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14. ABSTRACT
The goal of this proposal was to determine how brain networks are modulated during learning and performance of skilled tasks. We used cutting-edge techniques to measure brain activity at the level of individual neurons and cortical networks, as mice learn and perform visual discrimination tasks. These studies revealed distinct "channels" of information in different neurons, and demonstrated that these channels undergo specific patterns of modulation corresponding to learning and task engagement. Our findings suggest novel targets for intervention to improve human task performance, as well as novel computational mechanisms that could be implemented to improve robust performance in machine vision systems.

15. SUBJECT TERMS
Skill learning; task engagement; attention; cognitive performance; neuromodulation

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Final technical report

Large-scale neural circuits underlying skilled task performance
N00014-16-3154

Cristopher M. Niell
University of Oregon

Major goals

Performing a skilled task requires coordination of neural computation across brain-wide circuits. Although research in cognitive neuroscience has revealed psychological principles of task learning and has localized specific cognitive functions to particular brain regions, our understanding of skilled task performance at the neural level lags far behind. Two primary reasons for this are the challenge in studying direct neural activity in humans with non-invasive measures, and the limitation of invasive animal studies to observing activity in relatively limited brain regions. However, recently developed techniques for observing and manipulating neural activity in mice, combined with training on specific visual tasks, can overcome these obstacles.

In particular, we have implemented a combination of imaging methods that allow us to directly observe the flow of neural activity brain-wide networks, then zoom in to key regions to measure dynamics of neural activity across hundreds of individual neurons simultaneously. Notably, both of these imaging modalities can be performed during learning and performance of different visual tasks. Furthermore, novel computational methods allow us to analyze the high-dimensional activity patterns in large populations of neurons as a subject learns and performs a task. Finally, using optogenetic techniques we can manipulate activity in putative control circuits to test their role in skill learning and task performance.

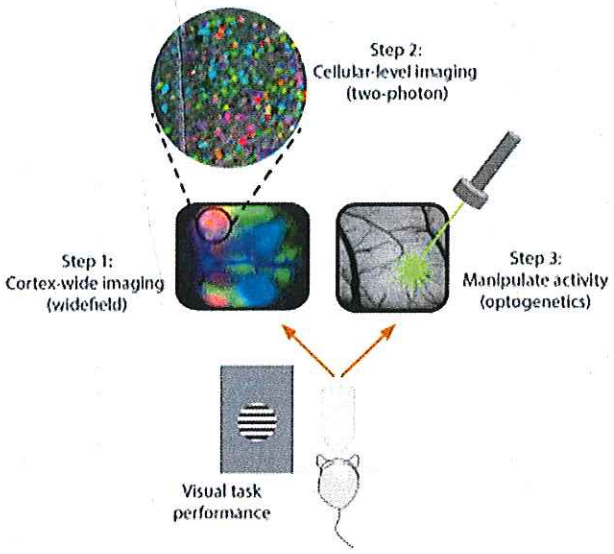

Figure 1. Schematic of technical approach. Widefield imaging is used to identify brain areas that show significant changes in activity, which can then be targeted for cellular-level 2-photon imaging and modulated by optogenetic stimulation.

Together, these approaches allow us to investigate neural function from the level of brain-wide networks down to activity in individual neurons, along with the ability to causally test the insight gained from neural recordings. In this project, we will use this approach in two aims that address key aspects of skilled task performance.

Project 1: How is sensory information encoded and routed appropriately based on learning of specific tasks?

Project 2: How is cortical information flow disrupted during lapses in performance?

Answering these basic research questions at the neural level will greatly expand our understanding of how the brain functions to enable learning and performance of a wide range of tasks. Importantly, these studies can also lead to direct impact on human task performance, by enabling the development of training strategies or technological and pharmacological interventions to target the neural circuit mechanisms that we identify. Finally, incorporating the high-dimensional dynamics we observe in vivo into in machine learning systems may provide a means to increase robust performance, particularly across multiple tasks.

Accomplishments under goals

We previously implemented novel methods to image neural dynamics across multiple length scales – from the entire brain down to individual neurons. Furthermore, optogenetics allows precise manipulation of activity in specific sets of neurons. In this project, our goal was to apply these approaches in 3 stages, summarized in Figure 1.

