BIOGRAPHICAL SKETCH

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NAME**: Kendall Han Lee**

eRA COMMONS USERNAME: **KENDALLLEE1**

POSITION TITLE: **Professor and Consultant of Neurosurgery, Physiology and Biomedical Engineering, and Physical Medicine and Rehabilitation**

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of Colorado at Denver	B.A.	1987-1990	Biology
Yale University Graduate School	M.Phil.	1991-1994	Neurobiology
Yale University School of Medicine	M.D.	1991-1998	Medicine
Yale University Graduate School	Ph.D.	1994-1998	Neurophysiology

A. PERSONAL STATEMENT

I have extensive research expertise in neuroscience, specifically in electrophysiology, stereotactic and functional neurosurgery, and electrochemistry. I received my M.D. and Ph.D. degrees from Yale University in 1998. My doctoral dissertation was on the neurochemical modulation of synchronized oscillations in the thalamus (Department of Neurobiology). I was a neurology resident at Harvard Medical School and completed my neurosurgery residency at Dartmouth-Hitchcock Medical Center, emphasizing stereotactic and functional neurosurgery and deep brain stimulation (DBS). During my residency, I also completed a postdoctoral research fellowship in electrophysiology. For the past fifteen years, my research has focused on elucidating the therapeutic mechanisms of electrical stimulation in restoring function in both the brain and spinal cord. In 2006, I joined Mayo Clinic as a stereotactic and functional neurosurgeon with a clinical emphasis on DBS and now am 50% clinical and 50% research. I founded and have been co-director of the Mayo Neural Engineering Laboratories (NEL) for fifteen years. Under my leadership, the laboratory has mentored 14 graduate school and medical school students. In 2015, I became the chair of Enterprise Neurosurgery Research across Mayo's three sites, and I was a sitting member of the BNVT study sections for NIH.
The lab's endeavors have included intensive collaboration with Mayo's Division of Engineering to develop novel research devices such as wireless fast-scan cyclic voltammetry designed for use during human and animal DBS surgery to monitor the neurochemical and electrophysiological bases of DBS, as well as research tools and novel stereotactic headframes and M.R. imaging strategies to investigate effects of DBS in large animal (swine and nonhuman primates). I have served as M.D./PhD Director at Mayo Clinic from 2017 to 2021. I was the P.I. on a T32 Medical Scientist Training Program at Mayo Clinic, funded by the National Institute of General Medical Sciences. (T32 GM 65841). I have extensive research expertise in neuroscience, specifically in electrophysiology, stereotactic and functional neurosurgery, and electrochemistry.

1. **Lee KH**, McCormick DA. Abolition of spindle oscillations by serotonin and norepinephrine in the ferret lateral geniculate and perigeniculate nuclei in vitro. Neuron. 1996 17(2):309-21.
2. **Lee KH**, Broberger C, Kim U, McCormick D. Histamine modulates thalamocortical activity by activating a chloride conductance in ferret perigeniculate neurons. Proc Natl Acad Sci USA. 2004 101:6716-21.
3. Chang SY, Kim I, Marsh MP, Jang DP, Hwang SC, Van Gompel JJ, Goerss SJ, Kimble CJ, Bennet KE, Garris PA, Blaha CD, **Lee KH**. Wireless fast-scan cyclic voltammetry to monitor adenosine in patients with essential tremor during deep brain stimulation. Mayo Clin Proc. 2012 87(8):760-5.
4. Min H-K, Ross EK, Jo HJ, Cho S, Settella ML, Jeong JH, Duffy PS, Chang S-Y, Bennet KE, Blaha CD, **Lee KH**. Dopamine release in the nonhuman primate caudate and putamen depends upon site of stimulation in the subthalamic nucleus. J Neurosci 2016 36(22):6022-6029.

B. POSITIONS AND HONORS

Positions

1994 - 1996	Instructor: Neurobiology 500b, Yale University School of Medicine
1994 - 1998	Student Editor: The Yale Journal of Biology and Medicine
1998 - 1999	Hospital of St. Raphael, Affiliate of Yale University School of Medicine Internship in Internal Medicine, Outstanding Intern of the Year
1999 - 2000	Harvard Medical School, Partners' Neurology program, Resident in Neurology
2000 - 2001	Internship in General Surgery, Dartmouth-Hitchcock Medical Center
2001 - 2006	Resident and Chief Resident in Neurosurgery Dartmouth-Hitchcock Medical Center
2006 - 2009	Assistant Professor in Neurosurgery, Physiology, and Biomedical Engineering Mayo Clinic
2009 - 2014	Associate Professor in Neurosurgery, Physiology, and Biomedical Engineering Mayo Clinic
2014 - present	Professor in Neurosurgery, Physiology, and Biomedical Engineering Mayo Clinic

