BIOGRAPHICAL SKETCH

NAME: Daniel A. Dombeck

eRA COMMONS USER NAME: DOMBECK

POSITION TITLE: Associate Professor, Department of Neurobiology, Northwestern University

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Illinois, Urbana-Champaign, IL	B.S.	05/2000	Physics
Cornell University, Ithaca, NY	M.S.	04/2003	Physics
Cornell University, Ithaca, NY	Ph.D.	05/2005	Physics
Cornell University, Ithaca, NY	Postdoctoral	06/2005-06/2006	Physics/Neuroscience
Princeton University, Princeton, NJ	Postdoctoral	07/2006-01/2011	Neuroscience

A. Personal Statement

The major research goal of my laboratory is to determine the cellular, circuit, and plasticity mechanisms underlying the neuronal activity patterns that allow mammals to navigate within their environment. My background in physics and biophysics, along with my training under two leaders in the field, has provided me with the skills to tackle the experimental challenges of studying neuronal activity at the level of individual dendritic branches in awake behaving animals. I obtained my PhD with Dr. Watt Webb, one of the inventors of two-photon microscopy. While in his lab during my PhD work followed by a one year postdoc, I developed new non-linear optical methods for functional imaging of neural systems. My second postdoc was spent in the lab of David Tank, one of the early adapters of two-photon microscopy to study neural dynamics in vivo. While in his lab, I designed and implemented new imaging technologies that have triggered the next generation of experiments to study the neural basis of behavior. For example, I developed the first method capable of functional imaging at cellular resolution in awake, mobile mice. Prior to my work, this type of high-resolution imaging was only possible in anesthetized rodents. Building on this work, my colleagues and I in the Tank Lab then developed a visual virtual reality system for head-fixed mice that was compatible with my cellular resolution imaging techniques. Since establishing my lab at Northwestern University I have applied this unique approach to in vivo imaging (combined with powerful new genetic tools) to study the signaling of neurons in the hippocampus of mice navigating in virtual reality environments. This approach has proven fruitful in deepening our understanding of how cellular and circuit dynamics give rise to place cell firing properties.

B. Positions and Honors

Positions

2005-2006	Post-doctoral Assistant, Watt W. Webb advisor, Cornell University.
2006-2011	Post-doctoral Assistant, David W. Tank advisor, Princeton University.
2011-2017	Assistant Professor, Department of Neurobiology, Northwestern University.
2017-Present	Associate Professor, Department of Neurobiology, Northwestern University.

Honors

2001-2004	Ruth L. Kirschstein National Research Service Award (Molecular Biology NIH Training Grant), Cornell University.
2004-2005	Cellular and Molecular Neurobiology NIH Research Training Grant, Cornell
2006-2007	Neurobiology NIH Research Training Grant, Princeton University.
2007-2009	Patterson Trust Postdoctoral Fellowship Program in Brain Circuitry.
2007	Research Award for Innovation in Neuroscience, Society for Neuroscience.
2010	Searle Leadership Fund award, Northwestern University.

2010 Chicago Biomedical Consortium (CBC) Junior Investigator Award.
2011 Klingenstein Fellowship, Esther & Joseph Klingenstein Foundation.
2011 Whitehall Research Grant Award, Whitehall Foundation.
2015 McKnight Scholar Award, McKnight Endowment Fund for Neuroscience.
2017 AT&T Research Fellow.

C. Contribution to Science

- I developed the first method capable of cellular-resolution functional imaging in awake, mobile mice (Dombeck et al, Neuron 2007; Dombeck et al, J Neurosci 2009). Prior to my work, this type of high-resolution imaging was only possible in anesthetized rodents, thus my methods have extended cellular-resolution functional imaging into the realm of behavior. This has led to a revolution in using microscopy to understand brain function during behavior in the neuroscience community.

    - Dombeck DA, Khabbaz AN, Collman F, Adelman TL, Tank DW (2007) “Imaging large-scale neural activity with cellular resolution in awake, mobile mice.” Neuron 56, 43-57. (PMCID: PMC2268027).
    - Dombeck DA, Graziano MS, Tank DW (2009) “Functional clustering of neurons in motor cortex determined by cellular resolution imaging in awake behaving mice.” J Neurosci 29(44), 13751-13760. (PMCID: PMC2872549).

