BIOGRAPHICAL SKETCH

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NAME: YASSA, MICHAEL A.

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

POSITION TITLE: Professor and Chancellor's Fellow, Neurobiology and Behavior, Neurology, Psychiatry
Director, Center for the Neurobiology of Learning and Memory

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Johns Hopkins University, Baltimore, MD	B.A.	05/2002	Neuroscience
Johns Hopkins University, Baltimore, MD	M.A.	05/2007	Cognitive Psychology
University of California, Irvine	Ph.D.	05/2010	Neurobiology & Behavior

A. Personal Statement

This high-risk high-impact Center renewal proposes that unpredictable, fragmented environmental sensory signals (FRAG), constitute a previously unrecognized indicator of early-life adversity. The overarching goal of the Neuroimaging Core is to address the as yet unknown mechanistic pathways by which FRAG may lead to anhedonia and vulnerabilities to psychopathology. I am interested in understanding how our brains can store and retrieve massive amounts of information and using this knowledge ultimately to improve the human condition. My research group uses cutting-edge human neuroscience tools to understand learning and memory in healthy and diseased brains. In particular, the lab is trying to uncover ways in which our memory abilities change throughout the lifespan from childhood to older adulthood, particularly in the context of vulnerability to psychopathology, including early life adversity. My work also focuses heavily on the development of novel neuroimaging techniques for acquiring high-resolution fMRI and DTI data. My lab has demonstrated a record of accomplished and productive research projects in the fields of both psychiatric imaging (in particular depression and anxiety) as well as biomarker development for cognitive dysfunction. My lab collaborates vigorously and widely with investigators across the globe and provides support with open tool development and data banks to facilitate discovery science. Outside of my own research and imaging leadership at UCI, I also have a track record in leading large-scale international efforts to harmonize imaging techniques such as the Hippocampal Subfield Segmentation Group (HSG), which I co-founded in 2013. Finally, I serve on several advisory committees for major multisite imaging projects in the US, Europe and Japan. I am also Director of the Center for the Neurobiology of Learning and Memory (CNLM), a renowned research institute that fosters multi-disciplinary collaborations in studies of learning and memory. Currently, there are over 70 faculty fellows of the CNLM from across the country and internationally, including the Conte Center PI Prof. Baram. Thus, my expertise and experience have prepared me to lead the Neuroimaging Core for the Conte Center's renewal.

B. Positions and Honors

Positions and Employment

1999 - 2005 Senior Imaging Technologist, Psychiatry, Johns Hopkins School of Medicine, Baltimore MD
2005 - 2007 Graduate Research Fellow, Neurobiology and Behavior, University of California, Irvine CA
2008 - 2010 Graduate Research Fellow, Psychology, Johns Hopkins University, Baltimore MD
2008 - 2010 Adjunct Professor, School of Social Sciences, Irvine Valley College, Irvine CA
2011 - 2013 Assistant Professor, Psychology, Johns Hopkins University, Baltimore MD
2014 - 2016 Assistant Professor, Neurobiology and Behavior, Neurology (Joint), UC Irvine, Irvine CA
2014 - 2016 Fellow, Center for the Neurobiology of Learning and Memory (UCI CNLM)

2014 - Member, Institute for Memory Impairments and Neurological Disorders (UCI MIND)
2016 - Associate Professor, Neurobiology and Behavior, Neurology, UC Irvine, Irvine CA
2016 - Visiting Professor, Faculty of Health and Sport Sciences, University of Tsukuba, Tsukuba, Japan
2016 - Director, Center for the Neurobiology of Learning and Memory (UCI CNLM)
2017 - 2020 Chancellor's Fellow
2018 - Professor, Neurobiology and Behavior, Neurology, Psychiatry and Human Behavior, UC Irvine

Professional Activities and Memberships

American Psychological Association (1999 – present), Society for Neuroscience (1999 – present), International Neuropsychological Society (2000 – present), Faculty for Undergraduate Neuroscience (2005 – present), Cognitive Neuroscience Society (2005 – present), International Society to Advance Alzheimer's Research and Treatment (2010 – present), Faculty of 1000 (elected member 2015 – present), Memory Disorders Research Society (elected member 2015 – present)