Honors and Other Professional Activities

2001	New England Neurosurgical Society: William Scoville Resident Award
2002	Thomas P. Almy, M.D. Resident Teacher of the Year Award: Dartmouth Medical School
2004	Dartmouth Neuroscience Day Outstanding Presentation Award
2004	American Association of Neurological Surgeons: Phillip Gildenberg Award
2005	Academic Enhancement Grant-Dartmouth Medical School
2005	Hitchcock Foundation Research Grant
2005	Neurosurgery Research and Education Foundation / Medtronic Grant
2006	Mayo Foundation Grant
2007	Mayo New Investigator Grant
2008 - 2011	Research Early Career Development Award for Clinician Scientists - Mayo Clinic
2015	Distinguished Team Science Award, Mayo Clinic Enterprise wide
2001 - present	Congress of Neurological Surgery, resident member
2001 - present	American Association of Neurological Surgery, resident member
2003 - present	American Society for Stereotactic and Functional Neurosurgery, member
2003 - present	Young Neurosurgeons Executive Committee, member
2004 - present	Society for Neuroscience, regular member

C. CONTRIBUTIONS TO SCIENCE

1. DBS-evoked neurochemical recording in animals and humans.

With its potential to individualize treatment, improve outcomes, and save costs, the development of a "smart" closed-loop DBS system with brain-based feedback control has generated great attention and interest. To initiate this research, my laboratory developed a neurochemical sensing device called WINCS (Wireless Instantaneous Neurochemical Concentration Sensing) and a neural stimulator called MINCS (Mayo Investigational Neuromodulation Control System). WINCS uses fast-scan cyclic voltammetry for real-time monitoring of the release of a variety of neurochemicals *in vivo*, including dopamine and adenosine. WINCS is wireless, has adjustable stimulation and acquisition parameters, and can transmit a graphical representation of neurochemical release data via a Bluetooth transceiver. MINCS is a wireless stimulator that can generate user-defined patterns of stimulation that can be integrated with the WINCS chemical sensing protocols. This allows the detection of neurochemical changes in the brain during the application of DBS and has allowed us to study the relationships between patterns of neural stimulation and neurochemical release. These studies will eventually provide information necessary for a smart DBS system in which control over neural stimulation is based on brain activity. We have now developed the next generation of WINCS, called WINCS Harmoni for animal research, which combines WINCS and MINCS capabilities in a miniaturized integrated circuit format. The new design has four neurochemical sensing channels, a customizable neurostimulator, and is consistent with all current industry standards for medical device safety. We have tested and evaluated the functionality and safety in small (rodent) and large animal models (swine).

a. Bledsoe JM, Kimble CJ, Covey DP, Blaha CD, Agnesi F, Mohseni P, Whitlock S, Johnson DM, Horne AE, Bennet KE, **Lee KH**, Garris PA. Development of the Wireless Instantaneous Neurochemical Concentration Sensor system for intraoperative neurochemical monitoring using fast-scan cyclic voltammetry. J Neurosurg. 2009 111(4):712-23.
b. Van Gompel JJ, Chang SY, Goerss SJ, Kim IY, Kimble CJ, Bennet KE, **Lee KH**. Development of intraoperative electrochemical detection: Wireless Instantaneous Neurochemical Concentration Sensor for deep brain stimulation feedback. Neurosurg Focus. 2010 29(2): E6.

c. Griessenauer CJ, Chang SY, Tye SJ, Kimble CJ, Bennet KE, Garris PA, **Lee KH**. Wireless Instantaneous Neurochemical Concentration Sensor system: electrochemical monitoring of serotonin using fast-scan cyclic voltammetry—a proof-of-principle study. J Neurosurg. 2010 113(3):656-65.
d. Chang SY, Kimble CJ, Kim IY, Paek SB, Kressin KR, Boesche JB, Whitlock SV, Eaker DR, Kasasbeh A, Horne AE, Blaha CD, Bennet KE, **Lee KH**. Development of the Mayo Investigational Neuromodulation Control System: toward a closed-loop electrochemical feedback system for deep brain stimulation. J Neurosurg. 2013 119(6):1556-65.