- I pioneered an approach combining virtual reality and cellular-resolution functional imaging (Dombeck et al, Nature Neuroscience 2009; Harvey et al, Nature 2009). Although spatial navigation is one of the most widely studied behavioral paradigms in neuroscience, before my research nearly all functional recordings of the neuronal circuitry underlying mammalian navigation involved electrode recordings. Powerful genetic and microscopy based tools had been developed to dissect and study neural circuits, but technical limitations prevented their application to the navigation circuitry. This research was the first to combine virtual reality and cellular-resolution functional imaging, thus allowing for optical studies of the navigation circuitry and use of optical based genetic tools (such as genetic cell type specific labeling and genetically encoded functional fluorescent probes). The methods allowed us to settle a long-standing debate about place cell functional organization that had existed since the cells were discovered in the 1970s: are place cells anatomically organized in the hippocampus according to their environment firing location or are they randomly organized in the hippocampus? Using our new imaging methods, we demonstrated that place cells are not functionally organized, but instead are randomly organized, in the hippocampus.

    - Dombeck DA, Harvey CD, Tian L, Looger LL, Tank DW (2010) "Functional imaging of hippocampal place cells at cellular resolution during virtual navigation." Nature Neuroscience 13(11), 1433-1440. (PMCID: PMC2967725).
    - Harvey CD, Collman FC, Dombeck DA, Tank DW (2009) "Intracellular dynamics of hippocampal place cells during virtual navigation." Nature 461(7266), 941-946. (PMCID: PMC2771429).

- My lab established the dendritic activity patterns associated with place cell formation and firing. This was accomplished by developing methods to simultaneously monitor somatic and dendritic activity in hippocampal place cells—the first recordings of this kind in any mammalian species (Sheffield and Dombeck, Nature 2015; Sheffield et al, Neuron 2017). The results from this research essentially overturned the conventional dogma of how Hebbian plasticity occurs. For decades, the Hebbian framework has dominated the landscape of proposed models for how the brain learns complex associations during behavior, defining the learning rules neurons can use to strengthen their interconnections. For example, “Classical” Hebbian models proposed that widespread regenerative dendritic mechanisms (back-propagating action potentials) provide the key informational link to inform all synapses of post-synaptic firing. In contrast, slice recordings demonstrating more local regenerative dendritic mechanisms (dendritically generated spikes) implied that learning rules may operate on a scale finer than the whole neuron. However, all Hebbian models had been operating uninformed about the uniformity or reliability of regenerative dendritic events in animals performing natural behaviors; it was

entirely unclear if the “Classical” Hebbian theory was accurate. The “dream experiment” in the field had been to visualize dendritic activity in awake behaving animals in which plasticity was actually taking place. This is exactly what we accomplished in this research; our results revealed for the first time that regenerative dendritic events do occur, across multiple branches, during behavior and learning. Our observations yielded surprising results: the dendritic events that define a neuron’s window for plasticity are far more temporally variable and spatially granular than expected. This was contrary to the textbook model of Hebbian plasticity, and went against the expectations of many experts in the field. Importantly, our results demonstrated that the process by which place cells orchestrate plasticity signals (regenerative dendritic events) are variably, rather than consistently, linked to their mode of information transmission (the somato-axonal action potential). To study the mechanisms of dendritic integration used to merge multimodal sensory information, we then developed the first olfactory virtual reality system for mice (Radvansky and Dombeck, 2018). This olfactory system allows for defining an olfactory landscape and can be used to complement our visual virtual reality simulations, either through making the simulation more immersive or by generating cue conflicts (between visual and olfactory cues). This system is fully compatible with our dendritic imaging methods, allowing for measurements of the functional tuning properties of different place cell dendritic branches to olfactory and/or visual stimuli.