Professional Honors and Awards

National Science Foundation Graduate Research Fellowship (2007-2010), Carl W. Cotman Scholar's Award in the Study of Neurodegenerative Disorders (2009), Roger W. Russell Scholar's Award in the Neurobiology of Learning and Memory (2010), University of California, Irvine Fine Science Tools Award in Neuroscience (2010), Ossoff Scholars Award, Alzheimer's Treatment Center, Johns Hopkins University (2011), Excellence in Teaching Award (2015), Departmental Service Award (2015), Robert Newcomb Interdisciplinary Team Science Award – 90+ Study (2016), UCI Chancellor's Fellow (2017-2020), Quad-L Early Career Award in Learning, Memory and Cognition (2017), CNS Young Investigator Award (2018), Robert Newcomb Interdisciplinary Team Science Award – Conte Center (2018).

C. Contributions to Science:

Area 1: Psychiatric Neuroimaging of memory and emotion in anxiety and depression. We have applied our pattern separation framework to individuals with depressive symptoms, and have uncovered a cluster of network aberrations that were highly predictive of depressive symptom severity, associated with the amygdala and hippocampal dentate and CA3. Based on this work, we were recently awarded a five year R01 by NIMH to study depression using our high-resolution neuroimaging tools. We have also used our approach to examine these networks in older adults with depression, and most recently Kraguljac et al. (*Biological Psychiatry,* below) has translated our model to schizophrenia.

a. Leal, S.L., Tighe, S.K., Jones, C.K., **Yassa, M.A.** Pattern separation of emotional information in hippocampal dentate and CA3. *Hippocampus.* 2014; 24(9): 1146-55. PMC417260.
b. Leal, S.L., Tighe, S.K., **Yassa, M.A.** Asymmetric effects of emotion on mnemonic interference. *Neurobiol Learn Mem*. 2014; 111:41-8. PMC419406
c. Leal SL, Noche JA, Murray EA, **Yassa MA**. Disruption of amygdala-entorhinal-hippocampal network in late-life depression. *Hippocampus.* 2017; 27(4): 464-476. PMC5858586
d. Kraguljac, N., Carle, M., Frölich, M., Tran, S., **Yassa, M.A**., White, D.M., Reddy, A., Lahti, A.C. Mnemonic Discrimination Deficits in First Episode Psychosis and a Ketamine Model Suggests Dentate Gyrus Pathology Linked to NMDA-Receptor Hypofunction. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging.* 2018; 3:231-238. PMC5836317

Area 2: Neuroimaging investigations of medial temporal lobe contributions to episodic memory. The hippocampal circuitry is complex with multiple input/output pathways. Work in my lab has contributed evidence to the role of the hippocampal dentate and CA3 regions in pattern separation and has further identified (1) a division of labor in the medial temporal lobes where the perirhinal and lateral entorhinal cortices are involved in object pattern separation, whereas the parahippocampal and medial entorhinal cortices are involved in spatial pattern separation; and (2) a longitudinal axis specialization where the anterior (ventral) hippocampus is preferentially involved in retrieval of online representations (i.e. rapid pattern completion), whereas the posterior (dorsal) hippocampus is preferentially involved in reconstructing episodic representations.

a. Reagh, Z.M., Watabe, J., Ly, M., Murray, E., **Yassa, M.A.** Dissociated signals in human dentate gyrus and CA3 predict different facets of recognition memory. *J Neurosci.* 2014; 34(40): 13301-13. PMC4180469.

