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Sensory Representation of Stimulus Features in the Rodent Whisker-Responsive Trigeminal Brainstem

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Abstract

Sensorimotor integration is a general term to describe how task-specific motor output is generated from the selective and rapid processing of sensory and motor information. The rodent vibrissal (whisker) system is an important model for the study of sensorimotor integration and active tactile sensing. This research uses the rodent vibrissal system as a model to study sensorimotor integration at the level of the brainstem.

Angular tuning is a property of whisker-sensitive neurons that describes the way a neuron responds when a single whisker is stimulated in a preferred direction. While this property can partially inform how individual whisker deflections shape the neural response to multi-whisker deflections, the study of global motion can sometimes be more ethologically relevant to the type of stimulation that a rodent experiences across the array. Specifically, my thesis investigates how neurons of the trigeminal brainstem encode stimulus speed and the extent to which they exhibit tuning for the direction of global motion. Direction of global motion tuning could aid in whisker-mediated orientating behaviors. The thesis reviews the literature on speed, angular tuning, and direction of motion tuning, and describes novel experiments to assess speed and direction of global motion tuning.

Experiments on the vibrissal system often require highly repeatable stimulation of multiple whiskers and the ability to vary stimulation parameters across a wide range. The stimulator must also be easy to position and adjust, while providing real time information about whisker contact. Developing a multi-whisker stimulation system that meets these criteria remains challenging. We describe a novel multi-whisker stimulator to assess neural sensitivity to the direction of global motion. The device can generate repeatable, linear sweeps of tactile stimulation across the whisker array in any direction and with a range of speeds. A fiber optic beam break detects the interval of

whisker contact as the stimulator passes through the array. We demonstrate the device's function and utility by recording from a small number of multi-whisker-responsive neurons in the trigeminal brainstem. Neurons had higher firing rates in response to faster stimulation speeds; some also exhibited strong direction-of-motion tuning. The stimulator complements more standard piezoelectric stimulators, which offer precise control but typically stimulate only single whiskers, require whisker trimming, and travel through small angles. It also complements non-contact methods of stimulation such as air-puffs and electromagnetic-induced stimulation. Tradeoffs include stimulation speed and frequency, and the inability to stimulate whiskers individually. The stimulator could be used – in either anesthetized or awake, head-fixed preparations – as an approach to studying global motion selectivity of multi-whisker sensitive neurons at multiple levels of the vibrissal-trigeminal system.

Acknowledgments

It takes a village to raise a child. No truer words have been spoken; kids are wild. The totally 'I-just-made-this-up' adage "It takes a village to get a PhD" also holds true. These past few weeks I've been reflecting on my seven-year journey in the academy and all of my musings boil down to one question: Was it worth it? Honestly, I don't know, and I may not know for a while. What I do know is that there are so many people in my life who have made this possible.

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List of Abbreviations

SpV …… spinal trigeminal nucleus

SpVi …… spinal trigeminal subnucleus interpolaris

SpVir …… rostral portion of the spinal trigeminal subnucleus interpolaris

SpVic …… caudal portion of the spinal trigeminal subnucleus interpolaris

SpVo …… spinal trigeminal subnucleus oralis

SpVc …… spinal trigeminal subnucleus caudalis

PrV …… principal trigeminal nucleus

VPM …… ventral posterior medial nucleus of the thalamus

PoM …… medial posterior nuclear group in the thalamus

TPR …… toe pinch reflex

DSI …… directional sensitivity index

PSTH …… peristimulus time histogram

Dedication

To my family.

For without you, I am nothing.

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Chapter 1: Introduction

1.1 Sensorimotor Circuits of the Whisker System

The exploration and navigation of an environment requires a sensory system that samples enough information from that environment to rapidly extract meaning from behaviorally relevant features and guide specific needs. For instance, the tactile guidance of prey capture via the rapid orienting and localization behavior is the consequence of fast motor control circuits that allow animals to detect, track, and orient towards an external moving stimulus. How sensory organs control the input they receive and determine which input is most relevant to behavior is a vital question in sensory physiology. This is best studied through the lens of sensorimotor integration.

Sensorimotor integration is a process by which sensory and motor information are rapidly integrated to produce task-specific motor output. This process can also involve the extrapolation of the features to unknown conditions and the cancellation of sensory expectation in the case of distinguishing self-generated movement from external stimuli (Curtis and Kleinfeld, 2006). The central nervous system integrates different sources of stimuli, and in parallel, transforms these inputs into motor actions. One excellent model for the study of sensorimotor integration is the rodent vibrissal system.

The rodent vibrissa (whisker) system is one of the most valuable models for the study of active tactile sensing and sensorimotor integration (Ahissar and Kleinfeld, 2003; Bosman et al., 2011; Kleinfeld and Deschenes, 2011). It is an anatomically well established and well-organized system that gives rise to complex behaviors. The whisker system is an ideal system to study sensorimotor circuits because it heavily relies on sensor movement to gather sensory information from the environment, integrates it with motor information, and guide animal movement. The whiskers themselves are specialized, tactile hairs that provide accurate somatosensory input via

the existence of mechanoreceptors at their follicles (Bosman et al., 2011). During exploratory behaviors, rats actively sweep their whiskers through space and across objects in a behavior known as “whisking” (Berg and Kleinfeld, 2003; Carvell and Simons, 1990; Welker, 1964). The classical description of a whisk cycle is a protraction followed by a retraction back to the rest position on the caudo-rostral plane, generating unique kinetic signatures of whisker vibrations when contact is made on a surface (Arabzadeh et al., 2005). During exploratory behaviors, rats make large whisker movements at a frequency of 5-15Hz and when they’ve contacted an object of interest, these movements become smaller and increase their frequency to 15-25Hz (Bosman et al., 2011). Rats produce spatiotemporally complex sequences of tactile contacts during whisking which they use to discriminate between objects (Jacob et al., 2008). The signals that occur at the level of the whisker convey sufficient information to the animal to be able to distinguish between objects of different shapes and textures.

There are five horizontal rows composed of 30 distinct whiskers that are arranged in a grid-like manner on each side of the rat’s snout (Fig. 1.1; Belli et al., 2018; Brecht et al., 1997; Brecht et al., 2006; Towal et al., 2011; Simons et al., 1983). One can identify each whisker using a unique letter-number combination corresponding to its row, A to E from dorsal to ventral, and column identified as numbers starting at 1 from caudal to rostral with four straddlers between rows named alpha, beta, gamma, and delta, from dorsal to ventral. Tactile information is acquired through this array and is represented in a robust and expressive way in whisker-sensitive circuits.

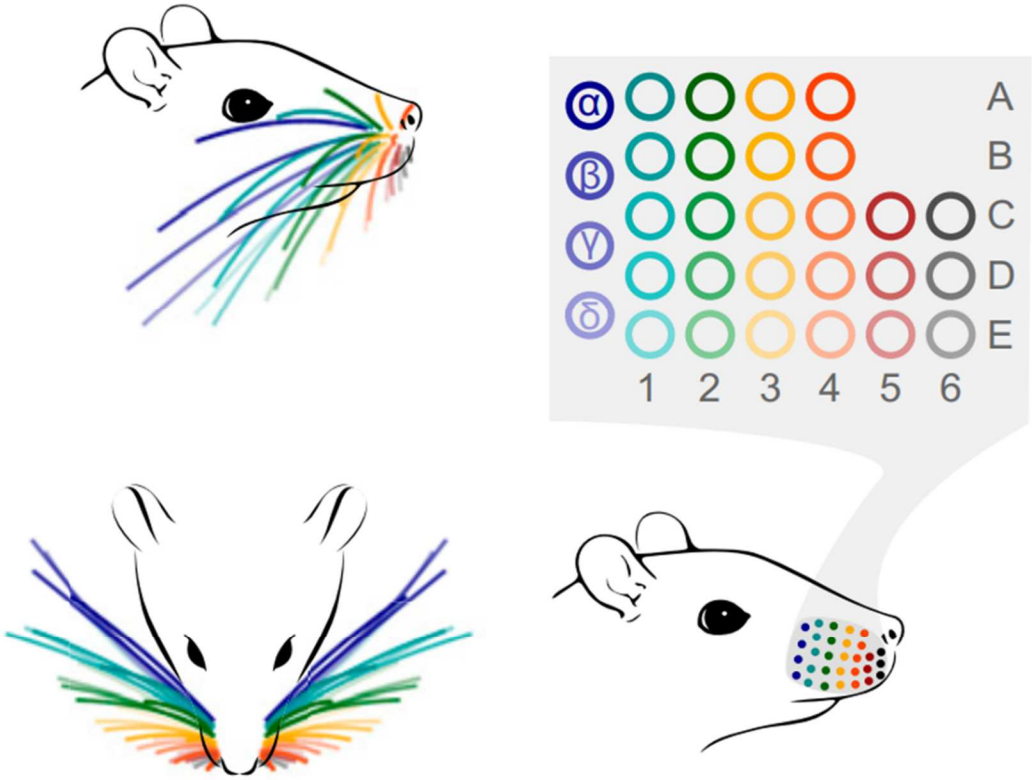

Figure 1.1 - A schematic depicting the rat whisker array. The whiskers are organized in rows (A to E) and columns (1 to 6) with straddler whiskers caudal to and in between rows that are denoted by Greek letters (α, β, γ, δ). Figure from Zweifel, 2021.

This arrangement of the vibrissal pad is mapped in the same grid-like manner at every step along the whisker pathway.

At every stage of processing, there are anatomical and functional topographic maps of whiskers (Fig. 1.2). These clusters are referred to as “barrels” in the cortex, “barreloids” in the thalamus, and “barrelettes” in the brainstem. While there are multiple maps in the thalamus and cortex, this work focuses on the trigeminal brainstem. Because of this topographic arrangement, the whisker system in rodents has become one of the most important models of research in sensory physiology and it allows us to study sensorimotor integration at different levels of the brain.

The structure that anchors a whisker within the skin is called a follicle. Each whisker is embedded in a follicle in the skin on the rat’s face and it gives tactile sensitivity and motion to the whisker. The follicles are surrounded by a dermal blood sinus which is thought to aid in modulating the dynamic range of the whisker (Bosman et al., 2011; Gottschaldt et al., 1973). Whiskers have no sensors along their length. Instead, each vibrissal base is embedded within a follicle that is densely innervated by the peripheral branches of about 200-300 cells of the trigeminal ganglion (Vg) (Ebara et al., 2002; Rice, 1993; Rice et al., 1997; Rice et al., 1986), and have mechanoreceptors that transduce vibrissal deformations into electrical signals that are sent to the Vg (Bush et al., 2016a; Bush et al., 2021; Campagner et al., 2016; Jones et al., 2004; Leiser and Moxon, 2007; Lichtenstein et al., 1990; Severson et al., 2017; Szwed et al., 2006).