- Sheffield ME, Dombeck DA (2015) “Calcium transient prevalence across the dendritic arbour predicts place field properties.” *Nature* 517, 200-204. (PMCID: PMC4289090).
- Sheffield ME, Adoff MA, Dombeck DA (2017) “Increased Prevalence of Calcium Transients across the Dendritic Arbor during Place Field Formation.” *Neuron* 96, 490-504. (PMCID: PMC5642299).
- Radvansky BA, Dombeck DA (2018) “An olfactory virtual reality system for mice.” *Nature Communications* 26, 839. (PMCID: PMC5827522)

- My lab developed the first methods capable of cellular-resolution imaging of grid cells in mammals (Heys et al, Neuron 2014). Grid cells have fascinated the general scientific community since their discovery in 2005 and grid cell research has been driven by a tight interplay between theory and experiment. Our research follows in this direction of informing network modeling with grid cell recording experiments, however, importantly, all previous grid cell recordings were made using electrode methods. This research details the first cellular-resolution imaging of grid cells in a behaving mammal and answers a long standing fundamental question about how grid cells are spatially arranged. By developing this novel imaging method, which provides information not readily available using any other technique, we provided evidence that grid cells are highly functionally arranged in the medial entorhinal cortex on the micro-circuit scale and further that nearby grid cells have similar spatial firing phase (these results and our manuscript, Heys, Rangarajan, Dombeck, were mentioned by Edvard Moser, one of the 2014 Nobel laureates in Physiology/Medicine, during his Nobel Prize acceptance speech). This micro-arrangement is consistent with the latest generation of continuous attractor network models of grid cell firing and implies that grid cells are anatomically arranged in the medial entorhinal cortex according to their network connectivity pattern. These results will be critical for establishing a micro-circuit level description of grid cell firing. Further, the methodology that we report in this research opens up an entirely new avenue for probing grid cell networks by providing high-resolution optical access to the medial entorhinal cortex with two-photon microscopy. This is important not only for studying the spatial micro-organization of grid cells, but also for allowing for the powerful combination of imaging and genetic fluorescent tools. We then applied these imaging techniques to identified a previously unknown representation of elapsed time in the medial entorhinal cortex that is largely distinct from the spatial representation in this region (Heys and Dombeck, Nat Neuro 2018).

  - Heys JG, Rangarajan KV, Dombeck DA (2014) “The functional micro-organization of grid cells revealed by cellular resolution imaging.” Neuron 84, 1079-90. (PMCID: PMC4360978).
  - Heys JG, Dombeck DA (2018) “Evidence for a subcircuit in medial entorhinal cortex representing elapsed time during immobility.” *Nature Neuroscience,* 21: 1574-1582. (PMCID: PMC6352992.)
  - Heys JG, Wu Z, Allegra-Mascaro AL, Dombeck DA (2020) “Inactivation of the Medial Entorhinal Cortex Selectively Disrupts Learning of Interval Timing.” Cell Reports, 32 (108163). (PMID: 32966784; PMCID: In progress).

- My lab has developed a novel 2-photon imaging approach, which provides unprecedented measurements of dopamine signaling in single axons innervating the mouse striatum during behavior. Using our methods, we have discovered highly unexpected dopamine dynamics that directly contradict the current widespread view of dopamine signaling. First, we show that the majority of dorsal striatum targeting dopamine axons display a robust and previously unknown phasic signal that is locked to mouse accelerations during normal, non-task dependent locomotion. Second, we show that sparse reward signaling axons are also present, but these axons do not strongly signal during locomotion, indicating a clear functional heterogeneity in the projection axon population with an inverse relationship between an axon's movement and reward responsiveness. This directly contradicts the prominent view in the field of homogeneous reward signaling across the dopamine population. Third, we reveal that the two functional axon populations originate largely from different midbrain nuclei (SNc and VTA for locomotion acceleration and reward, respectively). Fourth, we establish that dopamine signaling exhibits functional topography across the dorsal-ventral axis of the striatum, with locomotion and reward signaling dominating the dorsal and ventral striatum, respectively. Together, these results have widespread implications for dopamine signaling and will require a major rewrite of the current textbook descriptions and a rethinking of current treatment strategies for dopamine disorders.

