younger adults, a previous study found reduced ventral striatal activation in older adults engaged in a reward reversal learning task[8]. In that study, however, older subjects also performed more poorly on the task. In the present experiment, the simpler design of the MID task elicited equivalent performances from younger and older adults. Together, these findings suggest that ventral striatal activation during reward anticipation may not be as compromised by age as are the neural substrates recruited in the course of reversing reward associations (for example, ventrolateral prefrontal cortex[17]). Future research will have to specifically disentangle reward anticipation from reward reversal to fully test this possibility.

Although older adults did not differ significantly from younger adults during gain anticipation, they did differ during loss anticipation. Specifically, affective data indicated that older adults experienced less negative arousal (**Supplementary Results**), and neural data indicated that they showed less activation of the insula and caudate when exposed to loss cues. It is unlikely that the reduced neural activation during loss anticipation was a result of a general lack of response in these brain regions in older adults, as the same regions showed significant activation during gain anticipation. An asymmetry between positive and negative emotional experience has been documented in older adults in a number of behavioral studies using a variety of tasks[18]. Interpreted through the lens of socioemotional selectivity theory, age-related sparing of positive emotional experience may be related to efforts to optimize emotional experience as one approaches the end of life[4]. One aspect of this optimization may involve reducing negative arousal during anticipation of negative events. Notably, older adults did not show reduced neural responsiveness to loss outcomes themselves, as both older and younger adults had similar responses to loss outcomes (**Supplementary Results**). Although the present findings cannot establish whether reduced neural and affective responsiveness to loss anticipation results from effortful processing on the part of older adults, these findings are consistent with other reports indicating that older adults experience reduced negative emotion[19,20].

Recent evidence distinguishes brain mechanisms involved in learning about positive and negative incentives[21], and it is possible that older adults' reduced neural and affective responses during loss anticipation resulted from slower learning of the significance of loss cues, even though all participants received training on the task before scanning. However, a second experiment indicated that there were no differences between age groups in overall performance for learning of either gain or loss contingencies (**Supplementary Results**, **Supplementary Table 3** and **Supplementary Figs. 13** and **14** online). Reduced responsiveness to potential loss in the absence of cumulative learning deficits is consistent with a previous study comparing the performance of younger and older adults in a gambling task. That study[22] found that older adults performed as well as younger adults on a gambling task, despite showing skin conductance responses before choosing options associated with higher gains rather than losses[22]. Even after learning has taken place (or in the absence of learning), incentives still may vary in their impact. Regardless of the source, reduced responsiveness to anticipated loss may still have significant consequences for decision-making in older adults. Future research will have to explore this possibility.

Although an asymmetry in loss anticipation may enhance well-being in older adults, it may also engender biases in certain decision-making scenarios. For instance, risk assessment might be altered. Findings from this line of basic research may have implications for scientists' understanding of how processes underlying decision-making change with age, and might eventually facilitate the identification of markers for suboptimal decision-making in older adults[23].

METHODS

Participants. Twelve younger adults (age 19–27, six female) and 12 older adults (age 65–81, six female) participated in a MID task while undergoing fMRI. All participants gave written informed consent, and the experiment was approved by the Institutional Review Board of the Stanford University Medical School.

Care was taken to assess potential confounding baseline differences in both self-reports and neural activation between age groups. The two groups did not differ in years of education ($P > 0.05$), in trait measures of affect ($P > 0.05$), in personality variables ($P > 0.05$) or in blood oxygen level–dependent (BOLD) signal amplitude ($P > 0.05$) as assessed by a visual localizer task (**Supplementary Methods**, **Supplementary Table 4** and **Supplementary Fig. 15** online).

MID task. A canonical version of the MID task[24] was modified in two ways. First, the display duration of each frame of the task was lengthened to accommodate differences in vision and reading time among younger and older participants. Second, the traditionally used abstract symbolic cues (that is,