2. Combining DBS with neuroimaging in animals and humans (NIH R01 NS 70872-1)

To better understand the fundamental relationships between neural activation, neurochemical transmission, and clinical outcomes of DBS, our laboratory has combined two powerful technologies—blood oxygen level-dependent, fMRI (BOLD signal) to monitor neural network activation, and wireless instantaneous neurochemical concentration sensing (WINCS). Used together, these two techniques can give an accurate real-time picture of the DBS-evoked circuitry activation and the neurochemical changes that are likely involved in this activation. We began by using fMRI-BOLD brain regions that are activated during DBS in a large animal (swine and non-human primate). Having characterized the DBS response in the animal brain and similar experiments in patients undergoing DBS surgery for Parkinson's disease, we are now extending these experiments to study brain circuitry activation and neurochemical release in patients undergoing DBS surgery for neuropsychiatric disorders. Using a multi-voxel pattern analysis, we have found that areas of BOLD activation change as a function of DBS electrode activated (e.g., target) and stimulation parameters used (e.g., limbic/association cortex vs somatomotor cortex) with implications for clinical outcomes and adverse effects. These studies have provided, and will continue to provide, important insights into the optimal targets within a targeted brain structure and represent a first step toward the development of an objective functional biomarker for clinical DBS.

a. Min HK, Hwang SC, Marsh MP, Kim I, Knight E, Striemer B, Felmlee JP, Welker KM, Blaha CD, Chang SY, Bennet KE, **Lee KH**. Deep brain stimulation induces BOLD activation in motor and non-motor networks: an fMRI comparison study of STN and EN/GPi DBS in large animals. Neuroimage. 2012 63(3):1408-20.
b. Knight EJ, Testini P, Min H, Gibson WS Gorny KR, Favazza CP, Felmlee JP, Kim I, Welker KM, Clayton DA, Klassen BT, Chang S-y, **Lee KH**. Motor and nonmotor circuitry activation induced by subthalamic nucleus deep brain stimulation in Parkinson's disease patients: Intraoperative functional magnetic resonance imaging for deep brain stimulation. Mayo Clin Proc. 2015 90(6):773-85.
c. Paek SB, Min HK, Kim I, Knight EJ, Baek JJ, Bieber AJ, **Lee KH**, Chang SY. Frequency-dependent functional neuromodulatory effects on the motor network by ventral lateral thalamic deep brain stimulation in swine. Neuroimage. 2015 105:181-8.
d. Min H-K, Ross EK, Jo HJ, Cho S, Settella ML, Jeong JH, Duffy PS, Chang S-Y, Bennet KE, Blaha CD, **Lee KH**. Dopamine release in the nonhuman primate caudate and putamen depends upon site of stimulation in the subthalamic nucleus. J Neurosci 2016 36(22):6022-6029.

3. Diamond electrodes for neurochemical sensing (NIH R01 NS 75013-1).

The overall goals of our laboratory in determining DBS mechanisms require chronic studies of neurochemical changes evoked by DBS under various conditions (e.g., stimulator on and off; stimulation parameter changes; contacts activated). In addition, should a future closed-loop device use neurochemical feedback, a recording electrode with proven longevity and durability will be a requirement. By its very nature, recording neurochemical changes exposes electrodes to the extracellular environment in the brain. Today's micro-carbon fiber electrodes cannot long survive that corrosive environment and exhibit relatively low tensile strength.

Diamond is highly resistant to corrosion. Pure diamond is an insulator, but when adding small amounts of boron, gives it conductive properties while retaining its strength and corrosion resistance. The coating of diamond with other materials is a well-known industrial process. Our laboratory, with the Mayo Division of Engineering, has built a reactor for the chemical vapor deposition of boron-doped diamond, and we have manufactured our first diamond-coated electrodes specifically for DBS research. In 2014, we received a BRAIN Initiative grant from the NIH to continue this work and now have successfully generated a unique set of electrodes that demonstrate versatility and sensitivity in the laboratory. Following animal tests, this electrode would have wide applicability for use in DBS research aimed at understanding mechanisms of pathologic neural activity, DBS mechanisms, and as potential input for a closed-loop DBS system.

a. Marsh MP, Koehne JE, Andrews RJ, Meyyappan M, Bennet KE, **Lee KH**. Carbon nanofiber multiplexed array and Wireless Instantaneous Neurotransmitter Concentration Sensor for simultaneous detection of dissolved oxygen and dopamine. Biomed Eng Lett. 2012 2(4):271-277.
b. Bennet KE, **Lee KH**, Kruchowski JN, Chang SY, Marsh MP, Van Orsow AA, Paez A, Manciu FS. Development of conductive boron-doped diamond electrode: a microscopic, spectroscopic, and voltammetric study. Materials. 2013;6(12):5726-41.
c. Bennet KE, Tomshine JR, Min HK, Manciu FS, Marsh MP, Paek SB, Settell ML, Nicolai EN, Blaha CD, Kouzani AZ, Chang SY, **Lee KH**. A diamond-based electrode design for detection of neurochemicals in the human brain. Front Hum Neurosci. 2016 Mar 15; 10:102. PMID: 27014033.

