BRITTON A. SAUERBREI

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EDUCATION

California Institute of Technology *September 2009 - December 2015*
Ph.D. in Computation and Neural Systems
Dissertation: *Firing Patterns of Cerebellar Purkinje Cells During Locomotion and Sleep*
Supervisor: Prof. Athanassios Siapas

University of Chicago *September 2005 - June 2009*
B.A. in Mathematics and Psychology

EMPLOYMENT

Postdoctoral Associate, Janelia Research Campus *January 2016 - Present*
Laboratory of Dr. Adam Hantman

PUBLICATIONS

Sauerbrei BA*, Guo J-Z*, Cohen JD*, Mischiati M, Guo W, Kabra M, et al. Cortical pattern generation during dexterous movement is input-driven. ***Nature*** 2020; 577:386-91.

Guo J-Z*, **Sauerbrei BA***, Cohen JD, Mischiati M, Graves A, Pisanello F, et al. Dynamics of the Cortico-Cerebellar Loop Fine-Tune Dexterous Movement. ***bioRxiv*** 2020; 637447. Currently in revision at ***eLife***.

Steinmetz NA*, Aydin C*, Lebdeva A*, Okun M*, Pachitariu M*, ..., **Sauerbrei BA**, ..., Harris TD. Neuropixels 2.0: A miniaturized high-density probe for stable, long-term brain recordings. ***bioRxiv*** 2020; 358291. Currently in revision at ***Science***

Sauerbrei BA, Lubenov EV, Siapas AG. Structured Variability in Purkinje Cell Activity during Locomotion. ***Neuron*** 2015; 87:840-52.

PRESENTATIONS

Talks

· Session organizer and speaker: *The motor thalamus in limb control - subcortical influences and contribution to cortical dynamics.* Annual meeting of the Society for the Neural Control of Movement, Dubrovnik, Croatia (2020). Cancelled due to COVID-19. Title of talk: *Input-driven pattern generation in mouse motor cortex during reaching.*

· Selected speaker, meeting on *Mechanisms of Dexterous Behavior.* Janelia Research Campus (2018). Title of talk: *Normal and perturbed neural dynamics in motor cortex during a reach to grab task.*

Abstracts

· **B. Sauerbrei**, J.-Z. Guo, M. Mischiati, W. Guo, M. Kabra, N. Verma, B. Mensh, K. Branson, A. Hantman. Motor cortex is an input-dependent dynamical system controlling dexterous movement. Poster. Toyama, Japan: meeting of the Society for the Neural Control of Movement, 2019.

· J.-Z. Guo , **B. Sauerbrei**, J. Cohen, M. Mischiati, F. Pisanello, K. M. Branson, A. Hantman. The pontine nuclei as a link for corticocerebellar communication in the control of dexterous movement. Program No. 227.12 / M22. Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2019.

· **B. Sauerbrei**, J.-Z. Guo, J. Zheng, W. Guo, M. Kabra, N. Verma, M. Mischiati, K. Branson, A. Hantman. Normal and perturbed neural dynamics in motor cortex during a reach-to-grab task. Program No. 587.09/QQ21. Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2018.

TEACHING AND MENTORSHIP

· Graduate program interview preparation with Brianna Ramos (California State University, Channel Islands) and Mariela Lopez Valencia (UC San Diego). Organized through the Cientifico Latino Graduate School Mentorship Initiative (2021).

· External committee member for PhD oral exam, Angel Garcia de la Garza (supervised by Prof. Jeff Goldsmith), Department of Biostatistics, Columbia University (2020).

· Mentorship of undergraduate student Matteo Alleman in the Hantman lab (2017).

· Mentorship of high school student Chase Dawson in the Hantman lab (2017).

· Teaching Assistant for Topics in Systems Neuroscience (Bi250c), California Institute of Technology (2014).

OTHER PROFESSIONAL ACTIVITIES

· Reviewer for *Proceedings of the National Academy of Sciences*, *Journal of Neurophysiology*, and *Experimental Brain Research*.

· Co-reviewer (with Adam Hantman) for *Nature*, *Cell*, *Nature Neuroscience*, *Neuron*, *eLife*, and *Nature Communications*.