    - Howe MH, Dombeck DA (2016) "Rapid signaling in distinct dopaminergic axons during locomotion and reward." *Nature* 535, 505–510. (PMCID: PMC4970879).
    - Poulin J-F, Caronia G, Hofer C, Cui Q, Helm B, Ramakrishnan C, Chan CS, Dombeck DA, Deisseroth K, Awatramani R (2018) "Mapping projections of molecularly defined dopamine neuron subtypes using intersectional genetic approaches." *Nature Neuroscience*, 21:1260-1271. (PMCID: PMC6342021).
    - Patriarchi T, et al (2018) "Ultrafast neuronal imaging of dopamine dynamics with designed genetically encoded sensors." *Science*, 360(6396). (PMCID: PMC62877650).
    - Howe M, Ridouh I, Allegra Mascaro AL, Larios A, Azcorra M, Dombeck DA (2019) "Coordination of rapid cholinergic and dopaminergic signaling in striatum during spontaneous movement". *Elife*. (PMCID: PMC6457892).

Complete List of Published Work:
https://pubmed.ncbi.nlm.nih.gov/?term=dombeck+da

D. Research Support

Ongoing

NIH-NIMH 2R01-MH101297 Dombeck (Role: PI) 8/16/13-1/21/24
Behavioral relevance of active dendritic mechanisms of integration and plasticity
The goal of this study is to determine the behavioral relevance of active dendritic mechanisms in the hippocampus.

NSF/NCS-FO MacIver (PI), Dombeck (co-PI) 01/2019-12/2022
How Ecology Induces Cognition: Paleontology, Machine Learning, and Neuroscience
The goal of this study is to characterize predator-prey interactions in controlled lab experiments involving virtual reality. The brain regions involved in these interactions will then be studied using imaging and targeted manipulations.

NIH-NIMH R01-MH110556 Dombeck (PI), Awatramani (PI) 3/22/17-1/31/22
Molecular, anatomic, and functional characterization of midbrain dopamine neuron subtypes
The goal of this study is to deconstruct the midbrain dopamine system into its constituent components, by identifying molecularly distinct dopamine neuron subtypes and then characterizing their anatomic projections and functional properties during behavior.

Completed

McKnight Endowment Fund for Neuroscience Dombeck (Role: PI) 7/1/15-6/30/19, Functional dynamics, organization and plasticity of place cell dendritic spines. The goal of this study is to establish the changes in synaptic strength and presynaptic activity associated with encoding new spatial memories.

NSF 1516235, CRCNS: Functional imaging and computational models of place field integration in pyramidal cell dendrites, Dombeck (Role: PI; Kath Co-PI), 9/1/15-4/31/19, The goals of the project are to develop improved computational models of dendritic place cell firing constrained by current imaging data, establish new experimental techniques to image the inputs to pyramidal cells in the dendritic tree, at single spine resolution, during place field firing and to determine the degree to which local dendritic processing is involved in place cell firing.

Simons Foundation, Dombeck (Role: PI), 3/1/15 – 2/28/18, “Optical Imaging and Manipulation of Medial Enterhinal Cortex Mid Cells”, The experiments proposed in this application tested a key prediction made by a computational model of medial entorhinal cortex whose results determined how the medial entorhinal cortex is functionally organized and how this brain region could be used in spatial navigation and spatial memory.

Whitehall Foundation, Dombeck (Role: PI), 01/2012-02/2015 “Dissecting the cellular and circuit mechanisms underlying place field firing”, The goal of this study was to determine both the mode of dendritic integration in place cells and the pattern of inhibitory input from local interneurons in order to gain a more complete understanding for why place cells fire in place fields.

Klingenstein Foundation, Dombeck (Role: PI), 07/2011-06/2015, “Two-photon imaging of dendritic integration in place cells”, The major goal of this project was to develop methods for functional dendritic imaging in behaving mice in order to characterize how place cells sum their excitatory inputs to cause place field firing.