Vg neurons are the primary sensory neurons of vibrissal tactile sensing. The cell bodies of these neurons make up the Vg (Bosman et al., 2011) and their peripheral axons innervate one whisker (Kerr & Lysak, 1964; Zucker &Welker, 1969). Vg neurons encode single whisker deformations, meaning that every whisker-responsive cell in Vg responds to the movement of one

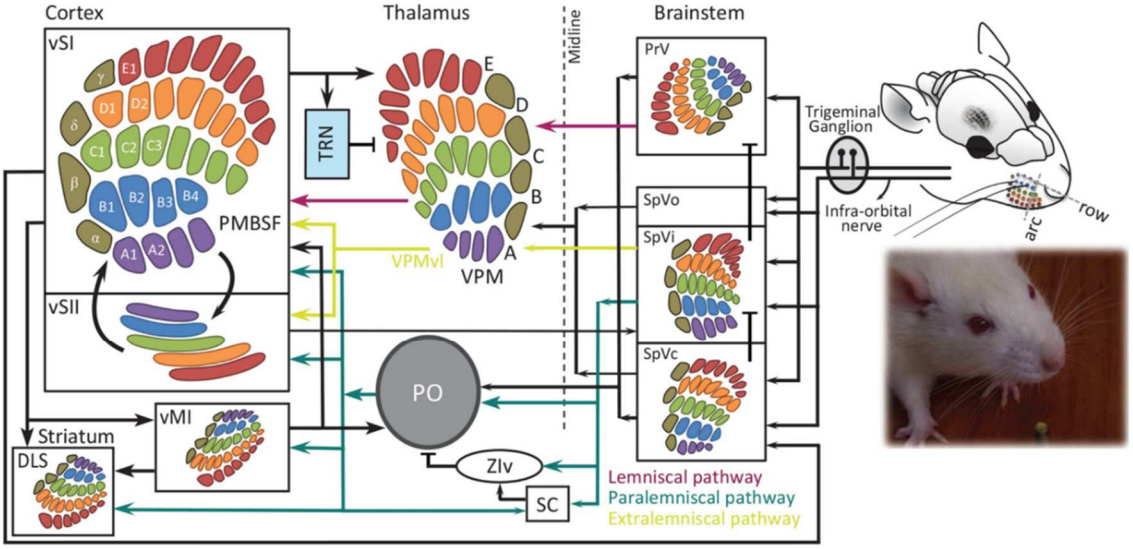

Figure 1.2 – Schematic representation of somatotopy in the whisker-barrel system. At every stage of processing, one can identify anatomical and functional topographic maps of whiskers. These clusters are referred to as "barrelettes" in the brainstem, "barreloids" in the thalamus, and "barrels" in the cortex. Figure from Adibi, 2019, based on the original figure from Durham and Woolsey (1984).

and only one whisker. Different Vg units show various tuning properties with sensitivity to parameters such as direction of whisker deflections and motions, acceleration, and amplitude, which all provide information regarding how these features are represented further along the pathway. The responses of these first-order neurons with their single-whisker receptive fields, constrain all subsequent somatosensory processing.

Signals from the Vg then ascend via multiple parallel pathways through the trigeminal brainstem, thalamus, and cortex (Ahissar and Kleinfeld, 2003; Bosman et al., 2011). The whisker-sensitive nuclei of the trigeminal brainstem are the first processing stage in the rodent vibrissal system. The trigeminal sensory nuclei are made up of two different nuclei: the principal trigeminal nucleus (PrV) and the spinal trigeminal nucleus (SpV) which is further divided into three subnuclei – oralis (SpVo), interpolaris (SpVi), and caudalis (SpVc). Most projections to the thalamus occur through three pathways that originate in these nuclei.

The first is the lemniscal pathway. This pathway, which is thought to be responsible for tactile discrimination (Carvell and Simons, 1990; Krupa et al., 2001b; Ebara et al., 2002; Arabzadeh et al., 2003; Moore et al., 2015), arises from the PrV, projects to the contralateral dorsomedial portion of the ventral posterior medial nucleus (VPMdm) of the thalamus (Erzurumlu et al., 1980; Hayashi, 1980), and terminates in the granular zone of the cortical barrel field (Deschenes et al., 2005). This pathway predominately conveys single-whisker input (Bosman et al., 2011). The second pathway, which is thought to be involved in localization and orienting behaviors (Knutsen et al., 2006; Mehta et al., 2007; O'Connor et al., 2010), is the paralemniscal pathway which originates from the rostral portion of SpVi (SpVir), travels through the medial posterior nuclear group in the thalamus (PoM) and terminates with multiple collaterals in the

dysgranular zone of the cortical barrel field (Bosman et al., 2011). This pathway conveys multi-whisker input to higher structures (Bosman et al., 2011). The third pathway is the extralemniscal pathway. This pathway originates in the caudal portion of SpVi (SpVic), projects to the ventrolateral VPM (VPMvl), and continues to the somatosensory cortices (Pierret et al., 2000). The input of this pathway originates from multi-whisker cells, though its function has yet to be elucidated (Bosman, et al., 2011). These trigemino-thalamo-cortical pathways play a central role in the sensory information processing of whisker movements.

Projections from the trigeminal brainstem travel to many different parts of the brain, most notably the lateral facial nucleus. The lateral facial nucleus neurons can evoke either the protraction of a single whisker or the retraction of multiple whiskers (Herfst and Brecht, 2008). Motor commands are delivered to whisker muscles via the facial nerve by the motor neurons located in the lateral facial nucleus (Ashwell, 1982; Klein and Rhoades, 1985; Herfst and Brecht, 2008; Dörfl, 1985; Haidarliu et al., 2010). While other connections to the lateral facial nucleus will not be discussed here, the convergence of those inputs with that of motor commands allow for the integration of whisker movements (Bosman et al., 2011).

The vibrissal-trigeminal loop, which goes from the whisker to the trigeminal ganglion to the trigeminal nuclei to the lateral facial nucleus to whisker muscles, is thought to be responsible for reflexive whisker retraction upon encountering a novel tactile stimulus (Tsur et al., 2019). We are interested in how this circuit is involved in whisker-mediated localization and orienting behaviors; specifically, how trigeminal brainstem neurons respond to global motion. Global motion is an apparent motion in a given direction when several whiskers are stimulated together (Jacob et al., 2008). Information about global motion is acquired through multiple whiskers (Jacob

et al., 2008). Quantifying global motion tuning is an approach towards understanding the neural basis for behaviors such as orienting (Arkley et al., 2014; Cohen et al., 2008) and gating incoming sensory input (Chakrabarti and Schwarz, 2018; Furuta et al., 2010; Urbain and Deschenes, 2007).

Most neurons in central vibrissal-sensitive structures integrate information from multiple whiskers, and it is a long-standing experimental challenge to quantify their integrative properties (Benison et al., 2006; Cohen et al., 2008; Deschenes et al., 2003; Goldin et al., 2018; Jacob et al., 2008; Jacob et al., 2017; Jouhanneau et al., 2014; Le Cam et al., 2011; Lyall et al., 2021; Pluta et al., 2017; Rodgers et al., 2006; Timofeeva et al., 2004; Veinante and Deschenes, 1999; Whitmire et al., 2021). To quantify these neurons' integrative properties, it would be useful to have a stimulation tool that could deliver repeatable stimuli to multiple whiskers, that allowed stimulation parameters to be varied across a wide range, that detected contact with the whiskers, and that was easy to position. The present work describes the construction and validation of a stimulation system that meets these requirements.

Understanding how trigeminal brainstem neurons encode tactile information from multiple whiskers is essential for understanding how that integration occurs in higher brain structures and how the vibrissal-trigeminal circuit represents the external world.

1.2 Studying Global Motion in the Vibrissal-Trigeminal System

To understand the integrative properties of vibrissal trigeminal neurons, we must first understand the type of stimulus that evokes these responses, specifically, the motion of whisker deflection that evokes this activity. Researchers have studied these whisker motions at the level of a single whisker, multiple whiskers within a receptive field, and multiple whiskers across the array. Each level informs how neurons in the vibrisso-trigeminal pathway collect, integrate, and pass along whisker motion information.

To investigate whisker motion at the level of a single whisker, researchers often turn to the property of angular tuning. Angular tuning is the angle to which an individual whisker needs to be deflected in order for the neuron to respond optimally. Although a stimulus may move multiple whiskers in the same general direction, individual whiskers will be deflected against the stimulus in very different directions based on their geometry and orientation. Researchers typically investigate the property of angular tuning using a piezoelectric stimulator to passively stimulate the trimmed whisker of an anesthetized rat while recording single units in the whisker-barrel circuit (Bellavance et al., 2010; Furuta et al., 2006; Timofeeva et al., 2003; Bruno et al., 2003). For instance, using this method, Bruno and colleagues demonstrated that angular tuning could be found not only in primary afferents, but in thalamic and cortical neurons as well, meaning this property is conserved at every level of the whisker pathway (Bruno et al., 2003). Angular tuning experiments tell us that whiskers are very sensitive to the direction they are pushed in at the level of a single whisker. However, angular tuning has not been investigated in the behaving animal, so its ethological relevance is unclear (Bruno et al., 2003). In the behaving animal, multiple whiskers

are typically used when exploring. This led researchers to wonder if the neuron would respond in the same way if all whiskers in its receptive field were deflected in the same direction.

Direction tuning is the consistency of angular tuning across the receptive field of a neuron. It is assessed for multiple whiskers and asks whether the direction of motion that elicits the largest neural response is the same for all the whiskers in the receptive field of the neuron. For instance, the neurons in SpVi have been shown to integrate inputs from multiple whiskers and they have large, elliptical shaped receptive fields of up to about 15 whiskers. So, it is important to understand if the neuron responds in similar ways when the whiskers are being deflected in the same manner across the receptive field. The approach to studying direction tuning is quite similar to that of angular tuning, except that with direction tuning, researchers systematically evaluate the neuron's response to the deflection of each and every whisker in the neuron's receptive field. In their 2006 paper, Furuta and colleagues investigated the directional tuning of neurons in the SpVi. They found that the directional tuning of SpVir cells was not conserved across the receptive field, which while surprising, indicated that there is the integration of whisker motion signals from multiple whiskers that are then conveyed to higher level brain structures (Furuta et al., 2006). These studies shed light on response properties of neurons along the vibrisso-trigeminal pathway and informed us of how individual whisker deflections shape the neural response to multi-whisker deflections. As researchers began performing more behavioral studies within the whisker system, it opened up questions of how behaviorally relevant these multiple whisker deflections are.

Global motion tuning is the sensitivity of a neuron to an apparent motion in a given direction across the whisker array (Jacob et al., 2008). It is assessed for the entire whisker array, and it asks whether there is a global motion across the whisker array that will evoke the largest

response from a neuron. Because global motion deflects whiskers in similar ways as they would be deflected if they encountered a complex, natural stimulus, it could potentially give us insight into the integrative properties of neurons in the pathway. The structure of multi-whisker receptive fields is stimulus dependent (Vilarchao et al., 2018) so it is important that we are able to quantify stimulus properties to truly understand their impact on neural responses.

When discussing "global motion," researchers often point to the 2008 study done by Jacob et al. where they used multi-whisker motion patterns across the array to investigate how barrel cortex neurons combine and extract information from the whisker pad (Jacob et al., 2008). They evaluated eight different global directions and demonstrated that barrel cortex neurons are indeed tuned to the global direction of a tactile stimulus, further supporting the notion that tactile perception is dependent on the neural representation of the collective features of a stimulus (Jacob et al., 2008). Another study that looked at global motion in the barrel cortex was done by Vilarchao and colleagues who investigated the cortical integration of multi-whisker inputs in response to global motion (Vilarchao et al., 2018). They were interested in whether barrel neurons extracted the global properties of complex tactile inputs and they found that these neurons were able to extract global motion direction information from a multi-whisker, moving stimulus (Vilarchao et al., 2018). These studies have demonstrated that the cortical response of whisker sensitive units to multi-whisker stimulation depends heavily on the direction of global motion.