4. DBS for the treatment of psychiatric disorders.

DBS is currently approved for the treatment of certain movement disorders such as Parkinson's disease and is under investigation as a treatment option for other neurologic conditions. We are working to expand the application of DBS technology for the treatment of a range of psychiatric conditions, including OCD, depression, chronic pain, and addiction, as well as Tourette's syndrome. Recent advances in brain imaging techniques and pharmacotherapies have helped elucidate the biological changes that are associated with complex psychiatric conditions. Current evidence proposes that these disorders are not simply a dysfunction of any single region but rather a failure in the coordination between specific brain regions. Research efforts have therefore focused on defining the organization and structural connectivity of neural circuits associated with these conditions. Metabolic imaging of brain activity by BOLD-fMRI has helped identify cortical and subcortical regions presenting abnormal activity. We have used our expertise in imaging brain activity and in the real-time analysis of neurochemical release to examine changes that take place following the stimulation of DBS targets that might be used for the treatment of neuropsychiatric disease. This information will guide the development of effective therapies for these conditions using the WINCS Harmoni technology described above.

a. Chopra A, Tye SJ, **Lee KH**, Sampson S, Matsumoto J, Adams A, Klassen B, Stead M, Fields JA, Frye MA. Underlying neurobiology and clinical correlates of mania status after subthalamic nucleus deep brain stimulation in Parkinson's disease: a review of the literature. J Neuropsychiatry Clin Neurosci. 2012 24(1):102-10.
b. Anderson RJ, Frye MA, Abulseoud OA, **Lee KH**, McGillivray JA, Berk M, Tye SJ. Deep brain stimulation for treatment-resistant depression: efficacy, safety, and mechanisms of action. Neurosci Biobehav Rev. 2012 36(8):1920-33.
c. Kim JP, Min HK, Knight EJ, Duffy PS, Abulseoud OA, Marsh MP, Kelsey K, Blaha CD, Bennet KE, Frye MA, **Lee KH**. Centromedian-parafascicular deep brain stimulation induces differential functional inhibition of the motor, associative, and limbic circuits in large animals. Biol Psychiatry. 2013 74(12):917-26.
d. Gibson WS, Cho S, Abulseoud OA, Gorny KR, Felmlee JP, Welker KM, Klassen BT, Min HK, **Lee KH.** The impact of mirth-inducing ventral striatal Deep Brain Stimulation on functional and effective connectivity. Cereb Cortex. 2016 Mar 21. [Epub ahead of print] PMID: 27001680

5. Limb Reanimation.

Neuroprosthetic devices can restore motor function following spinal cord injury by direct electrical stimulation of the neuromuscular system. Unfortunately, conventional neuroprosthetic techniques are limited by a myriad of factors that include, but are not limited to, a lack of characterization of non-linear input/output system dynamics, mechanical coupling, a limited number of degrees of freedom, power consumption, device size, and rapid onset of muscle fatigue. Our lab is working to improve intraspinal microstimulation (ISMS), which is believed to be capable of producing longer-lasting muscle contractions, at least in part, by the lower stimulation amplitudes associated with direct stimulation of spinal circuits. However, ISMS relies on external anatomical landmarks and can only provide 1-2 mm of accuracy. As a result, anatomical differences and variations in surgical strategy and skill can affect neuronal targeting and activation, which can compromise functional outcomes and prevent the translation of this technology into clinical applications. Our laboratory has developed an image-guided system for the targeted delivery of microelectrodes into the spinal cord. This system will ensure optimal microstimulation of target motor neuron populations, improve selectivity and control of motor function, maximize clinical benefits, and minimize adverse effects. Moreover, this stereotactic delivery system is adaptable for a host of clinical applications such as chemotherapy, gene therapy, and stem cell transplantation.

