**BIOGRAPHICAL SKETCH**

NAME: Karl Deisseroth, MD PhD

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POSITION TITLE: D.H. Chen Professor of Bioengineering and Psychiatry, Stanford University
Investigator, Howard Hughes Medical Institute

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 | Completion | FIELD OF STUDY |
|---|---|---|---|---|
| Harvard College | Cambridge, MA | A.B. | 1992 | Biochemical Sciences |
| Stanford University | Stanford, CA | Ph.D. | 1998 | Neuroscience |
| Stanford University | Stanford, CA | M.D. | 2000 | Medicine |
| Stanford University | Stanford, CA | Postdoctoral | 2004 | Physiology |

**A. Personal Statement** I am currently an HHMI Investigator and hold the D. H. Chen Chair at Stanford, serving as Professor of Bioengineering (where I teach optics and physiology courses to undergraduates, and direct the undergraduate major program in Bioenegineering), and with a joint appointment in the Department of Psychiatry and Behavioral Sciences (where I teach residents and treat patients using medications and brain stimulation techniques). We have developed and applied high-resolution tools for controlling (e.g. optogenetics) and observing (e.g. CLARITY, next-generation fiber photometry, next-generation light sheet microscopy) specific elements of intact biological systems; we develop and apply these and other tools for the study of physiology and behavior in health and disease, and support researchers around the world by disseminating the reagents and techniques. These optical methodologies have greatly advanced the exchange of high-resolution information with intact tissue, including from adult mammalian brains. We have over the past ten years focused our basic biology investigations using these tools within the realm of motivation, reward, and anxiety. I also have leveraged and expanded my longstanding technology-dissemination infrastructure for hands-on technology training for the community at large. Beyond the teaching of neuroscience methods, I have a long history of mentoring on undergraduate, graduate, post-doctoral, and medical resident levels, helping guide student career development as scientists, engineers, and clinicians in an interdisciplinary environment.

**B. Positions and Honors**

**Positions and Employment**

2000-2004 MD internship/licensure and psychiatry residency, Stanford University
7/04-12/04 Principal Investigator and Clinical Educator, Department of Psychiatry, Stanford
2004- Attending physician, inpatient and outpatient service; interventional psychiatry clinic
2005-2008 Assistant Professor of Bioengineering and Psychiatry, Stanford University
2006- Diplomate, American Board of Psychiatry and Neurology
2009-2012 Associate Professor of Bioengineering and Psychiatry, Stanford University
2009-2013 Howard Hughes Medical Institute Early Career Investigator
2010- Director of Undergraduate Education in Bioengineering, Stanford University
2012- Professor of Bioengineering and Psychiatry, Stanford University
2012- D.H. Chen Chair, Stanford University
2013- Foreign Adjunct Professor, Karolinska Institutet, Stockholm
2014- Howard Hughes Medical Institute Investigator

**Synergistic Activities**

2007-2009 Member, NIH Molecular Neurogenetics study section (MNG)
2008- Cold Spring Harbor and Woods Hole, summer optogenetics teaching
2008- Stanford, biweekly optogenetics course for visiting national/international students
20013- Stanford, biweekly CLARITY course for visiting national/international students
2005- Peer Reviewer: *Nature, Science, Cell, Neuron, Nature Neuroscience, Nature Methods, Nature Biotechnology, PNAS, Journal of Neuroscience, Biological Psychiatry, Journal of Neurophysiology*, others
2009- Member, Brain and Behavior Research Foundation (NARSAD) Council
2013- Editorial Board Member, *Cell*
2016- Editorial Board Member, *Neuron*
2013-2014 Member, US BRAIN Initiative Working Group, NIH