Global motion has also been studied at different levels of the whisker-barrel pathway. Ego-Stegnel and colleagues studied whether VPM neurons demonstrate global motion tuning in response to multi-whisker stimuli (Ego-Stengel et al., 2012). They tested the response of VPM neurons to global motion in eight different directions and found that their responses not only

depended on the direction of global motion, but these neurons selectively increased their firing rate during their preferred stimulus direction (Ego-Stengel et al., 2012). Studies of global motion tuning in the trigeminal brainstem have also been done. In their work investigating speed and direction coding in the trigeminal brainstem, Kaloti et al. used a global motion stimulus to generate an overall direction of deflection across the array (Kaloti et al., 2016). They passed a vertical post through the whisker array in the rostral-caudal and caudal-rostral directions and found that many neurons had a higher spike rate during caudal-rostral stimulation than during rostral-caudal stimulation. In addition, they found that many neurons had higher firing rates for slower stimulus speeds (Kaloti et al., 2016). The present work confirms that many neurons in the trigeminal brainstem are sensitive to the direction of global motion, but somewhat contradictory results for speed tuning, something that is discussed in *Discussion*. The studies presented here have studied global motion at every level of the whisker-barrel pathway, yet we still have little understanding of how global motion information is transformed in these circuits. It is imperative that we continue to study this phenomenon in the trigeminal brainstem because this is the first processing site in the whisker-barrel pathway and understanding how neurons respond to global motion stimuli could help the facilitation of studies about the integrative properties of trigeminal brainstem neurons.

Global motion tuning complements angular tuning and direction tuning of whisker-sensitive neurons (Furuta et al., 2006). Knowing how neurons respond to single whisker deformations can inform how the entire array responds to a global motion stimulus. Global motion simulates complex, natural stimuli interacting with the whisker array and it is necessary that we have a device that could replicate this stimulus experimentally. The present work describes the

development of such a system and its subsequent use to investigate tuning of global motion in multi-whisker responsive neurons.

1.3 Contributions to the Field

The previous work reviewed here discusses the properties of trigeminal brainstem neurons and their responses to global motion. This thesis performs a literature review on the trigeminal brainstem to describe speed tuning, angular tuning, and direction of global motion tuning. In this work we developed and tested a novel stimulator that could deliver complex, naturalistic mechanical stimulation to investigate speed tuning and direction of global motion tuning in the trigeminal brainstem, with the goal of understanding the global motion selectivity of multi-whisker sensitive neurons. We demonstrate the device's function and utility by recording from a small number of multi-whisker-responsive neurons in the trigeminal brainstem and found that neurons had higher firing rates in response to faster stimulation speeds and some exhibited strong direction-of-motion tuning. The stimulator could be used – in either anesthetized or awake, head-fixed preparations – as an approach to studying global motion selectivity of multi-whisker sensitive neurons at multiple levels of the vibrissal-trigeminal system.

Chapter 2: Research Strategy

Portions of this chapter from:

Dorizan S, Kleczka KJ, Resulaj A, Alston T, Bresee CS, Hartmann MJ (2022) A novel stimulator to investigate the tuning of multi-whisker responsive neurons for speed and the direction of global motion. Accepted with revisions.

2.1 Problem Statement

My thesis research uses the rodent vibrissal system as a model to study sensorimotor integration at the level of the brainstem. Figure 2.1 illustrates the vibrissal-trigeminal brainstem loop, which goes from the whiskers to the Vg to the SpV to the lateral facial nucleus to the whisker muscles. Vibrissal-sensitive structures integrate information from multiple whiskers, and before we can begin to quantify those responses, we need a tool specifically designed to investigate tuning to the direction of global stimulation across the entire whisker array. Therefore, we developed a system that would allow one to investigate the integrative properties of these neurons to further our understanding of their role in encoding spatial information. The present work describes the construction and validation of such a device.

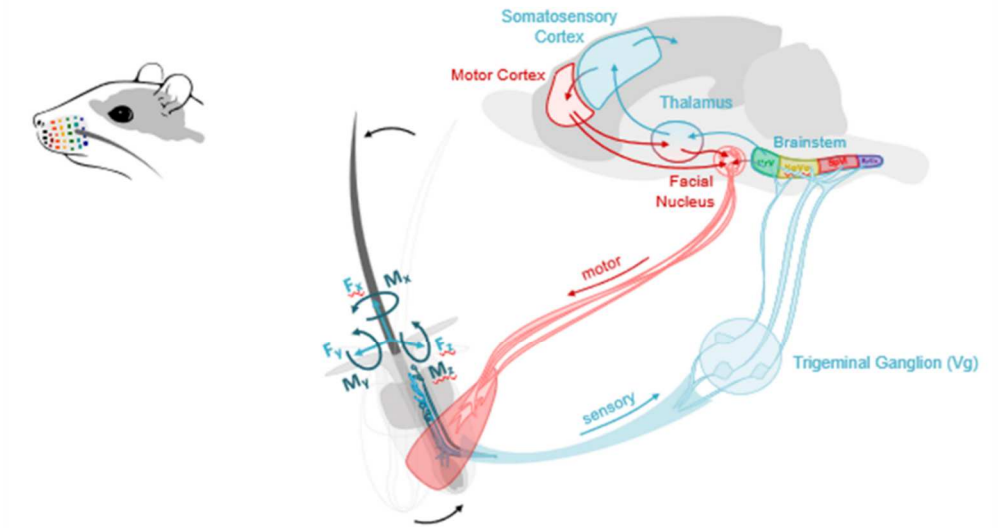

Figure 2.1 - Schematic of vibrissal-trigeminal brainstem sensorimotor loop. This three-synapse loop goes from the whiskers to the trigeminal ganglion (Vg) to the spinal trigeminal nuclei to the facial motor nucleus to the whisker muscles. This three-synapse loop is thought to be responsible for reflexive whisker retraction upon encountering a novel tactile stimulus. Figure adapted from Zweifel, 2021.

2.2 Overview of Objectives

This thesis work passively stimulated the rodent whiskers while recording from an isolated single unit in the trigeminal brainstem. Doing this, we were able to probe the relationship between this stimulation and the responses of whisker-responsive trigeminal neurons. We first developed a tool that would allow us to stimulate the whiskers systematically and reliably in a range of directions and speeds. Then we examined the responses of these whisker-sensitive units to the different combinations of speed and directions to determine whether these units are direction or speed selective. To that end, we set out to accomplish the following objectives:

To develop a multi-whisker stimulation system that can be controlled to generate repeatable, linear sweeps of tactile stimulation across the whisker array in any direction and with a range of speeds. We developed a multi-whisker stimulator that reliably stimulates and detects whiskers across conditions in a consistent manner. We validated the use of this system by demonstrating the function and utility of the stimulator by recording from a small number of multi-whisker-responsive neurons in the trigeminal brainstem.

To determine if a novel, multi-whisker stimulation system can be used to investigate the tuning of multi-whisker responsive neurons for speed and direction of global motion tuning. While used mainly to validate the stimulation device, we recorded from a small number of multi-whisker responsive neurons in the trigeminal brainstem and determined their speed and direction-of-motion tuning.

How the features of a stimulus are integrated in these whisker-sensitive circuits is of great interest to those in the field and this work provides a tool by which researchers can begin to investigate this idea in earnest.

2.3 Approach

Animal experiments were approved by the Institutional Animal Care and Use Committee (IACUC) of Northwestern University. Neurophysiological data were obtained from four adult, female Long Evans rats (4 – 7 months). Rats were anesthetized with isoflurane, their body temperature maintained on a "PhysioSuite" heating pad (Kent Scientific), and they were checked every 15 minutes for a toe pinch reflex (TPR). The animal's head was stereotaxically immobilized using earbars and eye ointment was applied. The scalp was shaved, cleaned, and covered with lidocaine, and the head leveled by ensuring that the heights of bregma and lambda differed by less than 0.05mm. To access the trigeminal nuclei, a craniotomy was performed on the animal's left side, between 11.9 and 13.3mm caudal to Bregma, and between -2.45 and -3.35mm lateral to the midline. Three holes were drilled to accommodate skull screws and ground wires were implanted.

The rat was then moved to a taller surgical stage to accommodate the stimulator height and to expose whiskers for stimulation. Deep anesthesia was achieved using an intraperitoneal injection of ketamine hydrochloride, xylazine HCl, and acepromazine maleate as the isoflurane gradually wore off. After anesthesia stabilized, the animal's head was re-leveled. A methyl methacrylate bridge was constructed between the skull screws and the surgical stage. After the bridge dried, the headgear was removed as well as the stereotaxic holder's left arm, exposing the left whisker array.

The stimulator, placed on a standard 3-DOF surgical micromanipulator, was then positioned and oriented to pass through the whisker array parallel to the rat's cheek. We paid particular attention to the distance between the stimulator and the rat's cheek. Placing the stimulator close to the cheek ensures that the nitinol wire makes contact with all macrovibrissae.

If the stimulator is moved further away but remains parallel to the cheek, some of the more rostral (shorter) macrovibrissae are not contacted during the sweep. In the present experiments, care was taken to ensure that all whiskers in the neuron's receptive field were contacted, and whiskers were always stimulated approximately halfway along their length or close to their tips.

A tungsten microelectrode (1-2MΩ; FHC, 15mm, Cat. #: UEWSFGSE7N1M) was lowered until the trigeminal brainstem was reached (~6.5mm from brain surface). The trigeminal brainstem was identified first, by the presence of multi-whisker receptive fields and second, by confirming that receptive fields gradually and systematically shifted from the E row to the A row as the electrode descended. As the electrode was lowered, whiskers on the ipsilateral side of the face were manually deflected to detect whisker sensitive units. Once a whisker-responsive neuron was identified, a battery of 24 different stimulus conditions was run. The stimulator was swept through the array at three speeds (150 mm/s, 113 mm/s, and 75 mm/s; Figure 2.3) and eight directions (0° - 315° in 45° increments; Fig. 2.2). Ten trials were run for each stimulus condition. After all 240 trials finished, an additional ten trials were completed at 0° at all three speeds to ensure that the spike shape had not changed during recording.

Neural recordings were collected using the open-access neural acquisition software, NeuroRighter (v1.1.0.564). Neural signals were amplified with a gain of 1,000 (AM Systems 1700) and filtered between 300 and 10,000 Hz before acquisition on a National Instruments™ BNC-2090 board at 40,000 Hz. Analog signals from the slide potentiometer and fiber optic amplifier (see *Chapter 3.2*) were recorded simultaneously on the same system. During experiments, the whisker stimulator was controlled via an Arduino Mega with an Adafruit motor

shield (part number 1438). Python scripts controlled the movement of the stimulator, while Arduino firmware handled low-level motor control.

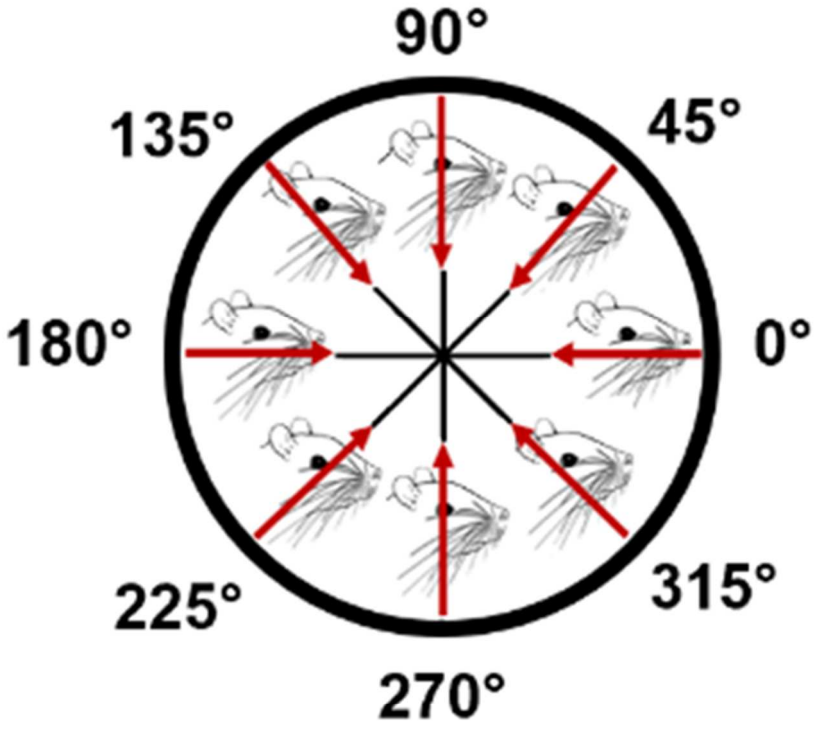

Figure 2.2 - Eight stimulation directions across the whisker array. The stimulator traversed the whisker array in eight different directions, as indicated by the red arrows through each whisker array cartoon.

