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January 16, 2018

Re: Cognitive Aging and Memory Intervention Core Pilot Proposals

Dear Dr. Dockery and MBRF Trustees,

Members of the Cognitive Aging and Memory Intervention Core met to discuss the pilot grant proposals submitted to the Core, including the input that we obtained from external reviewers. To summarize the results of that meeting, we are recommending that two of three submitted proposals be considered for funding by the MBRF. Below, we provide the scores obtained from external reviews and a summary of the impact statement and key points from the review and our Core committee discussion. Proposals were rated on a 1-9 scale, with 1 being the best overall score.

| PI | <u>Proposal</u> | <u>R1</u> | <u>R2</u> | Mean |
|------------|----------------------------------|-----------|-----------|------|
| Levin | Scamming proposal | 3 | 3 | 3 |
| Bowers | NIRS intervention | 2 | 5 | 3.5 |
| Williamson | Vagal nerve stimulation proposal | 4 | 7 | 5.5 |

All three applications were deemed to have merit according to reviewers. As evident from these scores, two of the three applications were rated significantly better than the third. The Williamson application, which received the weakest score, was rated less well in large part because plans for collaborative inter-institutional logistics had not been fully developed prior to the submission. Summaries of the two proposals that we are recommending for funding are provided below. The recommended proposals have similar overall mean impact scores.

Vulnerability of older adults to financial deception schemes. Levin, PI. This proposal from Dr. Levin and collaborators at Universities of Miami, Arizona and Florida aims to test an intervention to reduce susceptibility to financial scams in older adults. The application was judged to be significant because of its potential for clinical translational impact. Specifically, it was anchored in important social and cognitive issues associated with advanced age. The investigators provide evidence that age-associated declines in memory, attention, and certain executive functions contribute to increased vulnerability. The proposed study will develop a prototype scam detection intervention software that may be used in the future to help prevent seniors from being scammed. One reviewer noted that similar software exists, however, the members of the Core who evaluated the reviews concluded that this study could result in new and potentially more powerful methods and also would pilot the use of these in a small sample of older adults. They would also create in lab scamming susceptibility tools and ultimately evaluate cognitive, physical and socio-effective correlates

of scam susceptibility. In summary, the proposed study was judged to have considerable clinical and public health significance in the context of cognitive aging and memory. The approach was judged to be sound overall. Finally, it appears that this study has a high probability of leading to a future extramural funded clinical trial.

A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults. Bowers, Pl. This study will involve a collaboration between MBI investigators at the University of Florida and the University of Arizona. The goal of the study is to evaluate the potential of near infrared non-invasive brain stimulation for remediating age-related cognitive decline. This study proposes a neuromodulation method that is highly novel, based on use of infrared light to impact underlying mitochondrial activity in the brain. The investigators provided compelling pilot data to support the mechanistic action of the stimulation method. The proposed mechanism of action differs from other non-invasive neuromodulation approaches that focus on synaptic plasticity (e.g., transcranial direct current stimulation). This study proposes to evaluate this method in a pilot clinical trial of 52 older adults, of whom half will receive active intervention vs. a sham intervention procedure. At baseline, prior to the intervention, cognitive and neuroimaging assessments will be performed, with assessments repeated immediately post intervention and at 8 weeks after intervention completion. Although one reviewer expressed the need for more initial pilot work, the Core committee felt that the innovation of the method and the potential for high impact provided added justification and support for the approach. The proposal was judged to be clinically and scientifically significant given that there is a need for additional approaches to remediate cognitive decline in older adults and its focus on modulation of cerebral metabolic factors underlying age-associated cognitive dysfunction. The approach was deemed sound and highly innovative. The study was judged to have a high probability of leading to future extramural funded clinical trial.

We will not provide an impact statement on the third proposal given that our evaluation of the reviews suggest that this proposal will likely be viable in the future, but that the principal investigator needs to address logistical concerns regarding inter-institute collaboration. There were also some details in the proposal that the Core committee felt needed to be addressed before this application could be viewed as viable for potentially moving forward in the process.

To summarize, based on the reviews and adjudication of the proposals that have been invited and submitted for consideration, the Cognitive Aging and Memory Intervention Core voted unanimously that the two proposals described above be recommended for consideration for funding. The budgets requested for these proposals appear well justified and reasonable given the scope of work required for each study. If both are funded, we would request a total budget of \$120,000/year for two years with this amount divided between the two studies equally.

We appreciate your support and encouragement regarding the Cognitive Aging and Memory Intervention Core and also with respect to the pilot proposal process. We look forward to your consideration of the two recommended proposals and would be happy to discuss them in greater detail.

Best wishes,

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PROJECT SUMMARY

Scamming, the cheating of people out of money or information, is a pressing public health problem associated with decreased quality of life, functional dependence, and negative health outcomes. Individuals in late middle and late adulthood are at particular risk for scamming, but the cognitive, socio-affective, and neurobiological mechanisms underlying this increased risk with advanced age are unclear. Moreover, there are currently no effective interventions to reduce scam susceptibility in these age groups. The long-term goal of this multisite collaboration is to propose such an intervention; specifically, we will develop and validate a decisionsupportive device to reduce online scam susceptibility in late midlife and old age. The web tool MERLIN (Merlin, according to the legend, served as advisor to King Arthur) will alert Computer users to the possibility that an email is a scam and assist them, in an age-tailored fashion, in the art of scam detection. As summarized in Figure 1, the goals of this pilot grant are to develop a prototype of the MERLIN web tool (Aim 1), build the experimental infrastructure required to test its efficacy in the lab (Aim 2), and investigate the cognitive, socioaffective, and health-related functional correlates of scam susceptibility of late midlife and older adults to provide a more comprehensive understanding of susceptibility profiles (Aim 3) and to generate data that will allow finetuning of MERLIN to age-group specific vulnerabilities. Achieving these integrated aims across the three collaborating sites will provide a strong foundation for an R01 funding application. Successful completion of this pilot project will show feasibility of the study approach, demonstrate an organized and effective multi-site data collection strategy, and provide the crucial pilot data and effect sizes to determine sample size and design characteristics for an R01 submission. Importantly, NIH currently has a particular interest in deception and aging as reflected in recent calls (e.g., PAR16-448: Decision Making and Aging in Alzheimer's Disease; RFA-AG-18-010: Uncovering the Causes, Contexts, and Consequences of Elder Mistreatment). Our proposed research to deploy and study the efficacy of MERLIN as an intervention tool to reduce online deception in late midlife and aging falls directly into this realm. For an R01 submission we plan an extension of the proposed work in a large and more diverse sample (including independent adults living with mild MCI) for a full validation of the MERLIN

tool in-depth investigation of cognitive, socioaffective, and neurobiological brain structure (e.g., function)[1] susceptibility profiles in late midlife and old age. The long-term goal of our collaboration is to implement a comprehensive risk assessment and warning framework against scamming in advanced age.

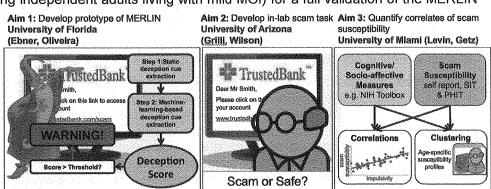


Figure 1. Overview of grant aims

SPECIFIC AIMS

Aim 1 (Ebner/Oliveira, University of Florida): Develop a prototype of MERLIN, an automated warning tool to support decision-making online. The browser plug-in MERLIN will scan email text to deliver alerts when an email is deemed suspicious, by combining methods from machine learning with our previous work identifying the particular psychological principles of influence or "weapons" (e.g., authority, commitment, liking, social proof) [2] used by scammers to lure users into visiting web pages that procure personal information or into clicking on links to malicious downloads. Aim 2 (Grilli/Wilson, University of Arizona): Develop the in-lab Scam Identification Task (SIT), a new behavioral task to effectively "scam people in the lab" and will allow validation of the efficacy of MERLIN under controlled conditions. Aim 3 (Levin/Getz, University of Miami): Quantify the cognitive, physical, and socio-affective correlates of scam susceptibility to tailor MERLIN to age-specific user profiles. Scam susceptibility will be measured using self-reported measures, SIT (from Aim 2), and performance on our previously developed Phishing Internet Task (PHIT) [3], an ecologically valid task to elicit scam-related behavior in the real world, by sending simulated phishing emails to participating Computer users, unbeknownst to them, and measuring the extent to which users fall for the "attacks" (i.e., clicking on the link present in the emails).

SIGNIFICANCE

Scamming is a major issue and late midlife and older adults are at particular risk. In 2010, financial fraud cost older adults \$2.9 billion [4]. Metropolitan Insurance Company data from 2010 showed that one in five Americans aged 65 years or older fell victim to some form of financial abuse [5-7]. These estimates, combined with the rapidly growing proportion of older adults in the US and other industrialized nations projected by the Census Bureau, raise concern that increased vulnerability to deception will directly impact quality of life, lead to loss of independence, and produce significant financial hardship for a large segment of the aging population. Scamming is prevalent at all ages but the age 50+ years demographic is most vulnerable [8-10].

The internet has increased the reach and dangers of scamming. Scam-related deception is becoming increasingly sophisticated and difficult to track. Phishing programs, defined as computerized software designed to deceive and exploit individuals through fraudulent electronic media such as emails and pop-up messages, are particularly insidious and effective, especially in older individuals, given that older compared to younger adults have less experience with computers and lower confidence in their IT skills [11, 12].

Our preliminary data using the PHIT task on 52 younger (18–31 yrs.) and 31 older (61–89 yrs.) participants showed that older Computer users clicked on more links in simulated phishing emails (number of clicks M=1.71, SD=1.14) than younger users (M=1.33, SD=0.64; t=-2.93, p=0.008). This was combined with significantly lower susceptibility awareness in older than younger adults. Further,

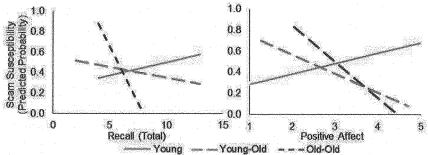


Figure 2. Associations between susceptibility to deception online and cognitive and socio-affective capacities

greater susceptibility to phishing was associated with lower memory recall, lower positive affect, and higher levels of state anxiety in old-old (75–89 yr.) participants (*N*=17) [13] (**Figure 2**).

Age-related change in cognitive, physical, socio-affective, and neurobiological systems may underlie increased scam susceptibility with advanced age. Multidisciplinary evidence from cognitive neuroscience, psychology, and economics offers an intriguing neurobiological framework for understanding why late midlife and older adults are at greater risk for scams [3, 14]. Recent research suggests an age-related asymmetry wherein younger and older adults experience similar levels of positive affect, but older adults report lower levels of negative affect [15]. Similarly, older adults show reduced attention to and memory for negative material [16]. Neuroimaging data further reveals that in anticipation of a monetary gain, younger and older adults show recruitment of the same brain region (nucleus accumbens), however, during loss anticipation, younger, but not older adults, show recruitment of the anterior insula [17]. This age-related asymmetry in loss anticipation may increase susceptibility to scams [18] and could be one of the contributing factors to the alarmingly high rates of scamming among older adults.

INNOVATION

The proposed interdisciplinary project combines research in experimental aging with recent advances in decision-making and cybersecurity. It conceptually, methodologically, and translationally extends previous work: (i) The development of MERLIN is based on a paradigm shift in cybersecurity research. It proposes that technical defense solutions alone cannot combat cyber social engineering attacks—rather, human behavior must be considered to bring security information to users in a user-friendly, age-tailored fashion. (ii) In targeting late midlife and older adults, our studies will investigate scam susceptibility in age cohorts that have received little attention with regard to cognitive, physical, and socio-affective changes in their impact on decision-making. In this effort, our project has great potential to conceptually advance a new model of decision-making in aging that considers interpersonal difference variables relating to fraud susceptibility and poor decision-making. (iii) MERLIN will be the first intervention aimed at reducing scam susceptibility in late midlife and old age. The savings to society would be substantial: If this intervention leads to even a 10% decline in scam susceptibility among older Computer users, it could save millions of dollars every year, and therefore have a large translational impact. (iv) In a multi-methods approach to measuring scam susceptibility, the newly developed in-lab SIT will allow for efficient assessment of susceptibility under controlled lab conditions, facilitating an in-depth characterization of susceptibility profiles in the targeted age groups.

APPROACH

Aim 1: Develop a prototype of MERLIN, an automated machine learning-based browser plugin that warns onthe-spot about cues to deception in email messages in an age-targeted and user-friendly fashion. This pilot version of MERLIN will be developed as a Chrome browser extension for Gmail. Future work will extend the tool to other browsers and email programs as part of our R01 proposal for broader application. In a typical use case, a user will install the MERLIN tool by clicking on a single link on our website. As part of the installation process, the user will be prompted to input their age, gender, and other demographic information which will ultimately be used to tailor the parameters of MERLIN to a personalized profile. MERLIN will run in the background automatically scanning the text of emails whenever the user opens an email on the Gmail webpage (Figure 3). Based on text analysis, MERLIN will assign the email a "Deception Score" ranging from 0 (low likelihood of scam) to 100 (high likelihood of scam). If the Deception Score passes a threshold, MERLIN will pop up a warning message indicating that the email is suspicious. For the prototype version of MERLIN, both the threshold for determining whether an email is suspicious and the content of the warning message will be identical for all users. As we learn more about the factors associated with scam susceptibility (by leveraging data collected under Aims 2 and 3), the levels of these thresholds will be set according to age-group specific user profiles pertaining to cognitive and socio-affective measures (towards a personalized use of MERLIN). As an example of age-group specific behavior of MERLIN, our data analysis from Aims 2 and 3 may determine the old-old (75+ yrs.) profile as particularly susceptible to the weapons of authority and reciprocation and characterized by executive function

deficits. MERLIN will tailor its behavior accordingly toward an oldold user by, for example, only generating warnings for authority and reciprocation, using color highlight for weapons in the email, and employing a high frequency of brief warnings in large font size in light of cognitive and sensory impairments in this age cohort. **Our pilot data supports the feasibility of developing MERLIN.** Ebner and Oliveira asked users to forward emails present in their spam folder [3]. A random selection of spam emails was used as a training set for development of a machine-learning classifier. Using the Random Forest algorithm, we predicted with 90% accuracy which age group (young vs. old) a spam email targeted. In addition to demonstrating feasibility of the proposed tool development, these data show that email-based social engineering attacks are already age-tailored to deceive users.

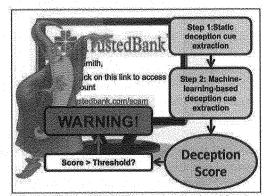


Figure 3. The MERLIN warning tool architecture

Aim 2: Development of in-lab assessment of scamming susceptibility and investigation of MERLIN's warning efficacy. We will develop and validate a lab task, the Scam Identification Task (SIT), to effectively measure individual differences in susceptibility to scam emails. This task will allow us to assess the efficacy of MERLIN under controlled conditions. We hypothesize that older relative to younger adults will perform worse on the SIT when unaided, and MERLIN will improve scam detection among late middle-aged and older adults.

<u>Participants.</u> 80 healthy young (18-30 yrs.) and 80 healthy middle-aged and older adults (50-90 yrs.) will be recruited from the Tucson community screened for neurologic, cognitive (cutoff score of 26 on the Montreal Cognitive Assessment; MoCA), and psychiatric conditions, leveraging existing recruitment logistics for these age groups at UA.

Scam Identification Task (SIT). The objective of the SIT is to efficiently measure individual differences in susceptibility to scam emails by simulating the real-world computing demands of the PHIT [3]. In SIT participants will make a series of forced-choice decisions about emails. On each trial of the task, participants will be presented with an email that they must classify as either a "scam" email they should ignore or a "safe" email they should reply to. In reality, 50% of the messages will be scam emails, which will be the most effective phishing emails from the PHIT, while the remaining 50% will be newly developed "safe" emails. "Safe" emails will be designed to mimic an important email that would normally require a response (e.g., an email from the electricity company about a late payment). To incentivize performance on the task, participants will be paid 10 cents for each correct answer and penalized 10 cents for each incorrect answer. To minimize learning effects, feedback on performance will not be given after each trial, but will instead be presented as aggregate performance every 10 minutes. To ensure no participant loses money on the task, participants will start the game with a balance of \$10. Participants in the experimental condition will use a version of SIT with the MERLIN plugin and will receive targeted warnings as they work through the emails. Participants in the control condition will do a standard version of SIT, with no MERLIN plugin.

Analysis. Our main analysis will focus on the experimental vs. control between-group comparison of false negative rates (scam emails classified as safe) and false positive rates (safe emails classified as scams). We predict that older individuals in the control group will be more likely to classify emails as safe leading to a higher false negative rate and lower false positive rate, relative to older individuals in the experimental group (MERLIN). Whether younger adults in the control group demonstrate similar performance relative to the experimental group is an empirical question. Assuming that MERLIN has a moderate to large effect on false negative rates in older adults (effect size of 0.35), our sample size of 40 participants per cell will give us 87% power to detect this effect at a threshold of p=0.05. In addition we will compare behavior between age groups in the control condition. Assuming a similar age effect to that observed in the PHIT (effect size 0.31), 40 participants in each group will give us 78% power to detect such an effect at a threshold of p=0.05.

Aim 3: Quantify cognitive, physical, and socio-affective correlates of scam susceptibility. We will employ a selected test battery to identify correlates of deception susceptibility among cognitively healthy late middle and older adults. Within this aim, we will measure participants' actual behavioral response when faced with deceptive stimuli and their self-reported level of scam susceptibility. We hypothesize that older compared to younger adults, and those with evidence of executive dysfunction, increased frailty symptoms, and a negative socio-affective profile (e.g., more negative affect, more loneliness) will show higher scam susceptibility.

<u>Participants.</u> 100 healthy middle-aged and older adults (50–90 yrs.) will be recruited from the community and the Memory Disorders Clinic at UM, Miller School of Medicine. Participants will be screened to rule out neurologic, cognitive (cutoff of 26 on the MoCA), and psychiatric conditions, applying recruitment logistics in place at UM.

In addition to well-validated screening measures of cognition (MoCA) [19] and intelligence (The National Adult Reading Test-Revised) [20], we will administer the NIH Toolbox-Cognitive Module and the Hopkins Verbal Learning Test-Revised (HVLT-R) [21]. Mood will be assessed with: (i) the Beck Depression Inventory-II (BDI-II) [22] and (ii) the Beck Anxiety Inventory (BAI) [23]. Socio-affective function will be measured with: (i) the General Trust Scale [24] and (ii) the Social and Emotional Loneliness Scale for Adults [25]. Physical/health functional status will be assessed with Fried's criteria [26], based on: (i) weight loss, (ii) fatigue, (iii) weakness (grip strength), (iv) slow gait speed, and (v) low physical activity. We will measure scam susceptibility in three ways: (i) a self-reported measure of scam susceptibility (What Would You Do (WWYD) questionnaire; developed by Levin et al.), which consists of 29 items that present various common scamming scenarios; (ii) the SIT developed in Aim 2, and (ii) the previously developed PHIT [3].

Analysis. Multiple linear regressions, with age as covariate, will be used to investigate the relationship between the cognitive, physical, and socio-affective measures to performance on the three scam susceptibility tasks (WWYD, SIT, PHIT). 100 participants will allow us to detect small to moderate effects (r=0.275) between scam susceptibility and the other variables at 80% power and a threshold of p<0.05. Further, as a test of the validity of SIT, we will investigate correlations between the different measures of scam susceptibility, i.e. SIT, PHIT and self-reported scam susceptibility. If SIT behavior is truly capturing scam susceptibility then we predict strong correlations between the SIT false negative rate and the likelihood of clicking on simulated phishing emails in PHIT. Conversely, in line with preliminary data from Ebner and Oliveira, we do not predict strong correlations between participants' subjective assessment of scam susceptibility and either their SIT and PHIT behavior.

Anticipated Challenges and Alternative Strategies. The proposed work fits the MBRF Clinical Intervention core call for pilot funding particularly well in its conceptual and methodological innovation and significance in developing an intervention with potential for broad application and translational impact. We recognize that there will be challenges and outline them briefly here, along with potential remediation strategies. Infrastructure and study logistics for PHIT are complex. However, the task has been implemented successfully at UF, including IRB approval. We will leverage implementation at UF for task transfer to UM where we have a broader catchment area of late midlife and older adults. Measurement and analytic approach. Machine-learning approaches complement (or can substitute) conventional statistical analysis to generate profiles based on data collected under Aims 2 and 3 for fine-tuning of MERLIN (Aim 1). Machine-learning models for MERLIN can be trained on existent pilot data from Ebner and Oliveira and other online text sources (e.g., online ads), should Aims 2 and 3 not generate the expected outcomes. However, this significantly smaller and less diverse training data set would result in less accurate and robust algorithms. Study costs. To maximize knowledge gain, we will combine questions that are firmly grounded in the literature with novel, exploratory, and thus riskier questions (e.g., gender differences in scam susceptibility, consideration of age and gender as deceiver characteristics).

Bibliography

- 1. Spreng, R.N., et al., Financial Exploitation Is Associated With Structural and Functional Brain Differences in Healthy Older Adults. J Gerontol A Biol Sci Med Sci, 2017. **72**(10): p. 1365-1368.
- 2. Cialdini, R.B., Influence, Vol. 3, 1987; A. Michel Port Harcourt.
- 3. Oliveira, D., et al. Dissecting spear phishing emails for older vs young adults: On the interplay of weapons of influence and life domains in predicting susceptibility to phishing. in Proceedings of the 2017 CHI Conference on Human Factors in Computing Systems. 2017. ACM.
- 4. MetLife, The MetLife study of elder financial abuse crimes of occasion, desperation, and predation against America's elders. 2011, Metlife Mature Market Institute/National Committee for Prevention of Elder Abuse/Virginia Polytechnic Institute and State University, Metlife Mature Market Institute Westport, CT
- 5. Acierno, R., et al., *Prevalence and correlates of emotional, physical, sexual, and financial abuse and potential neglect in the United States: The National Elder Mistreatment Study.* American journal of public health, 2010. **100**(2): p. 292-297.
- 6. Amstadter, A.B., et al., *Prevalence and correlates of elder mistreatment in South Carolina: the South Carolina elder mistreatment study.* Journal of Interpersonal Violence, 2011. **26**(15): p. 2947-2972.
- 7. Roberto, K.A., P.B. Teaster, and J.O. Duke, *Older women who experience mistreatment:circumstances and outcomes*. J Women Aging, 2004. **16**(1-2): p. 3-16.
- 8. Ruffman, T., et al., Age-related differences in deception. Psychol Aging, 2012. 27(3): p. 543-9.
- 9. Stanley, J.T. and F. Blanchard-Fields, *Challenges older adults face in detecting deceit: the role of emotion recognition.* Psychol Aging, 2008. **23**(1): p. 24-32.
- 10. Sweeney, C.D. and S.J. Ceci, *Deception detection, transmission, and modality in age and sex.* Front Psychol, 2014. **5**: p. 590.
- 11. Dyck, J.L. and J.A.-A. Smither, *Age differences in computer anxiety: The role of computer experience, gender and education.* Journal of educational computing research, 1994. **10**(3): p. 239-248.
- 12. Marquié, J.C., L. Jourdan-Boddaert, and N. Huet, *Do older adults underestimate their actual computer knowledge?* Behaviour & Information Technology, 2002. **21**(4): p. 273-280.
- 13. Ebner, N.C.e.a., Uncovering susceptibility profiles to online deception in aging. In review.
- 14. Samanez-Larkin, G.R. and B. Knutson, *Decision making in the ageing brain: changes in affective and motivational circuits.* Nature Reviews Neuroscience, 2015. **16**(5): p. 278-289.
- 15. Carstensen, L.L., et al., Emotional experience improves with age: evidence based on over 10 years of experience sampling. Psychology and aging, 2011. **26**(1): p. 21.
- 16. Carstensen, L.L., *The influence of a sense of time on human development.* Science, 2006. **312**(5782): p. 1913-1915.
- 17. Samanez-Larkin, G.R., et al., *Anticipation of monetary gain but not loss in healthy older adults.* Nature neuroscience, 2007. **10**(6): p. 787-791.
- 18. Harlé, K.M. and A.G. Sanfey, Social economic decision-making across the lifespan: an fMRI investigation. Neuropsychologia, 2012. **50**(7): p. 1416-1424.
- 19. Nasreddine, Z.S., et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc, 2005. **53**(4): p. 695-9.
- 20. Blair, J.R. and O. Spreen, *Predicting premorbid IQ: a revision of the National Adult Reading Test.* The Clinical Neuropsychologist, 1989. **3**(2): p. 129-136.
- 21. Brandt, J. and R.H. Benedict, *Hopkins verbal learning test--revised: professional manual.* 2001: Psychological Assessment Resources.
- 22. Beck, A.T., R.A. Steer, and G.K. Brown, *Beck depression inventory-II*. San Antonio, 1996. **78**(2): p. 490-8.
- 23. Beck, A.T. and R. Steer, Beck anxiety inventory (BAI). BiB 2010, 1988. 54.
- 24. Yamagishi, T. and M. Yamagishi, *Trust and commitment in the United States and Japan.* Motivation and emotion, 1994. **18**(2): p. 129-166.
- 25. DiTommaso, E. and B. Spinner, *The development and initial validation of the Social and Emotional Loneliness Scale for Adults (SELSA).* Personality and Individual Differences, 1993. **14**(1): p. 127-134.
- 26. Fried, L.P., et al., *Frailty in older adults: evidence for a phenotype.* The Journals of Gerontology Series A: Biological Sciences and Medical Sciences, 2001. **56**(3): p. M146-M157.

