Carnegie Mellon University

Annual Progress Report: 2010 Formula Grant

Reporting Period

July 1, 2013 – June 30, 2014

Formula Grant Overview

The Carnegie Mellon University received $860,191 in formula funds for the grant award period January 1, 2011 through December 31, 2014. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Research Program in Sensory Computation - Sensory systems allow humans and other species to collect information about the world. Our brains then integrate information from a variety of sensory modalities with stored information to generate our beliefs about what is happening around us. For many kinds of stimuli – e.g., written words, voices, faces, smells – humans are much better at interpreting stimuli than any machine ever created. Our goal is to understand the kinds of computations that underlie our remarkable abilities to interpret complex stimuli. Improving our understanding of such sensory computations will allow us to better understand brain disorders that involve abnormal perception (such as hallucinations observed in epilepsy or schizophrenia or the heightened sensitivity to certain stimuli seen in autism) and also possibly to engineer devices to improve perceptual abilities in individuals who have impaired vision, audition or other sensory systems.

Duration of Project

1/1/2011 – 12/31/2013

Project Overview

Our long term goal is to understand how human sensory systems are able to collect, process and integrate information about the world. This process happens in the face of a highly variable and noisy sensory world, as well as in the face of growth, degradation and damage of peripheral sensory structures. Even the most sophisticated artificial sensory systems, such as airport scanners and face and speech recognition software fail or require human intervention when stimuli are embedded in noise or distorted. Human and animal sensory systems cope with or even exploit the variation seen in real world objects and conditions to improve their performance in a way that is unmatched by artificial systems.

The specific hypothesis that we plan to investigate is that the diversity in the individual neurons and in local neuronal circuits improves the brain's ability to effectively extract information from

sensory stimuli. This hypothesis highlights the differences between machines, in which variations in hardware degrade performance, and brains, where we have evidence that variation in neuronal properties reduces performance. We will address this hypothesis by experiments and analysis designed to achieve the following specific aims:

Aim 1: To understand how differences in the properties of cortical neurons contribute to accurate stimulus encoding in a variety of sensory systems.
Aim 2: To understand how trial-to-trial differences in neuronal responses influence performance in sensory systems.

In both these aims, in addition to collecting the data, we will develop approaches for using machine learning and information theoretic analyses to determine how the variability in neuronal responses contributes to or limits processing of sensory information.

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Expected Research Outcomes and Benefits

Understanding and treating the root causes of brain disorders requires an understanding of brain function and the relationship between brain function and perceptual and cognitive abilities. Many brain disorders include perceptual deficits as primary or secondary symptoms. Auditory hallucinations are a key symptom in schizophrenia, visual disturbances and auras are common in migraines, and olfactory and somatosensory abnormalities are commonly associated with seizures. Autism and dyslexia involve highly specific deficits in face and word recognition, respectively, along with abnormal sensitivities to certain kinds of stimuli. Many stroke and traumatic brain injury patients experience abnormalities in sensory perception. In some cases, these perceptual symptoms are among the most prominent and debilitating (such as the voices heard in schizophrenia), whereas in other cases they are not (such as in seizures). Nonetheless, in all cases perceptual symptoms can readily be studied both in patients and also in animal models of disease and thus can provide important insights into cellular and circuit level abnormalities that may be common across many brain areas. The proposed work will allow us to generate models of how diverse types of neurons and circuits are harnessed to improve perceptual abilities, especially in the context of discrimination and recognition of complex stimuli. We believe that understanding these models of perception will provide insights into the causes of and treatments for perceptual symptoms of many brain disorders.

Summary of Research Completed

Aim 1 in the original proposal was to "To understand how differences in the properties of cortical neurons contributes to accurate stimulus encoding in a variety of sensory systems."

In pursuit of this aim we have undertaken a large scale effort to quantify differences in the properties of neurons from a variety of brain areas by a large number of electrophysiological recordings. Specifically, the goals of this work were to develop a large data set of electrophysiological properties from many types of neurons in order to determine 1) the cell-type to cell-type differences that may determine how different neuron types may respond to different stimulus properties and 2) to provide information that would facilitate the specific collection of additional physiological data on neuronal properties.