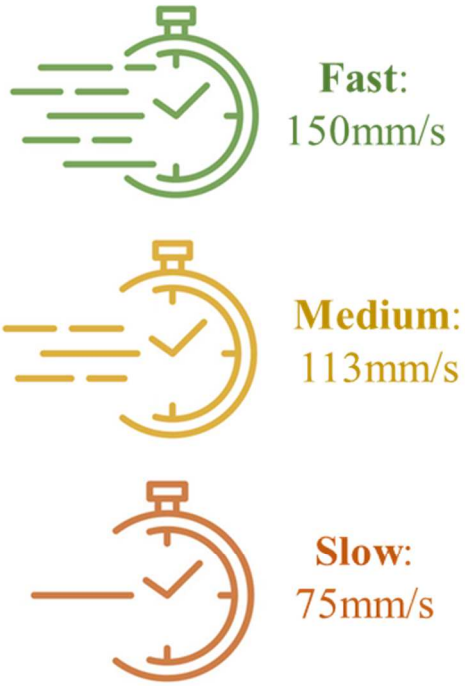

Figure 2.3 – Three speeds across the whisker array. The stimulator traversed the whisker array at three different speeds, a range of speeds that mimic natural tactile interactions.

Chapter 3: Development of a Novel Multi-Whisker Stimulator

Portions of this chapter from:

Dorizan S, Kleczka KJ, Resulaj A, Alston T, Bresee CS, Hartmann MJ (2022) A novel stimulator to investigate the tuning of multi-whisker responsive neurons for speed and the direction of global motion. Accepted with revisions.

3.1 Introduction

Repetitive contact with multiple whiskers is how rodents acquire tactile information (Carvell and Simons, 1990; Harvey et al., 2001; Sachdev et al., 2001) and to accurately discriminate between objects, the contact of multiple whiskers with an object is necessary (Jacob et al., 2010). Most neurons in central vibrissal-sensitive structures integrate information from multiple whiskers and it has been a long-standing experimental challenge to quantify their integrative properties (Benison et al., 2006; Cohen et al., 2008; Deschenes et al., 2003; Goldin et al., 2018; Jacob et al., 2008; Jacob et al., 2017; Le Cam et al., 2011; Rodgers et al., 2006; Timofeeva et al., 2004; Veinante and Deschenes, 1999; Whitmire et al., 2021). Rats have been shown to alter their whisking movement strategies during discriminative task acquisition which included changes in the frequency, velocity, amplitude, duration, and the amount of whisking (Benison et al., 2006; Harvey et al., 2001). It is therefore necessary to have a stimulation system where we can implement changes in these stimulus parameters that can replicate the different features of natural stimuli in accordance with experimental need. There have been several types of whisker stimulators with capabilities that support the aforementioned parameters, though not without limitations.

In the late 1970's, researchers used electric and manual stimulation to mimic the natural movement of the whisker. Axelrad and colleagues did this in two ways: 1) the electrical stimulation of a dissected follicle nerve and 2) by gluing a whisker at its resting position to a probe that was controlled by a custom-built stimulator (Axelrad et al., 1976). This stimulator offered precise control of direction, duration, amplitude, rise time, and fall time of the stimulus (Axelrad et al., 1976). While electrical stimulation directly activated the whisker, the response of units of interest

were directly affected by the strength of stimulation itself (Axelrad et al., 1976). Larger whisker displacements tended to produce larger neural responses, though whether this increase was due to the movement of the whisker or to the activation of more follicles is not clear. Similarly for manual stimulation, it was not clear whether the observed responses were due to the manual stimulation or to the varying amplitude of movement which stimulated more follicle receptors. Trimming and gluing the whisker to the probe also changes the whisker response to external stimuli so the responses seen may not accurately reflect what is happening on the circuit level.

Piezoelectric stimulators, the most common type of contact-based stimulator, have been used to induce single whisker and multi-whisker deflections in studies of the whisker system. One of the first piezoelectric stimulators was used by Simons when investigating the effects of multi-whisker stimulation on whisker-sensitive units in the somatosensory cortex (Simons, 1983). This "multiangular, piezoelectric stimulator" was an array of independently controlled whisker deflectors (Simons, 1983). After trimming the whiskers to a length of 7mm, they inserted the terminal 2mm of the whisker into a piece of Teflon tubing that protruded from a grass probe (yes, grass: "dried grass was used because it is strong and rigid but light in weight" (Simons, 1983)). Individual stimulators were then positioned over the whiskers via an anchored micromanipulator with a dissecting microscope attached (Simons, 1983). The advantages of this stimulator design were that a whisker could be deflected in any direction over 360°, the behavior of the stimulator was highly reproducible, the individual stimulators could be controlled simultaneously, and the stimulator was compact enough to allow whiskers that were no more than 2mm apart to be attached (Simons, 1983). One disadvantage, however, was that there was a need to calibrate the stimulator with a phototransistor circuit and a compound microscope (Simons, 1983), necessitating the use

of additional equipment outside of the stimulator itself to ensure delivery of stimulation and stimulation contact. Another disadvantage was that the stimulator needed to be repositioned often so as to stimulate the whisker array in different directions. This, of course, is cumbersome, not to mention potentially inconsistent as it is difficult to maintain the same stimulation conditions throughout the experiment. Finally, they used ramp-and-hold "trapezoid" as stimulus signals which does not cover the full range of relevant parameters for whisker deflection in a natural context (Simons, 1983; Jacob et al., 2010).

Most piezoelectric stimulators today (Fig. 3.1) were built following the design structure used by Simons. For example, Deschenes and colleagues built a whisker stimulator with a ceramic bimorph bender glued to a thin straw (Deschenes et al., 2003). At the free end of the straw, the tip of the whisker would be inserted into a tiny cone-shaped, glass bead that prevented any dead space (Deschenes et al., 2003). The piezo amplifier was then driven by bandpass-filtered sinusoidal or triangular waveforms and positioned to deflect the principal whisker in different directions (Deschenes et al., 2003). They too required additional equipment in the form of a microscope with an attached digital camera and used a stimulus that may not accurately reflect stimuli that these animals would encounter naturally. Whisker stimulators around this time also suffered from "ringing" at the resonance frequency due to the high-speed deflection of the bender. To prevent ringing at lower frequencies, the Deschenes group blocked the bimorph at mid-length, reducing how far the probe could displace the whisker. To compensate for this limitation, they stimulated the whiskers 5mm from the whisker pad, which restricted the type of response they could evoke with stimulation.

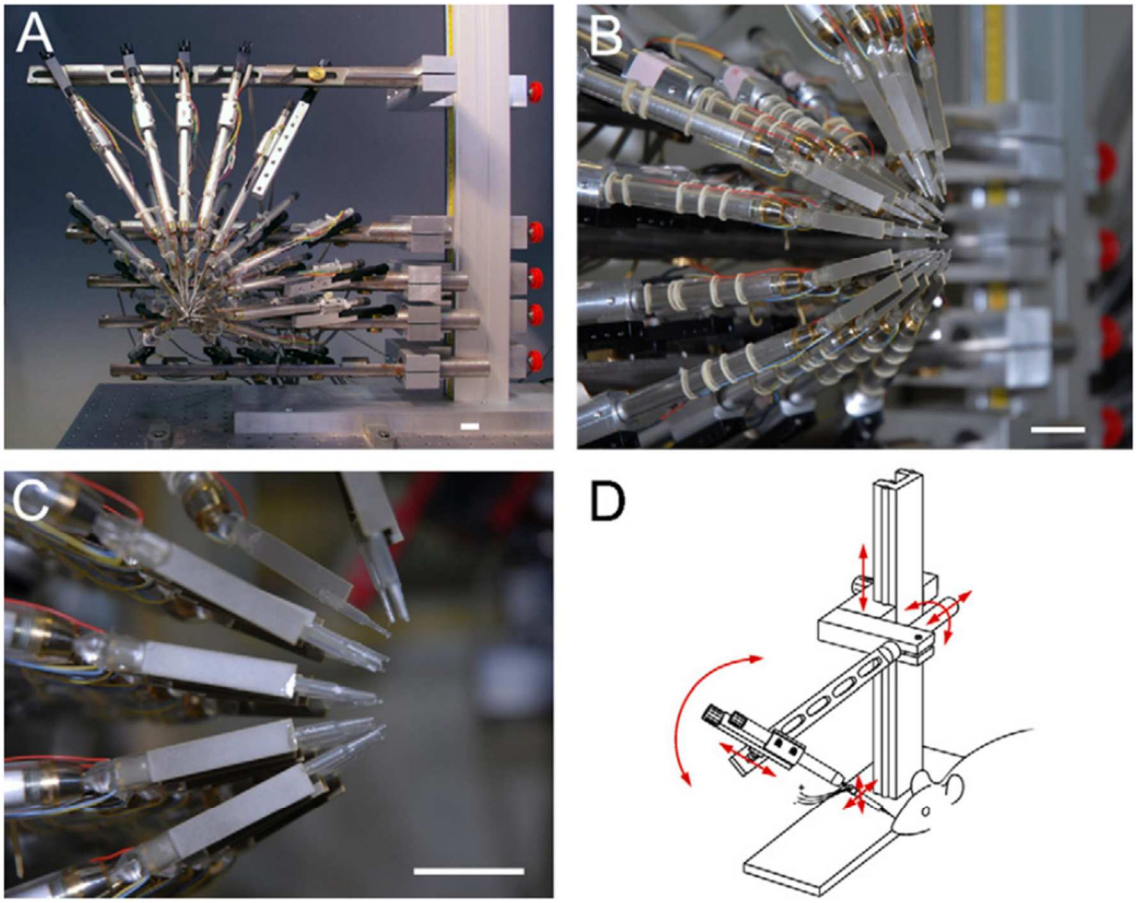

Figure 3.1 – Multi-directional, piezoelectric whisker stimulator. Currently the most widely used technology for producing mechanical deflections of whiskers. 24 independent piezoelectric benders contact 24 vibrissae to deliver a large scale of natural patterns of whisker deflections. Figure from Jacob et al., 2010.

Piezoelectric stimulators evolved from using one piezo to stimulate one whisker, to multiple piezos stimulating multiple whiskers simultaneously, though independently of one another. In their first iteration of such a device, Jacobs and colleagues built a stimulator of 24 independent piezoelectric actuators assembled to match the arrangement of the whisker array that allowed for deflections in the rostro-caudal axis at lower frequencies (Jacob et al., 2008). The second iteration of this device included multi-directional piezoelectric benders that allowed for the deflection of up to 24 whiskers in any direction (Jacob et al., 2010). Predecessors of this device demonstrated that piezoelectric bimorphs could be used to stimulate a large number of whiskers and did as few as 4 whiskers and as many as 16 whiskers (Krupa et al., 2001a; Krupa et al., 2004; Benison et al., 2006; Jacob et al., 2010).