MCKNIGHT CROSS-SITE COLLABORATION

Our team is well placed to conduct the planned studies towards our integrated aims. Our group brings together a unique skill set on experimental aging research (Ebner, Grilli, Levin, Getz), decision making (Wilson, Ebner). and computer science (Oliveira), including machine learning approaches for a comprehensive cross-site data collection and data analysis towards a joint R01 grant submission. With regard to clinical translatability, we are operating at the interface of basic and applied human cognitive neuroscience/psychology with ecologically valid tasks. Our collective areas of expertise, in addition to clinical neuropsychology (Grilli, Levin) and computer program development (Ebner, Oliveira), will be major assets for ensuring that we remain on a clear path towards clinical translation and implementation. In regard to our trajectory towards R01 funding, the proposed research will collect the necessary preliminary data and determine effect sizes for MERLIN's efficiency and for uncovering cognitive, physical, and socio-affective mechanisms underlying scam susceptibility. These data will directly relate to a future R01 proposal in which we will study the efficacy of MERLIN in the real world and extend the investigation of cognitive and socio-affective risk profiles to neurobiological factors contributing to scam susceptibility in midlife and old age (PAR16-448: Decision Making and Aging in Alzheimer's Disease; RFA-AG-18-010: Uncovering the Causes, Contexts, and Consequences of Elder Mistreatment). The proposed aims, each developed by PIs with unique expertise at one of the three MBRI sites, will develop a different part of the infrastructure required to test, tailor, and ultimately deploy the MERLIN tool. We expect to complete the proposed three Aims in the two-year time period (see Table 1). Monthly Skype calls, along with two in-person meetings (in Florida to reduce travel costs), will coordinate research across sites and ensure a coherent approach to the joint R01.

Word count: 292 (max 300)

| Site | Year 1 Goal | Site | Year 2 Goal |
|------|---|------|--|
| UF | Build MERLIN prototype | UF | Fine-tune MERLIN; publish tool and apply for patent |
| UA | Develop SIT; run 40 younger and 40 older participants; begin analyzing data | UA | Run 40 younger and 40 older participants; complete data analysis; write up results for publication |
| UM | Run 50 late midlife and older participants; begin analyzing data | UM | Run 50 late midlife and older participants; complete data analysis; write up results for publication |
| | | All | Write and submit R01 proposal |

Table 1. Cross-site goals for Years 1 and 2.

BUDGET AND BUDGET JUSTIFICATION

| Site | Year 1 | Year 2 |
|-------------------------------|-------------|--|
| University of Florida (Aim 1) | | |
| Personnel | \$21,053.61 | \$21,952.01 |
| Supplies | \$1,000.00 | |
| Other costs | | |
| Travel | \$800.00 | and the state of t |
| Subtotal | \$23,053.61 | \$21,952.01 |
| University of Arizona (Aim 2) | | |
| Personnel | \$13,229.57 | \$13,725.56 |
| Supplies | \$1,000.00 | |
| Other costs | \$800.00 | \$800.00 |
| Travel | \$1,000.00 | \$1,000.00 |
| Subtotal | \$16,029.57 | \$15,525.56 |
| University of Miami (Aim 3) | | |
| Personnel | \$17,220.00 | \$17,736.60 |
| Supplies | \$1,000.00 | \$500.00 |
| Other costs | \$1,500.00 | \$1,500.00 |
| Travel | | \$800.00 |
| Subtotal | \$19,720.00 | \$19,936.00 |
| | | |
| Total Budget | \$58,803.18 | \$57,413.56 |

UNIVERSITY OF FLORIDA (UF)

Personnel

Natalie Ebner, PhD, Pl, Associate Professor, University of Florida Term Professor (no salary requested in budget periods 1&2), will, in conjunction with Dr. Oliveira, provide oversight of all aspects of this research project at UF, including communication with the research team at UF and the other sites, development and refinement of the MERLIN tool under Aim 1, and budget management. She will oversee training and mentoring of the participating postdoc and any lab managers and graduate and undergraduate students involved in the project. In close communication with all Pls across the three sites, she will work on data analysis, interpretation of the data, write up of reports, dissemination of the results, and R01 grant submission.

Daniela Oliveira, PhD, PI, Associate Professor, IoT Term Professor (no salary requested in budget periods 1&2), will, together with Dr. Ebner, serve as the liaison between psychology and computer engineering for the machine-learning approach toward MERLIN development. She will be responsible for the cyber-security aspects of the study design and data collection infrastructure. She will work closely with Dr. Ebner in supervision of the machine-learning postdoc. She will also actively participate in results interpretation and dissemination, including grant reports, manuscripts, and R01 submission.

TBA, PhD, Postdoc (40% salary requested in budget periods 1&2), under close supervision of Drs. Ebner and Oliveira, will develop machine-learning algorithms and pattern-recognition methods to identify risk profiles and to automatically discover potent deception cues for implementation of the warning solution, MERLIN. S/He will also actively participate in report and manuscript write up.

Supplies

Computer and computer supplies are requested including funds for hardware for machine-learning and pattern-recognition methods, server processing and storage, and software licenses for analysis.

Other costs

Travel

Travel funds are requested for collaborative meetings across sites. A kick-off collaborative meeting will take place at UM in January 2018; another collaborative meeting at UF will take place in March 2019 during the grant writing phase. Total travel funds in the amount of \$800 are requested in Year 1 for travel to UM.

UNIVERSITY OF ARIZONA (UA)

Personnel

Robert Wilson, PhD, PI, Assistant Professor (no salary requested in budget periods 1&2), will, in collaboration with Dr. Grilli, provide oversight of all aspects of this research project at UA, including development of SIT for Aim 2, and budget management. He and Dr. Grilli will be in close contact with the PIs at the other sites. His responsibility will include co-supervision of the to-be-named research assistant, who will lead data collection and day-to-day responsibilities for this project. Dr. Wilson will work closely with Dr. Grilli to ensure that SIT is methodologically and psychometrically sound. He also will actively participate in results interpretation and dissemination, including grant submission and manuscripts. He will also be responsible for data transfer from UA to UF and UM for cross-site analyses.

Matthew Grilli, PhD, Pl, Assistant Professor, Licensed Clinical Neuropsychologist (no salary requested in budget periods 1&2), will, in collaboration with Dr. Wilson, serve in the same oversite role for all aspects of the research conducted at UA. This will include development of SIT, co-supervision of research staff, and all aspects of results interpretation and dissemination. He also will provide access to his subject pool and outreach program for recruitment of older adults. As a clinical neuropsychologist, he will ensure that the SIT and MERLIN protocols are optimized for older adults and translatable to real-world contexts, as well as older adults with cognitive impairment for future translation of this research.

TBA, Research Assistant (40% salary requested in budget periods 1&2), will be responsible for managing the day-to-day duties of this project, including management of the participant database, scheduling participants, conducting behavioral tests, communicating with IRB, and managing results databases.

Supplies

We request funds to purchase a laptop dedicated to this project, primarily for administration of the SIT.

Other costs

Participant payment is requested in the amount of \$800 (80 participants at \$10 each) for each of Years 1 and 2.

Travel

Travel funds are requested for the collaborative meetings across sites. Total travel funds in the amount of \$2,000 are requested, \$1,000 for each of Years 1 and 2.

UNIVERSITY OF MIAMI (UM)

Personnel

Bonnie Levin, PhD, Pl, Alexandria and Bernard Schoninger Professor of Neurology and Director of the Division of Neuropsychology (no salary requested in budget periods 1&2), will, in collaboration with Dr. Getz, provide oversight of all aspects of this research project at UM, including communication with the research team at UM and the other sites, supervision of data collection, and budget management. This will include co-supervision of the to-be-named research assistant, who will lead data collection and day-to-day responsibilities for this project. Dr. Levin will actively participate in results interpretation, data analyses and dissemination, including the submission of the R01 funding and manuscripts.

Sarah Getz, PhD, PI, Postdoctoral Fellow (no salary requested in budget periods 1&2), will, in collaboration with Dr. Levin, serve in a similar oversite role for all aspects of the research conducted at UM.

This will include supervision of cognitive, physical, and socio-emotional data collection, co-supervision of research staff, and all aspects data collection. This will include co-supervision of the to-be-named research assistant, who will lead data collection and day-to-day responsibilities for this project, including data analysis. She will also be responsible for data transfer from UM to UF and UA for cross-site analyses.

TBA, Research Assistant (40% salary requested in budget periods 1&2), will be responsible for managing the day-to-day duties of this project, including the participant database, scheduling participants, conducting behavioral tests, communicating with IRB, and managing results databases.

Supplies

We request funds to purchase an IPad (\$500) and annual licenses (\$500 each of Years 1 and 2) for the NIH toolbox for data collection.

Other costs

Participant costs will amount to \$30 per participant, which includes payment for taking part in the experiment and parking costs. Funds are requested to run 50 participants per year, totaling \$3,000 overall (\$1,500 in each of Years 1 and 2).

Travel

Travel funds are requested for the collaborative meetings across sites. Total travel funds in the amount of \$800 are requested for Year 2 for travel to UF.

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.

Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

| NAME Bonnie E. Levin, Ph.D. | | POSITION TITLE Professor of Neurology and Psychology |
|---------------------------------------|--|--|
| eRA COMMONS USER NAME bonnie_levin | | |

| Legin 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 | |
| Georgetown University | BS | 1974 | Psychology | |
| Temple University | Ph.D. | 1983 | Psychology | |

A. Personal Statement

I hold the Bernard and Alexandria Schoninger Professorship in Neurology. I founded and currently lead the Division of Neuropsychology at the University of Miami Miller School of Medicine. I direct the Neuropsychology Program in the Dept of Neurology and supervise the clinical activities of PhD graduate students enrolled the Child and Behavioral Medicine tracks in the Department of Psychology. I have taught the graduate level course, Foundations of Neuropsychology, for over 25 years. I have a long history of collaborations with interdisciplinary research teams in neurology, psychology, radiology and neurosurgery, and participate in multiple projects examining cognitive, behavioral and imaging changes associated with normal aging, acquired brain trauma and neurodegenerative disease. I am currently the site PI of the Mcknight Oldest Old Cognitive Core. Recently, I initiated the Mcknight Frailty Study, a clinic based and community outreach program to examine the association between symptoms of frailty and cognitive impairment and to educate those at risk on the detection and prevention of this symptom complex. I am particularly interested preventive health science and participate in several funded projects examining early biomarkers of cognitive change, including the NIH-funded population based Northern Manhattan Study (NOMAS), in which I am a member of the neuropsychology team and the dementia adjudication consensus panel, the Bugher AHA exercise grant, a Dept of Defense(DOD) study examining MRS brain metabolites underlying pain in traumatic injury and a funded study examining the role of cannabinoids in acquired brain injury in young and mid-life. The proposed project is focused on identifying the underlying basis of susceptibility to deception (scamming) in mid and later life. We have assembled a collaborative team with expertise in cognitive neuroscience, normative aging, and social cognition to tackle this growing public health crisis. My experience in cognitive aging, developmental neuropsychology, and social neuroscience provides the necessary background and expertise to serve as the Miami site PI on the proposed study.

These peer reviewed publications highlight my experience and qualifications for this project:

- 1. **Levin BE**, Llabre MM, Dong C, Elkind MS, Stern Y, Rundek T, Sacco RL, Wright CB. Modeling metabolic syndrome and its association with cognition: the northern Manhattan study. J Int Neuropsychol Soc. 2014 Nov;20(10):951-60.
- 2. Maudsley A, Govind V, **Levin B**, Saigal G, Harris LT, Sheriff S. Distributions of MR Diffusion and Spectroscopy Measures with Traumatic Brain Injury.J Neurotrauma. 2014 Oct 21. [Epub ahead of print] PMID: 25333480
- 3. **Levin BE**, Katzen HL, Maudsley A, Post J, Myerson C, Govind V, Nahab F, Scanlon B, Mittel A.Wholebrain proton MR spectroscopic imaging in Parkinson's disease. J Neuroimaging. 2014 Jan-Feb;24(1):39-44
- 4. Getz, S., **Levin**, **B.** Cognitive and neuropsychiatric features of early Parkinson's disease. Archives of Neuropsychology (in press)

B. Positions and Honors POSITIONS AND EMPLOYMENT Academic Appointments

1979-1980

1979-1980

Fellow (Psychology) Dept of Psychiatry, Harvard Medical School, Boston, MA Intern, Clinical Pediatric Neuropsychology, Children's Hosp Med Ctr, Boston, MA.

1980 Extern, Boston Veteran's Administration Hospital, Boston, MA 1981-1982 Instructor, Department of Neurology, University of Miami

1981 Director, Division of Neuropsychology, Department of Neurology, University of

Miami

1986-1992 Assistant Professor, Department of Neurology, University of Miami

1992-2011 Associate Professor (with tenure), Department of Neurology, University of Miami

Miller School of Medicine

2011- Professor of Neurology, Department of Neurology, University of Miami Miller

School of Medicine

Honors

Cum Laude, Georgetown University; Psi Chi Honor Society1974

Fellow, Mahoney Residential College

International Neuropsychology Society (INS) Program Chair-1997

INS Board of Governors 1998-2001

NINDS Study Section Member NSD-K, 2001-2005

NINDS AD hoc Reviewer-NSD-A 2001, 2002

NINDS Special Emphasis Panels 7/1998, 8/1999, 12/1999, 5/2000, 8/2000, 10/2000, 12/2001, 6/2001, 10/2001, 8/2002, 12/2002, 1/2004, 8/2004, 12/2004, 2/2005, 1/2006, 10/2006, 11/2006, 11/2006,

6/2007, (6/24 & 6/29) 3/2008, 4/2008.

NINDS Ad hoc reviewer, NSD-K, 2006 - 2008

Alzheimer Association Medical and Scientific Council Reviewer, 1999, 2002

Consultant: University of Miami Brain Endowment Bank, Department of Neurology; Clinical

Neuroscience Unit, UM Department of Neurology

Member, National Acute Brain Injury Study: Hypothermia II: Data Safety of Monitoring Board

Pediatrics; UM Sleep Center, Department of Neurology.

Professional Advisory Board: Epilepsy Foundation of South Florida

Editorial Boards: Neuropsychology, Journal of International Neuropsychology Society, Neuropsychology

Review, Aging, Neuropsychology and Cognition

Alexandria and Bernard Schoninger Endowed Professorship in Neurology, 2009

C. Contributions to Science

- C.1. Over the past 30 years, I have focused on cognitive and behavioral changes over the life course. My research projects are largely in the field of aging, examining age related cognitive decline and early biomarkers of behavioral and cognitive decline in normal aging and neurodegenerative disease. As the Schoninger Professor or Neurology, I oversee the Division of Neuropsychology, a major training and research site that evaluates over 300 patients a year examining age related cognitive change as well as pathological behavioral alterations associated with degenerative disease. I have published extensively on cognitive change across the lifespan.
- 1. Kelley, R.E., Chang, JY, Scheinman, NJ, **Levin, BE**, Duncan, RC, Shih-Chang, L: Transcranial doppler ultrasonographic assessment of cerebral artery flow velocity during cognitive activity. Stroke, 1992; 23:9-14.
- 2. Tomer, R, Levin, BE, Differential affects of aging in two verbal fluency tasks. Perceptual and Motor Skills, 1993; 76: 465-466
- 3. Levin, BE, Katzen, H.L., Klein, B., Llabre, M. Cognitive decline affects subject attrition in longitudinal research. Journal of Clinical and Experimental Neuropsychology. 2000, 22 (5), 580-586.
- 4. Grossman A, Levin B, Katzen H, Lechner S. PTSD symptoms and onset of neurologic disease in elderly trauma survivors. Journal of Clinical and Experimental Neuropsychology 2004: 26(5): 698-705.
- C.2.Our group was among the earliest investigators to document and describe non-motor changes in Parkinson's disease. I have also examined how gait and other lateralized motor changes are linked to cognitive and behavioral symptoms and PD progression. These studies reflect my longstanding interest in gait, movement and cognition.
- 1. **Levin, BE**, Llabre, MM, Weiner, WJ: Cognitive impairments associated with early Parkinson's disease. Neurology, 1989, 39:557-561.
- 2. Levin, BE, Llabre, MM, Weiner, WJ, Brown, MC: Visuospatial decline in Parkinson's disease. Neurology, 1991; 41:365-369.
- 3. Tomer, R, Levin, BE, Weiner, WJ: Side of motor onset influences cognition in Parkinson's disease. Annals of Neurology, 1993; 34:579-584.
- 4. Katzen, H, Levin, BE, Llabre, M: Age of onset influences cognition in Parkinson's disease. Journal of International Neuropsychological Society, 1998, 4, 285-290.

- C.3. I am currently involved in several studies examining the relationship between MRS metabolites and cognitive changes in normative aging, TBI, ALS and Parkinson's disease. These studies utilize a unique whole brain analysis that permits a study of a large fraction of the brain volume, including the cortical mantle. My role as the neuropsychologist on these projects is to identify sensitive outcome measures and to work with my collaborators linking the behavioral presentation associated a traumatic injury or neurologic illness with distributions of proton magnetic resonance spectroscopy (MRS) observed metabolites throughout the whole brain.
- 1. **Levin BE**, Katzen, HL, Maudsley, A, Post, J, Myerson, C, Govind, G, Nahab, F, Scanlon, B, Mittel. A Whole-brain proton MR spectroscopic imaging in Parkinson's disease. Journal of Neuroimaging, 2014, 24, 39-44
- 2. Maudsley, A, Govind, V, Levin, BE, Saigal, G, Harris, L, Sheriff, S Distributions of MR Diffusion and Spectroscopy Measures with Traumatic Brain Injury. J. Neurotrauma. 2015; 32 (14): 1056-1063
- 3. Widerstrom-Noga, E, Govind, VB, Adcock, J, Levin, BE, Maudsley, A Subacute Pain after TBI is associated with lower insular N-acetyl-aspartate concentrations. Journal of Neurotrauma (in press)

Complete List of Published Work at NCBI:

http://www.ncbi.nlm.nih.gov/pubmed/?term=(%22levin%2C%20bonnie%22%5BAll%20Fields%5D)&cmd=DetailsSearch

D. Research Support

Ongoing Research Support

Scythian Bioscience 08/01/2016-7/30/2021

The Effects of Cannabinoids on TBI

(B. Levin, Co-Investigator, Director of Clinical Trials)

This study will examine the inflammatory properties of cannabinoids and determine whether they can be used as a therapeutic intervention in traumatic brain injury

7 R01 NS 029993 (PI, Sacco) NIH/NINDS

02/01/03-03/31/21

1.20 calendar

Stroke Incidence and Risk Factors in a TriEthnic Region

\$1,795,509

(B. Levin, Co-Investigator)

The goals of this project are to determine the effects of risk factors for stroke, MI, and vascular death, as well as evaluate predictors of cognitive impairment and the importance of subclinical MRI findings in a prospective cohort study of 3300 persons from 3 race-ethnic groups from Northern Manhattan.

National Multiple Sclerosis

09/28/12-09/27/15

1.20 calendar

sis \$169,003

Fast Forward a Randomized Double Blind Placebo Controlled (PI: Ortega; B. Levin, Co-Investigator) To evaluate the therapeutics effects of caprylic triglyceride administered once a day for 90 days on cognitive impairment in subjects with multiple sclerosis.

AHA/ASA 14BFSC1759000 (PI: Sacco)

AHA (B. Levin, Co-Investigator)

04/01/14 - 03/31/18

0.6 calendar

\$234,667

Bugher Center Foundation Center of Excellence in Stroke Award

This award will conduct two projects evaluating the effects of physical activity and cognitive training on animals and stroke survivors on cognitive recovery

DoD/CDMRP/USAMRMC (PI: Widerstrom-Noga)

11/2015-10/2018

.84 calendar

(B. Levin, Co-Investigator)

\$977,099 (direct)

Utility of MRS Brain Biomarkers of Pain Phenotypes after TBI

Goals are to evaluate advanced metabolic imaging methods for injury assessment and prognosis following mild and moderate traumatic brain injury.

BIOGRAPHICAL SKETCH

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

NAME: Ebner, Natalie C

eRA COMMONS USER NAME (agency login): NATALIE.EBNER

POSITION TITLE: Associate Professor of Psychology

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

include postdoctoral training and residency training if applicable.)

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|--------------------------------|------------------------|-------------------------|----------------|
| Free University Berlin, Berlin | BA | 04/1998 | Psychology |
| Free University Berlin, Berlin | MA | 03/2001 | Psychology |
| Free University Berlin, Berlin | PHD | 05/2005 | Psychology |

A. Personal Statement

I am an expert in experimental aging research using a multi-methods approach including self-report, cognitivebehavioral measures, and neuroimaging techniques. My body of work is documented in 47 publications. As a pre- and postdoctoral fellow at the Free University Berlin and the Max Planck Institute for Human Development, I have supervised behavioral research on emotion-cognition interactions across adulthood. As a postdoctoral fellow and later as Associate Research Scientist at Yale University and as faculty at University of Florida (UF), I expanded my research to examine neuropsychological changes associated with cognitionemotion interactions across adulthood using neuroimaging and eye tracking techniques as well as pharmacological interventions. In addition to my primary appointment in the Department of Psychology at UF, I hold a joint appointment as faculty in the Center for Cognitive Aging and Memory (CAM) in the Aging Department at the College of Medicine at UF. I am also affiliated with the McKnight Brain Institute (MBI) and the Florida Institute for Cybersecurity Research (FICS) on campus, where I work jointly with co-Is Oliveira and Woodard. I have received multiple awards such as the Young Research Scientist Award from the German Psychological Association, the International Max Planck Research School on the Life Course Outstanding Alumni Award, the UF Assistant Professor Excellence Award, and the UF College of Liberal Arts and Sciences International Educator of the Year Award. Since 2015, I have been a Kavli Fellow of the National Academy of Sciences. The proposed project is focused on uncovering fraud susceptibility profiles in aging towards implementation of effective surveillance and warning of financial deception risk. We have put together a superb research team of investigators with outstanding, complementary expertise. We have demonstrated feasibility of the proposed work by (i) developing the study logistics and infrastructure needed to determine real-life susceptibility to deception via simulated spear-phishing email attacks (with co-I Oliveira), including IRB and research compliance, and (ii) developing first machine-learning algorithms for profiling and automated detection/warning (with co-I Oliveira). My broad expertise in cognitive and socioemotional aging, decision making, and experimental aging neuroscience and my previous experiences as investigation leader across various research projects, including coordination across national and international sites, put me in an excellent position to serve as site PI on this grant.

Representative Publications:

- a. **Ebner**, **NC**, Chen, H, Porges, E, Lin, T, Fischer, H, Feifel, D, & Cohen, RA. Oxytocin's effect on resting-state functional connectivity varies by age and sex. Psychoneuroendocrinology, 2016 Apr, 69:50-59. PubMed PMID: <u>27032063</u>; PubMed Central PMCID: <u>PMC4942126</u>.
- b. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. otherage faces: neuro-behavioral correlates and effects of emotion. Neuroimage. 2013 Sep; 78:363-71. PubMed PMID: 23602923; PubMed Central PMCID: PMC3684564.
- c. Oliveira, D, Rocha, H, Yang, H, Ellis, D, Dommaraju, S, Muradoglu, M, Weir, D, Soliman, A, Lin, T, Ebner, NC. Dissecting spear phishing emails for older vs young adults: On the interplay of weapons of influence and life domains in predicting susceptibility to phishing. CHI'17: CHI Conference Proceedings on Human Factors in Computing Systems, 2017.

d. Chen, A, Brahma, P, Wu, DO, Ebner, NC, Matthews, B, Crandall, J, Wei, X, Faloutsos, M, <u>Oliveira, D.</u> Cross-layer personalization as a first-class citizen for situation awareness and computer infrastructure security. NSPW '16: Proceedings of the 2016 New Security Paradigms Workshop, 2016.

B. Positions and Honors

| <u>Positions</u> | | F22502 E | |
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| 2001 - 2005 | Predoctoral Fellow, Free University Berlin & Max Planck Institute for Human Development, |
|-------------|--|
| | Berlin |
| 2005 - 2007 | Postdoctoral Fellow, Max Planck Institute for Human Development, Berlin |
| 2007 - 2010 | Postdoctoral Fellow, Yale University, Department of Psychology, New Haven, FL |
| 2010 - 2011 | Associate Research Scientist, Yale University, Department of Psychology, New Haven, CT |
| 2011 - 2017 | Assistant Professor, University of Florida, Department of Psychology, Gainesville, FL |
| 2013 - | Adjunct Faculty, at Cognitive Aging and Memory Clinical Translational Research Program; CAM-CTRP, University of Florida, Gainesville, FL |
| 2017 - | Associate Professor, University of Florida, Department of Psychology, Gainesville, FL |

Other Experience and Professional Memberships

| 2000 - 2011 | Member, German Psychological Association |
|-------------|--|
| 2003 - | Member, Society for Personality and Social Psychology |
| 2003 - 2009 | Member, American Psychological Association |
| 2008 - | Member, Association for Psychological Science |
| 2009 - 2009 | Reviewer, Retirement Research Foundation Doctoral Dissertation Award in the Psychology of |
| | Aging (American Psychological Association) |
| 2010 - | Member, Society for Social Neuroscience |
| 2012 - | Member, Cognitive Neuroscience Society |
| 2012 - | Reviewer, Swiss National Science Foundation |
| 2012 - | Early Career Reviewer (ECR), National Institute ofHealth, Center for Scientific Review (CSR) |
| 2014 - | Member, Society for Affective Science |
| | |

<u>Honors</u>

| Participation of the Participa | |
|--|--|
| 2006 | Heinz-Heckhausen-Jungwissenschaftlerpreis (Young Research Scientist Award), German |
| | Psychological Association |
| 2014 | International Max Planck Research School on the Life Course (LIFE) Outstanding Alumni |
| | Award, APA Board of Educational Affairs Award to Advance Interdisciplinary Education and |
| | Training in Psychology |
| 2015 | Kavli Fellow National Academy of Sciences |
| 2016 | UF Excellence Award Assistant Professors |
| 2016 | UF College of Liberal Arts and Sciences International Educator of the Year Award |
| | |

C. Contribution to Science

My expertise in experimental behavioral aging research coupled with my background in affective, social, and cognitive neuroscience allows for a comprehensive view of brain-behavior relationships in the study of emotion, motivation, and social cognition in aging (Ebner & Fischer, 2014a, 2014b). I use a multi-methods approach in my research that combines convergent measures, including self-report, cognitive-behavioral measures, eye tracking, functional neuroimaging (fMRI, ERP), and as of recently, highly innovative pharmacological (oxytocin administration), neurofeedback training (real-time fMRI), and applied (cybersecurity related decision making) interventional approaches, with the aim to integrate introspective, behavioral, and neuropsychological data.

Representative Publications:

a. **Ebner NC**, Johnson MK. Young and older emotional faces: are there age group differences in expression identification and memory?. Emotion. 2009 Jun;9(3):329-39. PubMed PMID: <u>19485610</u>; PubMed Central PMCID: <u>PMC2859895</u>.