closed circles and open squares) were replaced with literal symbolic cues (Win $0.00, Win $0.50, Win $5.00, Lose $0.00, Lose $0.50, Lose $5.00) that explicitly stated whether the trial was a potential gain or loss trial as well as the amount of money at stake. Across both runs, the entire task included 180 10-s trials. During each MID trial, participants viewed one of six different cues displaying the amount of money that could be gained or lost on that trial (anticipation phase). If the participant responded quickly enough to a subsequent target, he or she either gained or avoided losing money (outcome phase) (**Supplementary Fig. 16** online). The six trial types were each presented 30 times (15 times per run) in an individually randomized order for each participant. The hit and miss rate for individual participants was manipulated by altering the average duration of the target with an adaptive timing algorithm that was originally set to the individual's mean reaction time in prescan practice, and then followed his or her performance across the scanned blocks, such that the individual would successfully hit the target on approximately 66% of the trials for each cue type. Individual functional volume acquisitions were time-locked to cue onsets using a drift adjustment algorithm, and thus coincided with each frame of the trials. After the MID task scan, participants rated their affective reactions to each of the cues on seven-point Likert scales (that is, valence from 'very negative' to 'neutral' to 'very positive' and arousal from 'not at all aroused' to 'highly aroused').

Hits were calculated as the percentage of correct responses per condition (that is, the button press occurred during target presentation). Ratings of cue-elicited valence and arousal were mean-deviated within individual across cues and plotted in a euclidean two-dimensional space. These dimensions were then rotated by 45° to derive measures of positive arousal (PA; PA = arousal/$\sqrt{2}$ + valence/$\sqrt{2}$] and negative arousal (NA; NA = arousal/$\sqrt{2}$ – valence/$\sqrt{2}$] (ref. 25). Actual hit rate, cue-elicited PA for gain cues and cue-elicited NA for loss cues were analyzed with mixed-model analyses of variance (ANOVAs) with incentive valence (gain, loss) and magnitude ($0.00, $0.50, $5.00) as within-subject factors, and age (younger, older) as the between-subject factor. In the event of a significant interaction, PA and NA ratings were compared across all magnitude conditions for each group with within-subject ANOVAs (corrected for four comparisons, $P < 0.013$) and direct comparisons were made between groups for each cue with between-subject *t*-tests (corrected for six comparisons, $P < 0.008$). Further analyses isolated differences within groups in both valence and arousal using *t*-tests (corrected for eight comparisons, $P < 0.006$).

fMRI acquisition and analysis. Imaging of the MID task was done using a 1.5-T General Electric MRI scanner with a standard quadrature head coil. Twenty-four 4-mm-thick slices (in-plane resolution, 3.75 × 3.75 mm; no gap) extended axially from the midpons to the top of the skull; this volume provided adequate spatial resolution of subcortical regions of interest (for example, midbrain, ventral striatum) while omitting only the base of the cerebellum or crown of the skull in some participants. Functional scans of the entire brain were acquired every 2 s (repetition time, 2 s) with a T2*-sensitive in-out spiral pulse sequence (echo time, 40 ms; flip, 90°) specifically designed to minimize signal dropout at the base of the brain[26]. High-resolution structural scans were subsequently acquired using a T1-weighted spoiled gradient recalled acquisition in steady state sequence (repetition time, 100 ms; echo time, 7 ms; flip, 90°), which facilitated subsequent localization and coregistration of functional data.

Analyses focused on changes in brain activation during anticipation (that is, after participants saw cues but before they responded to targets) and outcome (that is, after participants received feedback about their success and monetary gains/losses) for both gain and loss trials. All analyses were conducted using Analysis of Functional Neural Images software[27]. For preprocessing, voxel time series were concatenated across runs, sinc interpolated to correct for non-simultaneous slice acquisition within each volume and corrected for three-dimensional motion. Visual inspection of motion correction estimates confirmed that no subject's head moved more than 2 mm in any dimension from one volume acquisition to the next. Data were then bandpass filtered to admit frequencies between 10 and 90 s, and the percentage signal change was calculated for each voxel with respect to the mean activation over the entire experiment.