**Selected Honors**

1992 Phi Beta Kappa and *summa cum laude*, Harvard University

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|---|---|
| 2005 | McKnight Foundation Technological Innovations in Neuroscience Award |
| 2005 | NIH Director's Pioneer Award, for optogenetics |
| 2006 | Presidential Early Career Award in Science and Engineering (PECASE) |
| 2007 | McKnight Foundation Scholar Award, for optogenetics |
| 2008 | Lawrence C. Katz Prize in Neurobiology, Duke University, for optogenetics |
| 2008 | Schuetze Prize in Neurobiology, Columbia University, for optogenetics |
| 2009 | Society for Neuroscience Young Investigator Award, for optogenetics |
| 2010 | Koetser Prize, Zurich Switzerland, for optogenetics |
| 2010 | Nakasone Prize, Human Frontiers Scientific Program, for optogenetics |
| 2011 | Alden Spencer Prize, Columbia University, for optogenetics |
| 2011 | election to the National Academy of Medicine (NAM; former Institute of Medicine) |
| 2012 | Perl/UNC Prize, for optogenetics |
| 2012 | Zuelch Prize, Max-Planck Institute, for optogenetics |
| 2012 | election to the National Academy of Sciences (NAS) |
| 2013 | MERIT award, National Institute of Health |
| 2013 | Richard Lounsbery Prize, National Academy of Sciences, for optogenetics |
| 2013 | Pasarow Foundation Award, for neuropsychiatry |
| 2013 | BRAIN Prize, Lundbeck Research Foundation, for optogenetics. |
| 2013 | Premio Citta' di Firenze for Molecular Sciences, for optogenetics and CLARITY |
| 2013 | Gabbay Award, Brandeis University, for optogenetics |
| 2013 | Goldman-Rakic Award, Yale/NARSAD, for optogenetics and CLARITY |
| 2014 | Dickson Prize in Science, for optogenetics and CLARITY |
| 2014 | Keio Prize in Medical Science, for optogenetics |
| 2015 | Albany Prize in Medicine and Biomedical Research, for optogenetics |
| 2015 | Lurie Prize, FNIH, for optogenetics |
| 2015 | Breakthrough Prize in Life Science, for optogenetics |
| 2015 | Dickson Prize in Medicine, for optogenetics |
| 2016 | BBVA Award, for optogenetics |
| 2016 | Massry Prize, for optogenetics |
| 2017 | Harvey Prize, for optogenetics |

## C. Contribution to Science

**1) Understanding structure and function of channelrhodopsins** The channelrhodopsins have intrigued biophysicists since their prediction and discovery between 1995 and 2002, representing a paradigmatic light-activated cation channel. However, the nature of the light-activation and pore structure for these seven-transmembrane retinal-binding membrane proteins is without precedent and has been mysterious. Understanding the operation of these proteins is therefore of basic importance in itself, but also carries far-reaching implications for design and implementation of new classes of optogenetic tools. Accordingly I have directed my laboratory toward the structural and functional understanding of channelrhodopsins, beginning with our discovery of the first redshifted channelrhodopsin VChR1[1] and our development of corresponding models of the retinal binding pocket that led to creation of C1V1 (Yizhar et al., ***Nature*** 2011), which not only allowed the first combinatorial two-color optogenetic control *in vivo* (Yizhar et al., ***Nature*** 2011), but also allowed the first single-cell resolution neuronal control *in vivo* (Prakash et al., ***Nature Methods*** 2012) via two-photon illumination, and the first all-optical (Rickgauer et al., ***Nature Neuroscience*** 2014; followed by Grosenick et al., ***Neuron*** 2015; Rajasethupathy et al., ***Nature*** 2015; Kim et al., ***Nature Methods*** 2016) control/readout in behaving mammals. We continued this work with creation of step-function channelrhodopsins[2], which enabled the first bistable optogenetic control[2], and allowed orders of-magnitude greater light-sensitivity[2]; we also created chimeric opsins including C1C2 that enabled determination, with our collaborators, of the first high-resolution crystal structure of a channelrhodopsin[3]. Recently we built on our structural discoveries to build a detailed electrostatic model of channelrhodopsin pore function, and used this model to create iC1C2, a light-activated $Cl^-$ channel, in fast and bistable forms[4]. The resulting pore model appears to apply as well to naturally-occurring $Cl^-$ channels (Berndt and Deisseroth, ***Science*** 2015; Berndt et al, ***PNAS*** 2015). These findings and tools have been applied in thousands of laboratories around the world.

[1]Zhang F, Prigge M, Beyriere F, Tsunoda S, Hegemann P & **Deisseroth K** (2008). Red-shifted optogenetic excitation: a tool for fast neural control derived from Volvox carteri. ***Nature Neuroscience*** 11:631-3. *Free pdf at http://web.stanford.edu/group/dlab/media/papers/Zhang%20Nat%20Neurosci%202007.pdf.*

[2]Berndt A, Yizhar, O, Gunaydin LA, Hegemann P & **Deisseroth K** (2008). Bi-stable neural state switches.