- b. **Ebner NC**, Fischer H. Studying the various facets of emotional aging. Front Psychol. 2014a;5:1007. PubMed PMID: 25250008; PubMed Central PMCID: PMC4158868.
- c. **Ebner NC**, Fischer H. Emotion and aging: evidence from brain and behavior. Front Psychol. 2014b;5:996. PubMed PMID: 25250002; PubMed Central PMCID: PMC4158975.

2. Own-Age Bias in Attention, Memory, and Emotion Perception

One line of my research builds on the fact that our environment is complex and our cognitive system is limited so that not all stimuli can be fully and simultaneously analyzed. There is evidence that emotional and self-relevant information is preferentially processed, possibly due to the highly practiced and elaborate knowledge-structures associated with it and the greater personal and social costs of inattention or inaccurate memory. My research findings open new insights into how faces of different ages are processed and how they bias attention and memory. I show that this bias is affect by the emotional content of the faces and impacts memory for person-related information (e.g., personal goals and agendas). My results challenge and inform interpretations of face and emotion processing and age-related differences therein as older participants may be at a disadvantage relative to young participants when stimuli are faces of only young individuals. My findings are not only important from a developmental perspective but they also place constraints on general theories of attention and memory and have various important implications for social interactions, emotional regulation, self-perceptions, psychological well-being, and health in adults of different ages.

Representative Publications:

- a. Lin, T, Lendry, R, & Ebner, NC. Face likeability mediates the memory-enhancing effect of face attractiveness in young but not older adults. Memory, 2015 Nov, 30:1-11. PubMed PMID: 26619961.
- b. **Ebner NC**, He Y, Fichtenholtz HM, McCarthy G, Johnson MK. Electrophysiological correlates of processing faces of younger and older individuals. Soc Cogn Affect Neurosci. 2011 Sep;6(4):526-35. PubMed PMID: 21030480; PubMed Central PMCID: <u>PMC3150862</u>.
- c. **Ebner NC**, Johnson MK, Fischer H. Neural mechanisms of reading facial emotions in young and older adults. Front Psychol. 2012;3:223. PubMed PMID: 22798953; PubMed Central PMCID: PMC3394436.
- d. **Ebner NC**, Johnson MR, Rieckmann A, Durbin KA, Johnson MK, Fischer H. Processing own-age vs. other-age faces: neuro-behavioral correlates and effects of emotion. Neuroimage. 2013 Sep;78:363-71. PubMed PMID: <u>23602923</u>; PubMed Central PMCID: <u>PMC3684564</u>.

3. Oxytocin and Socioemotional Aging

As summarized in recent theoretical papers (Ebner, Diaz, Kamin, MacDonald, & Cohen, 2015; Ebner, Maura, MacDonald, Westberg, & Fischer, 2013), oxytocin is a neuropeptide with beneficial effects in social and emotional domains, mostly studied in young adults, schizophrenia, and autism. Our group is the first to comprehensively study acute and chronic oxytocin effects in the context of emotional, motivational, and social-cognitive aging. We have developed a theoretical framework that allows us to examine the extent to which the neuropeptide oxytocin is associated with improved functioning in aging, considering gene-brain-behavior relationships using behavioral, (epi)genetic, pharmacological, and neuroimaging techniques.

Representative Publications:

- a. Ebner, NC, Horta, M, Lin, T, Feifel, D, Fischer, H, Cohen, RA. Oxytocin modulates meta-mood as a function of age and sex. Front Aging Neurosci. 2015,7,175. PubMed Central PMCID: PMC4565056.
- b. Ebner NC, Maura GM, Macdonald K, Westberg L, Fischer H. Oxytocin and socioemotional aging: Current knowledge and future trends. Front Hum Neurosci. 2013;7:487. PubMed PMID: <u>24009568</u>; PubMed Central PMCID: PMC3755210.
- c. Ebner NC, Kamin H, Diaz V, Cohen RA, MacDonald K. Hormones as "difference makers" in cognitive and socioemotional aging processes. Front Psychol. 2014;5:1595. PubMed PMID: <u>25657633</u>; PubMed Central PMCID: <u>PMC4302708</u>.

4. Decision Making and Aging

We aim at identifying adult age differences in cognitive, affective, and social influences on decision making in the applied contexts of health and computer security. We have shown that young and older adults differ in their use of future time travel towards healthy decision making. In addition, we have developed an infrastructure that allows us to determine internet users' susceptibility to cyberattacks (e.g., spear phishing emails) in the natural setting of the participants' homes and have found evidence of a particular vulnerability in older compared to young internet users, combined with very low susceptibility awareness in the elderly.

Representative Publications:

- a. Chen, A, Brahma, P, Wu, DO, **Ebner, NC**, Matthews, B, Crandall, J, Wei, X, Faloutsos, M, <u>Oliveira, D.</u> Cross-layer personalization as a first-class citizen for situation awareness and computer infrastructure security. NSPW '16: Proceedings of the 2016 New Security Paradigms Workshop, 2016.
- b. Oliveira, D, Rocha, H, Yang, H, Ellis, D, Dommaraju, S, Muradoglu, M, Weir, D, Soliman, A, Lin, T, Ebner, NC. Dissecting spear phishing emails for older vs young adults: On the interplay of weapons of influence and life domains in predicting susceptibility to phishing. CHI'17: CHI Conference Proceedings on Human Factors in Computing Systems, 2017.
- c. Tasdemir-Ozdes, A, Strickland-Hughes, CM, Bluck, S., & **Ebner, NC**. Future perspective and healthy lifestyle choices in adulthood. Psychol Aging. 2016 Sep;31(6):618-30. PMID: 27064600.

D. Research Support

Ongoing Research Support

2017/03/01-2019/2/28

NIH/NIA - R21AG057200

Ebner, Natalie C. (MPI)

Determining Plasticity of Brain-Regulatory Mechanisms Related to Emotion Processing: A Neurofeedback Approach in Aging and Parkinson's Disease

The goal of this project is to determine plasticity in emotion processing regions in aging using neurofeedback based on real-time functional magnetic resonance imaging and to determine beneficial neurofeedback effects on emotion-regulatory skills in aging and Parkinson's Disease.

2017/01/01-2021/12/31

US DEPT OF DEFENSE DARPA HR0011-17-2-0020

Oweiss, Karim (PI) Role: Co-Investigator

OLPENS: Optimized Learning via PEripheral Nerve Stimulation

The goal of this project is to determine and optimize learning effects via peripheral vagus nerve stimulation.

2015/09/01-2019/08/31

National Science Foundation SaTC Medium 1513572

Ebner, Natalie C. (MPI)

Developer Crowdsourcing: Capturing, Understanding, and Addressing Security-related Blind Spots in APIs The goal of this project is to determine blind spots in programmer's attention when writing code.

2016/07/01-2017/12/31

PRICE-CTSI-IOA ARG DTD 03-26-2008

Ebner, Natalie C. (MPI)

Neurobiological Mechanisms of Oxytocin's Pain-Modulatory Role in Aging

The goal of this project is to determine the neurobiological mechanisms of chronic oxytocin nasal administration in aging.

2015/10/01-2017/09/30

Massachusetts Institute of Technology, Lincoln Laboratory & US Air Force 7000341318

Ebner, Natalie C. (MPI)

Enhanced Operating System Level User Profile Extraction

The goal of this project is to determine computer user profiles and to develop a tool to alert unusual use.

2013/01/01-2017/12/31

Swedish Research Council

Ebner, Natalie C. (MPI)

Effects of Oxytocin on Physical and Cognitive Functioning in the Elders

The goal of this project is to examine acute effects of intranasal oxytocin administration on cognition and social functioning in aging.

2013/10/01-2017/09/01

1R01AA022456-01, NIH/NIAAA

Nixon, Sara Jo (PI) Role: Co-Investigator

Neurobehavioral and Emotional Deficits in Male and Female Alcoholics

The goal of this project is to examine gender differences in deficits in cognitive and emotional functioning in alcoholics.

Completed Research Support

2014/09/01-2017/08/31

SaTC EAGERS NSF 13-037, National Science Foundation

Ebner, Natalie C (MPI)

Age-Targeted Automated Security Cueing Against Web-Based Social Engineering Attacks

The goal of this project is to develop and validate an open-source browser extension that provides visual security cues in an age-targeted fashion to protect older adults from web-based social engineering attacks during their everyday internet use.

2013/08/01-2017/03/31

P30AG028740, University of Florida Center for Cognitive Aging and Memory & Claude D. Pepper Older Americans Independence Center (sponsor: NIH/NIA)

Ebner, Natalie C. (PI)

Effects of Oxytocin on Physical and Cognitive Functioning in the Elders

The goal of clinical trial is to examine the effects of intranasal oxytocin administration on cognition, health, and socioemotional functioning in aging over time.

2014/09/01-2015/03/31

Scientific Research Network on Decision Neuroscience and Aging (SRNDNA; sponsored by NIH/NIA) Ebner, Natalie C. (MPI)

The Role of Oxytocin in Prosocial Decision Making in Aging Across Humans and Monkeys
The goal of this project is to compare the effects of the neuropeptide oxytocin on social preferences and altruism in young and older primates and humans.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Getz, Sarah J

eRA COMMONS USER NAME (credential, e.g., agency login):

POSITION TITLE: Postdoctoral Fellow

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

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completi on Date MM/YYY Y | FIELD OF STUDY |
|---------------------------------------|--|------------------------------------|---|
| Reed College, Portland, OR | ВА | 05/2004 | Psychology |
| Princeton University, Princeton, NJ | MA _{e e} | 09/2011 | Psychology and Cognitive Neuroscience |
| Princeton University, Princeton, NJ | | 09/2013 | Psychology and Cognitive Neuroscience |
| Suffolk University, Boston, MA | Respecialization Certificate in Clinical Psychology | 07/2016 | Clinical Psychology/ Neuropsychology Track |
| Miami VA Healthcare System, Miami, FL | Clinical Internship | 07/2016 | Clinical Psychology and Neuropsychology |
| University of Miami, Miami, FL | Postdoctoral Fellowship | 08/2018 | Neuropsychology |

A. Personal Statement

My research program has focused on the hypothesis that impulsive and maladaptive decision-making may result from an imbalance between motivational brain circuitry and regulatory control circuitry. In my post-collegiate work at the Sackler Institute for Developmental Psychobiology at Cornell Medical College, I published research that examined the neurobiology of impulsive decision-making in adolescents. This work underscored the importance of addressing individual differences in impulsivity. reward sensitivity, and cognitive control in the context of the developing brain. My doctoral research at Princeton focused on impulsivity and cognitive control in decision-making. I was awarded a dissertation grant from the Center for Health and Wellbeing's Demography of Aging Center, which is funded by the National Institute of Aging at the Woodrow Wilson School of Public and International Affairs, In other lines of my doctoral research, I examined working memory training and intelligence. After earning my PhD in 2013, I realized that combining clinical practice with research and pedagogy would offer me the greatest number of opportunities to directly improve the lives of others. I therefore began postdoctoral respecialization training at Suffolk University in Boston where I completed research interventions and advanced neuropsychology pratica, including training experiences at Brigham and Women's Hospital Harvard Medical School and Beth Israel Deaconess Harvard Medical School. As the Chief Intern and Neuropsychology Intern at the Miami VA, I evaluated patients with Alzheimer's disease, epilepsy. frontotemporal dementia, vascular dementia, multiple sclerosis, and stroke. Under the mentorship of

co-I Dr. Bonnie Levin in the Department of Neurology Division of Neuropsychology at the University of Miami, I have had a full range of clinical experiences, evaluating patients from diverse backgrounds and cultures who present with a wide range of neurologic and psychiatric disorders including epilepsy, neoplasms, closed head trauma, demyelinating and vascular disease, movement disorders, dementia, neuromuscular disease, epilepsy, and behavioral disorders. My specialized research background in decision making science and cognitive neuroscience combined with my clinical training in neuropsychology, make me uniquely qualified to serve as a co-I on this grant.

Representative Publications and Presentations:

a. Casey, B. J., Getz, S. Galvan, A. (2008). The adolescent brain. Developmental Review, 28, 62-77.

b. Mulder, M. J., Gold, J. I., Durston, S., Heasly, B., Millner, A., Simen, P., **Getz, S.**, Voss, H., Ballon, D., & Casey, B. J. (2009). BOLD Correlates of Reward-related Decision Bias on a Visual Discrimination Task. *Neuroimage*, 47 (Supplement 1).

c. Getz, S. J., Tomlin D., Nystrom, L. E., Conway, A. R. A., & Cohen, J. D. (2010, October). Executive control of intertemporal choice: Effects of cognitive load on impulsive decision-making. Poster

presented at Neuroeconomics. Evanston, IL.

d. Kool, W., Getz, S. J.*, & Botvinick, M. M. (2013). Neural Representation of Reward Probability: Evidence from the Illusion of Control. *Journal of Cognitive Neuroscience*, 25(6), 852-861. *Indicates co-first authorship

B. Positions and Honors

Research Positions and Employment

| Lescalell Los | mons and Employment |
|---------------|--|
| 2005-2006 | Research Assistant, Kosslyn Laboratory, Harvard University, Cambridge, MA |
| 2006-2008 | Senior Research Aide, Sackler Institute for Developmental Psychobiology, Weill Cornell |
| | Medical College, New York, NY |
| 2013 | Research Consultant at Educational Testing Services, Princeton, NJ |

Clinical Positions

| | 2013-2014 | Practicum Clinician, Center for Anxiety and Related Disorders (CARD), Psychological |
|---|--------------|---|
| | | Services Clinic, Boston University, Boston, MA |
| , | 2014-2015 | Research Interventionist, Department of Psychiatry/Behavioral Medicine, Brigham and |
| | | Women's Hospital/ Harvard Medical School, Boston, MA |
| | 2014-2015 | Advanced Neuropsychology Practicum Student and Technician, Child and Family |
| | | Psychological Services, Norwood, MA |
| | 2014-2015 | Advanced Neuropsychology Practicum Student, Cognitive Neurology Unit, Beth Israel |
| | | Deaconess Medical Center/ Harvard Medical School, Boston, MA |
| | 2015-2016 | Neuropsychology Intern and Chief Intern, Miami VA Medical Center, Miami, FL |
| | 2016-Present | Neuropsychology Fellowship, University of Miami/Miller School of Medicine, Department |
| | | of Neurology/Division of Neuropsychology, Miami, FL |

Honors and Awards

| 2005 | Mind and Life Summer Research Institute Fellow |
|------|---|
| 2005 | Mind and Life Initiative Grant (PI: Daniel Reisberg) |
| 2008 | Princeton University Admission Merit Award |
| 2008 | Princeton University Graduate Student Fellowship |
| 2012 | Princeton University Residential Graduate Fellow, Forbes College |
| 2013 | Dissertation Grant, Princeton Center for Health and Wellbeing, Demography of Aging |
| 20,0 | Center, Woodrow Wilson School of Public and International Affairs, Princeton University |
| 2015 | Women in Leadership Sponsorship, National Academy of Neuropsychology |

Other Experience

| 2009-2010 | Psychology Graduate Representative, Princeton University |
|-----------|---|
| 2010-2012 | Co-director of Neuroscience of Social Decision Making Speaker Series, Princeton |
| | University |
| 2012-2013 | Resident Graduate Fellow, Forbes College, Princeton University |
| 2015-2016 | Chief Intern, Miami VA Medical Center |
| | |

C. Contributions to Science

1. Impulsive decision making across the lifespan

This research examined the hypothesis that suboptimal decision-making may result from an imbalance between brain regions involved in reward and executive control processes. When this imbalance occurs, the reward-oriented system may override the control system, and give rise to impulsive decision-making. I examined this imbalance in both the developing brain as well as via experimental manipulations. Experimentally, I investigated intertemporal choice—decisions over time that involve trade-offs between costs and benefits. I hypothesized that choosing larger long- term rewards over smaller short-term rewards requires control mechanisms and preferentially recruits brain regions involved in cognitive control. Frequently, decisions are made while tasks that also require control are simultaneously performed, which can cause interference of limited capacity control mechanisms necessary for patient decision- making. My research examined how interference of control mechanisms leads to decisions that are impulsive, maladaptive, or suboptimal. There is still much work to be done in addressing the fundamental question of the role of cognitive control in impulsive decision-making processes, and I aim to continue focusing on this question as it pertains to the aging brain.

Representative Publications and Presentations:

- a. Casey, B. J., Getz, S. Galvan, A. (2008). The adolescent brain. Developmental Review, 28, 62-77.
- b. **Getz, S. J.,** Tomlin D., Nystrom, L. E., Conway, A. R. A., & Cohen, J. D. (2010, October). *Executive control of intertemporal choice: Effects of cognitive load on impulsive decision-making*. Poster presented at Neuroeconomics. Evanston, IL.

2. Cognitive training and rehabilitation

The scope of my research has expanded to focus on training of working memory. I am an author on an opinion paper and chapter that argue for a better understanding of the durability and transfer of working memory training to other cognitive domains. Specifically, in this work we argue that the efficacy of our current training paradigms—particularly those that focus on rehabilitation and enhancement of cognitive resources—warrant concerns about the construct measurement, underlying cognitive and neural mechanisms, and durability of cognitive gains. Accordingly, this line of research may produce a means of improving cognitive rehabilitation outcomes for the elderly as well as a range of neuropsychological conditions.

Representative Publications:

- a. Conway, A.R.A. & **Getz, S.** (2010). Cognitive ability: Does working memory training enhance intelligence? *Current Biology*, 20, 362-4.
- b. Conway, A. R. A., **Getz**, **S**., Macnamara, B., & Engel, P. (2011). Working memory and fluid intelligence: A multi-mechanism view. In R. Sternberg and S. B. Kaufman (Eds.). Cambridge Handbook of Intelligence.

D. Additional Information: Research Support and/or Scholastic Performance

BIOGRAPHICAL SKETCH

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

NAME: Grilli, Matthew

eRA COMMONS USER NAME (credential, e.g., agency login): mgrilli

POSITION TITLE: Assistant Professor

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

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|---|------------------------------|-------------------------------|-----------------------------|
| University of California, Irvine, Irvine, California | ВА | 06/2007 | Psychology |
| University of Arizona, Tucson, Arizona | MA | 05/2009 | Psychology |
| University of Arizona, Tucson, Arizona | PHD | 08/2013 | Clinical Psychology |
| VA Boston Healthcare System, Boston, Massachusetts | Postdoctoral Fellow | 08/2015 | Clinical Neuropsychology |

A. Personal Statement

I am an Assistant Professor in the Department of Psychology at University of Arizona and Director of the Neuropsychology Track of the Clinical Psychology Doctoral Program. I am also a licensed psychologist in Arizona. My research is broadly focused on the clinical and cognitive neuroscience of autobiographical memory, which is memory for real world events. I utilize a combination of cognitive, neuropsychological, neuroimaging (magnetic resonance imaging), genetic, and intervention methods. For the past five years, I have studied healthy adults and individuals with brain lesions to gain insight into the cognitive and neural bases of autobiographical memory. Since starting my position at University of Arizona in 2015, I have added a new line of research focused on autobiographical memory and aging, both normal and abnormal trajectories. This has become the primary line of research being conducted in my laboratory. As part of this new line of research, I have gained skills in genetic and neuroimaging methods. I also have worked on developing new cognitive tasks that have translational potential to clinical assessment. As demonstrated by my funding record, I am committed to studying cognitive aging. Although this line of work is relatively new for me, I have published research on memory and aging (reference [b] below). Finally, given my expertise in clinical neuropsychology, I believe I am in a strong position to ensure that the proposed line of research has the potential to be translated to improved assessment and intervention, as well as additional lines of research on the functional and wellbeing implications of disrupted scam detection and decision making (e.g., self, social, and future-oriented).

- a. **Grilli MD**, Verfaellie M. Personal semantic memory: insights from neuropsychological research on amnesia. Neuropsychologia. 2014;61:56-64. Epub 2014/06/17. doi: 10.1016/j.neuropsychologia.2014.06.012. PubMed PMID: 24949553.
- b. **Grilli MD**, Woolverton CB, Crawford M, Glisky EL. Self-reference and emotional memory effects in older adults at increased genetic risk of Alzheimer's disease. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn. 2017:1-14. Epub 2017/01/03. doi: 10.1080/13825585.2016.1275508. PubMed PMID: 28044474.

- c. Grilli MD. The association of personal semantic memory to identity representations: insight into higher-order networks of autobiographical contents. Memory. 2017:1-9. Epub 2017/04/17. doi: 10.1080/09658211.2017.1315137. PubMed PMID: 28415908.
- d. **Grilli MD**, Glisky EL. Imagining a better memory: Self-imagination in memory-impaired patients. Clinical psychological science: a journal of the Association for Psychological Science. 2013; 1(1):93-99.

B. Positions and Honors

Positions and Employment

| The state of the s | |
|--|---|
| 2012 - 2013 | Psychology Intern, Boston Consortium in Clinical Psychology, Boston, MA |
| 2012 - 2014 | Teaching Fellow in Psychiatry, Boston University School of Medicine, Boston, MA |
| 2012 - 2015 | Clinical Fellow in Psychology, Harvard Medical School, Boston, MA |
| 2014 – 2015 | Assistant Professor, Boston University School of Medicine, Boston, MA |
| | (Promoted while completing postdoctoral fellowship) |
| 2015 - | Assistant Professor, University of Arizona, Tucson, AZ |
| | Director of Neuropsychology Track for the Clinical Psychology PhD Program |
| | Director of the Neuropsychology Clinic, Evelyn F. McKnight Brain Institute |
| | Affiliate, Graduate Interdisciplinary Program – Cognitive Sciences |

Other Experience and Professional Memberships

| 2014 - | Member, Association for Psychological Science |
|--------|--|
| 2014 - | Member, International Neuropsychological Society |

Licensure

| 2015 | Clinical Psychologist (Arize | ana 447101 |
|------|------------------------------|--------------|
| 2013 | Cililical Psychologist (Anzi | 301a #47 121 |
| | | |

| <u>Honors</u> | | |
|---------------|---|--|
| 2007 | Summa Cum Laude, University of California Irvine | |
| 2007 | Undergraduate Investigator Spotlight, University of California Irvine | |
| 2007 | Order of Merit Scholar-Athlete of the Year, University of California Irvine | |
| 2007 | Undergraduate Research Fellowship, University of California Irvine | |
| 2008 | Community Outreach Fellowship, University of Arizona | |
| 2010 | Human Development and Aging Fellowship, Heidelberg University | |
| 2012 | College of Science Scholar of the Year, University of Arizona | |
| 2014 | Council of Graduate Schools Dissertation Nominee, University of Arizona | |
| | | |

C. Contributions to Science

1. Advanced understanding of the cognitive neuroscience of autobiographical memory. A major contribution of my research has been to show that the cognitive and neural bases of autobiographical memory blur the boundaries between episodic memory and semantic memory, which traditionally have been thought of as supported by distinct cognitive components and brain networks. I have been particularly interested in understanding how the medial temporal lobe (MTL), a brain region that is essential to episodic memory, also contributes to the storage, retrieval, and organization of semantic components of autobiographical memory. After I demonstrated that autobiographical facts, which are semantic memories about the self, depend on the MTL for retrieval (Grilli & Verfaellie, 2014), I developed a theoretical model explaining why this might be the case and revealed preliminary support for this framework. Specifically, I built on the idea that autobiographical facts range in the degree to which they have spatiotemporal qualities and demonstrated that only facts that are associated with episodic-like content depend on the MTL for retrieval (Grilli & Verfaellie, 2016). Recently, I extended this logic (Grilli et al., in press) and showed that the

organization of autobiographical memory also depends on the MTL, because this region supports relational processes that form the connections among autobiographical contents. My studies of neuropsychological patients also have shed light on the contributions of other brain regions to storage of autobiographical memory (Grilli et al., in preparation; Marquine, Grilli, et al., 2016). Broadly, this research has advanced our understanding of the specific roles of neural regions within the autobiographical memory network.

- a. **Grilli MD**, Verfaellie M. Experience-near but not experience-far autobiographical facts depend on the medial temporal lobe for retrieval: Evidence from amnesia. Neuropsychologia. 2016 Jan 29;81:180-5. PubMed PMID: 26721761; PubMed Central PMCID: PMC4738052.
- b. **Grilli MD**, Verfaellie M. Personal semantic memory: insights from neuropsychological research on amnesia. Neuropsychologia. 2014 Aug;61:56-64. PubMed PMID: 24949553.
- c. Marquine MJ*, **Grilli MD***, Rapcsak SZ, Kaszniak AW, Ryan L, Walther K, Glisky EL. Impaired personal trait knowledge, but spared other-person trait knowledge, in an individual with bilateral damage to the medial prefrontal cortex. Neuropsychologia. 2016;89:245-53. Epub 2016/06/21. doi: 10.1016/j.neuropsychologia.2016.06.021. PubMed PMID: 27342256; PMCID: PMC5119478.
 - * Co-first authors.
- d. **Grilli MD**, Wank AA, Verfaellie M. The life stories of adults with amnesia: Insights into the contribution of the medial temporal lobes to the organization of autobiographical memory. Neuropsychologia. 2017. Epub 2017/03/10. doi: 10.1016/j.neuropsychologia.2017.03.013. PubMed PMID: 28286259; PMCID: PMC5592132.
- 2. <u>Developed a cognitive strategy for improving memory.</u> Although much of my research has focused on advancing cognitive neuroscience models, I always consider how insights from basic research can inform the development of new interventions for memory disorders. My first line of research merged two largely separate literatures on self-referential processing and imagination to establish a new cognitive strategy for improving episodic memory in individuals with acquired brain injury, which I referred to as self-imagination. In a series of studies, I have demonstrated that self-imagination is a highly effective cognitive intervention for individuals with traumatic brain injury, capable of enhancing recognition, cued recall, free recall, and prospective memory across various delays and over and above a variety of cognitive strategies.
 - a. **Grilli MD**, Glisky EL. Self-imagining enhances recognition memory in memory-impaired individuals with neurological damage. Neuropsychology. 2010 Nov;24(6):698-710. PubMed PMID: 20873930; PubMed Central PMCID: PMC2970672.
 - b. **Grilli MD**, Glisky EL. The self-imagination effect: benefits of a self-referential encoding strategy on cued recall in memory-impaired individuals with neurological damage. J Int Neuropsychol Soc. 2011 Sep;17(5):929-33. PubMed PMID: 21729405.
 - c. **Grilli MD**, McFarland CP. Imagine that: self-imagination improves prospective memory in memory-impaired individuals with neurological damage. Neuropsychol Rehabil. 2011 Dec;21(6):847-59. PubMed PMID: 22150451; PubMed Central PMCID: PMC3296226.
 - d. **Grilli MD**, Glisky EL. Imagining a better memory: Self-imagination in memory-impaired patients. Clinical psychological science: a journal of the Association for Psychological Science. 2013; 1(1):93-99.
- 3. Demonstrated that autobiographical memory is necessary for maintaining the self-concept.