Preprocessed time series data for each individual were analyzed with multiple regression[28]. The regression model consisted of a set of four orthogonal regressors of interest: gain ($0.50, $5.00) versus nongain ($0.00) anticipation, loss ($0.50, $5.00) versus nonloss ($0.00) anticipation, gain (hit: $0.50, $5.00) versus nongain (miss: $0.50, $5.00) outcome, and nonloss (hit: $0.50, $5.00) versus loss (miss: $0.50, $5.00) outcome. Additional covariates included two orthogonal regressors highlighting the periods of interest (anticipation and outcome), six regressors describing residual motion and six regressors modeling baseline, linear and quadratic trends for each experimental session. Regressors of interest were convolved with a gamma-variate function that modeled a prototypical hemodynamic response[29] before inclusion in the regression model. Maps of *t*-statistics representing each of the regressors of interest were transformed into *z*-scores, slightly spatially smoothed to account for anatomical variability (kernel full-width half-maximum = 4 mm), resampled at 2 mm^3 and spatially normalized by warping to Talairach space. Statistical maps were then generated for the younger and older age groups using one-sample *t*-tests. Thresholds for statistical significance within the predicted volumes of interest (that is, striatum, anterior insula and mesial prefrontal cortex) were determined by a local small-volume correction (six 6-mm-diameter spheres or approximately ten 4-mm^3 voxels corrected at $P < 0.05$, yielding a threshold z of 2.81, $P < 0.005$, uncorrected) and required a minimum cluster of eight face-to-face, contiguous 2-mm^3 resampled voxels. Thresholds for statistical significance outside of the predicted volumes of interest were set using a global family-wise error rate that corrected for gray matter volume in subcortical and mesial prefrontal cortical regions (approximately 500 4-mm^3 voxels corrected at $P < 0.05$, yielding a threshold z of 3.89, $P < 0.0001$, uncorrected[13]) and required a minimum cluster of eight face-to-face, contiguous 2-mm^3 resampled voxels.

Group analyses consisted of two types: localization and decomposition. For the localization analyses, direct *t*-tests compared contrast coefficient maps within each group. The goal of the localization analysis was to verify that a priori regions of interest were activated in both age groups, as well as to identify new regions that might be correlated with regressors of interest for one group but not the other. For the decomposition analyses, VOIs were specified by imposing 6-mm-diameter spheres at foci defined a priori in regions of interest in the ventral striatum, medial caudate, anterior insula and mesial prefrontal cortex[24,30]. Care was taken to ensure that data from VOIs included only gray matter for each individual (see **Supplementary Methods** and **Supplementary Table 5** online). Activation time courses were extracted and averaged from these VOIs by trial type. Peak anticipatory signal change (at a 6-s lag) was then compared using mixed-model ANOVAs with incentive valence (positive, negative), magnitude ($0.00, $0.50, $5.00) and subsequent outcome (hit, miss) as within-subject factors, and age group (younger, older) as the between-subject factor for each VOI. Outcome was included in the model to verify that signals extracted during the anticipatory period were not related to outcome activation. In the event of a significant interaction, values were compared across incentive and nonincentive conditions for each group using within-subject ANOVAs (corrected for four comparisons, $P < 0.013$). Peak outcome signal change (at a 6-s lag) was also compared using mixed-model ANOVAs with incentive valence (positive, negative), magnitude ($0.00, $0.50, $5.00) and outcome (hit, miss) as within-subject factors, and age group (younger, older) as the between-subject factor for each VOI. In the event of a significant interaction, values were compared across hits and misses for incentive conditions (gain $0.50, $5.00 versus fail to gain $0.50, $5.00; avoid loss $0.50, $5.00 versus lose $0.50, $5.00) for each group with within-subject *t*-tests (corrected for four comparisons, $P < 0.013$). No direct tests between groups for each of the individual six trial types were performed to avoid confounding differences in hemodynamic modulation between age groups as suggested by a recent review of BOLD imaging and aging[31]. Therefore, *post hoc* VOI analyses for both anticipation and outcome focused on linear effects within groups.

Correlational analyses assessed the relationship between self-reported anticipatory affect and anticipatory activation in the ventral striatum, medial caudate and anterior insula. A measure of cue-elicited affect change (PA, NA, valence and arousal) was computed by averaging self-reports for incentive cues ($0.50, $5.00) and subtracting self-reports for nonincentive cues ($0.00). Similarly, a measure of anticipatory activation change (ventral striatum, medial caudate and anterior insula) was computed by averaging the activation for incentive cues ($0.50, $5.00) and subtracting activation for nonincentive cues ($0.00). The correlations between these change scores as reported are one-tailed as a

result of our a priori directional hypotheses that activation during gain would correlate with PA and activation during loss would correlate with NA.

For methodological details of the follow-up behavioral learning study, see the **Supplementary Methods** and **Supplementary Figure 17** online.

Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS

G.S.L., S.G., L.N., L.C. and B.K. designed the experiment. G.S.L., S.G. and K.K. collected and analyzed the data. All of the authors contributed to the preparation of the manuscript.

COMPETING INTERESTS STATEMENT

The authors declare no competing financial interests.