· Session moderator for 13th Annual Symposium on Motor Systems, 2020.

· Session moderator for Neurolaunchpad Online Seminar Series, 2020.

REFERENCES

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Research Statement

Britton Sauerbrei

1 Background

The ability to walk over complex natural terrain is a major achievement of biological control[1]. With each stride, the muscles must generate forces that lift the limbs against gravity, send them smoothly through the air, and plant them on the ground to support the body and propel the animal forward. As step falls after step, the limbs, trunk, and head oscillate, but their rhythm is not a clockwork repetition of the same movement. Instead, each step is exquisitely adapted to the changing environment. When a lump of mud clings to the foot, the muscles must push harder against the heavier load. As the body approaches a knee-high rock, the limbs must be lofted high to clear the obstacle. This behavior is controlled by the central nervous system, which receives sensory information from the muscles, skin, vestibular system, and eyes, and generates time-varying output patterns that drive the muscles. These patterns must be precisely controlled on a timescale of tens of milliseconds: if an animal fails to provide the right amount of drive to the right muscles at the right time, it will stumble.

How do neural circuits, which in the mouse contain tens of millions of neurons distributed across many brain regions, flexibly generate these output patterns? A powerful emerging approach to this problem is to measure coordinated patterns of activity in large ensembles of neurons with the aim of defining how these patterns are generated and how they contribute to behavior[2]. In a given brain area and task, the number of variables, or dimensions, that capture the patterns of spiking activity is much smaller than the number of neurons in that area[2,3]. Each dimension is a weighted average of the firing rates of many neurons, and may be related to a specific aspect of behavior. For instance, some dimensions are related to the initiation and timing of a movement, while others reflect movement direction[4]. Activity in these dimensions evolves over time as a result both of local interactions between neurons within the region and of time-varying inputs from other brain areas[2,5,6]. Different inputs may "push" specific dimensions, shaping different aspects of neural activity during behavior.

The central goal of my research program is to identify how multiple brain regions interact to adaptively control locomotion. Individual neurons in the cerebellum[7-9] and motor cortex[10,11] are rhythmically entrained to the step cycle, while cells in the posterior parietal cortex (PPC) reflect the planning of visually-guided modifications to the gait when the animal prepares to step over an obstacle[12-14]. **I am fascinated by the open problem of how interactions between these areas generate coordinated patterns of activity in the large ensembles of neurons they contain, and how these patterns control specific movement parameters.** I plan to approach this problem by simultaneously recording the activity of many neurons in multiple areas in freely-moving animals, experimentally perturbing each region using optogenetics to test how it "pushes" specific dimensions of activity in other areas and influences behavior, and using the resulting data to develop models of the neural control system.

2 Previous Research Experience

I first developed a passion for the neural control of movement during my PhD work with Prof. Athanassios Siapas at Caltech. As I learned the art of chronic electrophysiological recording, I decided to apply this technique to the cerebellum and motor control, and we performed the first recordings of Purkinje cell simple and complex spikes during locomotion in freely-moving rodents. Although we observed, consistent with earlier work in cats[7], that each Purkinje cell had a characteristic mean firing pattern across the step cycle, we found that this pattern was rescaled or shifted in amplitude from step to step depending on the animal's speed and posture[9]. This project convinced me of the importance of step-to-step adjustments to the locomotor program, and of identifying how specific temporal features of neural activity are shaped by movement parameters.

In my postdoctoral research with Dr. Adam Hantman at Janelia, I turned to the problem of how the brain coordinates reaching and grasping in mice, a dexterous behavior requiring precise control of the arm, hand, and fingers. While it was well established that patterns of neural activity in motor cortex drove reaching through projections to the spinal cord and brainstem, it remained unclear how these patterns were generated. A prevailing model suggested that inputs to motor cortex set its initial state during movement preparation, and that local cortical circuits generated the pattern relatively autonomously during movement execution[15]. However, when we recorded from cortical populations while optogenetically perturbing thalamic inputs, we found, by contrast, that strong, time-varying input from thalamus to cortex is required throughout the movement for cortical pattern

generation and successful execution of the reach[6].