***Nature Neuroscience*** 12:229-34.
*Free pdf at http://web.stanford.edu/group/dlab/media/papers/Berndt%20Nat%20Neurosci%202008.pdf.*
[3]Kato H, Zhang F, Yizhar O, Ramakrishnan C, Nishizawa T, Hirata K, Ito J, Aita Y, Tsukazaki T, Hayashi S, Hegemann P, Maturana A, Ishitani R, ***Deisseroth K** & *Nureki O (2012). Crystal structure of the channelrhodopsin light-gated cation channel. ***Nature*** 482:369-74. *Co-corresponding senior authors. PMCID: PMC4160518.
[4]Berndt A, Lee SY, Ramakrishnan C & **Deisseroth K** (2014). Structure-guided transformation of channelrhodopsin into a light-activated chloride channel. ***Science*** 344:420-4. PMCID: PMC4096039.

**2) Optogenetics** A basic need in the study of biological systems is for experimental power to control defined events, in defined cell types, at defined times, in intact systems. Such analyses are important because cellular events are typically most meaningful in the context of other events occurring in the rest of the tissue, the organism and the environment as a whole. Beginning in 2004 I have directed my laboratory in the development and application of optogenetics, with several key streams of work: 1) discovery and development of microbial opsin gene-based optical stimulation or inhibition of neurons[1,2]; 2) discovery and development of laser diode/fiberoptic neural interfaces that allow application of optical control to neurons anywhere in the brain, even in freely moving mammals[3]; and 3) discovery and development of targeting strategies for *in vivo* behavioral use, including recombinase-dependent opsin viruses[4] (Tsai et al., ***Science*** 2009; Fenno et al., ***Nature Methods*** 2014) and projection-based cell-type targeting in behaving mammals using the fiberoptic interface[3] (Gradinaru et al., ***Science*** 2009; Deisseroth et al., ***Nature*** 2014; ***Nature Neuroscience*** 2015). Together these three advances allow reliable control of spiking with light during behavior, with millisecond precision; after naming the approach "optogenetics" in 2006, my lab has since globally disseminated the tools, and now thousands of findings in health and disease have been published with this single-component control.
[1] Zhang F, Wang, L, Brauner M, Liewald J, Kay K, Watzke N, Bamberg E, Nagel G, Gottschalk A & **Deisseroth K** (2007). Multimodal fast optical interrogation of neural circuitry. ***Nature*** 446:633-9. *Free pdf at www.stanford.edu/group/dlab/papers/Zhang%20Nature%202007.pdf.*
[2] Boyden ES, Zhang F, Bamberg E, Nagel G & **Deisseroth K** (2005). Millisecond-timescale, genetically targeted optical control of neural activity. ***Nature Neuroscience*** 8:1263-8. *Free pdf at www.stanford.edu/group/dlab/papers/Boyden%20Nat%20Neurosci%202005.pdf.*
[3] Aravanis A, Wang LP, Zhang F, Meltzer L, Mogri M, Schneider MB & **Deisseroth K** (2007). An optical neural interface. ***Journal of Neural Engineering*** 4, S143-S156. *Free pdf at http://web.stanford.edu/group/dlab/media/papers/Aravanis%20J%20Neural%20Eng%202007.pdf.*
[4] Sohal VS, Zhang F, Yizhar O & **Deisseroth K** (2009) Parvalbumin interneurons and gamma oscillations synergistically enhance cortical circuit performance. ***Nature*** 459:698-702. PMCID: PMC3969859.

**3) Probing the causal circuit underpinnings of brain and behavioral states** The major promise of optogenetics has been to develop a causal understanding of how precisely defined neural circuit activity patterns in defined circuit elements give rise to behavior. Building on our tools developed above, I have accordingly directed my own laboratory in this direction, with a focus on the cells and projections in the brain that give rise to modulated brain states, measured as stable changes in adaptive or maladaptive behavior. We began this work with the first optogenetic control of behavior in mammals in 2007, delivering precise control of activity patterns in hypocretin neurons in the lateral hypothalamus[1] to identify the causal neuronal activity underpinnings of sleep-wake transitions. We followed this with causal testing of the different appetitive conditioning value of phasic or tonic spike patterns in VTA dopamine neurons (Tsai et al., ***Science*** 2009); with testing the conditioning value of optically recruited and defined signaling messengers in nucleus accumbens neurons, using our novel biochemical optoXR strategy (Airan et al., ***Nature*** 2009); with defining the role in cocaine reward of cholinergic neuron activity in the nucleus accumbens[2]; with identifying the causal real-time role of shifted excitation-inhibition balance in social behavior[3] and of hippocampal activity in recall of recent and remote memories (Goshen et al., ***Cell*** 2011; Rajasethupathy et al, ***Nature*** 2015); and with defining the role in behavioral state transitions of activity in projections from prefrontal cortex to subcortical structures, including dorsal raphe and lateral habenula (Warden et al., ***Nature*** 2012). Together these papers from my lab, and associated readouts including our optogenetic fMRI (ofMRI) methods[4], have helped define circuit dynamical patterns governing implementation of behavioral states and state transitions.
[1] Adamantidis A, Zhang F, Aravanis A, ***Deisseroth K** & *de Lecea L (2007). Neural substrates of awakening probed with optogenetic control of hypocretin neurons. ***Nature*** 450:420-4. *Co-corresponding senior authors.
[2] Witten I, Lin S, Brodsky M, Diester I, Anikeeva P, Ramakrishnan C, **Deisseroth K** (2010). Cholinergic interneurons control local circuit activity and cocaine conditioning. ***Science*** 330:1677-81. PMC3142356.