In our previous results, we used widefield imaging to identify cortical areas that change activity following learning of the location discrimination task, with the most significant being a decreased activation in primary visual cortex, V1 (Figure 2). This led us to target V1 for two-photon recordings during performance of the task.

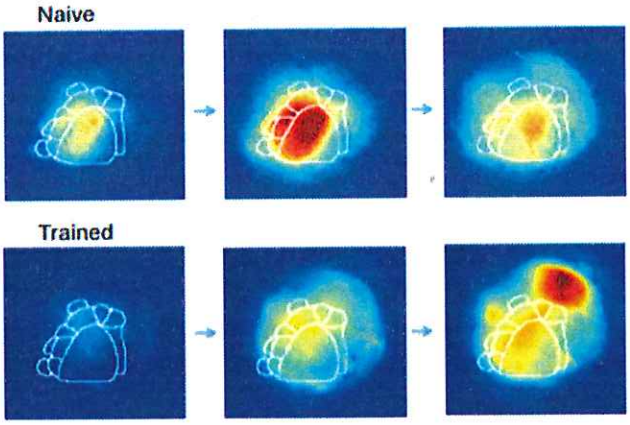

Figure 2. Widefield imaging of changes in cortical activity over learning. Activation of visual cortical areas during performance of a visual task (100, 200, and 300sec after stimulus onset) in trained vs naïve animals, showing decreased activation in visual areas after learning, accompanied by increased activation in sensorimotor areas.

Two-photon imaging of large populations during the location task revealed that neuronal responses could be clustered into three primary groups, which we termed "channels", based on the temporal dynamics of their response (Figure 3). We can thereby reduce the dimensionality of the population response by analyzing the weighted sum of response in these three clusters.

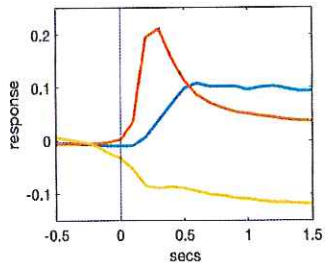

Figure 3. Three channels of visual information in V1. Based on clustering of cellular responses, we identified three channels with different temporal response dynamics to the visual stimulus – transient (red), sustained (blue), and suppressed (yellow).

Furthermore, each of these channels has distinct tuning for visual stimulus features and behavioral state. In particular, the "sustained" neurons carry the most information about the visual stimulus, the "suppressed" cells are modulated by alertness, and we expect that the "transient" cells may be signaling salience or novelty.

Using this channel-based analysis to study the changes over learning, we found that the decreased activation after learning observed in widefield imaging appears to be due to reduced activity in the population that responds transiently to stimulus onset (Figure 4). We hypothesize that this may reflect a reduction in nonspecific activation by the stimulus, preserving visual coding and behavioral state control.

We next trained mice on two additional tasks, an orientation discrimination and a non-discrimination task where mice are randomly rewarded. The first task revealed similar changes to previous location discrimination task, so we have restricted our subsequent analysis to the location task. The randomly rewarded task, which we refer to as "experienced", serves as a comparison for mice that have experienced the same visual stimuli over the same timecourse (one hour per day for several weeks) but do not learn an explicit rule. In this task we found that both transient and sustained populations showed a decrease over learning, suggesting that in the absence of learning a specific rule information about the stimulus itself is also reduced as a result of repeated visual stimulation.

We also performed imaging and data analysis to measure the response of trained mice during passive viewing of visual stimuli, to determine how neural activity is modulated by task engagement. This was a straightforward extension of our learning experiments, that complements the plans to study lapse trials explicitly. This revealed that all three channels had greater activity during task performance.

Together, these findings provide one of the first demonstrations of how different aspects of sensory information are encoded across the learning of a task, and how this information is modulated by repeated visual stimulation and by task engagement. These results have now been published online at bioRxiv, and are under revision at Journal of Neuroscience.