Experiments that use a piezoelectric stimulator or multiple piezoelectric stimulators aren't without difficulties. These stimulators are often hard to manually position, which can be time-consuming if there are multiple trials to done. The whiskers of the animal often need to be trimmed to use these stimulators, which can drastically change the response of whisker sensitive neurons to external stimuli. Experiments using a piezoelectric stimulator often place the probe along the shaft of the whisker (Axelrad et al., 1976; Simons, 1983) instead of at the tips or passing the stimulus through the array as an external natural stimulus would during typical exploratory behavior. And probably most notably, piezoelectric dynamics can cause artifacts. Piezoelectric stimulators offer precise control but travel only through small angles, and typically stimulate modified, trimmed whisker(s) (Axelrad et al., 1976; Deschenes et al., 2003; El-Boustani et al., 2020; Jacob et al., 2010; Simons, 1983).

While piezoelectric stimulators are the most ubiquitous, there are other types of stimulators that have been used that provide non-contact stimulation of whiskers: air current stimulators and magnetic-based stimulators.

In air current stimulators, sensory stimulation consists of puffs of compressed air delivered via a compressed air source or a repeatable pressure pulse system (Bernhard et al., 2020; Charpier et al., 2020; Sosnik et al., 2001; Yu et al., 2019). Air stimuli can be delivered at multiple directions and the pressure adjusted so as to deliver stimuli of different speeds, resembling the movement profile of natural whisking (Sosnik et al., 2001). Air puffs forced forward movement of the whiskers which allowed them to return to their rest position before the next stimulus. Much like there piezoelectric counterparts, however, there are also limitations to these types of stimulators. Air current stimulators require the calibration of airflow for each test condition (Yu et al., 2019) which can take up a lot of time during already time-sensitive electrophysiological experiments. Having to calibrate the stimulus signal after each administration could potentially lead to inconsistencies in stimulus intensity. Additional equipment is also necessary to measure whisker movement with air current stimulators. Lastly, the air puff does not always stimulate the entire whisker array simultaneously; it typically only deflects a select number of whiskers each time.

Magnetic-based stimulators offer non-contact stimulation of whiskers. Small metal pieces are glued to the desired set of whiskers and the animal is placed in a "Lausanne whisker stimulator," a cylindrical cage placed inside of an electromagnetic coil which delivers pulses of magnetic field bursts that deflect the metal pieces attached to the whiskers (Melzer et al., 1985; Welker et al., 1992). Magnetic-based stimulators allow experimenters to deflect the whisker while the animal is awake and freely behaving. A challenge to this approach is that the small metal pieces

must be constantly observed to ensure that they do not fall off or are replaced as soon as possible. Also, this method requires the whiskers to be glued to these small metal pieces which deform and can cause damage to the whisker, preventing an accurate reflection of the evoked neuronal responses to stimulation. Whiskers are also required to be clipped here, dampening potential responses to stimulation. While the magnetic field was homogeneous, the strength of stimulation was decreased the further the animal got away from the center, so it was difficult to keep the same stimulus intensity consistent throughout the experiment and it was difficult to ensure that the whiskers were appropriately stimulated at all. Lastly, it is hard to consistently stimulate multiple whiskers, let alone the entire whisker array. The magnetic-based stimulator is incompatible with experiments that necessitate the stimulation of more than three whiskers.

To overcome these challenges, there is a need for a stimulator that is more versatile, that can deliver real-time detection of whiskers, that offers high resolution control over stimulus parameters, and that can reliably replicate behaviorally relevant stimuli while recording the responses of whisker sensitive circuits. The present work describes the construction and validation of a stimulation system that meets these requirements.

3.2 Multi-whisker Stimulator

3.2.1 Stimulator Design and Control

We designed a closed-loop stimulator that repeatably and consistently stimulates the whisker array in a range of speed and directions which allows us to investigate the sensitivity of trigeminal brainstem neurons to these stimulus features. As shown in Figure 3.1A, the stimulator consists of a motorized slide potentiometer (Bourns®, PSM01-082A-103B2) attached to a stepper motor (Moons' Industries, MS17HD6P4150). The slide potentiometer permits controlled linear motion with simultaneous position readout. It supports a carriage holding a thin nitinol wire (0.01" diameter) that is swept through the whiskers. The stepper motor rotates the slide potentiometer and carriage as a unit, so the wire can sweep in any direction. The entire device can be mounted to a micromanipulator to position it relative to the animal.

To record the time interval when the nitinol wire contacts the whiskers a fiber optic emitter/detector pair (Banner™, DF-G3-NU-2M) is aligned coaxial with the wire. The emitter generates a collimated light beam, and the detector senses analog changes in light intensity. When the emitter-detector path is unobstructed, the detector voltage is constant. The voltage drops when the beam is interrupted. Although the work described in the present study was performed in rats, we fully expect the system to work for mice, as contacts were detected with even the smallest rat whiskers, which are approximately the same size as mouse whiskers (Belli et al., 2016; Hires et al., 2016). A bracket immobilizes the fiber optic cables relative to the slider as the mechanism rotates. Hardware to attach the slider to the stepper motor, to attach the fiber optic cables and nitinol wire to the slider, and to mount the stimulator are 3D-printed.

During experiments, both the slide potentiometer and the stepper motor were controlled via an Arduino Mega with an Adafruit motor shield (part number 1438). A capacitive absolute position rotary encoder (CUI, AMT203-V) allowed accurate, closed loop control of motor angle. Python scripts controlled the experiment, while Arduino firmware handled low-level motor control. The stimulator was briefly forced to its end of travel before each trial.

Files for stimulator construction and use are located at: https://github.com/SeNSE-lab/global_motion_stimulator. The repository includes a bill of materials, CAD drawings for each part, Arduino and python code, and instructions for assembly and use.

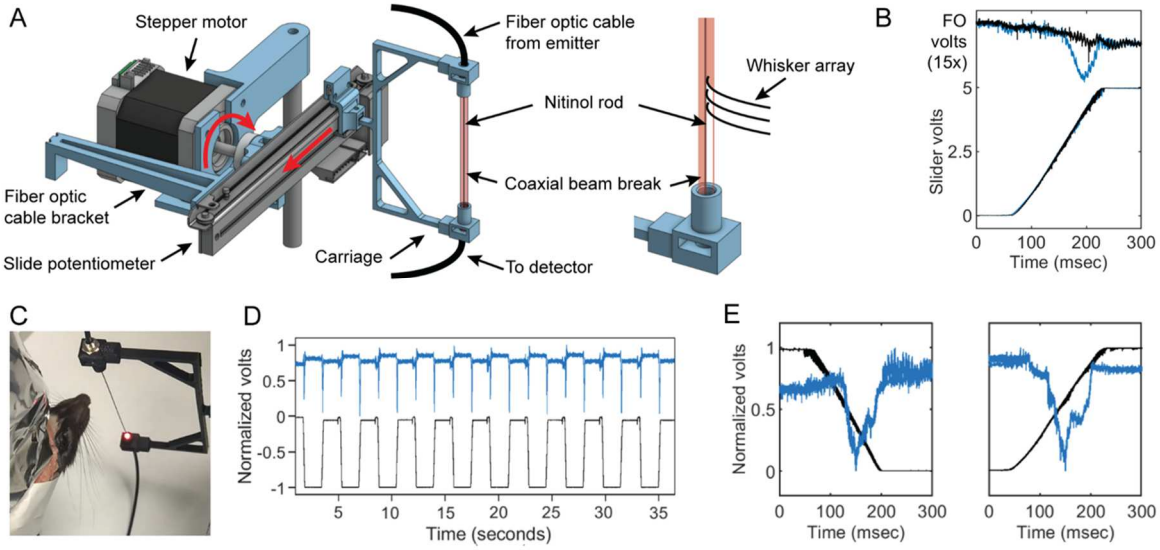

Figure 3.2 - Simultaneous whisker stimulation and contact detection. (A) Schematic of stimulator assembly and fiber optic sensor. The stimulus is a nitinol rod (wire) attached to a carriage controlled to sweep through the array. Speed is controlled by the slide potentiometer, which also gives a position readout. Direction is controlled by the stepper motor, which can rotate the slide potentiometer to any angle. A fiber optic emitter-detector pair, coaxial with the nitinol wire, detects occlusions by the whiskers. (Right) expanded view of nitinol wire and fiber optic. **(B)** Examples of the fiber optic signal when the nitinol wire does (blue) and does not (black) contact a single whisker. Position signals from the slide potentiometer for both trials are also shown ("Slider volts"). The position signal during contact (blue) is completely hidden by the position signal during non-contact (black), consistent with the high repeatability of the system. In this figure the slider traverses 10 cm at the slowest speed, ~75 cm/s. Fiber optic signal is 15x relative to slider voltage. **(C)** A photo of the stimulator next to the rat is shown for scale. **(D)** Slider position (black) and fiber optic signal (blue) during twenty sequential sweeps of the stimulator through the whiskers in alternating directions. On each trial the fiber optic voltage signal drops sharply during whisker contact. In this figure the slider traverses 10 cm at the slowest speed, ~75 cm/s. **(E)** Expanded view of ten fiber optic traces (blue) and ten linear actuator traces (black) superposed for the ten trials in the two directions shown in (C).

3.2.2 Stimulator Performance

First, we tested the system's ability to reliably detect single whisker contact with the nitinol wire. Figure 3.1B compares the fiber optic signal obtained when the stimulator brushed past a whisker with that obtained when the stimulator was pulled away from the face. The encoder (position) signal from the potentiometer for both trials is shown below the fiber optic signals. A voltage drop in the fiber optic signal is observed when a whisker is present, but not when the whisker is absent. The two encoder traces overlap, indicating that stimulator motion did not vary between trials even as the assembly was repositioned away from the whiskers.

Next, repeatability of stimulation and detection were assessed while running the stimulator through the full whisker array. A photo of the stimulator next to the rat is shown in Figure 3.2C for scale. The position and orientation of the stimulator relative to the bases of the whiskers will have a strong influence on the mechanical signals generated, as described further in the *Discussion*. Figure 3.2D shows fiber optic and potentiometer signals for ten sweeps back and forth (20 sweeps total) through the whisker array. The stimulator first traversed the array in one direction, and then in reverse, 180° opposite the original. To ensure that sequential sweeps did not interfere with each other, the stimulator was held fixed for ~1.5 s between sweeps. Thus, in Figure 3.2D stimulation durations appear as steep upwards and downwards slopes in the potentiometer trace, and durations of static hold appear flat. The small rectangular-shaped voltage pulse in the potentiometer trace at the start of each downwards slope indicates when the stimulator is forced to end-of-travel.

As expected, the fiber optic trace in Figure 3.2D is constant during times when the potentiometer is static, and shows large voltage drops during periods of whisker contact. Notably, the shape of the voltage drops differs considerably between the two stimulation directions. The

voltage drop is much larger for one direction (in this case, the direction with positive potentiometer slopes) than the other. These differences are expected, because the duration and timing of whisker contact will depend strongly on the positions and orientations of the whiskers relative to the stimulator. Importantly, however, although the fiber optic signal varies considerably between directions, it is extremely consistent for a single direction. This consistency is evident in Figure 3.2E, which overlays the twenty fiber optic voltage drops shown in Figure 3.2D, separated by stimulation direction.

3.3 Comparison with Other Whisker Stimulators

We describe a novel stimulator system with two important, distinct capabilities. First, the stimulator can be controlled to traverse either the full array or a subset of whiskers with multiple directions and speeds. It is intended for the study of tuning to global motion direction, not for experiments that require precise temporal control over individual whiskers. This capability complements more standard piezo-electric stimulators, which offer precise control but travel only through small angles, and typically stimulate only a single, trimmed whisker (Deschenes et al., 2003; El-Boustani et al., 2020; Simons, 1983). The present system is also safer and more versatile than a previous multi-whisker stimulator that relied on high-speed rotations to sweep a post through the array (Kaloti et al., 2016). The second, equally important capability of the system is real time, fiber optic detection of whisker contact. In the present work, this capability was used only during post-processing, to determine the interval of whisker contact. However, the real-time nature of the fiber optic signal means that the system could be used in closed-loop feedback experiments. For example, awake, head-fixed animals could be trained to whisk against the nitinol wire, and the stimulator moved in response with a chosen velocity.