[3] Yizhar O, Fenno L, Prigge M, Schneider F, Davidson T, O'Shea D, Sohal V, Goshen I, Finkelstein J, Paz J, Stehfest K, Ramakrishnan C, Huguenard J, Hegemann P & **Deisseroth K** (2011). Neocortical excitation-inhibition balance in information processing and social dysfunction. ***Nature*** 477:171-8. PMC4155501.
[4] Lee, J, Durand R, Gradinaru V, Zhang F, Goshen I, Kim D, Fenno L, Ramakrishnan C & **Deisseroth K** (2010). Global and local fMRI signals driven by neurons defined optogenetically by type and wiring. ***Nature*** 465:788-92. PMC3177305.

**4) Probing causal circuit dynamical underpinnings of neuropsychiatric disease models**

Just as important as determining the causal dynamics of normal or adaptive behaviors, will be determining the causal dynamics of pathological or maladaptive behaviors, which have been mysterious due to longstanding difficulties in achieving real-time control over the activity of precisely-defined cells and projections. Building on the tools described above, and my own clinical psychiatry training and practice, I have guided my laboratory in the investigation of circuit activity underpinnings of animal behaviors related to clinically-relevant states, symptoms, and treatments. We began this work with the first application of optogenetics to brain disease (Gradinaru et al., ***Science*** 2009), in which we systematically made light-sensitive diverse components of subthalamic nucleus circuitry in parkinsonian rodents, and identified afferent projections as a major causally-relevant direct target of point stimuli such as those used in deep brain stimulation. We also were able to discover a role for VTA dopamine neurons in modulating multiple symptom domains of stress-induced depression-like states (including anhedonia[1,3] and passive-coping/hopeless-like behavior[2] (Warden et al., ***Nature*** 2012); for projections from the BLA to the CeA in anxiolysis[1]; and for diverse projections to and from the extended amygdala in controlling and coordinating diverse features of anxiolysis[4] (Kim et al., ***Nature*** 2013). These papers laid groundwork for causal circuit-dynamics understanding of maladaptive behaviors.
[1] Tye KM, Mirzabekov JJ, Warden MR, Tsai HC, Finkelstein J, Kim SY, Ferenczi E, Adhikari A, Thompson KR, Andalman AS, Gunaydin LA, Witten IB & **Deisseroth K** (2013). Dopamine neurons modulate the neural encoding and expression of depression-related behavior. ***Nature*** 493:537-41. PMCID: PMC4160519.
[2] Tye K, Prakash R, Kim S, Fenno L, Grosenick L, Gradinaru V, Ramakrishnan C & **Deisseroth K** (2011). Amygdala circuitry mediating reversible and bidirectional control of anxiety. ***Nature*** 471:358-62. PMCID: PMC3154022.
[3] Ferenczi E, Zalocusky K, Liston C, Grosenick L, Warden M, Amatya D, Mehta H, Patenaude B, Ramakrishnan C, Kalanithi P, Etkin A, Knutson B, Glover G & **Deisseroth K** (2016). Prefrontal cortical regulation of brainwide circuit dynamics and reward-related behavior. ***Science*** 351(6268):aac9698. PMCID: PMC4772156.
[4]Adhikari A, Lerner T, Finkelstein J, Pak S, Jennings JH, Davidson TJ, Ferenczi E, Gunaydin LA, Mirzabekov JM, Ye L, Kim SY, Lei A & **Deisseroth K** (2015). Basomedial amygdala: deep brain target of prefrontal cortex for top-down control of anxiety and fear. ***Nature*** 527:179-85. PMCID: PMC4780260.