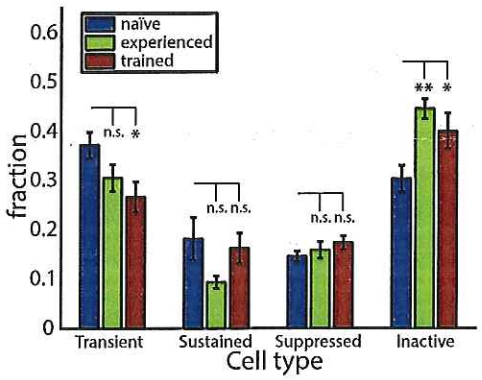

Figure 4. Changes across training for distinct cell types. Following learning of a discrimination task, the fraction of transient cells decreases, representing a specific modulation of one channel of information.

In the most recent period, we began to focus on novel analysis methods that will allow us to extract information relevant to neural network and machine vision models. In particular, these networks often do not include dynamics, so we seek to measure how activity and information encoding evolve over time, both within a trial and across learning. Furthermore, advanced machine learning systems deployed in complex environments may have to switch dynamically between tasks. Therefore, we are also examining how dynamics are impacted by task engagement to see how the biological network switches on and off of a task.

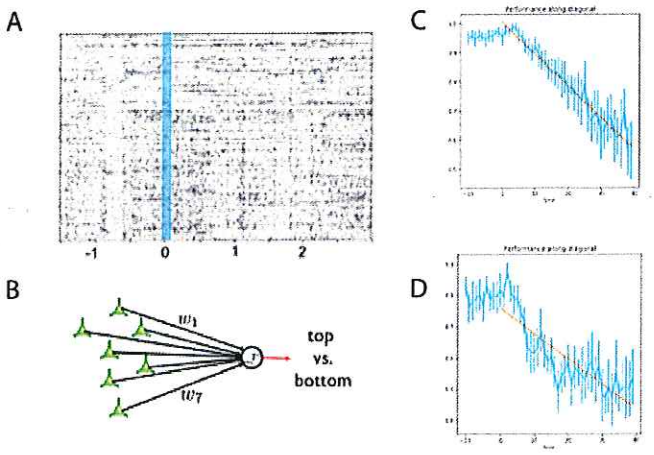

Figure 5. Decoding information encoded across a trial. Responses across the population at a specific timepoint (A) are used to train a linear decoder to classify stimulus properties (B). Following offset of the stimulus, information about the stimulus location is maintained (C), whereas information about orientation rapidly declines (D).

In collaboration with Dr. Yashar Ahmadian, a theoretical neuroscientist at University of Oregon, we have now implemented two different computational approaches – information decoding, and Poisson Linear Dynamical Systems (PLDS). The decoding approach allows us to measure the information represented in a large population of neurons, and how

this representation changes over time. To achieve this, we train a linear decoder to "read out" task variables, such as stimulus location/orientation (Figure 5A,B) The accuracy that the decoder can achieve provides a measure of the degree to which this task variable is explicitly represented in the population, and the weights of the decoder describe how it is represented. Using this approach, we have found that information about the visual stimulus location persists in the neural activity even after the end of the trial, when animal has made its response and the stimulus is no longer on the screen (Figure 5C). However, information about stimulus orientation rapidly decays (Figure 5D).

We can also test whether the population code for this stimulus information changes, by training a decoder at one timepoint and testing another (Figure 6A). This has demonstrated that the coding constant while stimulus is on the screen, but that this representation switches and becomes more dynamic (Figure 6B). Thus, the neural coding for a visible stimulus is different from the persistent activity after the stimulus is no longer present. is up, but switches and becomes more dynamics after.

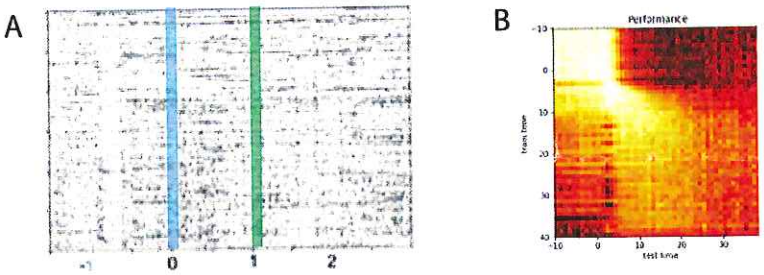

Figure 6. Dynamics of information encoding across time. A) The linear decoder is trained on population activity at one point (blue) and then tested on activity at another timepoint (green). B) Comparing performance across timepoints reveals that the information representation is constant while stimulus is present, while it shifts dramatically and becomes more dynamic after stimulus offset.