The present system complements several other stimulator types, some contact-based and others non-contact based. The most standard type of contact-based whisker stimulator is piezoelectric; this technology offers high resolution control over individual whisker motion (Armstrong-James, 1975; Cohen et al., 2008; Furuta et al., 2006; Ito, 1981; Jones et al., 2004; Kheradpezhouh et al., 2017; Laturnus et al., 2021; Lichtenstein et al., 1990; Shipley, 1974; Simons, 1983). However, it is challenging to manually position the stimulator and whiskers are often trimmed to ~1 cm. Piezoelectric dynamics can cause artifacts, and only small angle deflections are

possible. A few experiments have been performed with multiple piezoelectric (Estebanez et al., 2016; Jacob et al., 2010; Jacob et al., 2008; Jacob et al., 2017; Ramirez et al., 2014; Vilarchao et al., 2018) or solenoid-based (Krupa et al., 2001a; Rodgers et al., 2006) stimulators. These are tour-de-force experiments that have produced insights into response properties of whisker neurons that would not be possible with the stimulator described here.

Non-contact stimulation approaches include directing air at the whisker array (Bernhard et al., 2020; Charpier et al., 2020; Sosnik et al., 2001; Yu et al., 2019), or using magnetic-based stimulation (Melzer et al., 1985; Welker et al., 1992). Although air stimuli can be delivered at multiple directions and speeds, the mechanical response of whiskers is quite different than during contact and involves nonlinear effects (Yu et al., 2019). Thus, it can be difficult to correlate whisker motions with neural activity. Finally, the "Lausanne whisker stimulator" is a cylindrical enclosure surrounded by an electromagnetic coil that delivers magnetic field bursts that deflect metal filings attached to single whiskers (Melzer et al., 1985; Welker et al., 1992). An advantage of this approach is that animals can behave freely within the enclosure, but a challenge is ensuring that the filings are not removed during grooming. In addition, the metal filings slightly deform the whiskers, and it can be difficult to stimulate more than one whisker.

The present system permits repeatable, coherent-motion stimulation of multiple whiskers but sacrifices the ability to stimulate a single whisker with micron resolution, the ability to stimulate at high frequency, and to precisely control inter-whisker contact timing. In addition, the speeds generated by the device are relatively slow. Note, however, that when the nitinol wire makes contact with a whisker, the whisker will bend and then "slip" along the wire (Huet et al., 2015). Depending on the relative angle of contact, the speed of the whisker on the wire will be

greater than or equal to the speed of the stimulator. The slip of the whisker on the wire will be particularly significant given that the stimulator generates large angle deflections, except when positioned very close to the whisker tips. As the stimulator is moved closer to the whisker bases, larger angle deflections will be generated, and the mechanical signals (forces and torques) will be larger. Notably, although the stimulator can accurately indicate the time of first whisker contact, it cannot, by itself, be used to quantify whisker mechanical signals. To determine mechanical input, the stimulator must be used in conjunction with simulations (Zweifel et al., 2021) that establish error bounds on whiskers' mechanical responses. Thus, one of the most important future improvements is the incorporation of closed-loop speed control, to ensure that accurate speeds can be used in simulations.

3.4 Investigating the Tuning of Multi-whisker Responsive Neurons with the Multi-whisker Stimulator

Certain aspects of the sensory periphery make stimulating vibrissae difficult, so much so, that studies are often limited to stimulating one and only one whisker at a time (Simons, 1983). The size of the animal's face and the need for whiskers to be deflected in specific directions impose restraints on the physical dimension and dynamic properties of mechanical stimulating devices (Simon, 1983). The mechanical properties of the piezoelectric benders also limit what type of naturalistic whisker deflections are generated (Jacob et al., 2010). There is a need for a device that can consistently replicate and deliver behaviorally relevant stimuli while recording functional responses from whisker-sensitive regions (Jacob et al., 2010). To mimic these natural phenomena experimentally and to quantify whisker-sensitive neurons' integrative properties, a whisker stimulator that is designed to deliver careful sequences of multi-whisker stimulation is essential (Jacob et al., 2008). It would be useful to have a system that could deliver repeatable stimuli to multiple whiskers, that allowed stimulation parameters to be varied across a wide range, that detected contact with the whiskers, and that was easy to position. The present work describes the construction and validation of a stimulation system that meets these requirements.

To that end, we used this novel omni-directional, multi-whisker stimulator in the anesthetized rat preparation as a way to investigate multi-whisker sensitive neurons at the level of the brainstem. Our stimulator is designed to mechanically stimulate whiskers in any direction with a range of speeds that mimic natural tactile interactions; the stimulator traversed the array in eight stimulation directions, and in each direction, the stimulator was run at three different speeds. For each neuron recorded, ten trials were obtained for each speed/direction combination. The ability

to manipulate the spatial and temporal features of vibrissal stimuli is crucial for understanding how whisker-sensitive circuits integrate the various features of a stimulus.

Chapter 4: Direction and Speed of Global Motion in Trigeminal Brainstem Neurons

Portions of this chapter from:

Dorizan S, Kleczka KJ, Resulaj A, Alston T, Bresee CS, Hartmann MJ (2022) A novel stimulator to investigate the tuning of multi-whisker responsive neurons for speed and the direction of global motion. Accepted with revisions.

4.1 Introduction

Sensory physiology seeks to understand how responses to complex stimuli are generated (Ego-Stengel et al., 2012). The rodent vibrissa system is an ideal system for studying the spatiotemporal sequence of whisker deflections, though we still lack a full understanding of how responses to multi-whisker stimuli are collected, integrated, and processed in whisker sensitive structures.

When a rat explores an object, multiple whiskers simultaneously contact its surface (Ego-Stengel et al., 2012), which results in a complex sequence of whisker movements. In order to determine the functional properties of whisker-barrel units, one needs to be able to manipulate the spatial and temporal aspects of whisker stimuli (Simons, 1983). To that end, we developed a multi-whisker stimulation system that can vary stimulation parameters across a wide range, provides real time information about whisker contact, and is easy to position and adjust. We validated this stimulator by assessing the neural sensitivity of trigeminal brainstem neurons to the direction of global motion and speed of incoming stimuli. Understanding how trigeminal brainstem neurons represent tactile information is crucial for understanding the neuron's capacity to combine and extract information about the collective features of a stimulus from across the whisker array (Jacob et al., 2008) and for interpreting the responses and elucidating the functions of related, downstream structures.

The study of global motion is a means by which we can investigate the spatiotemporal structure of sensory information conveyed by the whiskers. Understanding the underlying mechanism of global motion sensitivity can help researchers examine the encoding properties of whisker-responsive units, particularly during behaviors that result in multi-vibrissae inputs,

understand whether relevant information from across the entire whisker array influences downstream responses, and for the overall investigation of the dynamics of spatiotemporal integration in the whisker-barrel pathway.

4.2 Methods

4.2.1 Data Acquisition

Neural signals were amplified with a gain of 1,000 (AM Systems 1700) and filtered between 300 and 10,000 Hz before acquisition on a National Instruments™ BNC-2090 board at 40,000 Hz. Analog signals from the slide potentiometer and fiber optic amplifier were recorded simultaneously on the same system.

4.2.2 Analysis

For each neuron and each speed, the directional sensitivity index (DSI) was computed by finding the vector sum of the mean firing rate in all directions (Mazurek et al., 2014). The mean firing rate was computed as the average (over 10 trials) of the number of spikes during contact divided by contact duration. The DSI was normalized by the summed firing rate in all directions. Thus, the DSI will have a magnitude of 0 if the neuron responds equally well in all directions and a magnitude of 1 if all responses are in a single direction. All neurons fired less than 0.8 spikes/second during non-contact periods. Most neurons did not respond during post-contact, when resonance is expected; those that did were excluded for future analysis. The resonance frequencies experienced during active whisking are different than the ones generated with passive stimulation. While we can accurately determine the interval of whisker contact and the response evoked within this timeframe, we did not measure the resonance frequencies of the post-contact response, thereby excluding them from our study.

4.3 Results

4.3.1 Speed and Direction Sensitivity of Multi-whisker Responsive Neurons

We used the stimulator to begin to explore speed and global-motion sensitivity of neurons in the trigeminal brainstem. Figure 4.2A illustrates the eight stimulation directions. In each direction, the stimulator was run at three different speeds. Ten trials were obtained for each speed/direction combination. Five neurons responsive to multi-whisker stimulation were recorded. Consistent with previous studies (Furuta et al., 2006; Timofeeva et al., 2004), each neuron had a "principal whisker" to which its response was maximal and several "surround" whiskers to which it responded more weakly as determined by manual stimulation of individual whiskers with a hand-held wooden probe. In the present study, neurons had principal whiskers D3, E2, and E6, and all had surrounds that included whiskers of the same row. Three of five neurons had surrounds that also included one or two whiskers in more dorsal rows, consistent with the elliptical, row-wise receptive fields commonly found in SpVi (Furuta et al., 2006; Timofeeva et al., 2004).

Responses of the five neurons are summarized in Figure 4.2B. Each panel in this row shows a polar plot in which the angular axis corresponds to the directions of stimulation shown in Figure 4.2A, and the radial axis indicates the mean firing rate (spikes/second). The three curves in each panel show the neuron's firing rate at each of the three speeds indicated as fast, intermediate, and slow. With few exceptions, the firing rate of all neurons is lower in response to slow stimulation than to faster stimulation in all directions – the black trace (slow speed) is enveloped within the responses to faster speeds.

In addition, visual inspection suggested that some neurons were tuned to the direction of global motion of the stimulator through the array. To more carefully quantify this effect, we

analyzed the neural responses after separating by speed, as shown in rows 2 – 4 of Figure 4.2B. The second row of Figure 4.2B shows the neural response at the fastest speed. Each panel shows the neuron's mean response, the mean ± standard error of the response, and the summed direction vector. The third and fourth rows of Figure 4.2B are identical to the second row, except that they show data for intermediate and slow speeds, respectively.

The plots reveal several important features of the data. First, for all neurons except neuron 4, the best direction is approximately the same across speeds. The probability of this occurring by chance is 3/82 = ~4.8%. Second, Cells 2 and 3 generally have direction vectors with magnitudes that exceed the standard error. To confirm that these two neurons were tuned to the direction of global motion we randomly shuffled the data 1,000 times. The last number in red at the bottom of each plot indicates the probability (expressed as a percent) that the observed direction vector could have occurred by chance. For example, there is a 3.2% chance that the DSI for neuron 3 at the slowest speed could have occurred by chance; probabilities are even lower for all other speeds for both neurons 2 and 3. A similar analysis showed that Cell 1 was not directionally tuned; the chances are 21%, 66%, and 14% that the observed DSI vectors could have resulted from a random distribution of firing rates. Tuning for the direction of global motion is more equivocal for Cells 4 and 5. Shuffling analysis showed that Cell 5 is not tuned at the fastest speed but may exhibit weak tuning at intermediate and slower speeds. Cell 4 exhibits weak direction tuning that gradually shifts with speed; this could result simply from chance.

To reveal spike timing information -- which cannot be observed in the polar plots of Figure 4.2B -- we computed peristimulus time histograms (PSTHs) for responses obtained when neurons were stimulated in their preferred directions (Figure 4.2C). The "preferred" direction for neuron 4

was ambiguous, so it was chosen based on results for fast stimulation. The plots show that the peak amplitude of the PSTH appears to occur at similar times across speeds for each neuron. Cell 3 exhibits a sharp onset response with rapid decay, while Cells 4 and 5 show a broader temporal distribution for some speeds. These types of temporal analyses will be interesting to investigate in future studies.