Following this work on the cortical patterns that initiate and drive reaching, I became interested in how the nervous system fine-tunes movement parameters during the behavior. In our next study[16], we focused on the neural circuit that runs from motor cortex through the pontine nuclei to the cerebellum and returns through thalamus to cortex, forming a closed loop. When we jammed the signals from motor cortex to cerebellum using optogenetic stimulation of the pontine nuclei, we found that animals were still able to initiate reaching, but their precision, accuracy, and success rate were impaired. Furthermore, when we recorded in the cerebellum and motor cortex, we found that pontine stimulation altered neural activity in both regions in a manner consistent with the effects of stimulation on hand kinematics for each mouse. Taken together, these studies have laid the groundwork for my future studies as a principal investigator, in which I will apply the same robust experimental and analytical approaches to investigate interactions between brain regions controlling adaptive locomotion.

3 Research Strategy, Years 1-5

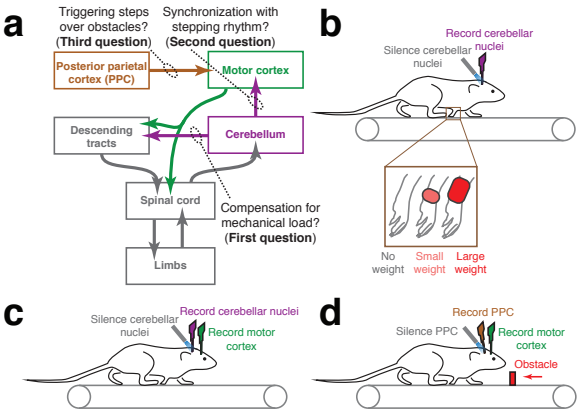

Figure 1: **(a)** Brain regions involved in the adaptive control of locomotion. Dotted lines indicate hypothesized functions, corresponding to the three questions described in the Research Strategy. **(b)** Experimental design for testing the cerebellar contribution to load compensation in mice. **(c)** Design for testing cerebellar entrainment of motor cortex. **(d)** Design for testing the role of PPC input to motor cortex in the control of steps over obstacles.

In the first five years of my research program, my lab will focus on three main questions aimed at defining how the cerebellum, cortical areas, and the body interact to achieve adaptive locomotion. These questions center on how descending signals from the cerebellum compensate for mechanical perturbations to the limbs, how ascending signals from the cerebellum pattern motor cortical activity, and how the posterior parietal cortex (PPC) modifies activity in motor cortex to coordinate steps over obstacles (see dotted lines in Fig. 1a). The **first question** I will address is: **how does the central nervous system adaptively adjust forces in the limb to compensate for changes in the mechanical load during walking** (Fig. 1b)? Previous work points to the cerebellum as a likely candidate for performing this function. During locomotion, the cerebellum receives rhythmic sensory and motor inputs from the spinal cord[17,18]. These inputs synchronize the activity of cerebellar neurons with the step cycle, and the cerebellum, in turn, imposes the stepping rhythm on descending tracts that project back to the spinal cord[18,19]. It has been proposed that this spinocerebellar loop may function as a feedback controller which fine-tunes limb forces to counteract changes in load and achieve smooth, accurate stepping[20]. I will test this hypothesis by training freely-moving mice to walk on a treadmill with bracelets of different mass attached to the wrist (Fig. 1b). I predict that as the load increases, neural activity in the cerebellar nuclei will increase in amplitude, providing stronger input to descending tracts and driving the muscles to push harder against the load. I expect this increase will be confined to neural dimensions in which activity is locked to the stepping rhythm, but will not appear in dimensions related to other factors, such as the initiation of locomotion. In addition, I predict that optogenetic stimulation of Purkinje cells, which suppresses firing in the cerebellar nuclei, will not alter the basic locomotor rhythm, but will decrease behavioral compensation for the imposed loads, reducing the amplitude of limb trajectories relative to steps with no optogenetic stimulation. **These experiments will reveal how the nervous system adaptively tunes movement parameters to compensate for external disturbances.**