b. Reagh, Z.M., **Yassa, M.A.** Object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortex in humans. *PNAS.* 2014; 111(40): E4264-73 PMC4210036
c. Reagh, Z.M., Noche, J.A., Tustison, N.J., Delisle, D., Murray, E.A., **Yassa, M.A.** Functional Imbalance of Anterolateral Entorhinal Cortex and Hippocampal Dentate/CA3 Underlies Age-Related Object Pattern Separation Deficits. *Neuron.* 2018; 97(5):1187-1198. Neuron. 2018; 7;97:1187-1198.e4. PMC5937538
d. Reagh, Z.M., Murray, E.A., **Yassa, M.A**. Repetition reveals ups and downs of hippocampal, thalamic, and neocortical engagement during mnemonic decisions. *Hippocampus*. 2017; 27:169-183. PMC5858562

Area 3: Bioinformatics and methods development in high-resolution neuroimaging. I have published extensively in the area of neuroimaging methods development and have pioneered novel methods for acquiring high-resolution fMRI and DTI data, some of which have been instrumental in identifying how the human brain learns to discriminate among similar experiences, such as in vivo ultra-high resolution (0.66 mm in-plane) microstructural DTI technique that we used to assess the perforant path. In collaboration with Dr. Craig Stark, we have also developed novel registration techniques for cross-participant alignment. In collaboration with Dr. Rene Vidal, we have developed new analytical techniques for high angular resolution diffusion imaging (HARDI) data.

a. **Yassa, M.A.**, Stark, C.E.L. A quantitative evaluation of cross-participant alignment techniques for MRI studies of the medial temporal lobe. *Neuroimage.* 2009; 44: 319-327. PMID: 18929669.
b. **Yassa, M.A.**, Muftuler, L.T., Stark, C.E.L. Ultrahigh-resolution microstructural diffusion tensor imaging (msDTI) elucidates perforant path degradation in aged humans in vivo. *PNAS.* 2010; 107: 12687-91. PMC2906542.
c. Schwab, E., Cetingul, E., Afsari, B., **Yassa, M.A.,** Vidal, R. Rotation invariant features for HARDI. *Inf Proc Med Imaging.* 2013; 23: 705-717. PMC4194072
d. Schwab E., **Yassa M.A.**, Weiner M., Vidal R. (2016) Using Automatic HARDI Feature Selection, Registration, and Atlas Building to Characterize the Neuroanatomy of Aβ Pathology. In: Fuster A., Ghosh A., Kaden E., Rathi Y., Reisert M. (eds) Computational Diffusion MRI. Mathematics and Visualization. Springer. 2016

Area 4: Clinical applications to cognitive dysfunction and memory enhancement interventions. Using high-resolution neuroimaging techniques that we developed, we were able to identify neurobiological features of the hippocampal network that degraded with age and Alzheimer's disease, e.g. perforant path integrity, dentate/CA3 hyperactivity, functional rigidity, and loss of functional connectivity between the entorhinal cortex and the hippocampus. We define a new Alzheimer's disease temporal biomarker model based on multimodal (structural, functional, diffusion) MRI data. We also show that certain interventions or pharmacological approaches can enhance memory and/or reverse age-related memory deficits, using our pattern separation paradigm as an outcome measure.

a. **Yassa, M.A.,** Mattfeld A.T., Stark, S.M., Stark, C.E.L. Age-related memory deficits linked to circuit-specific disruptions in the hippocampus. *PNAS.* 2011; 108(21): 8873-8. PMC3102362.
b. Bakker, A., Krauss, G., Albert, M.A., Speck, C.L., Jones, L.R., Stark, C.E., **Yassa, M.A.**, Bassett, S.S., Shelton, A.L., Gallagher, M. Reducing hippocampal hyperactivity improves cognition in mild cognitive impairment. *Neuron.* 2012*;* 74:467-474. PMC3351697.
c. Borota, D., Murray, E., Keceli, G., Chang, As., Watabe, J.M., Ly, M., Toscano, J.P., **Yassa, M.A.** Post-study caffeine administration enhances memory consolidation in humans. *Nat Neurosci.* 2014; 17: 201-3. PMC5909971.
d. Suwabe, K., Hyodo, K., Byun, K.H., Ochi, G., **Yassa, M.A.**, Soya, H. Acute moderate exercise improves mnemonic discrimination in young adults. *Hippocampus.* 2017; 27: 229-234. PMC5927776
e. Suwabe K, Hyodo K, Byun K, Ochi G, Fukuie T, Shimizu T, Kato M, **Yassa MA**, Soya H. (2017) Aerobic fitness associates with mnemonic discrimination as a mediator of physical activity effects: evidence for memory flexibility in young adults. *Scientific Reports.* 2017; 7:5140. PMC5506056.