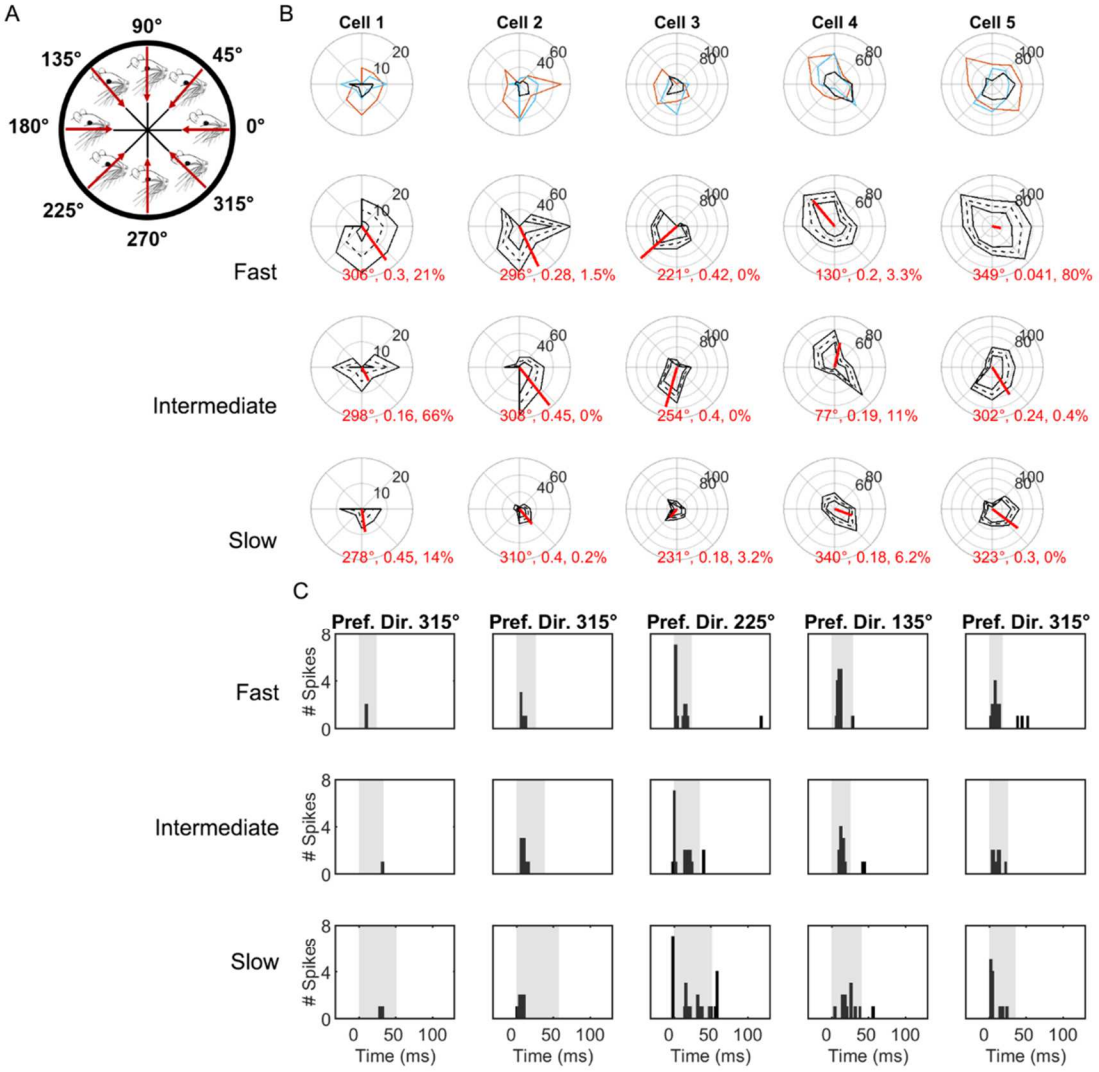

Figure 4.1 - Responses of five multi-whisker sensitive neurons in the trigeminal brainstem demonstrate the usefulness of the stimulator. (A) The stimulator traversed the array in eight different directions, indicated by red arrows through the eight figurines. **(B)** Polar plots illustrate directional sensitivity of the five neurons (Cell 1 – Cell 5). In all panels the radial axis represents the neuron's firing rate during contact, averaged across ten trials; the origin indicates a firing rate of zero. For visual clarity, only the outer two radial axis lines are labeled. The angular axis of each polar plot represents the stimulation directions shown in (A). **Top Row:** The three curves in each plot illustrate the neuron's firing rate when stimulated at different speeds: fast (150 mm/s; red), intermediate (113 mm/s; cyan), and slow (75 mm/s; black). **Rows 2 – 4:** Directional sensitivity of each neuron at each speed. In each panel the neuron's mean response is shown as a dashed black line. These mean response curves exactly match the corresponding curves in the top row. The mean plus and minus the standard error of the response are shown as solid black lines, and the (unnormalized) direction vector is shown as a red line. Notably, for all neurons except Cell 4, the best direction is approximately the same across speeds. At the bottom of each panel, the first number in red indicates the preferred direction in units of degrees (°), the second number indicates the normalized magnitude of the DSI, and the third number indicates the probability (expressed as a percent) that the observed DSI vector could have occurred by chance **(C)** PSTHs for the five neurons in (B). Histograms were computed for the stimulation direction that elicited the maximal firing rate; this direction is indicated in the top panel for each neuron. Top, middle, and bottom rows show histograms computed for fast, intermediate, and slow speeds, respectively. Bin size is 2ms. **Abbreviations:** #: number; *Pref. Dir.:* Preferred Direction.

Chapter 5: Discussion

Portions of this chapter from:

Dorizan S, Kleczka KJ, Resulaj A, Alston T, Bresee CS, Hartmann MJ (2022) A novel stimulator to investigate the tuning of multi-whisker responsive neurons for speed and the direction of global motion. Accepted with revisions.

5.1 Limitations

The sensory and motor systems of the whiskers are coupled together to allow the animal to adjust their whisker movements to sensory input (Bosman et al., 2011). Sensorimotor integration is a process in which sensory and motor information are integrated to guide the animal's behavior (Tsur et al., 2019). While the nature of sensorimotor integration is still under investigation, it is imperative that we begin to understand how sensory tactile stimuli can influence the neural responses of units along the vibrisso-trigeminal pathway.

We describe a novel stimulator system to begin to explore speed and global-motion sensitivity of neurons in the trigeminal brainstem. The stimulator has two important, distinct capabilities: 1) the stimulator can be controlled to traverse either the full array or a subset of whiskers with multiple directions and speeds and 2) it provides real time, fiber optic detection of whisker contact. It is intended for the study of tuning to global motion direction, not for experiments that require precise temporal control over individual whiskers.

The system does not stimulate individual whiskers; it is specifically designed to investigate tuning to the direction of global motion of stimulation (Vilarchao et al., 2018) across the entire whisker array. While the stimulator can traverse the array in any direction with a range of controllable speeds, with an optical detector to sense the duration of whisker contact, it sacrifices the ability to stimulate a single whisker with micron resolution, the ability to stimulate at high frequency, and to precisely control inter-whisker contact timing. In addition, the speeds generated by the device are relatively slow. Note, however, that when the nitinol wire makes contact with a whisker, the whisker will bend and then "slip" along the wire (Huet et al., 2015). Depending on the relative angle of contact, the speed of the whisker on the wire will be greater than or equal to

the speed of the stimulator. The slip of the whisker on the wire will be particularly significant given that the stimulator generates large angle deflections, except when positioned very close to the whisker tips. As the stimulator is moved closer to the whisker bases, larger angle deflections will be generated, and the mechanical signals (forces and torques) will be larger. Notably, although the stimulator can accurately indicate the time of first whisker contact, it cannot, by itself, be used to quantify whisker mechanical signals. To determine mechanical input, the stimulator must be used in conjunction with simulations (Zweifel et al., 2021) that establish error bounds on whiskers' mechanical responses. Thus, one of the most important future improvements is the incorporation of closed-loop speed control, to ensure that accurate speeds can be used in simulations.

5.2 Neural Representations of Global Motion in Trigeminal Brainstem Neurons

Most neurons along the vibrissotrigeminal pathway integrate information from multiple whiskers, and it is a long-standing experimental challenge to quantify their integrative properties (Benison et al., 2006; Cohen et al., 2008; Deschenes et al., 2003; Goldin et al., 2018; Jacob et al., 2008; Jacob et al., 2017; Le Cam et al., 2011; Rodgers et al., 2006; Timofeeva et al., 2004; Veinante and Deschenes, 1999; Whitmire et al., 2021). To demonstrate the stimulator's utility, we probed the directional sensitivity of multi-whisker responsive neurons in the trigeminal brainstem. Although stimulator motion will tend to push all whiskers in the same general direction, individual whiskers will deflect against the wire in very different directions based on their geometry and orientation. Thus, the present stimulation approach – which allows each whisker to interact with a stimulus that sweeps through the array – begins to quantify tuning for "global motion" (Vilarchao et al., 2018).

Global motion tuning complements "angular tuning" and "direction preference" of whisker-sensitive neurons (Furuta et al., 2006). Angular tuning refers to the neuron's response to the deflection of a single whisker in specific directions, while directional preference quantifies the extent to which the angular deflection that elicits the largest response is similar for all vibrissae in the neuron's receptive field. Direction preference is computed as the linear sum of individual angular tuning vectors (Furuta et al., 2006). Quantifying global motion tuning is an additional approach towards understanding the neural basis for behaviors such as orienting (Arkley et al., 2014; Cohen et al., 2008), gating incoming sensory input (Chakrabarti and Schwarz, 2018; Furuta et al., 2010; Urbain and Deschenes, 2007), and transforming between whisker, snout, and world coordinate systems (Bush et al., 2016b).

The small sample of neurons shown in Figure 4.2 suggests that neurons exhibit higher firing rates for faster stimulus speeds, appearing to contradict results of an earlier study done by our lab showing the opposite (Kaloti et al., 2016). One possible explanation for the discrepancy is that the slowest speed in the earlier study was much slower than that used here. Such a low speed could potentially cause higher firing rates as bending duration increases. A more likely explanation is that the two studies recorded from very few neurons and were biased towards recording from different brainstem regions.

When combined with appropriate simulations (Zweifel et al., 2021), the stimulator could be used to explore the extent to which neurons are tuned to the mechanics (forces and torques) at the whisker base. In the present study, whiskers were always stimulated approximately halfway along their length or close to their tips. Future work may include a systematic comparison of responses generated when whiskers are stimulated at different locations along their length, permitting a distinction between mechanical and kinematic signals.

5.3 Novel Multi-whisker Stimulator Utility

Through repetitive contacts with multiple whiskers, animals acquire tactile information about their environment (Carvell and Simons, 1990; Harvey et al., 2001; Sachdev et al., 2001). This information-seeking action using the entire sensory apparatus is known as "active sensing" (Adibi et al., 2019). Up until this point, we have studied whisker-mediated touch in a passive way. The stimuli delivered to animals in various preparations have delivered precisely controlled stimulation to an animal who isn't actively moving their whiskers. While we cannot use this novel stimulator to directly study "active sensing", we can use this stimulator in a variety of ways that will allow us to further our understanding of sensorimotor integration.