a. Hachmann JT, Jeong JH, Grahn PJ, Mallory, GW, Evertz LQ, Bieber AJ, Lobel DA, Bennet KE, **Lee KH,** Luján JL. Large animal model for development of functional restoration paradigms using epidural and intraspinal stimulation. PLoS One. 2013 8(12): e81443.
b. Grahn PJ, **Lee KH**, Kasasbeh A, Mallory GW, Hachmann JT, Dube JR, Kimble CJ, Lobel DA, Bieber A, Jeong JH, Bennet KE, Lujan JL. Wireless control of intraspinal microstimulation in a rodent model of paralysis. J Neurosurg. 2015 123(1):232-42.
c. Grahn PJ, Goerss SJ, Lujan JL, Mallory GW, Kall BA, Mendez AA, Trevathan JK, Felmlee JP, Bennet KE, **Lee KH**. MRI-guided, stereotactic delivery of intraspinal stimulating electrodes for selective activation of neuromuscular circuitry. Spine (Phila Pa 1976). 2015 Dec 14. [Epub ahead of print]
d. Gill ML, Grahn PJ, Calvert JS, Linde MB, Lavrov IA, Strommen JA, Beck LA, Sayenko DG, Van Straaten MG, Drubach DI, Veith DD, Thoreson AR, Lopez C, Gerasimenko YP, Edgerton VR, **Lee KH**, Zhao KD. Neuromodulation of lumbosacral spinal networks enables independent stepping after complete paraplegia. Nature Medicine. 2018 Sep 24

Additional information can be found at:
Lee, K. (2022). Bibliography. Retrieved from:
http://www.ncbi.nlm.nih.gov/pubmed?term=Lee%2C%20Kendall%20H[Author]

D. RESEARCH SUPPORT

Ongoing

NIH **1R01NS129549-01** (Lee, PI) 01/2023-11/2027
Development of an innovative in vivo voltametric technique for measurements of tonic serotonin concentrations in the mammalian brain.
The goal of this grant is to develop a novel neurochemical recording method called N-shaped Multiple Cyclic Square Wave Voltammetry to measure tonic serotonin concentrations in the brain.

NIH **1R42NS125895-01A1** (Bennet, PI; Lee, Co-PI) 10/2022 – 09/2026
An Integrated Neurochemical/Electrophysiological Recording and Neuromodulation System for Basic and Clinical Research
The goal of this NIH STTR grant is to partner WINCS International with Mayo Clinic Neural Engineering Laboratories to finalize the development of a novel neurochemical and electrophysiological recording and stimulating instrument.

NIH **1R01NS112176-01** (Lee, PI) 09/2019-08/2024
Development of Advanced Voltammetric Method for Basal Neurotransmitter Level Measurements
The goal of this project is to refine and improve our present electrochemical methods for monitoring basal concentrations of neurotransmitters in the brain.

NIH **T32 GM065841** (Lee, PI; Kaufmann, Co-PI) 07/2003 - 06/2023
Medical Scientist Training Program at Mayo Clinic.
This is a Training Grant for the MD/PhD Program at the Mayo Clinic

Completed

NIH **1R01NS107336-01** (Lujan, PI; Lee, Co-PI) 05/2018 - 06/2021
In Vivo Fluorescent Microscopy Analysis of Motor Cortex Activation by STN DBS
The goal of this grant is to directly image motor cortex neurons to study changes in their activity during movement in Parkinson's disease and deep brain stimulation-treated animals.

NIH **R01 NS 88260** (Chang, PI; Lee, Co-I) 02/2015 - 01/2019
Astrocytes and DBS
This project is examining the role that astrocytes play in the response to deep brain stimulation particularly with regards to the role of astrocytic release of adenosine.

NIH **U01 NS 090455** (Lee, PI) 09/2014 - 08/2019
Neurotransmitter Absolute Concentration Determination with Diamond Electrode
The goal of this project is to couple diamond-based electrodes with novel fast-scan cyclic voltammetry techniques to measure absolute concentrations of neurotransmitters in the chronically *in vivo* in animal models.

NIH **R01 NS 84975-1** (Lujan, PI; Lee, Co-I) 01/2014 - 12/2018
Neurochemical Closed-Loop Controller for Smart DBS
The goal of this study is to develop a closed-loop controller that uses neurochemical inputs to adjust stimulation parameters and improve therapeutic response to deep brain stimulation.

NIH **R01 NS 70872-1** (Lee, PI) 06/2011 - 05/2016
WINCS and DBS
This project is to understand the underlying mechanism of the therapeutic action of DBS, using simultaneous electrochemical measurement and fMRI methods.
NIH **R21 NS 87320** (Lujan, PI; Lee, Co-I) 04/2014 - 03/2016
Targeted Intraspinal Stimulation for Restoration of Limb Movement following Spinal Cord Injury
This project is developing a targeting strategy for identifying and stimulating motor neuron nuclei associated with specific target movements in a large animal (porcine) model.
NIH **R01 NS 75013-1** (Lee, PI) 08/2011 - 05/2016
WINCS/Nanotrode Development for DBS
This project is developing carbon nanotube-based electrochemical sensing electrodes for use as a nanotrode neurochemical recording electrode.