Area 5: MRI biomarkers for Alzheimer's disease. My laboratory has developed and optimized several structural measures of cortical thinning and volume loss in the medial temporal lobes and we are working towards harmonization and standardization of the techniques such that they can be used as outcome

measures in clinical trials and in large-scale natural history studies. These techniques are currently being employed in the UCI ADRC, in several NIH funded grants, including a recently funded major consortium on Alzheimer's disease biomarkers in Down syndrome. I am also a co-chair of an international organization devoted to the development of a harmonized protocol for segmentation of hippocampal subfields on MRI scans and designing automated tools to accomplish this. I have hosted several conferences dedicated to this topic and we have recently published two manuscripts discussing our work (*Hippocampus* and *Neuroimage*, below).

a. Yushkevich, P.A., Amaralm R.S., Augustinack, J.C., …, **Yassa M.A.**, Zeineh M.M.; Hippocampal Subfields Group (HSG). Quantitative comparison of 21 protocols for labeling hippocampal subfields and parahippocampal subregions in in vivo MRI: Towards a harmonized segmentation protocol. *Neuroimage.* 2015; 111:526-41. PMC4387011.
b. Wisse, LEM, Daugherty A, …, **Yassa, MA**, Yushkevich, P, la Joie, R, for the Hippocampal Subfield Group (HSG). A harmonized segmentation protocol for hippocampal and parahippocampal subregions: Why do we need one and what are the key goals? *Hippocampus*. 2016; 27: 3-11. PMC5167633.
c. Holbrook, A., Tustison, N., Roberts, J.M., **Yassa, M.A.,** Gillen, D., (2017) Lateral Entorhinal Cortical Thinning Predicts Cognitive Decline in MCI and AD Patients. *Poster presented at the Alzheimer's and Parkinson's Diseases Congress.*
d. Tustison, N., Avants, B., Wang, H., **Yassa, M.A.** (2017) Multi-Atlas Intensity and Label-Fusion with Supervised Segmentation Refinement for the Parcellation of Hippocampal Subfields. *Poster presented at the Alzheimer's and Parkinson's Diseases Congress.*

Full publication list available via **MyBibliography** at:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1JMgxEoSuJmAm/bibliograpahy/50407235/public/?sort=date&direction=ascending

D. Research Support

ACTIVE

Neural mechanisms of emotional memory modulation in major depressive disorder
R01 MH102392 (PI: Yassa MA) 9/5/2014 – 7/31/2019
NIH/NIMH
The goal of this study is to investigate emotional modulation of memory systems in healthy adults and adults with major depressive disorder using novel high-resolution neuroimaging tools geared to investigate the structure and function of the medial temporal lobe system.

Neuroimaging biomarkers for cognitive decline in elderly with amyloid pathology
R01 AG053555 (PI: Yassa, MA) 0 7/15/2017 - 04/30/2022
NIH/NIA
Our project goal is to determine the neural features (i.e. biomarkers) associated with amyloid pathology accumulation, and determine objectively how to combine these biomarkers to identify individuals with preclinical AD.

High-resolution neuroimaging biomarkers of preclinical Alzheimer's disease
P50 AG16573 (Project PI: Yassa MA; Program PI: LaFerla FM) 4/1/2015 – 3/31/2019
NIH/NIA
The goal of this study is to develop novel biomarkers for preclinical Alzheimer's disease using a combination of novel behavioral and cognitive tests sensitive to hippocampal function and high-resolution multimodal imaging tools of medial temporal structure, function, and connectivity in cognitively healthy and cognitively impaired individuals, focusing on the oldest old (90 plus) and Down syndrome, as models of disease resistance and vulnerability respectively.