By generating such a data-driven "parts list" of the brain we hope to provide scientists efficient access to available data on the properties of different neuron types so that mechanisms of reliability and stimulus coding can be efficiently studied. Generation of such a neuronal parts list, along with their properties will be a critical step in evaluating how sensory responses are generated in the brain and how computations are performed on these sensory representations. Currently, data on the properties of these neurons are effectively impossible to obtain without substantial effort and domain-specific expertise. We have developed methods for recording and compiling these data in highly standardized ways from many neurons in a variety of brain areas. Use of such a parts list will further help standardize both the characterization of new neuron types and the comparison of properties between control and manipulated animals

In the original proposal, the milestones for the past year were to work on and publish papers on "the mechanisms underlying neuron-to-neuron and trial-to-trial variability and describing models of how these sources of variability could contribute to deficits in sensory perception." Below we describe our progress toward this milestone.

In the past funding year, we collected and aggregated information on key biophysical properties and the experimental conditions under which they were collected for a variety of neuron types in the mammalian brain. After populating the database with our electrophysiological recording data, we assessed how experimental conditions systematically influence electrophysiological measurements across neuron types. We then explored the emergence of both intuitive and unexpected groups of neuron types according to commonalities in their biophysical properties and patterns of gene expression (as reported in the literature). As we indicated in the original proposal, "A key to our approach is that we use a combination of experimental methods that allow the collection of large data sets and also the most advanced analytic tools available to understand the relationship *between* activity and the stimuli that are presented."

Methods:

Mice with the C57BL/6 background were used in this study. Postnatal day 13–20 mice of both sexes were anaesthetized with isoflurane and decapitated into ice-cold oxygenated dissection solution containing (in mM): 125 NaCl, 25 glucose, 2.5 KCl, 25 NaHCO3, 1.25 NaH2PO4, 3 MgCl2 and 1 CaCl2. Brains were rapidly isolated and acute horizontal, sagittal and oblique slices

(310″ μm thick) of the MOB were prepared using a vibratome (VT1200S; Leica, Nussloch, Germany, or 5000 mz-2; Campden, Lafayette, IN, USA). Slices recovered for 15–30 min in ~37°C oxygenated Ringer solution that was identical to the dissection solution except for lower Mg2+ concentrations (1 mM MgCl2) and higher Ca2+ concentrations (2 mM CaCl2). Slices were then stored in room temperature oxygenated Ringer solution until recording.

Principal neurons in various areas were identified by: (1) cell body size, (2) cell body position within the relevant layer, (3) the presence of an apical and other dendrites consistent with classical classification schemes for the cell types being recorded.

Slices were continuously superfused with 37°C oxygenated Ringer solution. Cells were visualized using infrared differential interference contrast video microscopy. Whole-cell recordings were made from individual cells using electrodes filled with (in mM) 120 potassium gluconate, 2 KCl, 10 Hepes, 10 sodium phosphocreatine, 4 Mg-ATP, 0.3 Na3GTP, 0–0.2 EGTA, 0–0.25 Alexa Fluor 594 (Life Technologies, Carlsbad, CA, USA) and 0.2% Neurobiotin (Vector Labs, Burlingame, CA, USA). The liquid junction potential was 12–14 mV and was not corrected for. Cell morphology was reconstructed under a 100× oil-immersion objective and analyzed with Neurolucida (MicroBrightField, Inc., Williston, VT, USA). Data were low-pass filtered at 4 kHz and digitized at 10 kHz using a MultiClamp 700A amplifier (Molecular Devices, Sunnyvale, CA, USA) and an ITC-18 acquisition board (Instrutech, Mineola, NY, USA) controlled by custom software written in Igor Pro (WaveMetrics, Lake Oswego, OR, USA).