We have also implemented a PLDS approach, which provides a means to reduce the dimensionality of the neural activity, but in a way that respects the dynamics of the system. This method models the activity of a large population as a set of latent variables, which have interaction dynamics and can be driven by the visual input. Applying PLDS has shown different trajectories in a low dimensional space for different trial / stimulus conditions (Figure 7). The advantage of this method over other dimensionality reduction approaches is that we can now examine not only how the composition of the components changes over learning, but also how the dynamics that describe how they interact and evolve over the course of a task trial.

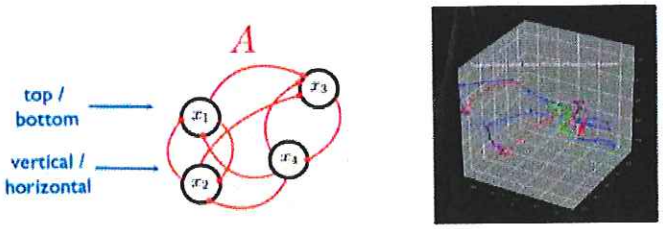

Figure 7. Poisson Linear Dynamical Systems (PLDS). This approach models the neural population activity as a set of latent dimensions representing weighted sums of neurons. The activity in these populations evolves following dynamics described by a matrix A. Right) Visualization of three dimensions shows distinct trajectories for different trial types.

During this most recent period, we also acquired additional data with pupil diameter in addition to neural activity, during behavior. We will use this in the analysis above to define behavioral lapses, as complement to error rate and reaction time measures. We also implemented a method stimulating serotonergic axons, which we hope to apply in future projects.

Future Goals

Although this is the end of the 3-year funded period for the Young Investigator Award, there are a number of promising directions that could be pursued in future projects. In particular, the unique signatures of different information channels could be implemented into computational approaches for machine vision. In particular, we expect that this may make them more robust during learning, particularly in complex visual scenes that real brains evolved for. Additionally, the approach we developed here could be applied to understand other brain regions and circuitry that has implications for improving intelligent sensing. In particular, mechanisms of predictive learning that have been proposed to be mediated by the pulvinar would be amenable to direct observation through our large-scale recording techniques.

Results dissemination

Publications

This work has been published online and is currently in revision at Journal of Neuroscience.

Wekselblatt JB and **Niell CM.** (2019) Distinct functional classes of excitatory neurons in mouse V1 are differentially modulated by learning and task engagement. *bioRxiv* doi.org/10.1101/533463

Presentations

PI Niell gave invited talks on this work at the following conferences and seminars

Conferences

2019	UT Austin - Natural Environments, Tasks, and Intelligence workshop
2018	CSHL Banbury workshop – Why does neocortex have layers?
2018	Pitt / CMU Neuro-learning Workshop
2018	Emory University – Mechanisms of Learning Forum
2017	European Visual Cortex Meeting – keynote speaker
2017	Allen Institute Summer Workshop - The Dynamic Brain

Seminars

2019	Fralin Medical Institute – Pioneers in Biomedical Research seminar
2019	Washington University ophthalmology seminar series
2018	Mt Sinai Friedrich Brain Institute seminar series
2018	University of Louisville seminar series
2018	Max Planck Florida seminar series
2018	CSHL Neuro seminar series
2018	UCSD Neuroscience seminar series
2017	OHSU Vollum Institute seminar series
2017	Champalimaud Institute seminar series

Honors and awards

2017	Medical Research Foundation of Oregon New Investigator Award (Niell)
2017	Promotion to Associate Professor with tenure (Niell)

Opportunities for training and development

N/A

Technology transfer

N/A