The **second question** I will address is: **how is the activity of high-level brain regions, such as motor cortex, synchronized with the stepping rhythm?** Motor cortex is not thought to be essential for normal walking on a flat surface, but is required for precise placement of the limbs (e.g., during walking on a horizontal ladder) and for visually-guided steps over obstacles[20,21]. To perform this function, motor cortex must have information about the phase of the step cycle; if an animal attempts to step over an obstacle and motor cortex alters muscle activity at the wrong time, the limb will collide with the obstacle. Neurons in motor cortex, like cerebellar neurons, are rhythmically entrained during walking[10,11], but the neural circuit that drives this entrainment remains a mystery. I hypothesize that the cerebellum, which projects to motor cortex through the motor thalamus, rhythmically drives cortical activity during locomotion. To test this hypothesis, I will record simultaneously in motor cortex and the cerebellar interpositus nucleus and transiently suppress cerebellar output by optogenetically stimulating Purkinje cells (Fig. 1c). I predict that step-to-step variability in motor cortical

activity will be strongly correlated with variability in the cerebellar interpositus nucleus, and that suppressing cerebellar output will reduce the amplitude of cortical activity. Furthermore, this reduction will be confined to cortical dimensions that are rhythmically active during stepping. **These experiments will reveal the principles by which locomotion-related signals propagate from the cerebellum into the forebrain.**

The **third question** focuses on **how multiple cortical regions interact to modify the gait as the animal steps over obstacles** (Fig. 1d). Previous work has shown that during such gait modifications, motor cortex exhibits an additional "boost" in activity that is superimposed on its normal step-related pattern[10,11]. It has been hypothesized that this "boost" may be driven by input from posterior parietal cortex (PPC)[21], which is reciprocally connected with visual, somatosensory, and motor areas[22] and contains neurons that discharge as the body approaches obstacles[12-14]. I will test this hypothesis by recording from neural ensembles in motor cortex and PPC during this behavior, and predict that PPC activity will be only weakly modulated by the locomotor rhythm. However, as the animal approaches obstacles, I expect to observe large transients in parietal activity that predict the timing and amplitude of the upcoming motor cortical transients. Furthermore, I predict that optogenetic silencing of PPC will not alter the rhythmic entrainment of motor cortex during normal walking (which I expect to be driven by the cerebellum), but will erase the motor cortical transient when the obstacle arrives, causing the animal to stumble. **This line of work will reveal how interactions between cortical areas allow an animal to adaptively modify the motor pattern in a dynamic environment.**

One major challenge in carrying out this research program will be to record simultaneously from many neurons in multiple brain areas in unrestrained mice. To establish the feasibility of this approach, I chronically implanted multiple next-generation, high-density electrophysiological probes in motor cortex and cerebellum and monitored neural activity and behavior during treadmill locomotion (Fig. 2a). This enabled the recording of a large number of cortical and cerebellar neurons (Fig. 2b, lower) and tracking of kinematic parameters such as wrist angle (Fig. 2b, upper). A second challenge will be to isolate dimensions of neural activity related to specific behavioral features from the resulting data. To illustrate this approach, I adapted modern methods for neural data analysis[23] to identify two dimensions in which activity oscillates in synchrony with the stepping rhythm (Fig. 3a, red and blue arrows; Fig. 3b, red and blue traces). In a third dimension, activity is unrelated to individual steps, but signals the transition from rest to locomotion onset (Fig. 3a, yellow arrow; Fig. 3b, yellow trace). Once such specific neural dimensions have been identified, it becomes possible to test how inputs from different brain regions drive these dimensions using optogenetic manipulations. For instance, because I hypothesize that the cerebellum drives step-related activity in motor cortex, I predict that optogenetic suppression of cerebellar output will attenuate the entrainment of motor cortex to the stepping rhythm, reducing the amplitude of the oscillations in the step-related cortical dimensions (c.f. **the second question**).

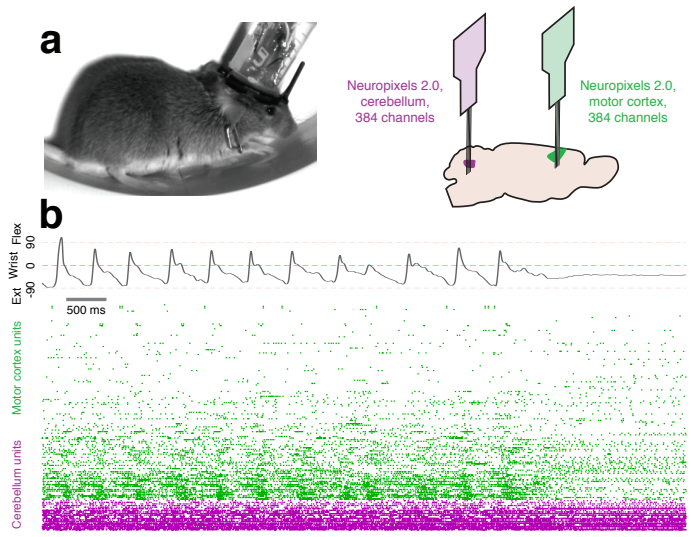

Figure 2: preliminary data demonstrating the feasibility of large-scale, multi-area, chronic recording in freely-moving mice. **(a)** Left: video frame showing unrestrained mouse walking on a treadmill. Right: location of Neuropixels 2.0 probes implanted in the left hemisphere of forelimb motor cortex and the right cerebellar paravermis and interposed nucleus. Each probe has four shanks and 3072 recording sites, and allows simultaneous acquisition from 384 channels. **(b)** Upper: wrist angle during a bout of locomotion. Lower: spike rasters from simultaneously-recorded cortical (n=122) and cerebellar (n=19) neurons.

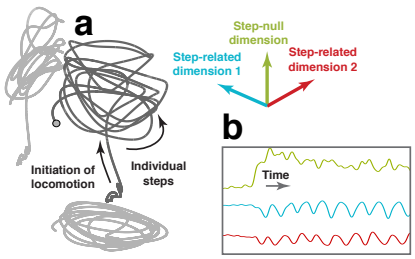

Figure 3: Preliminary data demonstrating the isolation of specific dimensions of mouse motor cortical activity. **(a)** Three-dimensional trajectory of neural population activity during walking. Each dimension in this space is a weighted average of the firing rates of 122 neurons. Movement along the step-related dimensions indicated by the red and blue arrows is locked to the locomotor rhythm; each step generates a rotation in the plane spanned by these two dimensions. The dimension indicated by the yellow arrow, on the other hand, is not related to the step cycle. Instead, the neural state moves upward along this dimension when the animal transitions from rest to walking. **(b)** The same data from **(a)**, where each of the three dimensions is now plotted against time. The red and blue dimensions oscillate with the stepping rhythm, while the yellow dimension increases at locomotion onset, but is not modulated by the stepping rhythm.

4 Research Vision, Year 6 and beyond

By the end of the fifth year of my research program, we will have identified how cerebellar and cortical areas interact to control several aspects of adaptive locomotion. These brain regions, however, do not function in isolation from the rest of the nervous system; rather, they receive extensive sensory input and project to the spinal cord

through monosynaptic and polysynaptic routes. Following year five, we will build on our earlier work to achieve three basic research goals. **First, we will determine how proprioceptive sensory inputs shape cerebellar population activity and influence adaptive locomotion**. The cerebellum receives proprioceptive signals related to the forelimbs and hindlimbs from the external cuneate nucleus and the dorsal nucleus of the spinal cord, respectively[24]. We will use large-scale recording in the cerebellar nuclei in conjunction with optogenetic and behavioral perturbations to determine how sensory signals influence specific dimensions of cerebellar output, and how these dimensions drive or fine-tune limb kinematics during locomotion. **Second, we will determine how the nervous system translates visual information about upcoming obstacles and information about the state of the limbs into a motor plan for stepping over the obstacles**. It has been proposed that the posterior parietal cortex (PPC) integrates signals from visual cortex, which represent object motion and distance, with signals from somatosensory cortex, which convey the limb and body state, to plan the step over the obstacle[21]. We will test this hypothesis by recording PPC population activity, identifying distinct dimensions of this activity that represent the object and the body, and testing the contribution of visual and somatosensory cortical inputs to these specific PPC dimensions and behavior by optogenetically silencing these inputs. **Third, we will define how the output of the cerebellum and motor cortex is transformed downstream in the reticular formation and red nucleus, which receive cortical and cerebellar input, project to the spinal cord, and are strongly modulated during locomotion and visually-guided gait modification**[25-27]. Taken together, this body of work will allow us to build a model of how sensory inputs influence specific dimensions of neural population activity, how activity propagates across cortical, cerebellar, and brainstem regions, and how interactions across brain circuits enable adaptive control of movement parameters in locomotion.