This novel stimulator could be used to study the context-dependent sensorimotor strategies of exploratory behavior. Exploratory behavior is an information-gathering venture that animals use to learn about their environment. This is a natural behavior for rodents that requires little to no training (Adibi et al., 2019). Other behaviors that do not require training include whisking, free navigation, and gap crossing (Adibi et al., 2019). If we combine these native forms of behavior with our stimulator, however, we can begin to elucidate the causal link between sensation and neuronal activity.

For instance, if we trained awake, head fixed animals to whisk against the nitinol wire, we could have the stimulator move at desired speeds across the whisker array while recording from regions of interest. While this would allow us to investigate questions of active sensing and allows us to observe whisker relevant circuits in their mostly, undisturbed state, having the animals be head-fixed takes away a major component of their whisking behavior: their head movement. There is a great deal of work that has been done that demonstrates that head movements play a crucial

role in determining how whiskers are brought into contact with an object of interest (Hobbs et al., 2016). If one wants to understand whisking behavior as it relates to head movement, they will not get very far with our stimulator. That goes to say that our stimulator would also not be able to help answer scientific questions regarding head movement, head position, head velocity, or head orientation in relation to whisking and exploratory behavior.

As the stimulator stands, we would not be able to easily investigate these questions in the awake, freely behaving animal. Our stimulator, which can traverse the array in a repeatable, controllable way with real-time whisker contact detection, was designed for the study of global motion tuning which has yet to be done in the awake, freely behaving animal. Our stimulator also provides complex stimuli that may be difficult to administer to freely moving animals. Also, recording neurons from a moving animal while accurately tracking whiskers is quite difficult. The best setup to date, in my opinion, that could be used to study these questions is a setup that has been used in our lab before.

Previous work from the Hartmann Lab has tracked rat whisking on the millisecond timescale with the use of a laser light sheet (Hobbs et al., 2016). They created a collimated plane of light using an infrared beam that was placed in front of a glass sheet and this plane of light was interrupted when the animal's whiskers contacted the glass sheet marking where the whiskers made contact (Hobbs et al., 2016). They used this setup to monitor head movements while also quantifying the complete sequence of vibrissal-object contact during exploratory behavior (Hobbs et al., 2016). While researchers of this study used a procedure to detect and quantify the sites of vibrissal-object contact, others can use a combination of these setups to answer questions of behavioral strategies used for exploratory behavior, head movement, position, and orientation,

motion of whisker contact, contact timing, contact patterns, and quantifying the spatiotemporal features of contact intervals.

One way that we would like to use this stimulator is to determine whether the generated mechanical signals at the base of the whisker are represented in the responses of trigeminal brainstem neurons, or any neuron along the vibrisso-trigeminal pathway. It is experimentally challenging to study this particular question because the tools that we would use to physically measure the mechanics of the whisker would also change what the mechanics look like (Whiteley et al., 2015). Using our stimulator combined with a biomechanical model, however, we can predict the forces and rotational moments that occur at the whisker given a set of stimulus parameters (Zweifel et al., 2021). For instance, we can use the stimulator to deliver complex, tactile stimuli to the full whisker array at different points along the whisker length (Fig. 5.1, unpublished). Stimulating the whisker array at these points along the length will change the forces and the moments acting on the whisker while minimally changing the kinematics of the stimulus, allowing us to see the difference, if any, in spike rate patterning as a function of distance. This, in conjunction with a biomechanical model that can simulate the natural sensory input and motor output of the whisker system, will simulate the complete loop of sensorimotor integration (Zweifel et al., 2021).

Largely, we are interested in how sensory organs control the massive amount of sensory information they receive and select the most relevant inputs for behavior. The whisker system is an ideal system to study sensorimotor integration and the relative simplicity of the whiskers allows us to study this complex process of rapid integration of stimulus features and the extrapolation of the features to unknown conditions.

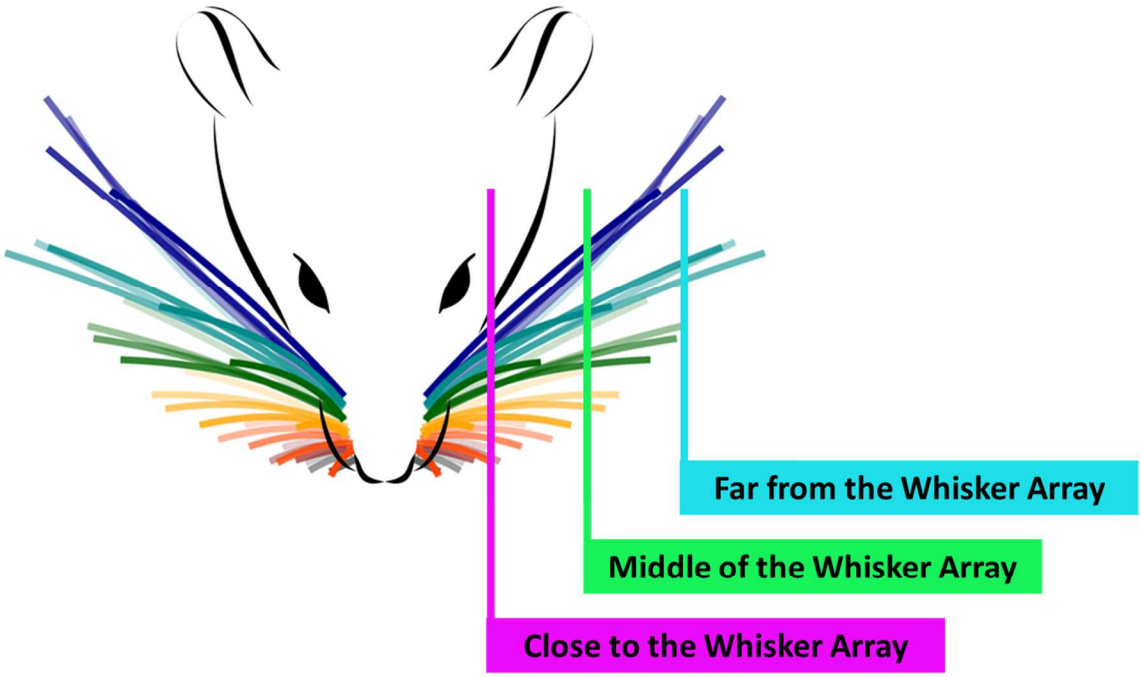

Figure 5.1 – Multi-whisker stimulation along the length of the whisker array. Stimulating the whisker array at these different points along the array will change the forces and moments acting on the whisker while minimally changing the kinematics of the stimulus. Figure adapted from Zweifel, 2021.

References

1. Adibi M. Whisker-Mediated Touch System in Rodents: From Neuron to Behavior. Front Syst Neurosci. 2019 Aug 21;13:40. doi: 10.3389/fnsys.2019.00040. PMID: 31496942; PMCID: PMC6712080.
2. Ahissar E, Kleinfeld D. 2003. Closed-loop neuronal computations: Focus on vibrissa somatosensation in rat. Cerebral Cortex; 13: 53-62.10.1093/cercor/13.1.53
3. Arabzadeh E, Zorzin E, Diamond ME. Neuronal encoding of texture in the whisker sensory pathway. PLoS Biol. 2005 Jan;3(1):e17. doi: 10.1371/journal.pbio.0030017. Epub 2005 Jan 11. PMID: 15660157; PMCID: PMC544542.
4. Arabzadeh, E., Petersen, R. S., & Diamond, M. E. (2003). Encoding of whisker vibration by rat barrel cortex neurons: implications for texture discrimination. The Journal of neuroscience: the official journal of the Society for Neuroscience, 23(27), 9146–9154. https://doi.org/10.1523/JNEUROSCI.23-27-09146.2003
5. Arkley K, Grant RA, Mitchinson B, Prescott TJ. 2014. Strategy change in vibrissal active sensing during rat locomotion. Current Biology; 24: 1507-12.10.1016/j.cub.2014.05.036
6. Armstrong-James M. 1975. Functional status and columnar organization of single cells responding to cutaneous stimulation in neonatal rat somatosensory cortex-s1. Journal of Physiology-London; 246: 501-38.10.1113/jphysiol.1975.sp010902
7. Ashwell KW. The adult mouse facial nerve nucleus: morphology and musculotopic organization. J Anat. 1982 Oct;135(Pt 3):531-8. PMID: 7153172; PMCID: PMC1169402.
8. Axelrad H, Verley R, Farkas E. Responses evoked in mouse and rat SI cortex by vibrissa stimulation. Neurosci Lett. 1976 Dec;3(5-6):265-74. doi: 10.1016/0304-3940(76)90053-7. PMID: 19604897.

9. Bellavance, M.A., M. Demers, and M. Deschenes, Feedforward Inhibition Determines the Angular Tuning of Vibrissal Responses in the Principal Trigeminal Nucleus. Journal of Neuroscience, 2010. 30(3): p. 1057-1063.
10. Belli HM, Bresee CS, Graff MM, Hartmann MJZ. 2018. Quantifying the three-dimensional facial morphology of the laboratory rat with a focus on the vibrissae. Plos One; 13.10.1371/journal.pone.0194981
11. Belli HM, Yang AET, Bresee CS, Hartmann MJZ. 2016. Variations in vibrissal geometry across the rat mystacial pad: Base diameter, medulla, and taper. J. Neurophysiol.; 117: 1807-20.10.1152/jn.00054.2016
12. Benison AM, Ard TD, Crosby AM, Barth DS. 2006. Temporal patterns of field potentials in vibrissa/barrel cortex reveal stimulus orientation and shape. J. Neurophysiol.; 95: 2242-51.10.1152/jn.01034.2005
13. Berg RW, Kleinfeld D. 2003. Rhythmic whisking by rat: Retraction as well as protraction of the vibrissae is under active muscular control. J. Neurophysiol.; 89: 104-17.10.1152/jn.00600.2002
14. Bernhard SM, Lee J, Zhu M, Hsu A, Erskine A, Hires SA, Barth AL. 2020. An automated homecage system for multiwhisker detection and discrimination learning in mice. PLOS ONE; 15: e0232916.10.1371/journal.pone.0232916
15. Bosman L, Houweling A, Owens C, Tanke N, Shevchouk O, Rahmati N, Teunissen W, Ju C, Gong W, Koekkoek S, De Zeeuw C. 2011. Anatomical pathways involved in generating and sensing rhythmic whisker movements. Frontiers in Integrative Neuroscience; 5.10.3389/fnint.2011.00053

16. Brecht M, Preilowski B, Merzenich MM. 1997. Functional architecture of the mystacial vibrissae. Behav. Brain Res.; 84: 81-97

17. Brecht M, Grinevich V, Jin TE, Margrie T, Osten P. Cellular mechanisms of motor control in the vibrissal system. Pflugers Arch. 2006 Dec;453(3):269-81. doi: 10.1007/s00424-006-0101-6. Epub 2006 May 31. PMID: 16736208.

18. Bush NE, Schroeder CL, Hobbs JA, Yang AET, Huet LA, Solla SA, Hartmann MJZ. 2016a. Decoupling kinematics and mechanics reveals coding properties of trigeminal ganglion neurons in the rat vibrissal system. Elife; 5.10.7554/eLife.13969

19. Bush NE, Solla SA, Hartmann MJZ. 2016b. Whisking mechanics and active sensing. Current Opinion in Neurobiology; 40: 178-86.10.1016/j.conb.2016.08.001

20. Bush NE, Solla SA, Hartmann MJZ. 2021. Continuous, multidimensional coding of 3d complex tactile stimuli by primary sensory neurons of the vibrissal system. Proceedings of the National Academy of Sciences of the United States of America; 118.10.1073/pnas.2020194118

21. Campagner D, Evans MH, Bale MR, Erskine A, Petersen RS. 2016. Prediction of primary somatosensory neuron activity during active tactile exploration. Elife; 5.10.7554/eLife.10696

22. Carvell GE, Simons DJ. 1990. