

BIOGRAPHICAL SKETCH

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NAME: Mackey, Sean, MD, PhD

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POSITION TITLE: Redlich Professor of Anesthesiology & Pain Medicine; Neurosciences; and Neurology;
Chief, Division of Pain Medicine

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania, Philadelphia, PA	BSE	05/1986	Bioengineering
University of Pennsylvania, Philadelphia, PA	MS	12/1986	Bioengineering
University of Arizona, Tucson, AZ	PhD	12/1994	Electrical Engineering
University of Arizona, Tucson, AZ	MD	05/1994	Medicine
Stanford University Medical Center, Stanford, CA	Residency	07/1998	Anesthesiology, Perioperative & Pain Medicine
Stanford University Medical Center, Stanford, CA	Fellowship	07/1999	Pain Medicine

A. Personal Statement

I have the leadership, resources and expertise to lead this proposed project. By way of introduction, I am currently the Chief for the Stanford Division of Pain Medicine. I oversee the research mission as the Director of the Stanford Systems Neuroscience and Pain Lab. I am PI on several NIH grants (P01, R01, T32). Additionally, I currently have an NIH K24 award, which provides with me with sufficient time and resources to provide mentoring for junior investigators. I also have an NIH T32 for postdoctoral trainees and a formal system in place to guide mentoring and evaluation (N.B. Our renewal T32 application was just reviewed and received a perfect 10 score). Finally, I hold two research endowments that provide the discretionary monies to help support novel spinoff projects that may come out of the projects proposed in this grant and allow for Dr. Salmasi to procure additional pilot data for his future R01 applications.

I am the PI and inventor of CHOIR (Collaborative Health Outcomes Information Registry), an open source and free platform for a learning healthcare system and platform for research discovery. CHOIR will serve as the informatics platform this pragmatic trial that addresses our specific aims and hypotheses.

Overall, I have a documented record of accomplishment in performing productive research, grants management and leadership in areas related to this research proposal and I can therefore provide the needed leadership for this important proposal.

B. Positions and Honors**Positions and Employment**

1996-1998 Resident, Anesthesia, Stanford University Medical Center, Stanford, CA
 1997-1998 Chief Resident, Anesthesia, Stanford University Medical Center, Stanford, CA
 1998-1999 Fellow, Pain Management, Stanford University Medical Center, Stanford, CA
 1999-2007 Asst. Prof. Anesthesia & Pain Management, Stanford University Medical Center, Stanford, CA
 2000-2006 Founder and Director - Regional Anesthesia Services, Stanford Dep. of Anesthesiology
 2002- Director, Stanford Systems Neuroscience and Pain Lab
 2004-2007 Associate Director – Pain Medicine Division, Stanford University Dep. Anesth., Stanford, CA
 2007- Chief – Division of Pain Medicine, Stanford University Dep. Anesth., Stanford, CA

2007-2012 Associate Professor. Anesthesiology, Perioperative and Pain Medicine, Neurosciences and (by courtesy) Neurology, Stanford Univ. Medical Center, Stanford, CA
 2007-2012- Program Director, Clinical Pain Medicine Fellowship Program, Stanford University, Stanford, CA
 Redlich Professor, Anesthesiology & Pain Medicine, Neurosciences and (by courtesy) Neurology, Stanford Univ. Medical Center, Stanford, CA
 2015-2017 Clinic Chief (Interim), Stanford Pain Management Center, Stanford Univ. Medical Center, Stanford, CA

Other Experience and Professional Memberships

2007- Member, American Society of Anesthesiology Pain Committee
 2008- Board of Directors, American Academy of Pain Medicine
 2008- Board of Directors, Association of Pain Program Directors
 2008-2009 International Association for the Study of Pain, Pain Clinic Guidelines Taskforce
 2008-2009 California Neuropathy Task Force
 2008-2012, 2016 National Institute on Drug Abuse, Career Award Scientific Review Committee
 2008-2015 Director at Large, American Academy of Pain Medicine
 2009- American Academy of Pain Research Committee
 2009-2011 Member, Institutes of Medicine, Committee on Advancing Pain Research, Care, and Education
 2009-2015 Executive Committee, American Academy of Pain Medicine
 2010- Senior Editor, Pain Medicine
 2011-2013 Vice President of Scientific Affairs, American Academy of Pain Medicine
 2011-2013 Committee Member, NIH Interagency Pain Research Coordinating Committee
 2012-2016 Co-Chair, NIH Prevention and Care Working Group for the National Pain Strategy Task Force
 2012 Co-Chair, American Academy of Pain Medicine Annual Meeting
 2012-2013 Committee Member, NIH Pain Consortium Chronic Low Back Pain Research Task Force
 2012-2013 President-Elect, American Academy of Pain Medicine
 2012-2016 Co-Chair, NIH Oversight Committee of the National Pain Strategy Task Force
 2013- Committee Member, National Comprehensive Cancer Network, Adult Cancer Pain
 2014-2015 President, American Academy of Pain Medicine
 2014-2016 NIH Healthy People 2020 Chronic Pain Workgroup
 2015-2016 Immediate Past-President, American Academy of Pain Medicine

Honors

1994 Eta Kappa Nu Electrical Engineering Honor Society
 2002, 2004 - 2016 Top Doctors in America published in "Guide to Top Doctors"
 2008, 2012 American Pain Society Clinical Center of Excellence Award
 2010 Ellis Cohen Achievement Award, Stanford Department of Anesthesia
 2012 American Academy of Pain Medicine Presidential Commendation
 2012 Top 1% Pain Medicine Physicians in America, US News & World Report Guide to Top Doctors
 2015 NIH Director's Award
 2016 American Pain Society Fordyce Award
 2017 American Academy of Pain Medicine, Distinguished Service Award

C. Contribution to Science (from over 130 peer-reviewed publications)

Our Stanford Pain Division's vision statement, "To Predict, Prevent, and Alleviate Pain through Science, Education and Compassion," encompasses my three research goals: (1) define the factors that cause pain or opioids use to become chronic after injury or surgery, (2) discover and implement novel methods to prevent the persistence or chronification of pain and opioid use, and (3) discover and test novel therapies to alleviate chronic pain and substance use disorders. This vision statement informs the multidisciplinary group I have assembled and the tools our team and I use: advanced neuroimaging, patient reported outcomes, psychophysical and neurobehavioral assessment, and genomics. Inherent within our vision is to develop a better mechanistic understanding of pain and biomarkers that can be translated clinically for safe and effective therapies.

Collaborative Health Outcomes Information Registry (CHOIR) and Big Data for Pain and Opioids: Most recently, my research and personal mission has been to develop an open source (free) learning health system

(LHS). Working in collaboration with the NIH (Pain Consortium), we have developed and implemented CHOIR (Collaborative Health Outcomes Information Registry; <http://choir.stanford.edu>), an open source, open platform and free health outcomes registry and platform for a learning health system. CHOIR is designed to provide a deep phenotype of every patient coming to the Stanford Pain Management Center across multiple domains of physical, psychological and social functioning – including substance use behaviors. It serves as a platform for point of care decision making, longitudinal patient tracking, comparative effectiveness research and large simple trial designs. We have disseminated CHOIR beyond Stanford to other clinical specialties and academic institutions nationally and internationally. Most recently, we have expanded CHOIR into the perioperative environment (Perioperative CHOIR) to deeply phenotype all patients coming to Stanford for surgery.

1. Sun, E.C., A. Dixit, K. Humphreys, B.D. Darnall, L.C. Baker and S. Mackey, "Association between concurrent use of prescription opioids and benzodiazepines and overdose: retrospective analysis". *BMJ*, 2017. 356: p. j760.
2. Sturgeon, J. A., Darnall, B. D., Kao, M. C., & Mackey, S. C. (2015). "Physical and psychological correlates of fatigue and physical function: a Collaborative Health Outcomes Information Registry (CHOIR) study. *J Pain*, 16(3), 291-298 e291. doi:10.1016/j.jpain.2014.12.004
3. Bhandari, R. P., A. B. Feinstein, S. E. Huestis, E. J. Krane, A. L. Dunn, L. L. Cohen, M. C. Kao, B. D. Darnall and S. C. Mackey (2016). "Pediatric-Collaborative Health Outcomes Information Registry (Peds-CHOIR): a learning health system to guide pediatric pain research and treatment". *Pain* 157(9): 2033-2044.
4. Sun EC, Jena AB, Kao MC, Darnall BD, Baker LC, Mackey SC. "Incidence of and Risk Factors for Chronic Opioid Use Among Opioid Naïve Patients in the Perioperative Period". *JAMA Intern Med*. 2016 Sep 1;176(9):1286-93. doi: 10.1001/jamainternmed.2016.3298.

Brain Neuroimaging of Pain: I have made significant contributions to our understanding that chronic pain can become its own disease, not just a symptom of another condition. Central neuroimaging has advanced our appreciation that pain is a subjective experience involving the brain. Our work in the following areas has shaped these advances: characterizing the neural correlates of the individual differences in pain perception due to fear, anxiety and catastrophizing; empathy of pain; cortical plasticity due to chronic pain (Younger, Shen et al. 2010) (Martucci, Shirer et al. 2015), abnormal neuroplasticity due to chronic opioid use (Younger, Chu et al. 2011), the intersection of reward and analgesic systems, and learned control of directed brain activity (deCharms et al, 2005). These studies and others have shaped our societal appreciation for the brain's role in pain. While my work has advanced our scientific knowledge, I am most pleased about the work's impact on our patients suffering from chronic pain, who now feel validated that their pain is "real."

1. Martucci, K. T., W. R. Shirer, E. Bagarinao, K. A. Johnson, M. A. Farmer, J. S. Labus, A. V. Apkarian, G. Deutsch, R. E. Harris, E. A. Mayer, D. J. Clauw, M. D. Greicius and S. C. Mackey (2015). "The Posterior Medial Cortex in Urologic Chronic Pelvic Pain Syndrome: Detachment from Default Mode Network. A Resting-State Study from the MAPP Research Network." *Pain*. 2015; 156(9):1755-64.. PMID: PMC4545714
2. Younger, J. W., Y. F. Shen, G. Goddard and S. C. Mackey (2010). "Chronic myofascial temporomandibular pain is associated with neural abnormalities in the trigeminal and limbic systems." *Pain* 149(2): 222-228.
3. Younger, J. W., L. F. Chu, N. T. D'Arcy, K. E. Trott, L. E. Jastrzab and S. C. Mackey (2011). "Prescription opioid analgesics rapidly change the human brain." *Pain* 152(8): 1803-1810.
4. deCharms C, Maeda F, Glover G, Ludlow D, Pauly J, Soneji D, Gabrieli J, Mackey S, Control Over Brain Activation and Pain Learned by Using Real-Time Functional MRI. *PNAS*, December 2005, 102:51; 18626-31. PMC1311906

Spinal Cord Neuroimaging of Pain: Working alongside Dr. Gary Glover and his team for many years, we have been developing methods and applications for spinal cord neuroimaging using BOLD fMRI. The spinal cord is typically a hostile environment from an imaging standpoint with large amounts of physiologic noise, spinal cord motion and its small size. We have overcome the methodological barriers and have been achieving consistently excellent imaging of the human cervical spine. Recently we were joined by Dr. Ken Weber as a postdoc from Northwestern where he had been performing spinal cord imaging. Combining his prior approaches with ours has helped advance the overall quality of our spinal imaging program.

1. Kornelsen J, Mackey S. Potential clinical applications for spinal functional MRI. *Current Pain and Headache Reports*. 2007; 11(3):165-70. PMID: PMC2914611
2. Nash P, Wiley K, Brown J, Shinaman R, Ludlow D, Sawyer AM, Glover G, Mackey S. Functional magnetic resonance imaging identifies somatotopic organization of nociception in the human spinal cord. *Pain*. 2013; 154(6):776-81. PMID: 23618495
3. Weber, K., Parrish, T., Bernadel-Huey, O., Sentis, A., Wang X., Mackey, S. Thermal Stimulation alters Cervical Spinal Cord Functional Connectivity in Humans. *Neuroscience*, 2017; 369:40-50 PMID: 29101078

Brain Based Biomarkers of Pain: I have been working to translate brain neuroimaging from a tool used to characterize brain systems related to pain, to that of a true predictive biomarker for a state of acute or chronic pain. There is a strong need for objective biomarkers of pain. Traditionally, we rely on self-report as the gold standard. However, self-report can fail us in circumstances (e.g. very young or old patients, those in the ICU) and can also be an incomplete measure of a person's experience of pain. Previous efforts to use physiological measurements (e.g. heart rate, blood pressure, pupillary response, etc) have all failed. We have developed methods using machine learning approaches to objectively use neuroimaging to detect the presence or absence of pain. In essence, we are developing a physiological "pain detector". We published the first paper using group data to predict individual acute pain experience and demonstrated an 87% accuracy (Brown, Chatterjee et al. 2011). We have extended this and have demonstrated the ability to detect the presence or absence of chronic low back pain (Ung, Brown et al. 2012), pelvic pain (Bagarinao, Johnson et al. 2014), fibromyalgia and to predict the natural history of pelvic pain. We are also addressing the profound ethical and legal implications of the use of these tools (Davis et al., 2017).