Results:

We have performed analyses on a variety of different neuron types (See figure 1) along with a more in depth analysis on a smaller set of neurons – namely mitral and tufted cells. These cell types, which are secondary sensory neurons, show similar properties, but differ in their excitability and their regularity of firing. To analyze the differences in stimulus coding properties of these neuron types we performed analysis of the responses of these neuron types to identical stimuli. Visual inspection of spiking patterns evoked by identical steady state current injections showed that mitral cells and tufted cells differ in their regularity of firing, in addition to their rate. This irregular firing, sometimes referred to as "stuttering" also seemed to differ between mitral and tufted cells. Specifically, TCs fired clusters of high-frequency action potentials separated by long ISIs between clusters (Fig. 2B). In contrast, MCs exhibited comparatively similar within-cluster and between-cluster inter-spike intervals (ISIs) (Fig. 2A). In other words, the instantaneous firing rate of TCs departed substantially from the mean rate for each spike train, while the instantaneous firing rate of MCs more closely tracked the mean rate. To quantify this effect, we calculated the instantaneous ISI variability normalized to the instantaneous ISI and averaged this across the spike train to yield a single value per spike train. This metric, called 'CV2' (where CV stands for coefficient of variation) is equivalent to the CV of the interspike interval for a regular spike train and for a perfectly random spike train (i.e. a homogeneous Poisson process) but is lower than CVISI for a slowly rate-modulated spike train (e.g. a spike train with highly discrete bursts). Confirming our initial observations, MCs exhibited nearly identical CVISI and CV2 (Fig. 2F). In contrast, TCs exhibited a markedly higher CVISI than

CV2 (Fig. 2H), especially at higher input strengths. Thus, the greater overall firing irregularity of TCs compared to MCs arises from a greater propensity of TCs to fire highly discrete clusters of action potentials. These clusters represent a kind of all-or-none firing that we believe decouples tufted cell firing from fast fluctuations in the stimuli, resulting in reduced capacity for coding of fast fluctuating stimuli.

We extended these experiments by identifying a type of ion channel that is responsible in part for the stuttering behavior of these neurons and blocking it. This is consistent with our proposed milestones having to do with sources of variability. We found that low concentration of 4AP – a blocker of A-type potassium channels, reduces stuttering, reduces trial to trial reliability and reduces the amount of information encoded in a spike train about a particular fluctuating stimulus. The magnitude of this reduction is about 20% in mitral cells and we predict that it will be somewhat higher in tufted cells, given their stronger propensity to fire in a stuttering fashion and evidence that they express higher densities of A-channels.

Aim 2: To understand how trial-to-trial differences in neuronal responses influence performance in sensory systems.

During the last funding period work completed on Aim 2 consisted of analysis of data on the properties of trial-to-trial reliability in human subjects performing sensory discrimination tasks. Stimulus strength, duration and familiarity were varied to determine their influence on the reliability of these responses. The goals of these analyses have been to develop models that explain the connection between neuron-to-neuron and the trial-to-trial variability to improve sensory discrimination (per the proposed milestone for 7/1/13-6/30/14).

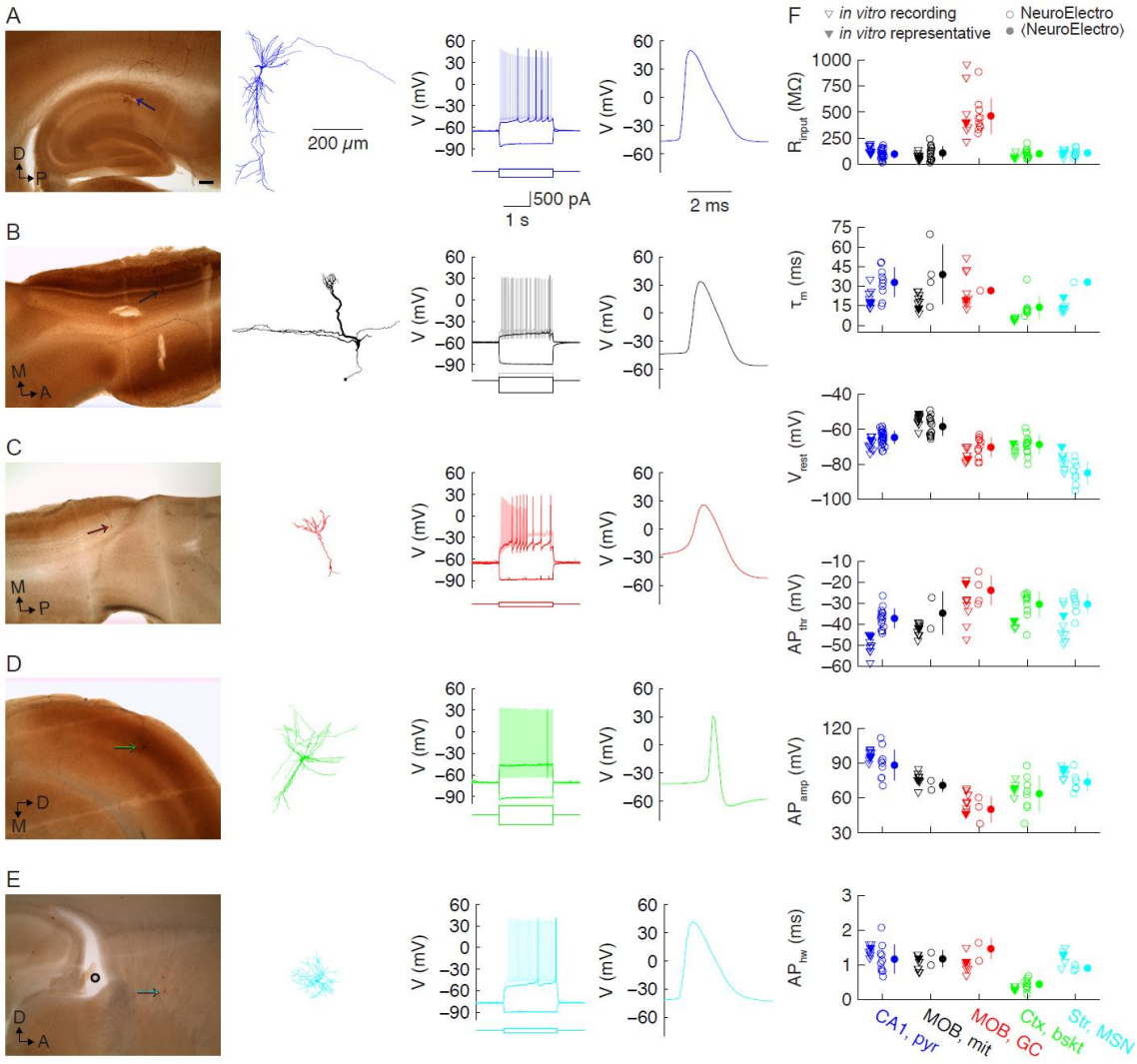

Figure 1: Validation of measurements of neuronal diversity by collecting data from 5 types of neurons.

A: Representative targeted recording of a hippocampal CA1 pyramidal cell ("CA1, pyr"), showing anatomical position and morphological reconstruction (left), response to hyperpolarizing and depolarizing rheobase and suprathreshold step current injections (middle), and action potential waveform (right). Anatomical scalebar: 200 μm.

B-D: Same as A for: main olfactory bulb mitral cell (B; "MOB, mit"), main olfactory bulb granule cell (C; "MOB, GC"), neocortical basket cell (D; "Ctx, bskt"), and striatal medium spiny neuron (E; "Str, MSN").

F: Summary of targeted in vitro recordings and comparison to text-mined, metadata-adjusted values from NeuroElectro. Abbreviations: dorsal (D), posterior (P), medial (M), anterior (A). Morphological reconstructions (except the representative granule cell) have been moderately thickened to aid visualization of thinner processes.