 Autobiographical memory, which is the repository of experiences and facts that are unique to each person, has long been thought to ground one's conceptualization of the self, which consists of higher-order knowledge structures about personal identity (i.e., traits and roles). My research has supported this idea. First, in a neuropsychological study, I demonstrated that MTL amnesics rely entirely on abstract personal semantic memories to ground their traits and roles, which comes at a cost: they cannot retrieve as many self-defining traits as healthy controls do. This indicates that episodic autobiographical memories serve a necessary role in grounding the self-concept. Second, I showed that the relative importance of episodic autobiographical memory and personal semantic memory depend on the stability of one's traits and roles. Specifically, I found that whereas healthy adults primarily rely on episodic and episodic-like autobiographical memories to ground recently formed traits and roles, they tend to ground remotely formed

traits and roles with abstract personal semantic memories more than other autobiographical contents. These studies provide important insight into the self-supporting function of autobiographical memory.

- a. **Grilli MD**, Verfaellie M. Supporting the self-concept with memory: insight from amnesia. Soc Cogn Affect Neurosci. 2015 May 11;PubMed PMID: 25964501.
- b. **Grilli MD**. The association of personal semantic memory to identity representations: insight into higher-order networks of autobiographical contents. Memory. 2017:1-9. Epub 2017/04/17. doi: 10.1080/09658211.2017.1315137. PubMed PMID: 28415908.

For a full list of my references, please see My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/matthew.grilli.1/bibliography/48613144/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Current Research Support

Arizona Alzheimer's Consortium Project Grant Grilli (PI)

7/01/2017 - 06/30/2018

Department of Health Services

"Forgetting one's past: Episodic autobiographical memory in ε4 carriers"

Specific aims: to reveal cognitive and neural mechanisms that contribute to disrupted memory in individuals at risk of Alzheimer's disease.

Arizona Alzheimer's Consortium Project Grant Grilli (Co-PI)

7/01/2017 - 06/30/2018

Department of Health Services

"Perirhinal cortical structure and function in older adults and its role in memory"

Specific aims: to elucidate the neural bases of impaired object recognition in aging and determine its relation to pattern separation and associative memory.

University of Arizona Faculty Seed Grant

Grilli (PI)

7/01/2017 - 06/30/2018

Research, Discovery, and Innovation

"Detecting the earliest signs of Alzheimer's disease: A new cognitive neuroscience approach"

Specific aims: to apply structural and functional MRI methods to understand the neural bases of a

Specific aims: to apply structural and functional MRI methods to understand the neural bases of disrupted autobiographical memory among older adults.

College of Science, University of Arizona

Grilli (PI)

08/30/2017 - 06/01/2018

Dean's Innovation and Education Fund

"Detecting the earliest signs of Alzheimer's disease"

Specific aims: to develop cognitive measurements for preclinical Alzheimer's disease.

Completed Research Support

P30 AG019610

Grilli (PI)

07/01/2016 - 06/30/2017

Arizona Alzheimer's Disease Core Center

"APOE status and emotional memory in cognitively healthy older adults"

Specific aims: determine whether emotional memory binding and detailed event retrieval are impaired in healthy middle-aged and older adult e4 carriers relative to non-carriers.

BIOGRAPHICAL SKETCH

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

NAME: Oliveira, Daniela

eRA COMMONS USER NAME (agency login): DANIELAOLIVEIRA

POSITION TITLE: Associate Professor

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

include postdoctoral training and residency training if applicable.)

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|-----------------------------------|---------------------------|-------------------------|------------------|
| Federal University of Minas | B.Sc. | 03/1999 | Computer Science |
| Federal University of Minas | M.Sc. | 02/2001 | Computer Science |
| University of California at Davis | Ph.D. | 06/2010 | Computer Science |

A. Personal Statement

I have extensive experience with cyber-security research from the technical to the human factors side and bring expertise to this team in identifying cyber-security risks in vulnerable populations (e.g., the elderly) and development of protection tools and trainings. My goal as a researcher is to improve the security of computer systems and to protect computer users from online deception. Society is dependent on networked computer systems and software, from running the smart grid that powers homes to social networking with family and friends. This societal dependency requires sound methods and practices to protect computer systems from attacks and to protect users against threats created by ubiquitous computer systems. These methods and practices must consider both threats from attackers looking to compromise systems and human factors.

Over the last several years, Dr. Ebner and I have been collaborating on various projects (including across-site collaborations) and have developed the infrastructure used in the proposed work (e.g., Chen et al., 2016; Oliveira et al., 2017). I, together with Dr. Ebner, am affiliate faculty in the Florida Institute for Cyber Security Research (FICS) at the University of Florida (UF). In this context, I serve as Diversity Director. I have received the NSF CAREER award in 2012, the Presidential Early Career Award for Scientists and Engineers (PECASE) in 2014 from President Obama, and the UF International Educator of the Year Award for junior faculty. Further I was one of the five US researchers selected by NSF to represent the United States at the Science and Technology in Society (STS) Young Leader's Program in Kyoto, Japan in 2014, where I discussed cyber-security issues with a community comprising state ministers, university and academy of sciences presidents, and Nobel Laureates. I am also a National Academy of Sciences Kavli Fellow.

Together with Dr. Ebner, I will serve as the liaison between psychology and computer engineering. My responsibilities will be related to the cyber-security aspects of the study design as well as assurance of data security throughout the entire project. I will work on development of the automated warning solution. I will be actively involved in results interpretation and dissemination, including manuscript and report write-ups.

Representative Publications:

a. Daniela Oliveira, Harold Rocha, Huizi Yang, Donovan Ellis, Sandeep Dommaraju, Melis Muradoglu, Devon Weir, Adam Soliman, Tian Lin, Natalie Ebner. Dissecting spear phishing emails for older vs young adults: On the interplay of weapons of influence and life domains in predicting susceptibility to phishing. ACM CHI'17: ACM CHI Conference Proceedings on Human Factors in Computing Systems, 2017.

- b. Chen, A, Brahma, P, Wu, DO, Ebner, NC, Matthews, B, Crandall, J, Wei, X, Faloutsos, M, Oliveira, D. Cross-layer personalization as a first-class citizen for situation awareness and computer infrastructure security. NSPW '16: Proceedings of the 2016 New Security Paradigms Workshop, 2016.
- c. Daniela Oliveira, Jedidiah Crandall, Harry Kalodner, Nicole Morin, Megan Maher, Jesus Navarro and Felix Emiliano. An Information Flow-based Taxonomy to Understand the Nature of Software Vulnerabilities. 31st International Conference on ICT Systems Security and Privacy Protection -Springer IFIP SEC 2016.
- d. Daniela Oliveira, Marissa Rosenthal, Nicole Morin, Martin Kuo-Chuan Yeh, Justin Cappos and Yanyan Zhuang. It's the Psychology Stupid: How Heuristics Explain Software Vulnerabilities and How Priming can Illuminate Developer's Blind Spots. Annual Computer Security Applications Conference (ACSAC) 2014. New Orleans, 8-12 December 2014.

B. Positions and Honors

Positions and Employment

| 2008 | Research Intern, Microsoft Research Redmond |
|-------------|--|
| 2009 | Associate Instructor, University of California at Davis |
| 2010 - 2014 | Assistant Professor of Computer Science, Bowdoin College |
| 0044 | A 1.4 mm a |

2014 - present Associate Professor, University of Florida

| Uther Experie | ence and Professional Memberships |
|----------------|---|
| 2011 - present | NSF panelist and reviewer |
| 2013 - present | Program Committee member for the Annual Computer Security Applications Conference |
| 2015 - present | Programmer Committee member for the USENIX ENIGMA Conference |
| 2015 - 2016 | Organizer – NAS Kavli Frontiers of Science Symposium |
| 2015 - 2016 | Organizer – NSF/Dept. of Homeland Security/Brazilian Ministry of Science and Technology US-Brazil Workshops on Cyber Security and Privacy |
| 2015 | Organizer NAE Frontiers of Engineering Symposium |
| 2016 | Florida Institute for Cyber Security Diversity Director |
| 2017 | CRA-W/ACSA Committee for the Scholarships for Women Studying Information |
| | Security (SWSIS) program |

Honors

- 2012 NSF CAREER Awardee
- 2014 Presidential Early CAREER Award for Scientists and Engineers (PECASE) from President
- 2014 NSF Young Leader Representative at the Science and Technology in Society (STS) forum in Kyoto, Japan
- 2014 NAS Kavli Fellow
- 2016 University of Florida International Educator of the Year Junior Faculty Award

C. Contribution to Science

My research is highly interdisciplinary and my research philosophy is to discover and employ successful ideas from other fields (psychology, neuroscience, economics, biology, etc.) to make computer systems more secure and to protect computer users from online deception. My work has focused on operating system-hardware collaboration, leveraging and understanding uncertainty at the operating system level for system security and software resilience, understanding and combating software vulnerabilities and deception in cyber-social engineering attacks, and leveraging cross-laver personalization to better detect anomalous events. My research approach focuses on extending operating systems, writing large prototypes, and conducting computer user studies that are

either remote, placed in the real-world (e.g., at participants' homes) or comprise in-lab assessments.

1. Cyber Deception Susceptibility in Vulnerable Populations

Older adults are a vulnerable and likely targeted population for spear-phishing attacks. In psychology, there is broad evidence of age-related declines in cognitive abilities, including deception sensitivity, while self-reported trust increases. This renders older adults particularly vulnerable to be misled by false information. The potential vulnerability of this segment of the population to cyber deception has many implications for cyber security. First, the risk behavior of specific age groups will likely be considered by the next generation of social engineering methods. Second, older adults are the fastest-growing segment of the U.S. population, control over half of the financial wealth, and occupy many powerful positions in finance and politics. My research seeks to understand older adults' susceptibility to cyber social engineering attacks and create machine learning based tools to alert Internet users about cyber deception in a personalized way.

Representative Publications:

a. **Daniela Oliveira**, Harold Rocha, Huizi Yang, Donovan Ellis, Sandeep Dommaraju, Melis Muradoglu, Devon Weir, Adam Soliman, Tian Lin, **Natalie Ebner**. Dissecting spear phishing emails for older vs young adults: On the interplay of weapons of influence and life domains in predicting susceptibility to phishing. ACM CHI'17: ACM CHI Conference Proceedings on Human Factors in Computing Systems, 2017.

2. Understanding and Addressing Software Vulnerabilities from a Developer's Perspective

I seek to understand software vulnerabilities from two distinct angles. The first insight is that vulnerabilities cross layers of abstraction, and this could shed light on why mitigation approaches fail and why, year after year, we have been witnessing security reports documenting a rise in the number of vulnerabilities in software. The second insight is that the rise in the number and type of vulnerabilities might be caused by security not being part of developers' heuristic-based decision-making process, and that cueing developers will trigger a security mindset in them. I posit that security information is not part of a developer's heuristics, and the cueing of developers on the spot about specific vulnerabilities that might arise in their current coding context can change their attitude towards a security mindset, which will lead to more secure software being developed.

Representative Publications:

- a. **Daniela Oliveira**, Jedidiah Crandall, Harry Kalodner, Nicole Morin, Megan Maher, Jesus Navarro and Felix Emiliano. An Information Flow-based Taxonomy to Understand the Nature of Software Vulnerabilities. 31st International Conference on ICT Systems Security and Privacy Protection Springer IFIP SEC 2016.
- b. **Daniela Oliveira**, Marissa Rosenthal, Nicole Morin, Martin Kuo-Chuan Yeh, Justin Cappos and Yanyan Zhuang. It's the Psychology Stupid: How Heuristics Explain Software Vulnerabilities and How Priming can Illuminate Developer's Blind Spots. Annual Computer Security Applications Conference (ACSAC) 2014. New Orleans, 8-12 December 2014.

3. Hardware-Software Collaboration for Systems Security

Today's computers do not collaborate and share intelligence to defend themselves against attacks. Many solutions focus on a single layer (application, operating system, or hardware) and fail to counter attacks that cross layers. This line of research involves building collaborative defense strategies encompassing intelligence from the operating system and hardware. The inspiration for this research was my observation of how the immune system works: it is distributed, with all layers cooperating and sharing intelligence to combat invaders, and it can coexist with untrustworthy but needed foreign

bodies. Remarkably, these successful immunity mechanisms have not been applied to computer systems security. The different players that make up a computer system, in particular the hardware and software, interact precariously with each other and do not cooperate, communicate, or learn from one another.

Representative Publications:

- a. **Daniela Oliveira** and S. Felix Wu. *Protecting Kernel Code and Data with a Virtualization-Aware Collaborative Operating System*. Annual Computer Security Applications Conference (ACSAC). Honolulu, Hawaii. December 2009.
- b. **Daniela Oliveira**, Jesus Navarro, Nicholas Wetzel, and Max Bucci. *Ianus: Secure and Holistic Coexistence with Kernel Extensions A Immune System-inspired Approach.* ACM SAC (Symposium on Applied Computing) Security Track. Gyeongju, Korea, March 2014.
- c. **Daniela Oliveira**, Nicholas Wetzel, Max Bucci, Dean Sullivan and Yier Jin. Hardware-Software Collaboration for Secure Coexistence with Kernel Extensions. ACM Applied Computing Review Journal, Fall 2014 Issue, Volume 14, Number 3.

D. Research Support Ongoing Research Support

09/01/15 - 08/31/19

National Science Foundation CNS 1513572

Oliveira, Daniela (PI)

TWC: Medium: Collaborative: Developer Crowdsourcing: Capturing, Understanding, and Addressing Security-related Blind Spots in APIs

This project captures developers' reasoning when faced with blind spots, and to identify common blind spot characteristics.

07/01/15 - 06/30/19

University of New Mexico

Oliveira, Daniela (PI)

FAROS: Beyond all-or-nothing DIFT via context-aware self-tuning operation.

The goal of this project is to develop the next generation of dynamic-information flow tracking systems.

09/01/16 - 08/31/17

National Science Foundation 1552059

Oliveira, Daniela (PI)

Workshop US-Brazil on Cyber Security Research

The goal of this workshop is to bring together, for the first time, American and Brazilian cyber security researchers to discuss the main challenges of the field, and to promote cross-collaboration and the building of ties among the attendees.

10/01/16 - 09/30/17

MIT PO NO 7000341318

Oliveira, Daniela (PI)

Enhanced Operating System Level User Profile Extraction

The goal of this project is to develop novel mechanisms for detection of insider threats using personalization.

Completed Research Support

03/01/12 - 02/28/17

National Science Foundation CNS 1464801

Oliveira, Daniela (PI)

CAREER: Bridging the Semantic Gap in Virtualization-Based Security via Collaboration between

Guest OS and VI

The goal of this project is to develop an architecture where guest OS and a VM actively collaborate requesting services and exchanging data and information through special instructions protected from tampering.

09/15/14 - 08/31/17

National Science Foundation SES 1450624

Oliveira, Daniela (PI)

EAGER: Age Targeted Automated Cueing Against Cyber Social Engineering Attacks
This project investigates the influence of user age on the type and the effectiveness of social engineering attacks through user studies involving young and older adults.

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Robert C. Wilson

eRA COMMONS USER NAME (credential, e.g., agency login): BOBWILSON

POSITION TITLE: Assistant Professor of Psychology and Cognitive Science

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

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|----------------------------|------------------------------|-------------------------------|--------------------------------|
| University of Cambridge | B.A. | 06/2002 | Natural Sciences |
| University of Cambridge | M.Sci. | 06/2002 | Chemistry |
| University of Pennsylvania | M.S.E. | 05/2003 | Bioengineering |
| University of Pennsylvania | Ph.D. | 05/2009 | Bioengineering |
| Princeton University | Postdoc | 12/2014 | Psychology and Neuroscience |

A. Personal Statement.

I am an expert in cognitive and computational neuroscience. I have modeled learning and decision making at a variety of levels – from low level neural networks to high level Bayesian inference – and have extensive experience linking theoretical models to behavioral and neural data. Most relevant to the current proposal is my work developing explore-exploit experiments (Wilson et al, JEP:General 2014), my work building cognitive models of complex tasks (Wilson, R. C., & Niv, Y., 2012), and my work linking models to behavioral and neural data (Wilson et al. Neuron 2014)

Wilson, R. C., Geana, A., White, J. M., Ludvig, E. A., & Cohen, J. D. (2014). Humans use directed and random exploration to solve the explore-exploit dilemma. *JEP:General*, 143 (6), 2074-2081.

Wilson, R. C., & Niv, Y. (2012). Inferring relevance in a changing world. Front Hum Neurosci, 5:189

Wilson, R. C., Takahashi, Y. K., Schoenbaum, G. & Niv, Y. (2014). Orbitofrontal cortex as a cognitive map of task space. *Neuron*, 81(2), 267-279

Zajkowski, W., Kossut, M., & Wilson, R. C. (2017). A causal role for right frontopolar cortex in directed, but not random, exploration. *In revision at eLife*

B. Positions and Honors.

Chronology of Employment

2003-2009 Graduate Student, Department of Bioengineering, University of Pennsylvania

2009-2014 Postdoctoral Research Associate, Princeton Neuroscience Institute

2015-present Assistant Professor of Psychology and Cognitive Science, University of Arizona

C. Contributions to Science.

1. How humans and animals solve the explore-exploit dilemma

Many decisions in life involve a tradeoff between exploring new options for information and exploiting known options for reliable reward. For example, when dining at a favorite restaurant do you explore the new ravioli that is sure to be informative, or exploit the known pizza that is sure to be good? Beyond eating out, the explore-exploit dilemma occurs at all levels of decision making, from picking a TV show to watch or a person to marry, and there are real advantages to solving it well. Yet despite its importance, solving the dilemma optimally is intractable in all but the simplest settings and so the question arises as to how we balance

exploration and exploitation in practice. In recent work I have shown that humans use two distinct strategies for solving the explore-exploit dilemma: a directed strategy in which information seeking drives exploration by choice, and a random strategy in which behavioral variability drives exploration by chance. In addition, initial studies from my lab and my collaborators suggest that these two strategies rely on dissociable neural networks, with directed exploration dependent of frontal pole, correlating with blink rate and developing over the course of adolescence, while random exploration appears to be tied to norepinephrine. The identification of the two strategies, in addition to experiments with which to quantify them, is already having a significant impact on the field and versions of my task are currently being run in at least nine different labs around the world to study exploration in mental illness, across development, in animals and in response to drugs.

- Wilson, R. C., Geana, A., White, J. M., Ludvig, E. A., & Cohen, J. D. (2014). Humans use directed and random exploration to solve the explore-exploit dilemma. *JEP:General*, 143 (6), 2074-2081.
- Somerville, L. H., Sasse, S. F., Garrad, M. C., Drysdale, A. T., Abi Akar, N., Insel, C., & Wilson, R. C. (accepted). Charting the Expansion of Strategic Exploratory Behavior During Adolescence. *JEP:General*
- Krueger, P. K., Wilson, R. C., & Cohen, J. D. (accepted). Directed and random exploration in the domain of losses. *Judgment and Decision Making*
- Zajkowski, W., Kossut, M., & Wilson, R. C. (in revision). A causal role for right frontopolar cortex in directed, but not random, exploration. *In revision at eLife*

2. Learning in the presence of abrupt change

Whether getting a new job or a new president, life is full of "change points" that cause the rules of the game to shift abruptly. Learning and making predictions in such circumstances can be challenging because change points can render much of the past irrelevant. In this work I developed a series of computational models to look at how humans and animals learn in the face of such environmental change points. These models ranged in scale from low level neural network models to high level cognitive models. All of these models made detailed experimental predictions some of which have been tested, and borne out, in experiments by my collaborators.

- Wilson, R. C., & Finkel, L. H. (2009). A neural implementation of the Kalman filter. *Advances in Neural Information Processing Systems* 22, 2062-2070
- Wilson, R. C., Nassar, M. R., & Gold, J. I. (2010). Bayesian online learning of the hazard rate in change-point problems. *Neural Computation*, 22 (9), 2452-2476
- Wilson, R. C., & Niv, Y. (2012). Inferring relevance in a changing world. *Front Hum Neurosci*, *5*:189 Wilson, R. C., Nassar, M. R., & Gold, J. I. (2013). A Delta-rule approximation to Bayesian inference in change-point problems. *PLoS Comp Biol*, *9* (7), e1003150

3. The role of orbitofrontal cortex in learning and decision making

Orbitofrontal cortex (OFC) has long been known to play an important role in learning and decision making. However, the exact nature of that role has remained elusive. I have recently proposed a new unifying theory of OFC function in which the OFC provides an abstraction of currently available information in the form of a labeling of the current task state. This "cognitive map" of "task space" in OFC is then used as a scaffold for learning and decision making throughout the brain. The theory accounts for many of the puzzling findings related to OFC such as its role in a number of behavioral tasks, as well as more recent findings showing the effect of OFC lesions on the firing of dopaminergic neurons in ventral tegmental area (VTA). This work has been well received by the field and has been cited over 100 times in just over two years.

- Takahashi, Y. K., Roesch, M. R., Wilson, R. C., Toreson, K., O'Donnell, P., Niv, Y., & Schoenbaum, G. (2011). Expectancy-related firing of midbrain dopamine neurons depends on orbitofrontal cortex. *Nature Neuroscience*, *14*, 1590-1597
- Wilson, R. C., Takahashi, Y. K., Schoenbaum, G. & Niv, Y. (2014). Orbitofrontal cortex as a cognitive map of task space. *Neuron*, *81* (2), 267-279

Links to a complete list of published work

- <u>Lab website</u> (also includes in press articles and conference papers)
 - http://www.u.arizona.edu/~bob/publications.html
- NCBI My Bibliography (published journal papers only)

http://www.ncbi.nlm.nih.gov/sites/myncbi/robert.wilson.3/bibliography/48037481/public/?sort=dat e&direction=ascending

D. Research Support.

Current Research Support

2017-2018

Principle Investigator with Ying-hui Chou (co-I)
The neural substrates of explore-exploit decisions in old age

Arizona Alzheimer's Disease Core Center pilot grant (P30 AG019610)

Total direct costs: \$30.000

2017-2018 Principle Investigator

The Neural Substrates of Exploration and Exploitation

University of Arizona, Faculty Seed Grant

Total direct costs: \$10,000

2017-2018 **Principle Investigator**

The High-Throughput Psychophysiology Lab - A cognitive neuroscience resource for research,

education and outreach

University of Arizona, Dean's Innovation and Education Fund

Total direct costs: \$10,000

Co-Investigator with Kobus Barnard (PI) 2017-2018

Building capacity for inferring facial communication from video data

UA Improving Health TRIF
Total direct costs: \$80,000

Co-Investigator with Mays Imad & David Kikuchi (PIs) 2017-2018

Integrative education mentoring in higher education
CIS Seed Grant
Total direct costs: \$10,000

CIS Seed Grant
Total direct costs: \$10,000

Completed Research Support 5T32 MH 65214 Cohen (PI) 04/1/12-9/30/13
Postdoctoral training grant

Application to the McKnight Inter-Institutional Cognitive Aging and Memory Intervention Core and Proposal for MBRF Funding

A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults

A Collaborative Study across the University of Florida and the University of Arizona 10/16/2017

Dawn Bowers, Ph.D.* University of Florida
Adam Woods, Ph.D. University of Florida
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A Pilot Intervention with Near Infrared Stimulation: Revitalizing Cognition in Older Adults

The proposed multi-site collaborative project will bring together research teams at the University of Florida (UF) and University of Arizona (UA) to test a novel, relatively low cost, low risk, though potentially <u>high impact</u> approach for a cognitive/mood intervention in older adults who are experiencing normal age-related memory and cognitive changes. The intervention involves transcranial and intranasal delivery of near infrared (NIR) light via light emitting diodes. Before describing the study design and hypotheses, we will briefly review the background and rationale for this unconventional, innovative approach and recent pilot data from 1 older adult.

Background: By history, current non-surgical device approaches to brain stimulation primarily involve magnetic (rTMS, TMS, deep TMS) or transcranial direct current stimulation (tDCS) which alter synaptic firing rates. In contrast, the *underlying mechanism of near infrared (NIR)* light stimulation is different. Application of light in red (630-700nm) and near-infrared wavelengths (808-904nm) appears to *improve mitochondrial function by promoting increased production of intracellular ATP*, important for cellular metabolism, respiration and oxygenation. It targets the cytochrome oxidase c integral membrane protein of the mitochondrial membrane (electron transport chain) and leads to increased intracellular levels of ATP (Mochizuka-Oda et al., 20002, Wong-Riley et al., 2005, Oron et al., 2007), increased expression of genes supporting cell proliferation and mitochondrial energy metabolism (Zhang et al., 2003), and decreased genes for pro-inflammatory proteins such as interleukin-1, interleukin10, and cytokine receptors (Whelan et al., 2003). Additionally, near infrared light may increase blood flow (Chung et al., 2012; Nawashiro et al., 2012) and up-regulate antioxidant genes (Chen et al., 2009). Thus, rather than directly modulating neural networks per se, application of NIR appears to create a supportive environment for optimal neuronal functioning that may lead to enhanced neural connectivity.