Once we have developed this model of the neural control system in healthy mice, we will use it to **identify possible intervention points and deep brain stimulation treatment strategies for spinocerebellar ataxia (SCA)**, a spectrum of neurodegenerative diseases that affects approximately 150,000 Americans. SCA results in the loss of neurons in multiple CNS regions, particularly the cerebellar cortex and its inputs, leading to a profound loss of coordination in walking and other movements. Several mouse models of SCA have been developed, which recapitulate key features of the disease pathology and phenotype, including gait abnormalities[28-31]. Our approach will first seek to **identify the specific deficits in neural activity that link pathology to phenotype, revealing possible intervention points for treatment**. We will identify which brain areas exhibit abnormal activity patterns in ataxic animals relative to healthy controls, and quantify the magnitude of these abnormal patterns in specific dimensions of neural activity. For instance, we predict that the exaggerated upward movement of the limbs during the swing phase in Purkinje cell degeneration (pcd)[31] and Lurcher[9] mice is caused by abnormally high levels of activity in flexor-related dimensions of activity in the red nucleus and reticular formation. After identifying these possible intervention points, we will **attempt to restore normal movement in ataxic mice by correcting the aberrant activity pattern** using real-time tracking of limb kinematics and closed-loop control of excitatory and inhibitory optogenetic actuators in sites that drive limb- or muscle-group-specific motor synergies[32-34]. In the case of pcd and Lurcher animals, this might be achieved by selectively silencing flexor-facilitory populations during swing to reduce the vertical overshoot of the limb. In the next stage of research, we will attempt to **develop a preclinical mouse model** using electrical microstimulation, which is more suitable for clinical applications than optogenetics, and targeting stimulation sites in motor cortex, which projects directly to midbrain, brainstem, and spinal centers and is more easily accessible in human neurosurgery. Finally, after achieving these goals, we will **collaborate with clinicians at the translational stage to apply our approach to the treatment of ataxic gait in human patients**.

5 References

[1] Bernstein, 1935 (trans. Pergamon Press, 1967). [2] Shenoy et al., Ann. Rev. Neurosci, 2013. [3] Yu et al., bioRxiv, 2017. [4] Kaufman et al., eNeuro, 2016. [5] Churchland et al., Nature, 2012. [6] Sauerbrei et al., Nature, 2020. [7] Armstrong et al., J. Physiol., 1984a. [8] Armstrong et al., J. Physiol., 1984b. [9] Sauerbrei et al., Neuron, 2015. [10] Beloozerova & Sirota, J. Physiol., 1984. [11] Drew, J. Neurophysiol., 1993. [12] Andujar et al., J. Neurophysiol., 2010. [13] Beloozerova & Sirota, J. Neurophysiol., 2003. [14] Marigold & Drew, eLife, 2017. [15] Pandarinath et al., J. Neurosci., 2018. [16] Guo et al., bioRxiv, 2020. [17] Arshavsky et al., Brain Res., 1972. [18] Arshavsky et al., Springer, 1984. [19] Orlovsky, Brain Res., 1972. [20] Orlovsky et al., Oxford, 1999. [21] Drew & Marigold, Curr. Op. Neuro., 2015. [22] Hovde et al., Eur. J. Neurosci., 2019. [23] Kaufman et al., Nat. Neurosci., 2014. [24] Oscarsson, Physiol. Rev. 1965. [25] Lavoie & Drew, J. Neurophys. 2002. [26] Drew et al., J. Neurophys. 1986. [27] Prentice & Drew, J. Neurophys. 2001. [28] Cendelin, Cerebell. Ataxias 2014. [29] Perdomini et al., J. Neurochem. 2013. [30] Fortier et al., Exp. Brain Res. 1987. [31] Machado et al., eLife 2015. [32] Orlovsky, Brain Res. 1972. [33] Drew, J. Neurophys. 1991. [34] Rho et al., J. Neurophys. 1999.