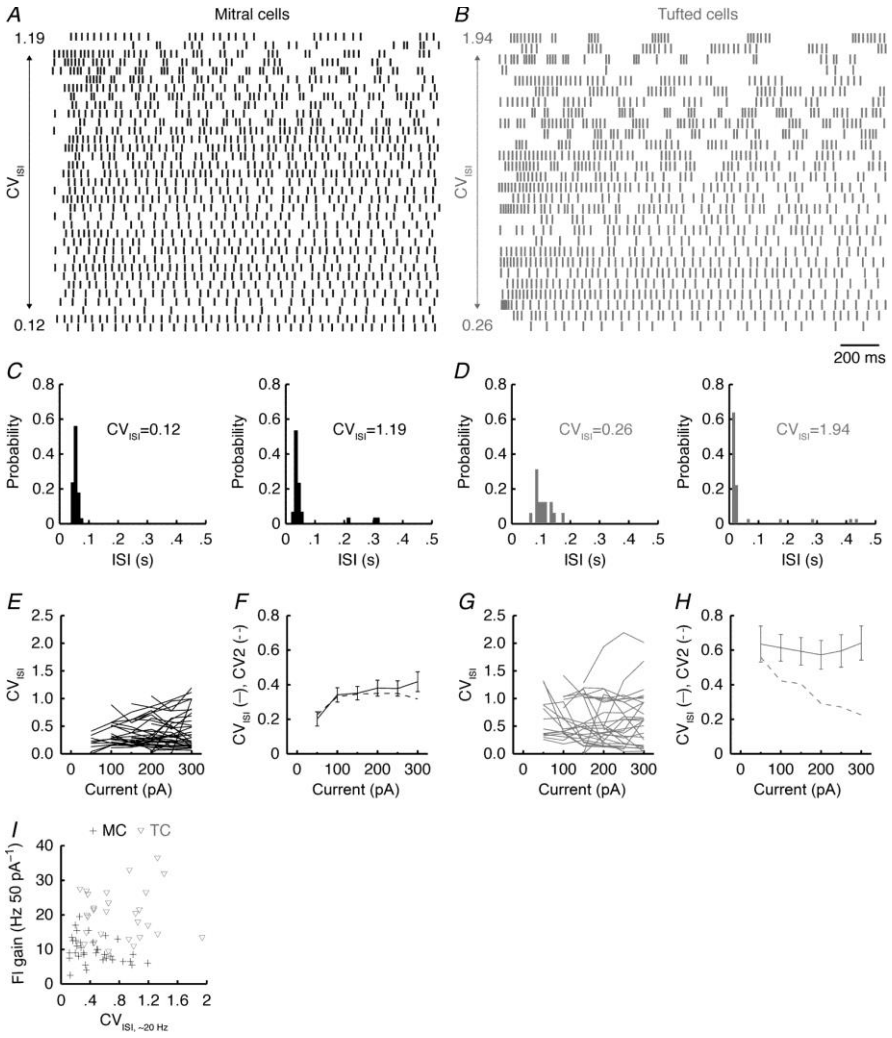

Figure 2. TCs exhibit diverse firing modes and more irregular firing than MCs

A & B: spike raster plots across 35 MCs (A) and 28 TCs (B) for firing responses to 2 s step current injections coming closest to 20 Hz. Spike trains are ordered according to CVISI, with minimum and maximum CVISI values shown.

C & D: ISI distributions of the most regular and irregular MC (C) and TC (D) spike trains shown in A and B.

E: CVISI across multiple step current injection amplitudes for MCs.

F: average CVISI across all MCs for multiple step current injection amplitudes. Error bars denote SEM.

G & H: as in E and F for TCs. Note that TCs demonstrated a significantly higher CVISI than MCs (compare F and H; $P = 5.8 \times 10{-}9$, two-way ANOVA with post hoc Tukey's test). Note also the close correspondence between the average CVISI and CV2 for MCs (F) but not for TCs (H).

I: FI curve gain vs. CVISI across MCs and TCs.