Recent animal and human studies have provided initial support for positive benefits of NIR stimulation on "brain and cognitive function". These studies include reports of reduced beta-amyloid load and neurofibrillary tangles in transgenic mice (APP/PSI and K3Tau) expected to develop Alzheimer's disease after exposure to real vs sham transcranial NIR stimulation (Purushothuman et al., 2013, 2014, Farfara et al., 2015), Others, using mouse and macaque models of Parkinson disease, have found that NIR stimulation via diodes implanted in the ventricles or midbrain protected dopaminergic neurons in the substantia nigra from MPTPinduced degeneration and also preserved locomotor activity (Moro et al, 2013, 2014, Reinhart et al., 2015; Darlot et al., 2016). Still others have reported that NIR stimulation attenuates post-stroke deficits in rabbits (Lapchak et al., 2007, 2010) and increases cortical metabolism and memory retention in healthy rats (Roias et al., 2012). In human studies, NIR stimulation has been delivered via light emitting diodes (LED) directly to the scalp and is thought to penetrate 1-3 centimeters deep, with approximately 2-3% of the light reaching the cortex (Wan, 1981; Tedford et al., 2015). Positive effects of NIR stimulation have been observed in individuals with chronic aphasia due to focal stroke (Naeser et al., 2012, 2013), in individuals with TBI undergoing six weeks of intervention (Naeser et al., 2014), individuals with Alzheimer's disease (Saltmarche et al., 2017), and in younger healthy adults (Barrett et al., 2013; Blanco et al., 2017). Effect sizes on memory and executive tasks in these groups have ranged from modest to large. In addition, a neuroimaging study of a single case has reported pre-post changes in resting state functional connectivity MRI (rs-fcMRI) following real vs. sham NIR (Naeser et al., 2013).

Statement of Problem and Specific Aims

Prior research in cellular and animal models suggests that NIR exposure may be neuroprotective and increases energy available to neurons. In humans, several preliminary studies have been conducted in healthy young adults and those with aphasia due to stroke, traumatic brain injury, and Alzheimer's disease. While findings from these studies are promising, it remains unclear whether this novel, unconventional approach might be useful for modifying age-related cognitive symptoms, such as memory or executive functions in older adults. Careful prospective sham-controlled studies are critical to determine if this NIR intervention might be beneficial to normal elderly who are beginning to experience early age-related cognitive changes. At UF, we have NIR instrumentation (MedX MCT502 Rehab Console) and a unique 31-P MRI coil that can be used to detect changes in magnetic resonance spectroscopy (MRS) based markers of ATP function. Using this coil, we have obtained initial *pilot imaging data* from one normal older adult (age 72 yrs)

who underwent 2 weeks of transcranial NIR stimulation (3 X a week) and showed changes in 2 of 3 markers of ATP function, primarily over the frontal cortex (mean ATP change effect size d = .6).

In light of this pilot observation, we propose to conduct a randomized, sham-controlled study in generally healthy, community-dwelling older adults to investigate whether NIR stimulation has beneficial effects on cognition, mood, and brain function. Our *overall hypothesis* is that exposure to NIR stimulation will have positive effects on brain health via influence on mitochondrial function as measured by changes in MRS-based markers of ATP, neural network changes (rs-fMRI), and improved cognitive performance. To test this hypothesis, we plan to randomize older adults, including those with age-related cognitive complaints but not cognitive impairment, to sham or real treatment groups and evaluate neuroimaging and cognitive outcome measures, before and after an 8-week intervention involving transcranial and intranasal NIR. The protocol will involve both "lab" and "home-based" NIR stimulation.

We have three specific aims:

- <u>Aim 1</u>: To evaluate whether NIR stimulation can enhance cognition in healthy aging. We <u>hypothesize</u> that NIR stimulation will result in greater pre-post intervention improvement on tasks of recent memory and executive function, relative to sham. This will be tested using novel tasks of recent memory that are sensitive to hippocampal function and amyloid load, including the LASSI-L (Curiel et al., 2013) and the Spatial Navigation Task (Thomas et al., 2001; Laczo et al., 2011). Executive function will be tested using composite scores from the NIH Examiner, a battery of executive function tests (Kramer et al., 2014) and traditional executive measures, the Trail Making Test (Reitan & Wolfson, 1985) and Stroop (Golden, 1978).
- <u>Aim 2:</u> To determine whether NIR stimulation can improve psychological well-being and mood in healthy older adults. We <u>hypothesize</u> that NIR stimulation will result in greater pre-post intervention improvements on measures of psychological well-being and negative affect. This will be tested using indices from the Emotion module of the NIH Toolbox (Salsman et al.,2013) and traditional measures of mood and emotion (Profile of Mood States, State-Trait Anxiety Inventory).
- <u>Aim 3:</u> To evaluate whether there are NIR intervention related changes in resting state functional connectivity in healthy aging. We <u>hypothesize</u> that NIR stimulation will show pre-post increases in functional connectivity in frontal and medial temporal lobe mediated resting state brain networks. We will also explore whether NIR stimulation leads to increases in MRS markers of ATP function, a presumed mechanism of NIR stimulation. This will be tested with rs-fcMRI and 31-P MRS.

Innovation: a) We are testing a novel intervention, NIR stimulation, for enhancing cognition in older adults with age-related cognitive changes; b) The proposed mechanism of change for NIR (i.e., ATP induced mitochondrial change) is promising in light of recent findings with animal models of Alzheimer's and Parkinson's disease; c) We have the unique opportunity to examine this potential mechanism in humans via use of MRS-phosphorous imaging, which targets changes in ATP and other metabolic markers. The use of rs-fcMRI enables us to identify intervention-related brain network changes in response to NIR intervention; d) Our primary cognitive outcomes include measures that are viewed as "cognitive biomarkers" due to their sensitivity to hippocampal function, amyloid burden, and early age-related cognitive changes; e) Methodologically, we have designed a randomized, blinded parallel group pilot study that includes a sham control group and will be carried out across 2 different McKnight Brain Institute sites (UF, UA). The multi-site design enables us to tease apart the potential influence of placebo and practice effects and examine reliability across sites, enhancing the impact of our findings; and f) The intervention is relatively low cost and low risk, and the technology used in this trial is safe, painless, and non-invasive. We expect that this pilot study will provide the basis for a larger scale NIH proposal; and if successful, this intervention could be ultimately adapted for 'in home' use.

Approach

<u>Participants</u>. Participants will include 52 healthy, community-dwelling older adults (age 65 yrs and older) who will be randomized to one of 2 intervention groups: a) active NIR stimulation (N=26) or (b) sham NIR (N=26). Half the participants (N=26) will be enrolled at the University of Florida and half at the University of Arizona. Participants can have subjective cognitive complaints (i.e., word finding, memory), as long as there is no psychometric evidence of impairment on cognitive screening measures.

<u>Inclusion criteria</u>: a) no evidence of dementia or MCI based on cognitive screening (i.e., MoCA scores within normal limits for age, education, and sex using the NACC Uniform Data Set (UDS) norms; age-

appropriate delayed story recall [WMS Logical Memory] and confrontation naming (Boston Naming Test); b) at least 8th grade education; c) willingness to be randomized to sham or real intervention; d) normal functional behaviors.

<u>Exclusion criteria</u>: a) history of brain abnormalities/neurological disorders affecting cognition (e.g., stroke, PD, MS, epilepsy, etc.); b) major psychiatric disturbance (e.g., schizophrenia, bipolar disorder, current major depression, current alcohol/substance abuse); c) use of psychotics, sedatives or other medications with anticholinergic properties; e) use of photosensitive medications within 15 days of intervention; d) active cancer diagnosis; and e) inability to undergo brain imaging due to metal, pacemakers, claustrophobia, etc.

<u>Sample Size, Attrition, Power, and Intent to treat</u>: We anticipate approximately 30% attrition rate for the 52 participants enrolled across the 2 sites, resulting in 36 participants who complete 8 weeks of intervention. With this sample (N=36), we expect to be able to detect a medium treatment effect on our primary cognitive/mood and brain imaging outcome measures with 83% power and p = 0.05, two tailed. Intent to treat analysis will be used to reduce selective attrition bias; participants who are unwilling/unable to continue with intervention will be encouraged to attend the post intervention testing, if possible.

<u>Screening and Pre-Post Outcome Measures</u>. Participants will be screened for inclusion/exclusion criteria, receive pre-post cognitive and imaging outcome measures before and after intervention. Resting state fMRI will be acquired at both sites (UF, UA), whereas MRS with a 31P coil will only be obtained at UF.

NIR Stimulation Intervention. We have previously used the MEDx console system for transcranial delivery of NIR light in pilot participants. Given the recent findings of Saltmarche et al. (2017), we have decided to use the Vielight system due to ease of standardizing LED clusters over the head and reduced cost. (See figure). Our NIR intervention protocol will span 8 weeks and includes:

- a) 10 stimulation sessions in the laboratory using the Vielight Neuro-Gamma system (Vielight, Inc); this system consists of a head frame holding 4 separate LED clusters plus 1 intranasal unit; each session will last approximately 1 hr and involves delivery of 810nm pulsed at 40 Hz for two 20 min periods; this results in total cranial dosage of 450j/cm² per session. During stimulation, participants will view clips from the BBC Life Series (Gunton, 2009) to standardize cognitive engagement. Following Saltmarche (2017), the lab sessions will occur twice a week during the initial 2 weeks and once a week thereafter.
- b) <u>daily home use of an intranasal NIR</u> stimulator (Intranasal only 810) for 25 min/day. To increase adherence, participants will keep a daily home journal logging times and other comments. They will not self-stimulate on days they come to the laboratory.



From Saltmarche et al., 2017

Sham NIR Condition and Blinding: Participants in the sham group will undergo identical informed consent, screening, pre-post testing, and NIR intervention sessions. The only difference is that "sham" Vielight devices will be used. These are identical in all respects to real devices except that they do not deliver NIR. The research assistant administering the lab stimulation session will be aware of the participant's treatment status, but will have no role in pre- or post-intervention assessments. The research assistant involved in testing and neuroimaging acquisition will be blinded to the treatment status of the participant.

<u>Imaging Protocol</u>: Imaging will be performed on 3T Siemens MRI systems (Prisma at UF and Skyra at UA). The protocols will be optimized for standardized acquisition across scanners for T1-weighted volumetric MRI, rs-fcMRI to examine functional connectivity, and MRS using a 31P coil (currently available at UF only) to assess region specific changes in markers of ATP, one of the presumed mechanisms of NIR stimulation.

Resting State fcMRI: We will perform an fcMRI resting state block with eyes open and visual fixation using echoplanar BOLD imaging (EPI; TR=2500ms, TE=16ms, FOV=192²mm, matrix=64², voxel size = 3.5mm³). Processing and analyses will use Statistical Parametric Mapping (SPM12). We will present one ten-minute block of rs-fcMRI before and after intervention to test stimulation related change in functional networks. We will construct time series datasets implementing preprocessing methods to minimize physiological and motion artifact. Whole-brain voxel-wise multiple regression analysis will verify activation patterns in resting state networks. Appropriate covariates, such as movement, for each participant's brain voxels will be included using the variation

in BOLD signal over time. The CONN toolbox and local specialized software will be used to obtain temporal correlation values to assess functional connectivity between nodes for resting state networks, with particular focus on change in frontal and hippocampal regional connectivity. Primary dependent measures will be beta weights between resting state ROI's per participant. Beta values will compare intervention-related changes in functional connectivity. Multiple comparisons will be addressed with a false discovery rate (FDR) threshold of p=0.05.

Phosphorous MRS: A 31P-MRS pulse sequence will be acquired from two 6-cm³ volumes centered in prefrontal cortex and left temporal lobe to assess region-specific change in phosphorous MRS-based markers of ATP function (TE=0.1ms; TR=4500ms; Spectral resolution=2.4 Hz/point; Spectral bandwidth=3000Hz; 7 min. duration). Spectra will be analyzed using jMRUI to give concentrations for the following phosphorous metabolites: nucleoside di- and tri-phosphate (gamma, alpha, beta-NTP), phosphoethanolamine (PEtn), phosphocholine (PCho), glycerophosphoethanolamine (GPEtn), glycerophosphocholine (GPCho), 2,3 diphospho-glyceride (DPG), inorganic-phosphate (Pi), membrane-bound phospholipid (MP), and phosphocreatine (PCr). The signal amplitudes of brain tissue and CSF will be derived (corrected for T2 decay), with brain water signal used to correct for partial CSF volume.

Outcomes: Change in performance on cognitive and mood measures and changes in imaging parameters (functional connectivity, MRS ATP markers) before and after intervention, relative to the sham control group. Intervention changes must exceed the effects of practice based on the sham control group. Aim 1 examines memory and executive function.

- Co-Primary Outcome: Changes in pre-post scores on a <u>verbal memory measure</u>, the LASSI-L (Curiel et al., 2013) and the <u>executive</u> composite and domain scores from the NIH Examiner (Kramer, et al., 2014).
- Secondary Outcome: Changes in pre-post treatment scores on the Spatial Navigation Task, a human Morris Water Maze analog sensitive to hippocampal function and traditional neuropsychological measures of executive function, Trail Making Test (Reitan & Wolfson, 1985) and Stroop (Golden, 1978).

Aim 2 examines well-being and mood variables.

- Primary outcome: Changes in pre-post treatment scores on the Negative Affect and Psychological Wellbeing scales from the emotion module of the NIH Toolbox (Gershon et al., 2013).
- Secondary outcome: Changes in pre-post treatment scores on traditional mood measures 1) State-Trait Anxiety Inventory (Spielberg, 1989), and 2) Profile of Mood States (POMS; Curan et al., 1995).

Aim 3 examines neuroimaging changes

- Primary outcome: Changes in frontal and medial temporal lobe mediated patterns of resting state functional connectivity.
- Secondary outcome: Changes in frontal and temporal lobe MRS, including markers of ATP function.

Limitations and Future Directions. There are several limitations. Ideally, we would like to follow participants for 3-6 months post intervention, but this is not possible given available resources. It is possible that we may find null cognitive/behavioral changes. This could arise because of inadequate penetrance of the signal through the skull and/or suboptimal dosing parameters. Currently, there are no standard empirically based guidelines for dosing in humans, and need exists for studies of dose-response relationships. However, we selected an 8 week intervention interval based on prior published findings and we observed MRS based changes in our initial preliminary findings with 1 older adult assessed over a 2 week interval. If results of this pilot study show efficacy in enhancing cognition and brain health, this technology could easily be used in larger trials and combined with other interventions; it represents an ideal approach because of its safety and limited side effects. Further, as a relatively inexpensive technology there is the potential for modifying NIR LED devices for widespread clinical use and/or as part of multimodal treatment programs. Because NIR light is applied with safe, non-thermal, and painless light emitting diodes (LEDs), this technology could also be modified for use by caregivers and patients at home. Based on the proposed mechanisms of action (i.e., neuroprotection, and increasing neuronal metabolism and blood flow), one possible outcome is that regular use of this technology may aid in altering the cognitive trajectory of age-related cognitive decline linked to structural and functional changes in the brain. Information learned from this study will be valuable in helping to establish the potential of this unique and innovative intervention as one of the first brain aging modifiers for healthy individuals at-risk for age-related cognitive decline with potential benefits for primary, secondary, and tertiary prevention in healthy and pathological aging

Multisite Collaboration

The University of Florida (Bowers/Woods) and University of Arizona (Alexander) will be equal partners in the proposed study. Drs. Bowers, Woods and Alexander together have extensive experience in the use of neuropsychological and neuroimaging measures to evaluate the effects of cognitive and brain aging, with the goal of identifying effective interventions for age-related cognitive decline. In the proposed study, participants will be enrolled similarly across both sites and undergo the same screening, baseline, and study intervention procedures. Similarly, pre-post imaging data will be collected from participants at both sites including structural and resting state fcMRI, thereby enabling examination of intervention related network changes. Only the UF site will collect pre-post MRS data due to the availability of a 31P coil for human use currently only at UF. We believe the proposed pilot project will provide the key information needed to support our plans for subsequent grant submissions. We anticipate frequent virtual meetings during the initial start up phase of this pilot study to ensure that all standardization and quality assurance procedures are in place; followed by biweekly to monthly meetings with at least one 'face to face' meeting at the yearly McKnight Inter-Institutional meeting. Moving forward, our ultimate goal is to obtain sufficient pilot data for submission of a multi-site NIH R01 application to more fully evaluate the potential impact of NIR stimulation as a promising intervention for the effects of brain aging, to enhance cognitive health and promote emotional well-being in the context of healthy aging.

References

- Barrett, D. W., & Gonzalez-Lima, F. (2013). Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience*, 230, 13–23.
- Blanco, N. J., Maddox, W. T., & Gonzalez-Lima, F. (2017). Improving executive function using transcranial infrared laser stimulation. Journal of neuropsychology, 11(1), 14-25.
- Chen, A. C. H., Huang, Y. Y., Arany, P. R., & Hamblin, M. R. (2009). Role of reactive oxygen species in low-level light therapy. Proceedings of the SPIE, 7165, Mechanisms for Low-Light Therapy IV, 716502.
- Chung H., Dai T., Sharma S. K., Huang Y. Y., Carroll J. D., Hamblin M. R. (2012). The nuts and bolts of low-level laser (light) therapy. Ann. Biomed. Eng. 40, 516–533.
- Crocco, E., Curiel, R. E., Acevedo, A., Czaja, S., & Loewenstein, D. A. (2013). An evaluation of deficits in semantic cueing and proactive and retroactive interference as early features of Alzheimer's disease. *American Journal of Geriatric Psychiatry* 22(9), 889-897.
- Curiel, R. E., Crocco, E., Acevedo, A., Duara, R., Agron, J. & Loewenstein, D.A. (2013). A new scale for the evaluation of proactive and retroactive interference in Mild Cognitive Impairment and Early Alzheimer's disease. *Journal of Aging Science*, 1(1), 2-5.
- Curran, S. L., Andrykowski, M. A., & Studts, J. L. (1995). Short form of the Profile of Mood States (POMS-SF): Psychometric information. *Psychological Assessment*, 7(1), 80–83.
- Darlot, F., Moto, C., Massri, N., Chabrol, C., Johnstone, Benabid, A. (2016). Near-infrared light is neuroprotective in a monkey model of Parkinson disease. *Ann. Neurology*, 79, 59-75.
- Farfara, D., Tuby H., Trudler D., et al. Low-level laser therapy ameliorates disease progression in a mouse model of Alzheimer's disease. (2015). *J. Mol Neurosci.* :55:430–436.
- Gershon, R. C., Wagster, M. V., Hendrie, H. C., Fox, N. A., Cook, K. F., & Nowinski, C. J. (2013). NIH Toolbox for assessment of neurological and behavioral function. *Neurology*, 80, S2–S6.
- Golden, C. J. (1978). Stroop Color and Word Test: A Manual for Clinical and Experimental Uses. Wood Dale, Illinois: Stoelting Company
- Gunton, M. (2009). *Life* [Television series]. In BBC Natural History Unit and The Open University. London, United Kingdom: British Broadcasting Corporation.
- Kramer, J. H., Mungas, D., Possin, K. L., Rankin, K. P., Boxer, A. L., Rosen, H. J et al. (2014). NIH EXAMINER: Conceptualization and development of an executive function battery. *Journal of the International Neuropsychological Society, 20*(1), 11-19.
- Laczó, J., Andel, R., Vlček, K., Macoška, V., Vyhnálek, M., Tolar, M., & Hort, J. (2011). Spatial navigation and APOE in amnestic mild cognitive impairment. *Neurodegenerative Diseases*, 8(4), 169-177.
- Lapchak, P. A., Salgado, K. F., Chao, C. H., & Zivin, J. A. (2007). Transcranial near-infrared light therapy improves motor function following embolic strokes in rabbits: An extended therapeutic window using continuous and pulse frequency delivery modes. *Neuroscience*, 148(4), 907-914.
- Lapchak, P. A., & De Taboada, L. (2010). Transcranial near infrared laser treatment (NILT) increases cortical adenosine-5'-triphosphate (ATP) content following embolic strokes in rabbits. *Brain Research*, 1306, 100–105.

- Lapchak, P. A., Boitana, P., Butte, P., Fisher, D., Holscher, T., Ley, E, et al. (2015). Transcranial near-infrared transmission (NILT) profiles (800nm): Systematic comparison in four common research species. *PLoS One*, *10*(6): e012758.
- Mochizuki-Oda, N., Kataoka, Y., & Cui, Y. (2002). Effects of near-infra-red laser irradiation on adenosine triphosphate and adenosine diphosphate contents of rat brain tissue. *Neuroscience Letters*, 323, 207–210.
- Moro, C., Torres, N., El Massri, N., Ratel, D., Johnstone, D. M., Stone, J., Benabid, A. L. (2013). Photobiomodulation preserves behaviour and midbrain dopaminergic cells from MPTP toxicity: Evidence from two mouse strains. *BMC Neuroscience*, *14*, 40. doi:10.1186/1471-2202-14-40
- Moro, C., Massri, N. E., Torres, N., Ratel, D., De Jaeger, X., Chabrol, C. Benabid, A. L. (2014). Photobiomodulation inside the brain: A novel method of applying near-infrared light intracranially and its impact on dopaminergic cell survival in MPTP-treated mice. *Journal of Neurosurgery*, *120*, 670–683.
- Naeser, M. A. (2012, October). Improved language after scalp application of red/near-infrared light emitting diodes: Pilot study supporting a new, noninvasive treatment for chronic aphasia. Poster presented at the 50th Annual Scientific Meeting of the Aphasia Society, San Francisco, CA.
- Naeser, M. A. (2013, February). Functional Connectivity (fcMRI) increase in language network after left scalp application of red/near-infrared, light-emitting diodes (LED) in Primary Progressive Aphasia Potential for Treatment Research. Poster presented at the 42nd Annual Meeting of the International Neuropsychological Society, Waikoloa, Hawaii.
- Naeser, M. A., Zafonte, R., Krengel, M. H., Martin, P. I., Frazier, J., Hamblin, M. R., Baker, E. H. (2014). Significant improvements in cognitive performance post-transcranial, red/near-infrared light-emitting diode treatments in chronic, mild traumatic brain injury: Open-protocol study. *Journal of Neurotrauma*, *31*(11), 1008–1017.
- Nawashiro, H., Wada, K., Nakai, K., & Sato, S. (2012). Focal increase in cerebral blood flow after treatment with near-infrared light to the forehead in a patient in a persistent vegetative state. *Photomedicine and Laser Surgery*, 30(4), 231–233.
- Oron, U., Ilic, S., De Taboada, L., & Streeter, J. (2007). Ga-As (808 nm) laser irradiation enhances ATP production in human neuronal cells in culture. *Photomedicine and Laser Surgery*, 25(3), 180–182.
- Purushothuman, S., Johnstone, D., Nandasena, C., Mitrofanis, J., & Stone, J. (2014). Photobiomodulation with near infrared light mitigates Alzheimer's disease-related pathology in cerebral cortex—evidence from two transgenic mouse models. *Alzheimer's Research & Therapy*, 6(2), 1–13.
- Purushothuman, S., Nandasena, C., Johnstone, D.M., Stone, J., and Mitrofanis, J. (2013). The impact of near-infrared light on dopaminergic cell survival in a transgenic mouse model of parkinsonism. *Brain Res.* 1535,61–70.
- Quirk, B., DeSmet, K., Henry, M., Buchmann, E., Wong-Riley, M., Eells, J., & Whelan, H. (2012). Therapeutic effect of near infrared (NIR) light on Parkinson's disease models. *Frontiers in Bioscience*, *E4*, 818-823.
- Reinhart, F., El Massri, N., Darlot, F., Torres, N., Johnstone, et al. (2015). 810nm near-infrared light offers neuroprotection and improves locomotor activity in MPTP-treated mice. *Neurosci.Res.* 92, 86–90.
- Reitan, R. M., & Wolfson, D. (1985). The Halstead–Reitan Neuropsychological Test Battery: Therapy and clinical interpretation. Tucson, AZ: Neuropsychological Press.
- Rojas, J. C., Bruchey, A. K., & Gonzalez-Lima, F. (2012). Low-level light therapy improves cortical metabolic capacity and memory retention. *Journal of Alzheimer's Disease*, 32, 741-752.
- Salsman, J. M., Butt, Z., Pilkonis, P. A., Cyranowski, J. M., Zill, N., Hendrie, H. C. et al. (2013). Emotion assessment using the NIH Toolbox. *Neurology*, *80* (11 Suppl 3), S76-86.
- Satlmarche, A.E., Naeser, M.A., Ho, K., Hamblin, M., Lim, L. (2017). Significant improvement in cognition in mild to moderately severe dementia cases treated with Transcranial plus intranasal phtobiomodulation: Case Series Report. *Photomedicine and Laser Surgery*, 35, 432-44.
- Spielberger, C. D. (1989). State-Trait Anxiety Inventory: Bibliography (2nded.). Palo Alto, CA: Consulting Psychologists Press.
- Tedford, C., DeLapp, S., Jacques, S., Anders, J. (2015), Quantitative analysis of transcranial and intraparenchymal light penetrating in human cadaver brain tissues. *Lasers Surg Medicine*, 47, 312-322.
- Thomas, K.G., Hsu, M., Laurance, H.E., Nadel, L., Jacobs ,W.J.. (2001). Place learning in virtual space. III: Investigation of spatial navigation training procedures and their application to fMRI and clinical neuropsychology. *Behav Res Methods Instrum Comput.* 33(1):21-37.
- Wan, S., Parrish, J., Anderson, R., & Madden, M. (1981). Transmittance of nonionizing radiation in human tissues. *Photochemistry and Photobiology*, *34*, 679–681.

Whelan, H., Desmet, K., Buchmann, E., Henry, M., Wong-Riley, M., Eells, J., & Verhoeve, J. (2008). Harnessing the cell's own ability to repair and prevent neurodegenerative disease. *SPIE Newsroom*, 1–3.

Wong-Riley, M. T., Liang, H. L., Eells, J., Chance, B., Henry, M., Buchmann, E. et al. (2005). Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: Role of cytochrome c oxidase. *Journal of Biological Chemistry*, 280(6), 4761-471.

Zhang, Y., Song, S., Fong, C.-C., Tsang, C.-H., Yang, Z., & Yang, M. (2003). cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light. *The Journal of Investigative*

Dermatology, 120(5), 849–857.