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Research Report

Individual Differences in Insular Sensitivity During Loss Anticipation Predict Avoidance Learning

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ABSTRACT—*The anterior insula has been implicated in both the experience and the anticipation of negative outcomes. Although individual differences in insular sensitivity have been associated with self-report measures of chronic anxiety, previous research has not examined whether individual differences in insular sensitivity predict learning to avoid aversive stimuli. In the present study, insular sensitivity was assessed as participants anticipated monetary losses while undergoing functional magnetic resonance imaging. We found that insular responsiveness to anticipated losses predicted participants' ability to learn to avoid losses (but not to approach gains) in a behavioral test several months later. These findings suggest that in addition to correlating with self-reported anxiety, heightened insular sensitivity may promote learning to avoid loss.*

Detecting and avoiding threats arguably are the most basic of survival skills. In humans, avoidance learning is necessary not only to ensure survival in the face of basic threats (e.g., predators, rotten food), but also to promote optimal responses to more abstract threats in social (e.g., enemies) and economic (e.g., risky investments) domains. Although the ability to anticipate and avoid danger is critical to survival, excessive anticipatory anxiety may contribute to psychopathology.

Scientists have recently used brain-imaging techniques with enhanced spatial and temporal resolution to characterize neural circuitry implicated in anticipation of threats. One region that has consistently been associated with anticipation of threat is the anterior insula (Seymour, Singer, & Dolan, 2007), a region of polymodal association cortex tucked deep within the lateral sulcus between the lateral prefrontal cortex and striatum. Activation of the anterior insula has been observed not only in response to emotionally negative events, but also during anticipation of those events (Kim, Shimojo, & O'Doherty, 2006; Nitschke, Sarinopoulos, Mackiewicz, Schaefer, & Davidson, 2006; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Samanez-Larkin et al., 2007; Seymour et al., 2005). In addition, anticipatory insula activation is associated with (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003) and predicts (Kuhnen & Knutson, 2005) behavioral avoidance of risky options in decision-making tasks.

Whereas insula activation exhibits within-individual variation related to task demands, chronic insular activation differs between individuals, and has been proposed as an endophenotypic marker of anxiety proneness (Paulus & Stein, 2006). Altered insular sensitivity has been observed in several clinical populations with anxiety disorders, including simple phobia, specific phobia, social phobia, posttraumatic stress disorder, obsessive-compulsive disorder, panic disorder, and generalized anxiety disorder (for a review, see Paulus & Stein, 2006). Moreover, studies of healthy, nonclinical samples have demonstrated significant relationships between insular sensitivity and self-report measures of anxiety, such as neuroticism and harm avoidance (Paulus et al., 2003; Stein, Simmons, Feinstein, & Paulus, 2007). In addition, animal studies have shown that specific lesions to insular cortex disrupt taste-aversion learning in rats (Cubero, Thiele, & Bernstein, 1999; Yamamoto, Shimura, Sako, Yasoshima, & Sakai, 1994).

Although there is converging evidence that activation of the insula plays a role in anticipatory anxiety, previous studies have not tested the functional hypothesis that anticipatory insular activation predicts learning to avoid loss. In the study reported

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here, we examined whether a neural index of insular sensitivity to anticipated loss would predict behavioral loss-avoidance learning several months later.

METHOD

Eleven younger (ages 19–27; 5 female, 6 male) and 12 older (ages 65–81; 6 female, 6 male) adults participated in two sessions. In the first, all 23 participants played a monetary incentive delay task while undergoing functional magnetic resonance imaging (fMRI) to localize brain regions involved in the anticipation of monetary incentives. On each trial, participants viewed one of six cues (lose $0.00, lose $0.50, lose $5.00, gain $0.00, gain $0.50, gain $5.00) on a computer monitor (2 s). After a delay (2–2.5 s), a star appeared briefly (100–400 ms), and participants attempted to press a button while the star was still present on the screen. An adaptive algorithm was used to control the hit rate by setting a deadline for each of the six trial types defined by the cues, such that individuals would respond while the star was present on approximately 66% of the trials for each cue type. When participants responded in time, they received feedback (2 s) that they had avoided losing ("−$0.00") or had gained ("+$0.00," "+$0.50," "+$5.00") the amount of money indicated by the preceding cue (in the loss and gain conditions, respectively); late responses produced feedback that participants had lost ("−$0.00," "−$0.50," "−$5.00") or had not gained ("+$0.00") money Participants were told that their goal was to earn as much money as possible, and they were subsequently paid in real cash the cumulative amount of money they had won, as indicated by the outcomes displayed. There were 30 trials for each condition, ordered randomly.