1. Bagarinao, E., K. A. Johnson, K. T. Martucci, E. Ichescio, M. A. Farmer, J. Labus, T. J. Ness, R. Harris, G. Deutsch, A. V. Apkarian, E. A. Mayer, D. J. Clauw and S. Mackey (2014). "Preliminary structural MRI based brain classification of chronic pelvic pain: A MAPP network study." *Pain* 155(12): 2502-2509.
2. Brown, J. E., N. Chatterjee, J. Younger and S. Mackey (2011). "Towards a physiology-based measure of pain: patterns of human brain activity distinguish painful from non-painful thermal stimulation." *PLoS One* 6(9): e24124.
3. Ung, H., J. E. Brown, K. A. Johnson, J. Younger, J. Hush and S. Mackey (2012). "Multivariate classification of structural MRI data detects chronic low back pain." *Cereb Cortex* 24(4): 1037-1044.
4. Davis KD, Flor H, Greely HT, Iannetti GD, Mackey S, Ploner M, Pustilnik A, Tracey I, Treede RD, Wager TD, Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations, *Nat Rev Neurol*. 2017 Oct;13(10):624-638. doi: 10.1038/nrneurol.2017.122. Epub 2017 Sep 8. Review. PMID: 28884750

List of Published Works:

<https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41145440/?sort=date&direction=ascending>
<https://profiles.stanford.edu/sean-mackey?tab=publications>

D. Research Support

Ongoing Research Support

P01 AT006651 PD: Mackey 9/1/11 – 5/31/16 (On NCX; Projected end mid-2018)
 Stanford Center for Back Pain

The purpose of this Center grant is to investigate cortical mechanisms of chronic low back pain (CLBP) and mechanisms of four therapies with the hypothesis that CLBP represents a dysfunction between pain modulatory and emotion regulatory circuits.

R01 HD082200 PI: Beth Darnall, Co-Investigator: Sean Mackey 9/1/15 – 6/31/20
 Maternal Chronic Pain: Risk for Pain and Poor Outcomes in Children

R01AT008561 PIs: Mackey and Darnall 9/1/15 - 5/31/20
 Single Session Pain Catastrophizing Treatment: Comparative Effectiveness & Mechanisms

The goals of this project are to develop and validate a short daily pain catastrophizing measure and to compare effectiveness of a brief, single-session pain catastrophizing treatment against an 8-session CBT class.

K23 AT008477 PI: Jiang-Ti Kong, Mentor: Sean Mackey Predicting Analgesic Response to Acupuncture – A Practical Approach	9/1/15 – 8/31/20
K99 R00 DA040154 PI: Katie Martucci, Mentor: Sean Mackey Impact of Opioids on Chronic Pain: Clinical Research and Career Training in Spinal Cord fMRI and Brain Reward Systems	7/1/15 – 6/31/20
R01DA035484 PI: Tor Wager (Univ Colorado); Site PI: Mackey “fMRI-Based Biomarkers for Multiple Components of Pain” The purpose of this grant is to combine fMRI and machine learning to identify objective biomarkers of pain.	8/1/13 – 3/31/18
K24 DA029262 PI: Mackey <i>Neuroimaging and Mentoring in Translational Pain Research</i>	03/31/15-4/1/20
T32 DA035165 PD: Mackey (resubmitted and reviewed with score = 10) <i>Interdisciplinary Research Training in Pain and Substance Use Disorders</i>	7/1/13 – 6/30/18
K23 DA035302 -PI: Jennifer Hah, Mentor: Mackey <i>Psychological Factors Contributing to Persistent Opioid Use After Surgery</i>	9/2013 – 9/2018
Chris Redlich Professorship in Pain Research This endowment supports pain medicine research efforts.	9/1/09 – Forever
Dodie and John Rosekrans Pain Research Endowment Fund This endowment supports pain medicine research efforts.	2001 – Forever
<u>COMPLETED RESEARCH SUPPORT</u>	
HHSN 271201200728P PI: Mackey <i>Development of an Open-Source National Pain Registry</i>	9/30/12 – 9/29/15
K23 DA031808 PI: Kevin Johnson, Mentor: Mackey <i>Research Training Using TMS to Study Pain Processing in Long-Term Opioid Use</i>	7/15/11 – 5/31/16
R01 NS053961 PI: Mackey <i>fMRI of Pain in the Human Spinal Cord</i> The major goal of this project is to utilize fMRI techniques to characterize neural plasticity and the processing of nociception in the human spinal cord.	1/9/06 – 12/31/12
Stanford CME Grant PI: Mackey <i>Safe Opioid Prescribing and Risk Evaluation and Mitigation Strategies (REMS)</i>	9/1/12 – 8/31/13