Total Budget - McKnight Near Infrared Intervention Project Combined Sites (U Florida & U Arizona)

| | | Year 1 | | | | Year 2 | | | Total |
|--------------------------------------|--|--------|--|--|---|--------|---------|------------------|---------|
| Personnel | UF | UA | Total | | UF | UA | Total | | |
| Site PI/MPI | 0 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| Study Coordinator (10%) | 5,000 | 5,450 | 10,450 | | 5,000 | 5,450 | 10,450 | | 20,900 |
| Research Assistant (10%) | 3,500 | 3,500 | 7,000 | | 3,500 | 3,500 | 7,000 | | 14,000 |
| Student hrs per subject | 1,300 | 1,300 | 2,600 | | 1,300 | 1,300 | 2,600 | | 5,200 |
| Subtotal Personnel | 9,800 | 10,250 | 20,050 | | 9,800 | 10,250 | 20,050 | | 40,100 |
| | | | | | | | | | |
| Fringe Benefits | | | | | | | | 15000 | |
| Site MPI/PI | 0 | 0 | 0 | | 0 | 0 | 0 | | 0 |
| Study Coordinator | 1,790 | 1,744 | 3,534 | | 1,790 | 1,744 | 3,534 | | 7,068 |
| Research Assistant | 357 | 1,120 | 1,477 | | 357 | 1,120 | 1,477 | | 2,954 |
| Student | 78 | 52 | 130 | | 78 | 52 | 130 | 3 A | 260 |
| Subtotal Fringe Benefits | 2,225 | 2,916 | 5,141 | | 2,225 | 2,916 | 5,141 | | 10,282 |
| | | | | | physical physical and the second control of | | vindő A | i dan sun san sa | |
| SUBTOTAL-PERSONNEL & BENEI | ITS 12,025 | 13,166 | 25,191 | | 12,025 | 13,166 | 25,191 | | 50,382 |
| | | | | Tenansanana | | | | lemental | |
| Supplies | UF | UA | Total | | UF | UA | Total | | Total |
| Supplies | 500 | 1,418 | 1,918 | 1 | 2,100 | 3,290 | 5,390 | | 7,308 |
| NIR Device | 3,036 | 3,036 | 6,072 | | 1,164 | 1,164 | 2,328 | | 8,400 |
| Neuropsychology Tests | 0 | | 0 | 1 | 0 | 0 | 0 | | 0 |
| Subtotal Supplies | 3,536 | 4,454 | 7,990 | | 3,264 | 4,454 | 7,718 | | 15,708 |
| | | | on New York of the State of the | Sanskateskannot H | | | | | |
| Operations | UF | UA | Total | • | UF | UA | Total | | Total |
| MRI (30/60min scan each, pre & post) | 10,400 | 5,980 | 16,380 | ı | 10,400 | 5,980 | 16,380 | | 32,760 |
| Subject Pay (\$250) | 3,250 | | 6,500 | 1 | 3,250 | 3,250 | 6,500 | | 13,000 |
| Advertising | 789 | | 3,289 | 1 | 1,061 | 2,500 | 3,561 | | 6,850 |
| Parking for Subjects | 0 | | 650 | 1 | 0 | 650 | 650 | | 1,300 |
| Subtotal Operations | 14,439 | 12,380 | 26,819 | | 14,711 | 12,380 | 27,091 | | 53,910 |
| ANATHA CATA | - | | | 71 - 10 - 10 - 10 - 10 - 10 - 10 - 10 - | | | | 1 amana | |
| Travel | UF | UA | Total | | UF | UA | Total | | Total |
| Travel | 0 | | | 1 | 0 | 0 | 0 | 1 | 0 |
| Subtotal Travel | 0 | 0 | 0 |] | 0 | 0 | 0 | | 0 |
| | Specific Control of the Control of t | | | 86 | 0.000/20122-7-0600-650-7- | | | | |
| TOTAL DIRECT COSTS | 30,000 | 30,000 | 60,000 | | 30,000 | 30,000 | 60,000 | Additional | 120,000 |
| | | | | | | | | | |

University Florida Site Budget McKnight Near Infrared Intervention Project

| | Year 1 | Year 2 | TOTAL |
|---|--|--------|---|
| Personnel | | | |
| Site MPIDawn Bowers (no salary requested) | 0 | 0 | 0 |
| Site MPI - Adam Woods (no salary requested) | 0 | 0 | (0) |
| Study Coordinator (10%) | 5,000 | 5,000 | 10,000 |
| Research Assistant (10%) | 3,500 | 3500 | 7,000 |
| Students hrs per subject-10hrs/13subjects | 1,300 | 1300 | 2600 |
| Subtotal Personnel | 9,800 | 9800 | 19,600 |
| Fringe Benefits | | | |
| Site MPI Dawn Bowers | 0 | 0 | 0 10 |
| Site MPI - Adam Woods | | 0 | - maj ij nar en o in |
| Study Coordinator | 1,790 | 1,790 | 3,580 |
| Research Assistant | 357 | 357 | 714 |
| Student 1 State of Page 1 State 1 | 78 | 78 | 156 · |
| Subtotal Fringe Benefits | 2,225 | 2,225 | 4,450 |
| SUBTOTAL OF PERSONNEL & BENEFITS | 12,025 | 12,025 | 24,050 |
| | | | |
| Supplies | manay eng away are a di Historia | | |
| Supplies | 500 | 2,100 | 2,600 |
| NIR Device | 3,036 | 1,164 | 4,200 |
| Neuropsychology Tests | | 0 | A 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 |
| Subtotal Supplies | 3,536 | 3,264 | 6,800 |
| | | | |
| Operations | | | |
| MRI (60min scan each, pre & post) | 10,400 | 10,400 | 20,800 |
| Subject Pay (\$250) | 3,250 | 3,250 | 6,500 |
| Advertising | 789 | 1,061 | 1,850 |
| Parking for Subjects | | 0 | . Para magazi 0 . ja |
| Subtotal Operations | 14,439 | 14,711 | 29,150 |
| Travel | | | |
| Travel | 1 | 0 | Seaste (.0 0) a |
| Subtotal Travel | 11-14-14-14-14-14-14-14-14-14-14-14-14-1 | 0 | <u> </u> |
| | | 0 | |
| TOTAL DIRECT COSTS | 30,000 | 30,000 | 60,000 |

University of Florida Budget Justification

Personnel:

Dawn Bowers, Ph.D., & Adam Woods, Ph.D., UF MPI (no salary support requested): Drs. Bowers and Woods will co-direct the project at the University of Florida and jointly supervise all aspects of the project. They will work closely with Dr. Alexander to ensure coordination across both the UF and UA sites. They will be jointly responsible for participant recruitment and insuring that the study complies with institutional, state, federal, and ethical guidelines. Together with Dr. Alexander, they will coordinate and prepare progress reports and work together to prepare manuscripts and complementary external grant proposals.

- <u>Dr. Bowers</u> will take the lead in providing oversight for personnel involved in subject recruitment, data collection, project management, and data analysis of behavioral/cognitive data. She will work closely with Dr. Alexander to ensure standardized implementation and administration of the near infrared (NIR) stimulation intervention across both sites. She will oversee procedures for participant screening and enrollment and will provide supervision for personnel performing screening, pre-post neurocognitive testing, and the intervention.
- <u>Dr. Woods</u> will take the lead in the neuroimaging aspects of this protocol, including MRI acquisition for all participants enrolled at UF. He will be responsible for the quality control of obtained scans, image processing and reduction, and all imaging analyses. He will work closely with Dr. Alexander at the UA site in terms of identifying site-specific imaging differences in data acquisition and analyses of the structural and functional imaging scans.

TBD, Study Coordinator (10% effort). The study coordinator will be responsible for coordinating and overseeing participant enrollment, scheduling, advertising, mailing, preparing fee payments, coordinating research assistant and student efforts, budget management, and arranging for project phone conferences and staff meetings. The Coordinator will assist with maintaining and supervising human subject certifications for the project and will work with Drs. Bowers and Woods to insure full compliance with university Institutional Review Board requirements and approvals. He/she will assist with project updates for preparation of status and progress reports and will generally assist and facilitate the day-to-day operations for data collection, data transfer, archiving, and data analysis for the study.

TBD, Project Research Assistant (10% effort). The research assistant (RA) will provide assistance in the overall operations of the study including scheduling, data entry, and maintaining participant records. S/He will schedule and perform the screening, baseline and post-intervention assessments and assist with quality control review of neuroimaging scans during the study. S/He will work with Dr. Bowers/Woods and the study coordinator to ensure that the blinded aspects of the intervention in the study are maintained. The RA will organize and review all outcome data for quality assurance and will work closely with other members of the study team to transfer data for central storage and processing for analyses.

TBD, Student Research Assistant (10 hours per subject). The student research assistants (RA) will assist by conducting phone screens, identifying participants, and scheduling study procedures. The student RA will administer the transcranial NIR intervention to study participants during the intervention visits according to the study protocol and will assist the participants in the use of the NIR stimulation procedures while at home during the intervention

study interval. They will assist with monitoring any adverse effects, should they occur, during the intervention session. They will not participate in post-intervention assessments.

Supplies

We request \$6800 over the course of the project for project-related expenses and supplies needed for intervention, creating participant files/charts, computer hardware and software, and supplies for scientific posters and manuscripts. This amount also includes costs for the NIR device.

<u>Transcranial NIR Stimulation Devices:</u> We anticipate spending \$3036 in year 1 of the project for the purchase of the Vielight NeuroGamma and 810 real and sham intranasal devices needed for the intervention. This amount includes \$1164 for the purchase of 13 intranasal leads for each participant (cost 249.50 per lead with academic research discount.) In Year 2, we will purchase additional intranasal leads for enrolled participants at cost of \$1164.

Operational Costs

MRI scans: 52 MRI scans (1 hr) @ \$400 = \$20,800. This includes time for structural and resting state fMRI, along with the MRS spectroscopy scans using the 31P coil.

<u>Subject payment and fees</u>: Subjects will receive \$250 in compensation for their completion of the study.

<u>Advertising & recruitment costs:</u> Additional monies are requested for advertising, including ads in local newspapers for recruiting participants.

University of Arizona Site Budget McKnight Near Infrared Intervention Project

| | Year 1 | Year 2 | TOTAL |
|--|---|--------|-------------------------------------|
| Personnel | | | |
| Site PIGene Alexander (no salary requested) | 0 | 0 | 0 |
| Study Coordinator-(10%) | 5,450 | 5,450 | 10,900 |
| Research Assistant (10%) | 3,500 | 3,500 | 7,000 |
| Students hrs per subject-10hrs/13subjects per year | 1,300 | 1,300 | 2,600 |
| Subtotal Personnel | 10,250 | 10,250 | 20,500 |
| | | | |
| Fringe Benefits | | | |
| Site PI - Gene Alexander | 4 1 4 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 | 0 | 0 |
| Study Coordinator | 1,744 | 1,744 | 3,488 |
| Research Assistant | 1,120 | 1,120 | 2,240 |
| Student | 52 | 52 | 104 |
| Subtotal Fringe Benefits | 2,916 | 2,916 | 5,832 |
| SUBTOTAL OF PERSONNEL & BENEFITS | 13,166 | 13,166 | 26,332 |
| ing the second of the second o | | | |
| Supplies | 1,418 | 3,290 | 4,708 |
| Supplies | 3,036 | 1,164 | 4,200 |
| NIR Device & Leads | 3,030 | 0 | -1,200 |
| Neuropsychology Tests Subtotal Supplies | 4,454 | 4,454 | 8,908 |
| Subjustance per an acceptance of the period of the control of the | | 4,434 | 0,300 |
| Operations | | | |
| MRI (30min scan each, pre & post) | 5,980 | 5,980 | 11,960 |
| Subject Pay (\$250) | 3,250 | 3,250 | 6,500 |
| Advertising | 2,500 | 2,500 | 5,000 |
| Parking for Subjects | 650 | 650 | 1,300 |
| Subtotal Operations | 12,380 | 12,380 | 12,800 |
| Travel | | | |
| Travel | 0 | 0 | 0 |
| Subtotal Travel | 0 | 0 | 1/2 / 1 H ₁ - 1/2 / H |
| | | | |
| Total Direct Costs | 30,000 | 30,000 | 60,000 |

University of Arizona Budget Justification

Personnel:

Gene E. Alexander, Ph.D. UA Site Principal Investigator (no salary support requested). Dr. Alexander will be responsible for the supervision of all aspects of the project at the University of Arizona (UA). He will work closely with Drs. Bowers and Woods to ensure coordination of the project across both sites. He will provide oversight for personnel involved in human subject recruitment, data collection, project management, data storage, and analysis at the UA. Dr. Alexander will work closely with Drs. Bowers and Woods to ensure standardized implementation and administration of the transcranial near infrared (NIR) stimulation intervention at the UA. Dr. Alexander will oversee implementation of procedures for participant screening and enrollment and will provide supervision for personnel performing the neuropsychological testing, intervention, and MRI acquisition for all subjects enrolled at the UA. He will assure that the study fully complies with all institutional, state, federal, and ethical guidelines and will work with the other research team members to insure that all safety and human subject compliance protocols are maintained. Dr. Alexander will work with Drs. Bowers and Woods in the coordination and preparation of progress reports and on the preparation of manuscripts and complementary external grant proposals.

Cortney Jessup, M.P.A., Study Coordinator (10% effort). Ms. Jessup will assist Dr. Alexander with project coordination at the UA and will be responsible for coordinating and overseeing participant enrollment and scheduling, advertising to support participant recruitment, preparation of subject mailings and fee payments, coordinating research assistant and student efforts, budget management, and arrangements for project phone conferences and staff meetings. She will work with other members of the UA research team to obtain project updates for preparation of routine status and progress reports. She will maintain and supervise the human subject certifications for the project and will work with Dr. Alexander to insure full compliance with university Institutional Review Board requirements and approvals. Ms. Jessup will work closely with staff at the UA to assist and facilitate the day-to-day operations for data collection, data transfer, archiving, and data analysis for the study.

TBN, Project Research Assistant (10% effort). The research assistant will provide assistance in the overall operations of the study including scheduling, data entry, maintaining participant records, and performing assessments according to study protocol. S/He will schedule and perform the administration of screening and neuropsychological assessments and be responsible for the acquisition and QC review of neuroimaging scans during the study. S/He will work with Dr. Alexander and Ms. Jessup to ensure that the blinded aspects of the intervention in the study are maintained. S/He will organize and review all outcome data for quality assurance and will work closely with other members of the study team to transfer data for central storage and processing for analyses.

TBN, Student Research Assistant (10 hours per subject). The student research assistants will assist the project research assistant with conducting phone screens, identifying participants, and scheduling study procedures. The student research assistants will administer the transcranial NIR intervention to study participants during the intervention visits according to the study protocol and will assist the participants in the use of the NIR stimulation procedures while at home during the intervention study interval.

Supplies

<u>Supplies</u>: We request \$4,708 over the course of the project for project-related supplies needed for intervention, creating participant files/charts, computer hardware and software, and supplies for scientific posters and manuscripts.

<u>Transcranial NIR Stimulation Devices:</u> During Year 1, we plan to purchase the Vlelight NeuroGamma system and 810 real and sham devices. We also request \$1164 in each of of year 1 and 2 for the purchase of individual intranasal leads for each subject.

Operational Costs

MRI scans: 52 MRI (30 min. session) scans @ \$230ea = \$11,960

Subject payment and fees: Subjects will receive \$250 in compensation for their completion of the study.

<u>Subject parking fees</u>: We request \$650 per year for the purchase of one leased parking space behind the Psychology Building for subject use during study visits.

Advertising & recruitment costs:

We request \$2,500 per year for placing ads in local newspapers to recruit participants for the study.

BIOGRAPHICAL SKETCH

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

NAME: Dawn Bowers, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): dbowers

POSITION TITLE: Professor, Clinical & Health Psychology, Neurology

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

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|--------------------------|------------------------------|-------------------------------|------------------------------------|
| Emory University | - | 1968-1970 | Chemistry |
| University of Florida | B.S. | 1972 | Psychology |
| University of Florida | M.S. | 1974 | Clinical Psychology |
| Boston University | internship | 1977 | Neuropsychology |
| University of Florida | Ph.D. | 1978 | Clinical & Health |
| University of Florida | Post-Doc | 1979 | Psychology Behavioral Neurology |
| | | | |

A. Personal Statement

I am a university professor, a cognitive neuroscientist, and a board certified clinical neuropsychologist. I have longstanding research and clinical expertise in cognitive and emotional changes that are associated with neurologic disease and aging, particularly apathy, depression, memory and executive function. I am the lead neuropsychologist for UF's internationally known Center for Movement Disorders and direct a NINDS-funded predoctoral T32 training grant. My current research focuses on emotion regulation and executive function in older adults, real time fMRI for modulating emotional responsivity, psychophysiologic signatures of apathy and depression, and interactive effects of cognitive training, mindfulness and novel therapies on mood and cognition in older adults. I have been funded by NIH for over 30 years. This has included support for several randomized clinical trials, one for treatment of apathy using rTMS, another for treatment of masked faces in Parkinson disease, and a 3rd involving combined cognitive training-exercise intervention with older adults. My laboratory has used various tools (startle, pupillometry, ERP, computational modeling, TMS and rTMS) to better understand neural mechanisms that underlie emotional and cognitive changes in older adults. As such, I have experimental tools/approaches and wealth of experience that can facilitate hypothesis driven research. both mechanistically and applied. The proposed project hopes to evaluate the viability of a novel noninvasive approach to cognitive enhancement and is designed to rigorously evaluate potential cognitive and neural benefits for older adults. The team assembled for this research project (Dr. Adam Woods from UF and Dr. Alexander from the University of Arizona), are leaders in the field in terms of age-related cognitive decline, intervention, neuroimaging, and brain stimulation and bring forth a wealth of experience and knowledge to this collaborative effort across two McKnight sites, the University of Florida and the University of Arizona.

B. Positions and Honors

Positions and Employment

| 1976-1977: | Teaching Fellow in Neurology, Boston University College of Medicine |
|------------|--|
| 1976-1977: | Internship in Clinical Psychology/Neuropsychology, Boston VAMC |
| 1976-1977 | Externship in Geriatric Neuropsychology, Framingham Heart Study, MA |
| 1979 | Post-doctoral Fellowship, Behavioral Neurology, UF College of Medicine |
| 1980- 1998 | Associate Professor in Neurology [Assistant 1980-85], UF College of Medicine |

| 1984-1998 Neuropsychologist, State of Florida Memory Disorders Clinic |
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| 1998- Professor of Clinical & Health Psychology [Associate 1998-2002] |
| 2006- Chief, Neuropsychology Division, Dept. Clinical & Health Psychology |
| 2006- Director, Neuropsychology Post-doctoral Program |
| |
| Other Positions and Professional Memberships (abbreviated) |
| 2011-12 Ad hoc Member, Special Emphasis Panel, Clinical and Imaging Translations Study Section (ZRG1 DTCS Y(81)]. |
| 2012-14 Chair & Vice Chair, Faculty Council, College of PHHP |
| 2012-15 Board of Governors, International Neuropsychological Society |
| 2012 Panel Member, NIH Review of LRP proposals |
| 2013-17 Merit Review Panel for Mental Health and Behavioral Sciences-B, BLRD and SCR&D |
| Department of Veterans Affairs |
| 2013- Fellows Committee, Division 40, APA (Member 2013-16)-) |
| 2016- Chair, APA Division 40 Fellows Committee |
| 2017 Panel Member, NINDS Review of T32 Programs, ZNS1 SRB 58 |
| Membership American Psychological Association (Divisions 12, 20, & 40), International Neuropsychology |
| Society, American Academy of Clinical Neuropsypchology, Society for Neuroscience, Cognitive |
| Neuroscience Society |
| <u>Honors</u> |
| 2006- UF Foundation Research Professor |
| Fellow, American Psychological Association, Division 40 |
| 2013 Board Certification in Clinical Neuropsychology (ABBP/cn) |
| 2014 Paul Satz Career Mentoring Award, International Neuropsychology Society |
| 2014 Edith Kaplan Neuropsychology Award, Massachusetts Psychological Society |
| 2015 Doctoral Mentoring Award, College of Public Health and Health Professions, UF |
| 2015 Audrey Shumacher Teaching Award, Department of Clinical & Health Psychology |
| 2015 Research Award, Department of Clinical & Health Psychology |
| 2016 University of Florida Doctoral Mentoring Award |
| 2017 University of Florida Term Professor Award |

C. Contributions to Science

Apathy/depression in Parkinson Disease. Much of my research over the past decade has focused on cognitive and emotional sequelae of Parkinson disease. One line of research has supported the view that apathy is the primary neuropsychiatric signature in Parkinson disease. We and others have shown that apathy is distinct from depression, affects between 30-70% of PD patients in cross-sectional studies and progressively worsens with disease severity. In my lab, we have examined psychometric properties of different apathy scales and shown how depression and apathy differentially predict cognitive, physiologic, and trajectory of motor decline in Parkinson disease. An initial study published over a decade ago in Brain found that Parkinson patients had muted physiological reactivity to emotional materials, as indexed by blunted startle eyeblink responses; we proposed this was due to aberrant amygdala gating. Importantly, this blunting was associated with apathy but not depression. These findings were replicated and similar apathy-depression dissociations were observed in our ERP studies, trajectory of decline studies, and by the differential influence of depression and apathy on cognition. What has emerged is the view that depression is a mood disorder, whereas apathy is motivational disorder. The importance of this perspective relates to diagnosis and treatment, as pharmacologic therapy for depression with SSRI's actually worsens apathy. Current efforts relate to non-pharmacologic treatment approaches for apathy, ranging from motivational telehealth interventions to emotion regulation. Currently, we are completing an NINDS funded ERP study examining the ability of Parkinson patients to 'intentionally" upregulate their emotional reactivity and whether success in doing so is related to executive dysfunction.

- Bowers, D., Miller, K., Mikos, A., Kirsch-Darrow, L., Springer, S., Fernandez, H., Foote, K., Okun, M.S. (2006).
 Startling facts about emotion in Parkinson disease: Blunted reactivity to aversive stimuli. *Brain, 129,* 3345-3365.
- Kirsch-Darrow, L., Fernandez, H., Okun, M., Bowers, D. (2006). Dissociating apathy and depression in Parkinsons's disease. *Neurology*. 67(1), 20-27.

- Zahodne, L, Marsiske, M., Okun, M.S., Rodriguez, R., Malaty, I, Bowers, D. (2012). Mood and motor symptoms in Parkinson's Disease: a multivariate latent growth curve modeling. Neuropsychology, 26, 71-80. PMID: 22142359
- Renfroe, J.B., Bradley, M.M., Okun, M.S., Bowers, D. (2016). Motivational engagement in Parkinson disease: perception and preparation for action. *International Journal of Psychophysiology*, 99, 24-32. PMID:26659013
- Mangal, P., Lafo, P., Scott, B., Okun, M.S., Bradley, M., Bowers, D. (2017, February). Intentional enhancement of electrocortical responses to emotional pictures by Parkinson patients: Relation to executive function. Presented at the 44th annual meeting of the International Neuropsychological Society, Boston, MA. (Abstract: Journal of the International Neuropsychological Society
- Butterfield, L., Ciminio, C., Salazar, R., Lee, C., Haley, W., Sanchez-Ramos, J., Okun, M.S., Bowers, D. (2017). The Parkinson Active living (PAL) Program: A behavioral intervention targeting apathy in parkinson's disease. J. Geriatric Psychiatry and Neurology, 30, 11-25.

<u>Vascular Comorbidities and Cognition in Parkinson Disease.</u> Despite clinical lore that patients with Parkinson disease are impervious to effects of hypertension due to the blood pressure lowering effects of various dopamine medications, we have shown that those with hypertension and other vascular comorbidities 'take a hit' in terms of executive function, similar to that of non-PD older adults.

- Jones, J., Malaty, I., Price CC, Okun, MS., Bowers, D. (2012) Health comorbidities and cognition in 1948 patients with idiopathic Parkinson disease. Parkinsonism and Related Disorders. 18 (10), 1073-1078 PMID:22776043
- Jones, J., Jacobson, C., Murphy, M.C., Price, C.E., Okun, M.S., Bowers, D. (2014). Influence of hypertension on neurocognitive domains in non-demented Parkinson's disease patients. Parkinson's Disease, 2014, Article ID 507529, [http://dx.doi.org/10.1144/2014/507529]. PMID: 24587937 PMCID: PMC3920751.
- Scott, B.M., Maye, J., Jones, J., Thomas, K., Mangal, P., Trifilio, E., Hass, C., Marsiske, M., Bowers, D. (2016).
 Post-exercise pulse pressure is a better predictor of executive function than pre-exercise pulse pressure in cognitively normal older adults. *Aging, Neuropsychology, and Cognition*. 23 (4), 464-476 PMID: 26629911
- Jones, J., Price, CE, Tanner, J., Okun, M.S., Bowers, D. (2017). Is cognition more vulnerable to the effects of cardiovascular risk in Parkinson patients versus controls: A neuroimaging and neuropsychological study. J. International Neuropsychology Society. 23, 1-10 PMID:28162137

Retrosplenial Amnesia. This body of work described the first human case of a pure amnestic syndrome due to an isolated lesion of the left retrosplenial region, located beneath the posterior cingulum; it receives direct input from the fornix of the hippocampus, projects forward via the cingulum and serves as way station for input from the adjacent parietal region. We conceptualized the amnesia induced by this lesion as a 'disconnection' variant, and a neuroimaging study (PET) of this patient showed hypometabolism of the thalamus and hypermetabolism of the ipsilateral frontal lobe. We and others subsequently described other cases of retrosplenial amnesia. More recent research has implicated this region in Alzheimer's disease.

- Valenstein, E., Bowers, D., Verfaellie, M., Heilman, K., Day, A., and Watson, R. (1987). Retrosplenial amnesia. *Brain, 110*, 1631-1646.
- Bowers, D., Verfaellie, M., Valenstein, E., and Heilman, K. (1988). Impaired acquisition of temporal information in retrosplenial amnesia. Brain and Cognition, 8, 47-66
- Heilman, K.M., Bowers, D., Watson, R., Day, A., Valenstein, E., Hammond, E., and Duara, R. (1990). Frontal hypermetabolism and thalamic hypometabolism in a patient with abnormal orienting and retrosplenial amnesia. Neuropsychologia, 28, 161-170.
- McDonald, C., Crosson, B., Valenstein, E., and Bowers, D. (2001). Verbal encoding deficits in a patient with retrosplenial amnesia. Neurocase, 7, 407-17.