Brain-imaging analyses focused on changes in activation during anticipation (i.e., after participants saw cues but before they responded to targets) and outcome (i.e., after participants received feedback about their success and monetary losses or gains), for both loss and gain trials. We conducted a whole-brain multiple regression analysis with four independent and orthogonal regressors of interest: loss versus nonloss anticipation, gain versus nongain anticipation, nonloss versus loss outcome, and gain versus nongain outcome.[1]

In the second session, administered 8 to 10 months later, participants performed a monetary incentive-learning task (functional imaging data were not collected in this session). On each trial, one of three pairs of fractal images was presented. In one pair (loss avoidance), choice of one image had a .6 probability of avoiding a $1 loss, and choice of the other had a .3 probability of avoiding a $1 loss. In a second pair (gain acquisition), choice of one image had a .6 probability of yielding a $1 gain, and choice of the other image had a .3 probability of yielding a $1 gain. In a third pair, neither image was associated with monetary outcomes. Assignment of pairs to conditions and images to outcomes was counterbalanced across participants.

Each trial began with a fixation cross (2 s), followed by a pair of images. Participants were given an unlimited amount of time to choose an image. The selected image was highlighted on the screen (2 s), and then the monetary outcome ("−$1," " $0," or "+$1") was displayed (2 s). There were 120 trials, consisting of 40 trials in each of the three conditions. Participants were urged to earn as much money as possible by learning to choose the image with the higher probability of avoiding a $1 loss when the loss-avoidance pair was presented and the image with the higher probability of a $1 gain when the gain-acquisition pair was presented. Participants were paid in real cash the cumulative amount of money they won, as indicated by the outcomes displayed. Performance was calculated as the percentage of correct choices (i.e., the high-probability cue) in each monetary condition (loss avoidance, gain acquisition). Unlike in the first session, hit rate was not manipulated in this session. Group differences in performance were examined with independent-sample t tests.

To explore the relationship between neural activation in the first session and behavioral learning in the second, we conducted a whole-brain regression analysis that identified brain regions whose activation correlated significantly with subsequent incentive learning (i.e., correlation between voxel coefficients, from the whole-brain regression model described earlier, during each condition of the incentive-anticipation task and performance in each condition of the incentive-learning task). The threshold for statistical significance was set using a global family-wise error rate ($z > 3.89$, $p < .0001$ uncorrected) and required a minimum cluster of fifteen 2-mm^3 voxels. Confirmatory partial correlational analyses (controlling for age) were performed by extracting mean peak anticipatory signal change from regions identified in the whole-brain analysis (adjusted within individuals to ensure that regions contained gray matter only). The signal change score for each individual was computed as a measure of sensitivity (signal change on $0.50 and $5.00 trials minus signal change on $0.00 trials, separately for loss and gain).

RESULTS

Younger and older adults did not differ in their performance in any condition of the learning task, and so these groups were combined in the following analyses. Results of the whole-brain analysis revealed a significant association between activation in the right anterior insula (peak-voxel Talairach coordinates: 30, 20, 3) during loss avoidance and loss-avoidance learning, $z = 4.71$, $p_{rep} = .999$, effect size: $R^2 = .62$ (Fig. 1a). No other brain regions showed a significant association with loss-avoidance learning.

This relationship was confirmed in a volume-of-interest analysis, which revealed a significant partial correlation (con-

[1]For a complete description of the task, fMRI acquisition parameters, and the full regression model used to localize changes in neural activation, see Samanez-Larkin et al. (2007).