Biomarkers for Alzheimer's Disease in Adults with Down Syndrome
U01 AG051412 (Imaging Core Director: Yassa MA, PI: Lott) 10/1/2015 – 9/30/2020
NIH/NIA/NICHD

The goal of this multisite consortium is to establish biomarkers for predicting onset and progression to Alzheimer's disease in individuals with Down syndrome using multimodal imaging, proteomics, lipidomics, pathological markers, and neuropsychological examinations. The consortium is a collaboration between UC Irvine, Columbia University, Harvard University, and Johns Hopkins University. UCI's Imaging team (Director: Yassa) handles all imaging data for the consortium.

High-resolution structural and functional brain imaging of the MTL in neurocognitive aging
R01 AG034613-02 (Co-I: Yassa MA; PI: Stark CEL) 9/30/2009 – 7/31/2019
NIH/NIA
This project aims to explore changes in the hippocampus, medial temporal lobe and frontal lobe associated with healthy aging. We have developed high-resolution fMRI and DTI techniques to interrogate small structures in vivo. In addition, we are extending our investigations to larger systems involved in memory encoding and retrieval. We will be enrolling healthy participants, ages 20-89 to evaluate these age-related changes.

Selective age-related vulnerability in human perirhinal and lateral entorhinal cortices
R21 AG049220 (PI: Yassa MA) 9/15/2015 – 9/14/2018 (in NCE)
NIH/NIA
The goal of this study is to identify the neural basis of selective age-related vulnerabilities in the lateral entorhinal cortex and peririhinal cortex in young and older adult humans using multimodal structural, functional and diffusion MRI.

Epigenetic PET Tracer for Cross-Species Investigation of Age-Related Memory Decline
Seed Grants Program (MPI: Yassa, M.A., Wood, M.) 6/1/2015 – 9/30/2018
Cal-BRAIN
The overall goal of this project is to examine the ability of a novel positron emission tomography (PET) imaging probe, called [^{11}C]Martinostat, to determine the activity of a specific epigenetic mechanism required for memory formation in rodents and humans. [^{11}C]Martinostat selectively binds key histone deactetylases (HDACs) with subnanomolar potency and fast binding kinetics. We will use [^{11}C]Martinostat to determine HDAC enzyme density in young and old rodents, as well as young and old humans and its relationship to object location memory formation. We will also analyze multimodal MRI data associated with the PET scans to determine the relationship between [^{11}C]Martinostat binding and structural and functional integrity of neural circuitry.

Advancing International Networks to Accelerate Circulation of Talented Researchers
JSPS Exchange Program (Co-I: Yassa MA; PI: Soya H) 8/1/2014 – 7/30/2020
Japan Society for the Promotion of Science
The aim of this exchange program is to foster international collaboration across institutions by providing funds for international joint research as well as opportunities for young scholars to travel from Japan to the US to work at US-based laboratories on neuroscience research as well as cover travel for US-based investigators to Japan for discussions and collaboration. This is a cross-institutional partnership between UC Irvine, the University of Tsukuba, Rockefeller University, and the Cajal Institute.

COMPLETED

Neural basis for language processes in acute stroke
NIH/NIDCD R01 DC005375 (PI: Hillis, A, Role: Co-I) 7/1/2012 – 12/31/2013
High-Resolution Neuroimaging Tools For Investigating Age-Related Memory Loss
NIH/NIA P50 AG05146 (Pilot PI: Yassa MA; P50 PI: Albert M) 7/1/2011 – 6/30/2012
Functional Imaging of Hippocampal Subfields in Healthy Aging
NIH/NIA R03 AG032015-01 (Co-I: Yassa MA; PI: Stark CEL) 9/1/2008 – 8/30/2010
Pathways to Brain Health for African Americans: A Community-Based Participatory Research Study
NIH/NIA R56 AG053961 (Co-I: Yassa MA; PI: Gluck MA) 9/15/2016 – 8/31/2017