Cortical Contributions to Emotion. During an early phase of my academic career, my interests focused on cortical contributions to emotion. This was done primarily using a 'stroke" or 'lesion' model. Much of this work predated fMRI. Some key findings, that have been replicated over the years, were that that posterior focal hemisphere lesions (temporo-parietal) induced defective perception of emotional faces and prosody (tone of voice) that was not due to basic visuoperceptual disturbances. Instead I proposed a model which involved a nonverbal affective lexicon that was moreso lateralized to the right than left hemisphere. This was initially inspired by observations of patient with a callosal disconnection and an affect specific anomia (Bowers & Helman, 1984); this observation led to the development of *The Florida Affect Battery* which enabled us to parcellate out various processing disturbances. What we know now is that more anterior cortical systems play a more direct role in modulating the underlying limbic system, whereas the posterior cortical systems are involved in emotional interpretation that feeds forward to assist in goal selection, with lateralized involvement.

- Bowers, D., Jones, J., Dietz, J. (2014). Assessment of emotion, mood, and affect associated with neurologic disorders. In Parsons, M. and Hammeck, T. (eds), Clinical Neuropsychology. *Pocket Handbook of Assessment*. American Psychological Press.
- Bowers, D., Bauer, R.M., and Heilman, K. (1993). The nonverbal affect lexicon: Theoretical perspectives from neuropsychological studies of affect perception. *Neuropsychology*, 7(4), 433-444.
- Bowers, D., Coslett, B., Bauer, R., Speedie, L., and Heilman, K.M. (1987). Comprehension of emotional prosody following unilateral brain damage: Processing versus distraction defects. Neuropsychologia, 25,317-328.
- Bowers, D., Bauer, R., Coslett, B., and Heilman, K. (1985). Processing of faces by patients with unilateral hemisphere lesions. I. Dissociation between judgments of facial affect and facial identity. *Brain & Cognition*, 4, 258-272.

<u>Pseudoneglect.</u> Early in my career, I described a mild asymmetry in spatial attention whereby normal individuals tend to favor the left side of space. I referred to this phenomenon as 'pseduoneglect', since the spatial error was opposite in direction to that observed in patients with right parietal strokes. Since the initial discovery, pseudoneglect (or spatial asymmetry) has been observed in 100's of studies ranging from judgements of brightness, numerosity, size, and representation to neuroimaging studies. The original study initially describing this phenomenon (Bowers & Heilman, 1980) has been cited almost 1000 times, and continues to be studied today.

- Bowers D, Heilman KM (1980) Pseudoneglect: effects of hemispace on a tactile line bisection task.
 Neuropsychologia 18: 491–498
- Heilman KM, Bowers D, Watson RT. (1984). Pseudoneglect in a patient with partial callosal disconnection. Brain. 107 (Pt 2):519-32.
- W atson RT, Heilman KM, Bowers D. (1985). Magnetic resonance imaging (MRI, NMR) scan in a case of caollosal apraxia and pseudoneglect. Brain, 108 (Pt 2):535-6

D. Research Support

Ongoing Research Support

R01 HD091658 PI: Hegland

2017-2020

Mechanisms of airway protection dysfunction in Parkinson's disease.

This project examines neural mechanisms underlying swallowing disorders in individuals with Parkinson disease, focusing on relationship between sensory signals and motor output.

Role: Co-I

NIH/R21-AG057200

MPI: Bowers/Ebner

2017-2019

Determining plasticity of brain-regulatory mechanisms related to emotion processing: A Neurofeedback approach in aging and Parkinson Disease

This project examines use of real time fMRI to provide neurofeedback for increasing limbic activation (anterior insula) and its influence cognitive and behavioral ratings.

T32- NS082168

MPI: Bowers & Vaillancourt

2015-2020

Interdisciplinary Training in Movement Disorders and Neurorestoration

This grant focuses on interdisciplinary training of predoctoral trainees across cognitive/movement science,

R03-MH109333

PI: Bowers

2017-2018

Dissociating Components of Anhedonia: Pilot Behavioral and fMRI Data for the Effort Expenditure for Rewards Task

The goal of this study is to examine the neural correlates of anhedonia in older and younger adults. (I took over this project when Dr. Dotson left UF)

ALZ67-State of Florida

PI: Bowers

2016-2018

Pilot Intervention in Mild Cognitive Impairment: A Proof of Concept Study with Transcranial Near Infrared Stimulation

This pilot study will test in a randomized sham controlled trial whether a novel intervention, near infrared brain stimulation, has potential for improving cognitive symptoms in individuals with amnestic mild cognitive impairment.

NIH/ R01-NS096008

MPI: Okun/Gunduz

2016-2021

The Human Thalamocortical Network in Tourette.

The goal of this study is to develop a closed loop neuromodulation solution for Tourette syndrome and to explore the humanthalamocortical newtwork in Tourette syndrome

Role: Co-I

UH3-NS095553

MPI: Gunduz/Foote

2016-2021

NIH/NINDS

Closing the Loop on Tremor: A Responsive Deep Brain Stimulator for Treatment of Tremor

This project examines the thalamocortical neurophysiology of tremor.

Role: Co-I

ALZ-121 State of Florida

PI: Wicklund

2016-2018

Consortium for Diagnostic Algorithm with Novel Markers in early Alzheimer's Disease

This Florida multisite study aims to 1) validate novel neuropsychological and imaging measures that are sensitive to the earliest cognitive changes associated with AD, and 2) develop algorithms for fitting patients into various diagnostic categories using multimodal clinical, neuropsychological, and neuroimaging data.

Role: Co-I

R01 NS082386

PI: Price

2013-2018

White Matter Connectivity and PD Cognitive Phenotype

This grant examines 3 cognitive subtypes of PD in relation to white matter connectivity using cognitive testing and multimodal imaging approaches (DTI, fMRI)

Role: CO-I

Michael J. Fox Foundation

PI; Okun

2015-2017

A Closed Loop Neuromodulation Solution For Parkinson's Disease Related Freezing

Role: Co-I

Completed Research Support

R21NS079767

PI: Bowers

2012-2015

Emotion Regulation, Executive Function, and Parkinson Disease.

This grant tests whether Parkinson patients can learn to "upregulate" their emotional reactivity, as measured by electrophyysiologicall measures (LPP, ERP), and whether the ability to do so is related to executive functioning.

Village-UF Partnership

MPI: Bowers & Marsiske

2014-2016

Vitality Mind-Brain Health: Re-Vitalize, Cedar, & Neuroadvantage

This project tests various hypotheses regarding the basis for cognitive improvement in older adults undergoing various cognitive and behavioral interventions i.e., mindfulness, exergames, etc.)

State of Florida

PI: Lowenstein/Wicklund

02/2015-03/30/15

Novel Markers in Alzheimer's Disease.

This multi-site project across 5 institutions in Florida focused on novel experimental measures that might be more sensitive in detecting preclinical changes associated with early Alzheimer's disease.

Role: CO-I

BIOGRAPHICAL SKETCH

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

NAME: Woods, Adam Joshua

eRA COMMONS USER NAME (credential, e.g., agency login): AJWOODS

POSITION TITLE: Assistant Professor, Clinical & Health Psychology, Aging and Geriatric Research

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

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date MM/YYYY | FIELD OF STUDY |
|-------------------------------------|---------------------------|-------------------------------|------------------------|
| University of Alabama at Birmingham | B.S. | 05/03 | Psychology |
| George Washington University | Ph.D. | 05/10 | Cognitive Neuroscience |
| University of Pennsylvania | Post-Doctoral | 06/13 | Cognitive Neuroscience |
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A. Personal Statement

Dr. Adam J. Woods is an Assistant Professor in the Department of Clinical and Health Psychology and the Assistant Director of the Center for Cognitive Aging and Memory in the McKnight Brain Institute at the University of Florida. His active program of research investigates precursors and neuroimaging-based biomarkers of cognitive impairment in older adults. Dr. Woods has a strong background using multi-disciplinary neuroscience methodologies (MRI/fMRI, electrophysiology, non-invasive brain stimulation), extensive experience with aging-related disorders, and past research with neurological diseases. His background, experience, and training in analysis of magnetic resonance neuroimaging and execution of non-invasive brain stimulation clinical trials will be central to his role in the present proposal. Dr. Woods leads two of the largest Phase II and Phase III non-invasive electrical brain stimulation trials - funded by NIA. The ACT study is the first ever phase III trial of this type and the Stimulated Brain study is one of the largest Phase II trials currently underway for non-invasive electrical stimulation. Both of these trials specifically target enhancing cognition in older adults. His experience with non-invasive brain stimulation in older adults as a treatment modality will be a strong foundation for success of this application. In addition, Dr. Woods is also an expert in multimodal neuroimaging (fMRI, sMRI, FLAIR, DWI, MRS). In the context of this work, he has established a multimodal semi-automated neuroimaging pipeline using 1000 cores of the HiperGator super-computer at the University of Florida, specifically dedicated to the Center for Cognitive Aging and Memory. In addition, Dr. Woods pioneered whole head 31P MRS at the University of Florida, not only obtaining funding for this relatively unique imaging modality (~5 whole head 31P MRS coils exist across the country), but also worked closely with Philips to implement optimized 31P sequences at UF for acquisition of phosphorous based cerebral metabolites. In addition, he Dr. Woods has developed state of the art processing pipelines for this unique data and Drs. Bowers and Woods have worked closely together on prior and ongoing projects to implement this modality in older adults undergoing NIRS intervention. Thus, Dr. Woods' knowledge and expertise in neuroimaging and non-invasive brain stimulation will serve to facilitate the success of the project.

- a. Bikson, M., Grossman, P., Thomas, C., Jiang, J., Adnan, T., Mourdoukoutas, P., Kronberg, G., Troung, D., Boggio, P., Brunoni, A., Charvet, L., Fregni, F., Fritsch, B., Gillick, B., Hamilton, R., Hampstead, B., Jankford, R., Kirton, A., Knotkova, H., Liebetanz, D., Liu, A., Loo, C., Nitsche, M., Richardson, J., Rotenberg, A., Turkeltaub, P., & Woods, A.J. Safety of transcranial Direct Current Stimulation (tDCS): evidence based update 2016. *Brain Stimulation. 9*(*5*): 641-661. PMCID: PMC5007190
- b. Woods, A.J., Antal, A., Bikson, M., Boggio, P.S., Brunoni, A.R., Celnik, P. Cohen, L.G., Fregni, F., Herrmann, C.S., Kappenman, E., Knotkova, H., Liebetanz, D., Miniussi, C., Miranda, P.C., Paulus, W.,

- Priori, A., Reato, D., Stagg, C., Wenderoth, N., Nitsche, M.A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology*. *127(2)*: 1031-1048. PMCID: PMC4747791
- c. Porges, E.C., Woods, A.J., Edden, R., Harris, A., Chen, H., Garcia, A., Lamb, D., Williamson, J.W., Cohen, RA. (2017). Frontal GABA concentrations are associated with cognitive performance in older adults. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging. 2(1):* 38-44. PMCID: PMC5312683
- d. Woods, A.J., Hamilton, R.H., Kranjec, A., Bikson, M., Minhaus, P., Yu, J., Chatterjee, A. (2014). Space, time, and causality in the human brain. *NeuroImage*, *92*, *285-297*. PMCID: PMC4008651

B. Positions and Honors

| <u>Positio</u> | | |
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| 2010-2013 | Post-Doctoral Fellow | , Department of Neurolog | y, University of Pennsylvania | , Philadelphia, PA |
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2013-2016 Assistant Professor, Department of Aging and Geriatric Research, University of Florida, Gainesville, FL

2013-2014 Cognitive Aging and Memory Clinical Translational Research Program Scholar, University of Florida, Gainesville, FL

2013-2014 Pepper Scholar, Institute on Aging, University of Florida, Gainesville, FL

2014- Assistant Director, Center for Cognitive Aging and Memory, Institute on Aging, University of Florida, Gainesville, FL

2016- Assistant Professor, Department of Clinical and Health Psychology, University of Florida, Gainesville, FL

Academic and Professional Honors

| National Science Foundation (NSF) Graduate Research Fellowship |
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| Research Enhancement Fund grant award for advanced dissertation research, GWU |
| Graduate Research Fellowship, GWU |
| Thelma Hunt Research Fellowship in Psychology, GWU |
| Post-Doctoral Fellowship, Intellectual and Developmental Disabilities Research Center, |
| Children's Hospital of Philadelphia |
| Pepper Center/CAM-CTRP Scholar, Cognitive Aging and Memory Clinical Translational |
| Research Program, University of Florida, Gainesville, FL |
| Appointed Assistant Director of the Center for Cognitive Aging and Memory |
| KL2 Scholar, Clinical Translational Science Institute |
| Junior Fellow of the World Academy of Arts and Sciences |
| Young Investigator Award in Neuromodulation, NYC Neuromodulation 2015, New York, NY, |
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C. Contribution to Science

Non-invasive Brain Stimulation. Over the past eight years, I have focused my research on the technical and basic science application of non-invasive electrical brain stimulation techniques as novel interventions for enhancement of cognitive function. This work includes both transcranial direct current stimulation, transcranial magnetic stimulation, and near infrared stimulation. To further the field, I co-founding a CME certified practical training course in transcranial electrical stimulation (tES) that has trained over 700 researchers and students to safely and consistently apply this method of non-invasive brain stimulation. I have published numerous papers aimed at enhancing replicability and safety for the method, in addition to exploring its impact on a variety of cognitive functions in the brain. In addition, I was awarded the 2015 NYC Neuromodulation Young Investigator Award for my technical and educational contributions to the field. Furthermore, I recently led a 20-author field consensus paper on technical and methodological standards in the field of tES, in addition to senior authorship on a 27 author field standards safety paper currently.

a. Minhas, P., Bikson, M., Woods, A.J., Rosen, A., Kessler, S. (2012). Transcranial direct current stimulation in the pediatric versus adult brain: A computational modeling study. *IEEE Xplore: EMBC*, 63: 859-862. PMCID: PMC3641645

- b. Kessler, S., Minhas, P., Woods, A.J., Rosen, A., Bikson, M. (2013). Dose considerations for transcranial direct current stimulation in children: a computational modeling study. *PLoS ONE*, *8*(9): e76112. PMCID: PMC3785412
- c. Woods, A.J., Bryant, V., Sacchetti, D., Gervits, F., Hamilton, R. (2015). Effects of electrode drift on transcranial direct current stimulation. *Brain Stimulation*. *8*(3): 515-519. PMCID: PMC4461479
- d. Szynkowicz, S.M., McLaren, M.E., Suryadevara, U., Woods, A.J. (2016). Transcranial direct current stimulation use in the treatment of neuropsychiatric disorders: A brief review. *Psychiatric Annals*, 46(11): 642-646. PMCID: PMC5117191

Neuroimgaing. My work in neuroimaging has focused on understanding what brain networks underlie cognitive processes and how these processes are altered by age and medical disorders exacerbating aging of the human brain. This work has primarily used structural and functional magnetic resonance imaging and diffusion weighted imaging, but now includes magnetic resonance spectroscopy. Through multimodal neuroimaging, this work aims to identify markers predictive of cognitive decline in older adults, as well as markers of intervention effectiveness. This work has been central to identification of neural intervention targets for tES.

- a. Dotson, V.M., Szymkowicz, S.M., Sozda, C.N., Kirton, J.W., Green, M.L., O'Shea, A., McLaren, M.E., Anton, S.D., Manini, T.M & Woods, A.J. (2015). Age differences in prefrontal thickness and volumes in middle aged to older adults. *Frontiers in Aging Neuroscience*. 7: 250. PMCID: PMC4717301
- b. Seider, T., Gongvatana, A., Woods, A.J., Porges, E., Chen, H., Cummings, T., Kahler, C.W., Monti, P.M., Cohen, R.A. (2016). Age exacerbates HIV associated white matter abnormalities. *Journal of Neurovirology*. 22(2): 201-212. PMCID: PMC4783252
- c. Szynkowicz, S.M., McLaren, M.E., Kirton, J.W., O'Shea, A., Woods, A.J., et al. (2016). Depressive Symptom Severity Is Associated with Increased Cortical Thickness in Older Adults. *International Journal of Geriatric Psychiatry*. 31(4): 325-333. PMCID: PMC4724336
- d. O'Shea, A., Cohen, RA, Porges, E.C., Nissim, N., Woods, A.J. (2016). Cognitive aging and the hippocampus in older adults. *Frontiers in Aging Neuroscience*, *8*: 298. PMCID: PMC5143675

Working Memory/Executive Function. One area of my work investigates the impact of aging and stroke on working memory and executive function. My recent work in age-related change in working memory/executive function includes both behavioral and neuroimaging based identification of therapeutic neural targets for tES. This work spans investigation of early development (age 2-18 years) to effects in later life (ages 60+) and following focal lesions to frontal and parietal brain systems.

- a. Mark, V.W., Woods, A.J., Ball, K.K., Roth, D.L., Mennemeier, M. (2004). Disorganized search is not a consequence of neglect. *Neurology*, *63(1)*, 78-84.
- b. Woods, A.J., Mark, V.W. (2007). Convergent validity of executive organization measures on cancellation. *Journal of Clinical and Experimental Neuropsychology, 29(7),* 719-723. PMCID: PMC3275913
- c. Woods, A.J., Goksun, T., Chatterjee, A., Zelonis, S., Mehet, A., Smith, S. (2013). The development of organized visual search. *Acta Psychologica*. *143*(2), 191-199. doi: 10.1016/j.actpsy.2013.03.008 PMCID: PMC3651801
- d. Nissim, N., O'Shea, A., Bryant, V., Porges, E., Cohen, R., Woods, A.J. (2017). Frontal structural neural correlates of working memory performance in older adults. *Frontiers in Aging Neuroscience, 8: 328.* PMCID: PMC5210770

Attention. Over the past ten years, I have studied attentional processes in the brain using a variety of tES and attention research methods in spatial neglect following stroke and health cognitive populations to understand the relative contributions of frontal and parietal systems in attention.

- a. Mennemeier, M., Pierce, C., Dowler, R., Chatterjee, A., Anderson, B., Jewell, G., Woods, A.J., Mark, V.W. (2005). Biases in attentional orientation and magnitude estimation explain crossover: neglect is a disorder of both. *Journal of Cognitive Neuroscience*, 17, 1194-1211.
- b. Woods, A.J., Mennemeier, M., Garcia-Rill, E., Meythaler, J., Mark, V.W., Jewell, G.R., Murphy, H. (2006). Bias in magnitude estimation following left hemisphere injury. *Neuropsychologia*, *44*, 1406-12.

- c. Woods, A.J., Lehet, M., Chatterjee, A. (2012). Context modulates the contribution of time and space in causal inference. *Frontiers in Psychology*, *3*, 371. doi: 10.3389/fpsyg.2012.00371 PMCID: PMC3498891
- d. Woods, A. J., Mennemeier, M., Garcia-Rill, E., Huitt, T., Chelette, K. C., McCullough, G., Munn, T., Brown, G., Kiser, T. S. (2012). Improvement in arousal, visual neglect, and perception of stimulus intensity following cold pressor stimulation. *Neurocase*, *18*, 115-122. PMCID: PMC3266979

Cognitive Aging Interventions. Much of my current and past work focuses on successful cognitive aging interventions, in a variety of populations. This work has evaluated not only the cognitive and functional consequences of aging and various disorders, but also improvement in these processes following intervention. This line of my research attempts to identify novel markers (e.g., neuroimaging, etc.) and methods for prevention (e.g., tES, anti-inflammatory intervention) of age and disease related cognitive.

- a. Mark, V.W., Woods, A.J., Mennemeier, M., Abbas, S., Taub, E. (2006). Cognitive assessment for CI therapy in the outpatient clinic. *Neurorehabilitation*, *21*, 139-46.
- b. Woods, A.J., Mark, V.W., Pitts, A., & Mennemeier, M. (2011). Pervasive cognitive impairment in acute rehabilitation patients "without" brain injury. *PM&R*, *3*(*5*), 426-432. PMCID: PMC3275913
- c. Woods, A.J., Cohen, R.A., Pahor, M. (2013). Cognitive frailty: frontiers and challenges. *Journal of Nutrition, Health, and Aging. 17, 741-743.* PMCID: PMC4471842
- d. Anton, S., Woods, A.J., Ashizawa, T., Barb, D., Buford, T., et al., Successful aging: Advancing the science of physical independence in older adults. *Aging Research Reviews*. 24, 304-27. PMCID: PMC4661112

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/adam.woods.1/bibliography/45511051/public/?sort=date&direction=descending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

NIA R01AG054077 (Woods/Cohen/Marsiske; MPIs) 09/01/16-08/31/21

National Institutes of Health

Augmenting Cognitive Training in Older Adults (ACT)

This study is a Phase III definitive multi-site randomized clinical trial with an adaptive design that will establish the benefit of delivering adjunctive transcranial direct current stimulation (tDCS) with cognitive training in older adults to combat cognitive aging. This trial measures both trial success and intervention mechanisms using multimodal neuroimaging and magnetic resonance spectroscopy, as well as comprehensive neurocognitive and functional assessment.

Role: PI

NIA K01AG050707-A1 (Woods; PI) 09/30/16-05/31/21

NIH

Neuromodulation of Cognition in Older Adults

The goal of this study will be to investigate the ability of transcranial direct current stimulation to enhance the effectiveness of cognitive training targeting attention, speed of processing, and working memory function in older adults. Training will focus on cognitive aging interventions and advanced magnetic resonance imaging and spectroscopy methods.

Role: PD/PI

NIMH RF1MH114290-01 (Sadlier; PI) 07/19/17-07/18/21

National Institutes of Health

Mechanism and dosimetry exploration in transcranial electrical stimulation using magnetic resonance current mapping methods

The goal of this project is to pioneer an objective measure of current flow in the brain using state of the art magnetic resonance imaging methods combined with in scanner application of tDCS and tACS. This project

will also assess the relationship between activation in working memory related regions from an NBACK fMRI task and correspondence of change following F3-F4 in scanner tDCS.

Role: Co-I (overlap covered by K01)

NIA R21AG053736-01A1 (Clark; PI) 07/01/17-06/31/19

National Institutes of Health

Combining tDCS and neurorehabilitation to treat age-related deficits of mobility and cognition

The goal of this study is to obtain pilot data for a full-scale clinical trial combining transcranial direct current stimulation (tDCS) and complex walking intervention to enhance mobility in older adults.

Role: Co-I (overlap covered by K01)

Industry Sponsored Trial (Woods; PI)

07/01/16-06/31/18

Osato Research Institute

Impact of Fermented Papaya Product on brain energetics, neuroinflammation, and cognition: The Efficient

Brain Study

The goal of this study is to perform a pilot clinical trial investigating the influence of Fermented Papaya Product on brain energetics, neuroinflammation, and cognition in older adults with elevated systemic inflammation using multimodal neuroimaging (fMRI, DWI) and spectroscopy (31P, 1H-MRS), as well as assessment of systemic inflammation and cognition. The project specifically focuses on enhancement of working memory function in older adults.

Role: Pl

Recently Completed Research Support

CTSI KL2TR001429-01 (Woods; PI)

03/15/14-03/15/16

NIH & Clinical Translational Science Institute KL2 Career Award

Neuromodulation of working memory function in older adults.

The goal of this funding is to provide investigators with further training in clinical translational science. The funded project will involve a randomized clinical trial pairing transcranial direct current stimulation with cognitive training to enhance working memory function in older adults.

Role: PI

Ethel Moore Fund (Bowers, PI)

02/01/16-08/31/16

State of Florida

Pilot Intervention in Mild Cognitive Impairment: A proof of concept study with Transcranial Near Infrared Stimulation

The goal of this study is to obtain pilot data for effectiveness of TNIS in treatment of cognitive impairment in MCI, with acquisition of mechanistic phosphorous magnetic resonance spectroscopy (31P MRS) data investigating change in brain ATP metabolism.

Role: Co-I

2 P30 AG028740-06 (Pahor; PI)

04/15/12-03/31/17

National Institutes of Health

UF Claude D. Pepper Older Americans Independence Center (OAIC) KL2 Award:

A study of cross-cultural differences in analgesic effects of transcranial direct current stimulation (tDCS) in white and Asian older adults with chronic pain: KL2 awardee (Ahn).

Role: Co-Mentor

NIA K99AG048762 (Fazeli; PI)

09/15/14-05/31/16

National Institutes of Health

A novel neurorehabilitation approach for cognitive aging with HIV

The goal of this study is to investigate the efficacy of cognitive training paired with tDCS on remediation of cognitive deficits in HIV positive older adults. Dr. Fazeli will receive training in aging and tDCS research methods.

Role: Co-mentor

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.

Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Gene E. Alexander, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): alexander

POSITION TITLE: Professor of Psychology, Psychiatry, Neuroscience, and Physiological Sciences

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

| INSTITUTION AND LOCATION | DEGREE (if applicable) | Completion Date | FIELD OF STUDY |
|---|---------------------------|--------------------|---------------------|
| Pomona College, Claremont, CA | B.A. | 5/1983 | Psychology |
| Loyola University of Chicago, Chicago, IL | M.A. | 5/1987 | Clinical Psychology |
| Loyola University of Chicago, Chicago, IL | Ph.D. | 1/1992 | Clinical Psychology |

A. Personal Statement

Gene E. Alexander, Ph.D. is Professor in the Departments of Psychology and Psychiatry, in the Evelyn F. McKnight Brain Institute, and in the Neuroscience and Physiological Sciences Graduate Programs of the University of Arizona. He is Director of the Brain Imaging, Behavior and Aging Lab, a member of the Scientific Advisory Committee for the Arizona Evelyn F. McKnight Brain Institute, Chair of the Research Committee in the Department of Psychology, and a member of the BIO5 Institute and the MRI Operations Committee at the University of Arizona. Prior to coming to Arizona, Dr. Alexander was Chief of the Neuropsychology Unit in the Laboratory of Neurosciences in the Intramural Research Program at the NIA. Dr. Alexander is a Fellow of the American Psychological Association (Division 40) Society for Clinical Neuropsychology and the Association for Psychological Science. His research has been supported by grants from the National Institutes of Health, McKnight Brain Research Foundation, and the State of Arizona. Dr. Alexander has over 20-years experience as a neuropsychology and neuroimaging researcher on the effects of aging and risk factors for age-related neurodegenerative disease. He uses structural and functional magnetic resonance imaging (MRI) and positron emission tomography (PET) with novel network analyses to investigate the effects of multiple health and lifestyle factors on the cognitive and brain changes associated with healthy and pathological aging, with the goal of developing new interventions for the effects of cognitive aging. Dr. Alexander's experience in the use neuroimaging and neuropsychological assessment in the context of brain aging make him well suited to serve as the University of Arizona site PI for this inter-institutional collaborative project to evaluate the effects of near infrared stimulation as an intervention for cognitive aging.