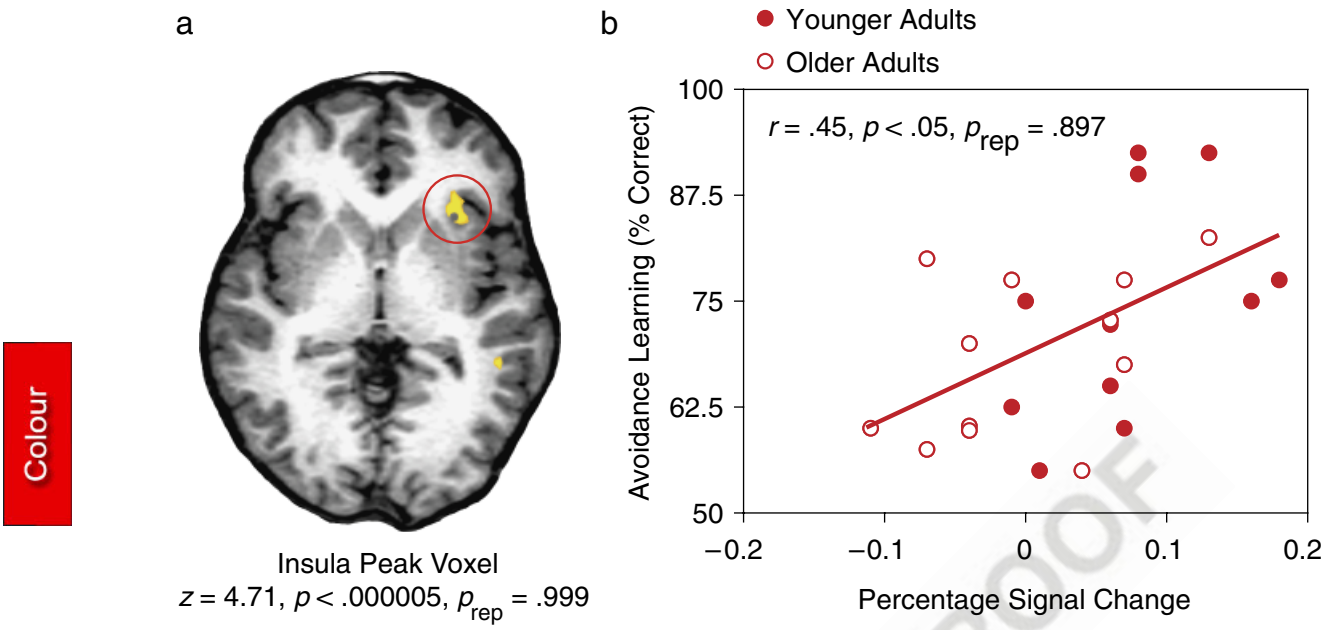

Fig. 1. Correlation between insular activation during loss anticipation and behavioral loss-avoidance learning. The illustration (a) depicts the location and corresponding statistics for the peak cluster of activation in the right anterior insula, identified during the whole-brain analysis (map threshold: $p < .0005$). The scatter plot (b) reveals the correlation (and corresponding statistics, controlling for age) between mean percentage signal change (*x*-axis) extracted from anatomically defined regions of interest in the anterior insula in individual participants and subsequent loss-avoidance learning (percentage correct; *y*-axis). The trend line depicts the correlation across all participants, but individual results for younger adults and older adults are labeled with separate markers.

trolling for age) between percentage signal change in the anterior insula during loss anticipation and subsequent behavioral loss-avoidance learning, $r = .45$, $p_{rep} = .897$ (Fig. 1b).[2] However, performance in gain-acquisition learning was not significantly correlated with activation in any brain region. Further, the correlation between insular activation during loss anticipation and future loss-avoidance learning ($r = .45$) was significantly greater than the correlation between insular activation during loss anticipation and future gain-acquisition learning ($r = -.10$), $z = 5.8$, $p_{rep} = .999$. Additionally, insular activation during gain anticipation was not significantly correlated with either gain-acquisition learning or loss-avoidance learning ($rs = .11$ and $.04$, respectively). The association between insular activation and loss-avoidance learning was specific to activation during anticipation, as insular activation in response to loss outcomes was not significantly related to learning of either gain acquisition or loss avoidance.

DISCUSSION

This is the first demonstration that individual differences in insular sensitivity presage future loss-avoidance behavior. Because the present study localized insular sensitivity with a task devoid of performance differences, individual differences in insular sensitivity cannot be attributed to differential incentive outcomes. The results are consistent with the recent hypothesis that a loss-prediction signal (i.e., heightened anxiety during loss anticipation), rather than global sensitivity to loss (i.e., heightened anxiety during both loss anticipation and loss outcomes), can promote avoidance behavior (Paulus & Stein, 2006). The findings also provide neural evidence consistent with the historic hypothesis that a loss-prediction signal that generates increased anxiety can promote instrumental avoidance behavior (Mowrer, 1956).

These results suggest that a neural endophenotypic marker of the affective experience of anxiety may also promote avoidance learning—a skill that can confer survival value in threatening environments. This potential functional advantage may help to explain why anxiety-related traits persist in humanity's genetic endowment, even as environmental threats vary.

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[2]Controlling for age did not reduce the significance of this effect. The simple correlation between anterior insular activation and avoidance learning was also significant, $r = .50$, $p_{rep} = .939$.

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