**5) Optical tools for observing structure and function**

Optogenetic control becomes even more powerful when applied in combination with advanced technologies for observing brain circuit structure and function. In my laboratory we have worked to develop and discover such new methodologies and apply them to the same experimental subjects and settings in which optogenetic control is applied. First regarding structural investigation, the difficulty of attaining detailed structural and molecular information from intact tissues has been a key challenge in studying biological systems in general, but is particularly acute for neuroscience given the density and complexity of brain tissue. CLARITY is a technique developed in my lab to transform intact tissue into an optically transparent and permeable hydrogel-hybridized form, that can undergo immunostaining and high-resolution 3-D imaging without damage to the sample. This process allows for marking and visualization of long-range projections and subcellular structures, multiple rounds of molecular phenotyping, and is applicable to multiple tissue types and sizes with no disruption or thin sectioning required to visualize whole intact tissue samples. By clearing while preserving fine structural details, CLARITY provides a technique now in wide use, with many papers already published from other labs, for obtaining high-resolution information from complex systems while maintaining the global perspective necessary to understand system function, and we have developed advanced light-sheet and computational methodologies to collect and analyze these new kinds of intact-system data[2]. Second, we have worked on a targeted intact-brain activity-imaging method called fiber photometry (which uses fiberoptics and lock-in amplifier methods to allow quantitative detection of activity along deep brain projections)[2,3] as well as closed-loop control for collecting and feeding back these activity data through the very same fiberoptic that is delivering optogenetic control. Fiber photometry has allowed direct comparison of time-varying activity along the VTA-to-accumbens projection during social or novel-object interaction, that was then controlled optogenetically, with the predicted causal effect on social behavior[3]; we have since used this method to identify

natural and causal neural circuit dynamics of risk-taking decisions (Zalocusky et al., ***Nature*** 2016) and published a second-generation form called Frame-projected Independent-fiber Photometry (Kim et al., ***Nature Methods*** 2016) which allows multisite optical play-in/readout in behaving rodents (e.g. for matching naturally-occurring signals in the same cells). Together these advances (CLARITY and fiber photometry) have substantially advanced optical resolution of activity and structure in defined cells and projections within intact mammalian brains. We have also developed next-generation forms of CLARITY suitable for nucleic acid labeling (EDC-CLARITY; Sylwestrak et al., ***Cell*** 2016) and for automated registration of cohorts of brains with each other and online brain atlases, automated cell counting and phenotyping, and quantifying brainwide activity traffic along projections; Ye et al., ***Cell*** 2016). We have also developed new forms of light sheet microscopy (COLM or CLARITY-optimized light sheet microscopy; Tomer et al., ***Nature Protocols*** 2014) and SPED light sheet microscopy[4] to greatly advance and accelerate the collection of high-resolution structural and functional data from intact tissue including CLARITY volumes. As with optogenetics, we run training workshops in these methods to facilitate dissemination and wide application in neuroscience and psychiatry.

[1] Chung K, Wallace J, Kim S, Kalyanasundram S, Andalman A, Davidson T, Mirzabekov J, Zalocusky K, Mattis J, Bernstein H, Ramakrishnan C, Grosenick L, Gradinaru V & **Deisseroth K** (2013). Structural and molecular interrogation of intact biological systems. ***Nature*** 497:332-7. PMCID: PMC4092167.

[2] Lerner TN, Shilyansky C, Evans K, Beier KT, Crow AK, Malenka RC, Luo L, Tomer R & **Deisseroth K** (2015). Intact-brain analyses reveal distinct information carried by SNc dopamine subcircuits. ***Cell*** 162:635-47. PMCID: PMC4790813

[3] Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, Adhikari A, Lammel S, Mirzabekov JJ, Airan RA, Tye KM, Anikeeva P, Malenka RC & **Deisseroth K** (2014). Natural neural projection dynamics underlying social behavior modulation. ***Cell*** 157:1535-51. PMCID: PMC4123133.

[4] Tomer R, Lovett-Barron M, Kauvar I, Andalman A, Burns V, Grosenick L, Broxton M, Yang S & **Deisseroth K** (2015). SPED light sheet microscopy: fast mapping of biological system structure and function. ***Cell*** 163:1796-806. PMCID: PMC4775738.

**Complete List of Published Work**

http://www.ncbi.nlm.nih.gov/pubmed?term=Karl%20Deisseroth