- 1. Kern KC, Wright CB, Bergfield KL, Fitzhugh M, Chen K, Moeller JR, Nabizadeh N, Elkind MSV, Sacco RL, Stern Y, DeCarli C, & **Alexander GE**. (2017) Blood pressure control in aging predicts cerebral atrophy related to small-vessel white matter lesions. <u>Frontiers in Aging Neuroscience</u>, 9, 132.
- 2. Cohen RA & **Alexander GE**. Using the Telephone Interview for Cognitive Status and Telephone Montreal Cognitive Assessment for evaluating vascular cognitive impairment: Promising call or put on hold? <u>Stroke</u>, in press. (Invited editorial)
- 3. **Alexander GE**. (2017) An emerging role for imaging white matter in the preclinical risk for Alzheimer disease: Linking β-amyloid to myelin. <u>JAMA Neurology</u>, 74(1), 17-19. (Invited editorial)
- 4. Raichlen DA & **Alexander GE**. (2017) Adaptive Capacity: An evolutionary neuroscience model linking exercise, cognition, and brain health. <u>Trends in Neurosciences</u>, 40(7), 408-421.

B. Positions and Honors

Research and Professional Experience

- 1988-1989 Clinical Psychology Intern, Dept of Psychiatry & Behav Sci, Univ of Washington, Seattle, WA
- 1989-1992 Research Fellow, Dept. of Brain Imaging, NYSPI and Columbia University, NY, NY
- 1991-1993 Research Scientist I, Dept. of Brain Imaging, NYSPI and Columbia University, NY, NY
- 1993-1999 Staff Fellow to Sr. Staff Fellow, Laboratory of Neurosciences, NIA, NIH, Bethesda, MD
- 1993-1999 Chief, Neuropsychology Unit, Laboratory of Neurosciences, NIA, NIH, Bethesda, MD
- 1999-2003 Research Associate Professor, Dept. of Psychology, Arizona State University, Tempe, AZ
- 2001-2009 Director, Data Management and Statistics Program/Core, Arizona ADC, AZ
- 2003-2007 Assoc. Professor with Tenure to Professor, Psychology Dept., Arizona State University, Tempe, AZ

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2007-Date Professor, Psychology Dept & Evelyn F McKnight Brain Institute, University of Arizona, Tucson, AZ
2007-Date Director, Brain Imaging, Behavior & Aging Lab, Psychology Dept, University of Arizona, Tucson, AZ
2007-Date Professor, Neuroscience Graduate Interdisciplinary Program, University of Arizona, Tucson, AZ
2008-Date Member, Scientific Advisory Board, Evelyn F. McKnight Brain Inst., University of Arizona, Tucson, AZ
2011-Date Professor, Physiological Sciences Graduate Interdisciplinary Program, University of Arizona, AZ
2017-Date Member, BIO5 Institute, University of Arizona, Tucson, AZ
2017-Date Professor, Department of Psychiatry, College of Medicine Tucson, University of Arizona, AZ
Selected Honors and Professional Activities
1995-Date Ad Hoc Reviewer, over 20 journals in Neuropsychology, Psychiatry, Neurology, and Neuroscience.
1996-1999 Staff Recognition Awards (annual), Laboratory of Neurosciences, IRP, NIA, NIH
2000-Date Reviewer, Alzheimer's Association Research Grant Program
2003-2007 Member, Study Section, Clinical Neuroscience and Disease, IRG, CSR, NIH
           Member, SEP, Women's Health Initiative Memory Study, Review Branch, NHLBI, NIH
2003
2004
           Member, Special Emphasis Panel, Alzheimer's Disease Center Grant Review, NIA, NIH
2004-2009 External Advisor, Aging Brain: Vasculature, Ischemia & Behav. Prog. Proj., UCSF/Davis
2005-2007 Member, Specialist Review Cmte, Psychology: Exp/Clinical, Fulbright Scholar Program
           Chair, SEP, Clinical Neuroscience & Disease, ZRG1 BDCN-E, IRG, CSR, NIH
2006
           Member, SEP, Prog Proj Review Group, Recovery from Illness, ZAG1 ZIJ-8 O1, NIA, NIH
2008
           Member, Study Section, Brain Injury & Neurovasc. Path., ZRB 1 BDCN-L (07), CSR, NIH
2008
           Member, SEP, SPRINT Center Review, ZHL1 CCT-B C2 1, NHLBI, NIH
2008
2008-Date Member, Neuroimaging Workgroup, International Conf. on Alzheimer's Disease/ISTAART
           Reviewer, SEP, Challenge Grant Panel #10, ZRG1 BDA-A 58 R, CSR, NIH
2009
           Member, SEP, P30 Faculty Recruitment in Biomedical Research Core Centers, NIA, NIH
2009
           Member, SEP, RC2 Grand Opport, Grants in Genetics, Epigenetics & Genomics, NIA, NIH
2009
2009
           Member, SEP, Program Project Review Group, Brain Dopamine, ZAG1 ZIJ-8 J3, NIA, NIH
           Member, SEP, Prog. Proj. Rev. Group, Neuroimaging and Aging, ZAG1 ZIJ-5 JF, NIA, NIH
2009
           Member, Neurological Sciences & Disorders K Review Committee, NSD-K, NINDS, NIH
2010
          Member, Neuroscience of Aging Review Committee, NIA-N, NIA, NIH
2010-2012
           Member, SEP, Prog. Proj. Rev., Exercise, Motor Deficits, & Aging, ZAG1-ZIJ-9, NIA. NIH
2010
           Member, SEP, Prog. Proj. Rev., Dopaminergic Dysfunct, Aging, ZAG1 ZiJ-6 J3, NIA, NIH
2010
           Chairperson, Member Special Emphasis Panel, ZAG1 ZIJ-7 (J1), NIA, NIH
2011
2011-2014 Advisory Editor, Neurobiology of Aging, Elsevier.
2011
           Member, VA MHBB Merit Review Subcommittee, Veterans Administration
           Member, SEP, Biobehav Res Award Innovat New Scientists (BRAINS), ZMH1ERBL04, NIMH, NIH
2011
2011-Date Reviewer, Alzheimer's Disease Pilot Grant Program, Arizona Alzheimer's Disease Center
2011-Date Fellow, Association for Psychological Science
           Member, Neurological Sciences & Disorders K Review Committee, NSD-K, NINDS, NIH
2012
2012-Date Member, Cognitive Workgroup, Evelyn F. McKnight Brain Institute
2012-Date Member, MRI Standardization Workgroup, Evelyn F. McKnight Brain Institute
2012-Date Co-Director, Annual Conference on Successful Aging, University of Arizona
2013
           Member, SEP, Neurodegen. & Neurodevelopmental Dis., ZRG1BDCN-Y(02), NIA, NIH
           Member, SEP, Psychol. Health, Development & Aging, 10 ZRG1 BBBP-D (02), NIA, NIH
2013
           Member, Alzheimer's Disease Research Centers Review, ZAG1ZIJ4J1, NIA, NIH
2013
2013-2019 Member, Neuroscience of Aging Review Committee, NIA-N, NIA, NIH
           Member and Chairperson, Biobehav & Behav, Processes Rev. Group, ZRG1BBBPY04, CSR, NIH
2014
2015-Date Guest Assoc. Editor, Neuroimaging Approaches to Cognitive Aging, Frontiers Aging Neuroscience
2015-Date Chair, Research Committee, Department of Psychology, University of Arizona
           Member, SEP, Alzheimer's Disease Center Review, ZAG1 ZIJ-1 M1, NIA, NIH
2016
           Member, SEP, Prevention Trial Review, ZAG1 ZIJ-1 M2, NIA, NIH
2016
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C. Contribution to Science

1. Brain Imaging and Cognitive Effects of Age-Related Dementia: My early research interests focused on understanding brain-behavior relationships in the context of Alzheimer's dementia with the use of functional and structural neuroimaging methods combined with measures of cognition and demographic characteristics (e.g., 1.b). My initial work in this area, with Dr. Yaakov Stern (1.a), led to the first functional neuroimaging findings to suggest the potential for a brain-based, cognitive reserve against the effects of Alzheimer's disease. My research then expanded to include measures of cerebral metabolism with PET, further supporting the

concept of cognitive reserve (1.c) and the use of PET as a method to evaluate treatments to delay or diminish declines in cerebral metabolism over time in Alzheimer's dementia (1.d).

- a. Stern Y, **Alexander GE**, Prohovnik I, Mayeux R. (1992). Inverse relationship between education and parietotemporal perfusion deficit in Alzheimer's disease. <u>Ann Neurol</u>, 32, 371-5.
- b. **Alexander GE**, Prohovnik I, Stern Y, Mayeux R. (1994). WAIS-R subtest profile and cortical perfusion in Alzheimer's disease. <u>Brain and Cognition</u>, 24, 24-43.
- c. **Alexander GE**, Furey M, Grady CL, Pietrini P, Brady D, Mentis MJ, Schapiro MB. (1997). Association of premorbid function with cerebral metabolism in Alzheimer disease: Implications for the cognitive reserve hypothesis. <u>Am J Psychiatry</u>, 154, 165-172. (Article featured in journal editorial)
- d. **Alexander GE**, Chen K, Pietrini P, Rapoport SI, Reiman EM. (2002). Longitudinal PET evaluation of cerebral metabolic decline in dementia: A potential outcome measure in Alzheimer's disease treatment studies. <u>Am J Psychiatry</u>, 159, 738-745. (Article featured on journal cover & editorial)
- **2. Brain Imaging and Cognitive Effects of Healthy Aging:** In more recent years, my research program has focused on the effort to better understand heterogeneity across the spectrum from successful to pathological aging. This work includes studies of healthy aging across the adult age range using structural and functional brain imaging methods combined with standardized and computerized measures of cognition. Additionally, I have an interest in extending my research in humans to non-human animal models of aging (e.g., 2.c; 3.d) and age-related disease. The following publications provide examples of my work using both univariate and novel multivariate network analysis methods to evaluate patterns of brain structure in older adults (2.a; 2.b), as well as functional brain regions (2.d) and cognitive processes (2.c) impacted by brain aging.
 - a. **Alexander GE**, Chen K, Merkley TL, Reiman EM, Caselli RJ, Aschenbrenner M, Santerre-Lemmon L, Lewis DJ, Pietrini P, Teipel SJ, Hampel H, Rapoport SI, Moeller JR. (2006) Regional Network of MRI Gray Matter Volume in Healthy Aging. NeuroReport, 17, 951-6.
 - b. Bergfield KL, Hanson KD, Chen K, Teipel SJ, Hampel H, Rapoport SI; Moeller JR, **Alexander GE**. (2010) Age-related networks of regional covariance in MRI gray matter: Reproducible multivariate patterns in healthy aging. <u>NeuroImage</u>, 49, 1750-9.
 - c. **Alexander GE**, Ryan L, Bowers D, Foster TC, Bizon JL, Geldmacher DS, Glisky EL. (2012) Characterizing Cognitive Aging in Humans with Links to Animal Models. <u>Frontiers in Aging Neuroscience</u>, 4, 21.
 - d. Ryan L, Cardoza JA, Barense MD, Kawa KH, Wallentin-Flores J, Arnold WT, **Alexander GE**. (2012) Age-related impairment in a complex object discrimination task that engages perirhinal cortex. <u>Hippocampus</u>, 22, 1978-89.
- 3. Method Development, Evaluation, and Implementation for Neuroimage Analysis Approaches: My work also includes the development, evaluation, and implementation of novel analysis methods for neuroimaging data. Early in the course of my research, I recognized the importance of applying analysis methods that have the potential to more fully capture the rich regional information obtained within functional and structural brain images. My work in this area has focused on the application of novel multivariate network analysis methods to characterize regional patterns of covariance in brain scans to better understand the effects of brain aging and age-related disease. I have applied this approach to PET cerebral metabolism (e.g., 3.a), functional MRI (3.c) and multimodal approaches that combine across imaging modalities (e.g., 3.b). I have also performed the first application of this approach to structural MRI in both humans and in a non-human primate model of aging (e.g., 2.a; 3.d). The example publications below illustrate my research efforts in this area.
 - a. **Alexander GE**, Moeller JR. (1994) Application of the Scaled Subprofile Model to functional imaging in neuropsychiatric disorders: A principal component approach to modeling regional patterns of brain function in disease. <u>Human Brain Mapping</u>, 2, 79-94. (Article featured on journal cover)
 - b. Chen K, Reiman EM, Zhongdan H, Caselli RJ, Bandy D, **Alexander GE**. (2009) Linking functional and structural brain images with multivariate network analyses: A novel application of the partial least square method. Neuroimage, 47, 602-10.
 - c. Smith JF, Chen K, Johnson SC, Morrone-Strupinsky J, Reiman EM, Nelson A, Moeller JR, **Alexander GE** (2006) Network analysis of single-subject fMRI during finger opposition task. Neuroimage,32,325-32.
 - d. **Alexander GE,** Chen K, Aschenbrenner M, Merkley TL, Santerre-Lemmon LE, Shamy JL, Skaggs WE, Buonocore MH, Rapp PR, Barnes CA. (2008) Age-related regional network of magnetic resonance imaging gray matter in the rhesus macaque. <u>Journal of Neuroscience</u>, 28, 2710-8.
- **4. Large Multi-Institutional Collaborative Projects:** Additionally, my research has included participation in several large multi-institutional collaborative research projects that have had a significant impact on the field, including supporting efforts to identify imaging methods for the evaluation of treatments, to aid diagnosis, and

to enhance prevention research for Alzheimer's disease and dementia. These projects have included the Alzheimer's Disease Neuroimaging Initiative (ADNI), for which I served as a member of the MRI (e.g., 4.b; 4.d) and PET Cores, as well as other multi-institutional projects on APOE risk (e.g., 4.c) and pathology confirmed dementia (4.a). Examples of some of my collaborative publications are illustrated below.

- a. Silverman DHS, Small GW, Chang CY, Lu CS, Kung de Aburto MA, Chen W, Czernin J, Rapoport SI, Pietrini P, **Alexander GE**, Schapiro MB, Jagust WJ, Hoffman JM, Welsh-Bohmer KA, Alavi A, Clark CM, Salmon E, de Leon MJ, Mielke R, Cummings JL, Kowell AP, Gambhir SS, Hoh CK, Phelps ME. (2001) Neuroimaging in evaluation of dementia: Regional brain metabolism and long-term outcome. <u>JAMA</u>, 286, 2120-7. (Article featured in press release)
- b. Jack CR Jr, Bernstein MA, Fox NC, Thompson P, **Alexander G**, Harvey D, Borowski B, Britson PJ, L Whitwell J, Ward C, Dale AM, Felmlee JP, Gunter JL, Hill DL, Killiany R, Schuff N, Fox-Bosetti S, Lin C, Studholme C, DeCarli CS, Krueger G, Ward HA, Metzger GJ, Scott KT, Mallozzi R, Blezek D, Levy J, Debbins JP, Fleisher AS, Albert M, Green R, Bartzokis G, Glover G, Mugler J, Weiner MW. (2008) The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. <u>J Magn Reson Imaging</u>, 27, 685-91.
- c. Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, Ayutyanont N, Keppler J, Reeder SA, Langbaum JB, **Alexander GE**, Klunk WE, Mathis CA, Price JC, Aizenstein HJ, DeKosky ST, Caselli RJ. (2009) Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. Proceedings of the National Academy of Sciences U S A,106, 6820-5.
- d. Leow AD, Yanovsky I, Parikshak N, Hua X, Lee S, Toga AW, Jack CR, Bernstein MA, Britson PJ, Gunter JL, Ward CP, Borowski B, Shaw LM, Trojanowski JQ, Fleisher AS, Harvey D, Kornak J, Schuff N, **Alexander GE**, Weiner MW, Thompson PM; for the ADNI study. (2009) Alzheimer's Disease Neuroimaging Initiative: A one-year follow up study using tensor-based morphometry correlating degenerative rates, biomarkers and cognition. Neuroimage, 45, 645-55.
- **5. Health, Lifestyle, and Genetic Risk Factors for Pathological Aging:** A major focus of my current research interests includes integrating health status, lifestyle characteristics, and genetics with brain imaging and cognitive testing to investigate healthy and pathological brain aging. For example, my work was the first demonstrate an interaction between age and hypertension on brain volume in aging (5.a), and has contributed to our understanding of how the APOE ε4 allele impacts cognition and brain structure over the adult lifespan (5.b; 5.c). I have also recently proposed a new hypothesis suggesting that demands for exercise may have interacted with APOE status to influence the evolution of the human lifespan (5.d), which was recently featured on the cover of *Trends in Neurosciences*.
 - a. Strassburger TL, Lee HC, Daly E, Szczepanik J, Krasuski JS, Mentis MJ, Salerno JA, DeCarli C, Schapiro MB, **Alexander GE**. (1997) Interactive effects of age and hypertension on structural brain volumes. <u>Stroke</u>, 28, 1410-1417. (Article featured in journal editorial & AHA press release)
 - b. Alexander GE, Bergfield KL, Chen K, Reiman EM, Hanson KD, Lin L, Bandy D, Caselli RJ, Moeller JR. (2012) Gray matter network associated with genetic risk for Alzheimer's disease in young to early middle-aged adults. Neurobiology of Aging, 33, 2723-32.
 - c. Caselli RJ, Reiman EM, Osborne D, Hentz JG, Baxter LC, Hernandez JL, **Alexander GE**. (2004) Longitudinal changes in cognition and behavior in asymptomatic carriers of the APOE ε4 allele. Neurology, 62, 1990-5.
 - d. Raichlen DA, Alexander GE. (2014) Exercise, APOE genotype, and the evolution of the human lifespan. Trends in Neurosciences, 37, 247-55. (Article featured on journal cover)

<u>Publications above selected from over 143; Complete list of published work in MyBibliography:</u>
http://www.ncbi.nlm.nih.gov/sites/myncbi/gene.alexander.1/bibliography/41140485/public/?sort=date&direction=ascending [Google Scholar H-Index = 65]

D. Research Support

Ongoing Research Support

NIA R01 AG049464-01 Alexander, Barnes, Coleman (MPIs)

8/1/14-3/31/20

Epigenetic, Neuroimaging and Behavioral Effects of Hypertension in the Aging Brain

The goal is to determine epigenetic changes induced by hypertension in brain regions important for cognition. Role on Project: Dr. Alexander is Contact Pl.

McKnight Brain Research Foundation Alexander, Cohen, Levin, Wadley (MPIs)

9/1/15-12/31/18

McKnight Inter-Institutional Cognitive Aging Assessment Core

The goal is to provide standardized clinical and cognitive measures for multi-institutional brain aging research. Role on Project: Dr. Alexander is a Pl.

McKnight Brain Research Foundation Alexander, Cohen, Rundek, Visscher (MPIs) 1/1/15-12/31/18 McKnight Inter-Institutional Neuroimaging Core and Brain Aging Registry

The goal to establish neuroimaging acquisition and a multi-site brain aging registry to study brain aging. Role on Project: Dr. Alexander is a PI.

NIA R01 AG054077-01 Cohen, Marsiske, Woods (MPIs)

9/1/16-8/31/21

Augmenting Cognitive Training in Older Adults – The ACT Grant

This multi-site RCT will evaluate cognitive training and transcranial direct current stimulation for brain aging. Role on Project: Dr. Alexander is PI of the UA Field Center and UA subcontract.

State of Arizona/Banner Health Subcontract Alexander (PI).

Reiman (PI)

7/1/11-6/30/18

Risk Factors for Brain Aging and Cognitive Health

(Continuing Annual State Appropriation)

The goal is to study cerebrovascular risks for brain aging and cognitive health in humans and animal models. Role on Project: Dr. Alexander is Pl.

NIA R03 AG055020-01 Su (PI)

NIA P30 AG019610-17

7/15/17-4/30/19

Ultra-sensitive and label-free detection of Alzheimer's disease biomarkers

This goal is to evaluate a highly sensitive method to identify Alzheimer's biomarkers in fluid samples. Role on Project: Dr. Alexander is Co-Investigator.

Troic of Froject. Dr. Alexander is Co-investig

7/1/16-6/30/21

Arizona Alzheimer's Disease Core Center

This center provides core resources to support Alzheimer's disease research in the Arizona region.

Role on Project: Dr. Alexander is Co-Investigator and member of the Data Management and Statistics Core.

NIH 3 R01 AG031581 Reiman, Caselli (MPIs)

4/1/14-3/31/19

Brain Imaging, APOE & the Preclinical Course of Alzheimer's disease

The goal is to characterize the brain changes in those at risk for Alzheimer's disease with the APOE e4 allele. Role on Project: Dr. Alexander is Co-Investigator and PI of the UA subcontract.

NIH R01 AG049465-01 Barnes (PI)

8/1/14-3/31/19

Neural System Dynamics and Gene Expression Supporting Successful Cognitive Aging

The goal is to use cognitive, neurobiological and molecular methods to test reserve in a rodent model of aging. Role on Project: Dr. Alexander is Co-Investigator.

UA15-011 Alexander, Raichlen (MPIs)

2/5/15-12/31/17

Tech Launch Arizona Wheelhouse

Evaluation of the aerobic training system for enhancing cognitive performance in older adults The goal of this project is to evaluate the benefits of exercise on cognitive function in healthy aging Role on Project: Dr. Alexander is a Pl.

Selected Completed Recent Research Support

NIH 1 R01 AG025526

Alexander (PI)

4/1/07-7/31/14

Neuroanatomical substrates of aging & cognitive decline

(w/ NCE)

The goal is to study how health status and genetic risk for AD affect the brain and cognitive changes in aging. Role on Project: Dr. Alexander is the project Pl.

NIMH/NIA 2 R01 MH57899-01A1 Reiman (PI)

7/1/98 - 6/30/13

PET, APOE, & the Preclinical Course of Alzheimer disease

The goal is to characterize the brain changes in individuals at risk for Alzheimer's disease with APOE e4. Role on Project: Dr. Alexander is Co-Investigator and PI of the UA subcontract.

NIA 1 UO1 AG024904-01 Weiner (PI)

10/1/04-9/30/10

Alzheimer's Disease Neuroimaging Initiative (ADNI)

The goals are to test the ability of MRI and PET to track the brain changes in MCI and Alzheimer's dementia. Role on Project: Dr. Alexander is Co-Investigator, member of MRI and PET Cores, and PI for UA subcontract.





March 15, 2018

Dear Dr. Dockery and McKnight Brain Research Foundation Board of Trustees,

We thank you so very much for your letter dated February 26, 2018 with comments regarding our 2017 Annual Progress Report. We truly appreciate your thorough review of our Report and your continued support and encouragement for our plans to reorganize our program and expand our Scientific Advisory Board. We thank you for recognizing our accomplishments in a transition plan and enhancement of our educational program activities, including implementation of Cognitive Fellowship and Small Pilot Collaborative Research Award Program.

We also recognized one point of your critique related to our clinical translational program not reaching its full potential. In order to reach our full potential, our major goal in the next year is to develop and implement a strategic plan with clear short and long-term research and educational priorities. This will help us steer a successfully and sustained research program in age-related memory loss. We believe our new, focused and energized clinical translational research and educational strategic program led by an extended Scientific Advisory Board will considerably advance our mission to accelerate discovery of the causes, treatment and prevention of age-related memory loss and enhance brain health.

We thank you again for your continued support, vision, and valuable guidance to our clinical translational research program and educational activities.

Sincerely,

Ralph Sacco, MD, MS

Executive Director

Evelyn F. McKnight Brain Institute

UM Miller School of Medicine

Tatjana Rundek, MD, PhD

Tapana Dundel

Scientific Director

Evelyn F. McKnight Brain Institute

UM Miller School of Medicine

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GIVE SOMETHING CHANGE EVERYTHING

March 28, 2018

The McKnight Brain Research Foundation c/o Ms. Melanie Cianciotto
Vice President for Foundations and Endowments
SunTrust Bank
200 South Orange Avenue
SOAB 10th Floor
Orlando, Florida 32801

Dear Ms. Cianciotto,

Thank you for your letter dated February 26 in follow-up to UAB's annual report for 2017. We, too, are excited about the future of the Evelyn F. McKnight Brain Institute (EMBI) at UAB under the leadership of Drs. Lazar and Standaert, and we remain grateful for our ongoing partnership with the Evelyn F. McKnight Brain Research Foundation.

Relative to the trustees' question regarding Dr. Virginia Wadley Bradley's work, the acronym CARDIA stands for Coronary Artery Risk Development in Young Adults. This study, started in 1985/86, is examining the development and determination of clinical and subclinical cardiovascular disease and their risk factors.

Regarding the two endowed chair positions in our Department of Psychiatry dedicated for EMBI Investigators, the F. Cleveland Kinney Endowed Chair in Geriatric Psychiatry and the Geropsychiatry Research Chair, the occupants of these positions will be critical to our clinical translational research efforts. As approved by the Foundation and the University's Board of Trustees, the EMBI has been organizationally restructured under the Department of Neurology versus Neurobiology. This move, in part, was in response to the Foundation's goal of having the EMBI enterprise increase its focus on clinical intervention. The EMBI space in the Shelby Building remains active; Dr. Lazar's primary office is located nearby in the Sparks Center where the Department of Neurology is located; and similarly, the psychiatry positions will be located in the Sparks Center where the Department of Psychiatry is housed. Dr. Lazar's vision for these positions is that certain psychiatric illnesses induce premature cognitive aging, allowing us to study potential treatment targets for age-related cognitive decline without the confound of cardiovascular and other systemic conditions prevalent in older age.

If the trustees have further questions, please don't hesitate to let us know. Dr. Lazar would be happy to discuss this further with you in person next week. We look forward to hosting the McKnight Inter-Institutional Meeting and having you and the other trustees at UAB. Thank you again for all the Foundation does for the EMBI at UAB.

Sincerely,

Tom Brannan

Vice President for Development and Alumni

cc:

Dr. Ronald M. Lazar

Dr. James H. Meador-Woodruff

Ms. Daphne B. Powell

Dr. Eric Roberson

Dr. David G. Standaert

Dr. Selwyn M. Vickers

Dr. Ray L. Watts