Caltech Statement of Purpose
Neuroscience, PhD
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My path into neuroscience began with the realization that people can share a room yet experience entirely different worlds. In *[redacted]*, I worked with a first-grader named *[redacted]*, who saw doors and train tracks mapped across the ceiling tiles, guiding him through patterns invisible to the rest of us. Later, when my *[redacted]* began experiencing psychosis, I watched him whisper to voices no one else heard and scrub spilled milk into the floor to "keep us safe from harm". These experiences showed me that perception is not a passive process but an active construction shaped by circuits. Individuals may share an environment yet form distinct internal models that govern how they perceive evidence, assign value, and update beliefs. **I want to understand how these models change across aging and disease, and expand our ability to study them by integrating genomic insights to improve molecular tools.**

To investigate these mechanisms, I turned to mice. Their conserved cortical circuits allow us to measure how learning unfolds in real time, and their decision-making changes across age in ways that mirror our own. I began with development, a period when both behavior and its supporting circuits transform rapidly. In the Sabatini Lab, I studied how the maturation of inhibitory signaling in prefrontal cortex reshapes behavior.

I hypothesized that as animals mature, their approach to strategies for optimizing outcomes in a changing environment would shift from immediate, outcome-driven choices to more stable strategies. To test this, I trained mice from adolescence through adulthood on a two-armed bandit task (2ABT), where thirsty animals choose between probabilistic rewards that reverse in an uncued manner. Using a computational framework developed in the lab, I quantified variables guiding choice and found that **adolescents rely heavily on recent outcomes, whereas adults integrate evidence across longer histories.**

I next asked whether these behavioral differences arise from developmental changes in prefrontal circuitry. We focused on the prelimbic cortex (PL), the rodent analog of primate prefrontal cortex and a region required for strategy updating. Our group had shown that parvalbumin-positive (PV) interneurons exert progressively stronger inhibition onto PL pyramidal neurons from adolescence to adulthood. Whether this affects strategy was unknown. To test this, we transiently reduced PV activity in adult mice using chemogenetics and found that their gameplay reverted toward adolescent patterns. **This work, now in review, provides causal evidence that developmental changes in cortical inhibition shape decision strategy.**

I next examined whether PV interneuron activity during decision-making naturally differs across age. If inhibitory maturation supports more stable behavior, PV activity should shift in parallel with task strategy. I examined this possibility using dual color fiber photometry in PL, recording population excitatory activity and attempting to measure inhibitory signals during 2ABT. Excitatory signals were robust, but the reporter in inhibitory neurons did not yield useful signals,

preventing direct comparison of activity across cell types. I troubleshot viral integrity, optical alignment, autofluorescence, hemodynamics, and surgical parameters before confirming a failure of viral expression. Though disappointing, the process taught me how to diagnose complex experimental pipelines and reminded me that understanding failures can be as valuable as success. Still, the excitatory signals revealed an age-dependent pattern. During the reward encoding window, pyramidal activity in response to reward decreased with maturation. Although inhibition could not be measured directly, the data together indicate that **maturation of prefrontal circuitry alters reward encoding and drives the behavioral shift.**
Based on these observations during mouse development, I hypothesized that as these circuits continue to age, further reductions in reward responsiveness could contribute to the cognitive rigidity observed later in life. Therefore, I led a longitudinal study tracking behavior across the lifespan. Over three years, I collected >3 million 2ABT trials from mice spanning early adulthood (P90) through late aging (P750). Using the same behavioral modeling framework, I found that reinforcement strength (the parameter in our model that describes the weight given to recent outcomes) declined in the 18-24-month period. As each reward had less influence, animals updated their choices less often, adopting increasingly stereotyped strategies. This progressive rigidity reflected a loss of flexibility that extended beyond what cortical maturation alone could explain.

Because reinforcement strength depends on dopaminergic signaling in the nucleus accumbens (NAC), I investigated dopamine dynamics during aging. Using GRABDA sensors, I found that dopamine tracked recent reward history and that encoding strength varied across individuals. I then used fluorescence-lifetime photometry, which measures tonic and phasic dopamine independently of expression level. Preliminary analyses reveal that **tonic dopamine declines across adulthood while phasic responses remain stable, suggesting that older animals may still detect rewards but reach thresholds for updating behavior less frequently**. I am now using a lifetime-based PKA reporter to measure the intracellular signaling threshold at which dopamine drives plasticity, and manipulating this threshold to test causality. **This work remains ongoing and was recently presented at SfN2025.**

Extending this work highlighted a key methodological limitation: computation arises not from any single population but from *distributed* interactions. Standard optogenetic/chemogenetic tools can test a population's necessity, but offer limited insight into how processes unfold *across* interacting cell types. **New tools capable of perturbing gene programs across cell populations are needed to match the distributed architecture revealed by modern genomics.**

To learn viral and protein engineering, I joined George Church's lab and developed scalable viral genome engineering strategies that enable coordinated, multiplexed manipulation. My current work focuses on *[redacted]*. *[redacted]* enable therapeutic strategies for complex genetic disorders that cannot be addressed with current AAV or lentiviral tools, representing a translational direction that has become increasingly important to me.

Together, these perspectives shape my PhD goal. I hope to **understand how neuromodulators reshape distributed circuits to build and update internal models of action, affect, and social meaning**, and to **develop molecular tools that allow these processes to be read out and repaired with precision.**

Professor Viviana Gradinaru's work is the closest match I have found to the scientific future I hope to build. Her CREATE paper was one of the first viral engineering studies I read closely, and it showed me that delivery can be engineered rather than accepted as a fixed limitation. That insight shapes how I now think about my own platform. Although *[redacted].* What further draws me to Professor Gradinaru's lab is that her work extends far beyond delivery. She has built an integrated set of technologies that includes systemic, BBB-bypassing AAVs, spatial transcriptomic profiling of vector tropism, and advanced optical tools for reading and modulating neural activity. I want to learn from first principles how optical modulation can be improved, how gene transfer across the BBB can be made selective and scalable, and how these tools can deepen the neuromodulatory questions that motivate my neuroscience. In her lab, I hope to contribute as both a neuroscientist and engineer. My goal is to help develop next-generation, high-capacity platforms with refined tropism and reliable transcriptional behavior, and then use these technologies to investigate and eventually repair the distributed neuromodulatory circuits that shape maladaptive behavior in disease.

Professor David Anderson's work offers the complementary opportunity to investigate how internal states are computed at the circuit level. His studies of persistent defensive states in the hypothalamus and amygdala, and of Tac2-dependent states under chronic isolation, highlight mechanisms I want to test directly. I am curious whether tonic dopamine shifts the thresholds for entering or exiting these defensive and anxious states, and whether sustained changes in basal dopamine alter the persistence or generalization properties his lab identifies as emotional primitives. Additionally, I want to examine whether biased prediction error signals lead animals to over-assign threat to ambiguous cues, and whether these distortions may map onto specific microcircuits in the VMH, lateral septum, or extended amygdala. These hypotheses fit closely with my broader aim of identifying how neuromodulatory changes coordinate across distributed circuits to give rise to biased inference and affective symptoms of psychiatric conditions.

Together, these groups provide an ideal setting for my questions and goals. I would be grateful for the opportunity to contribute to Caltech's research community.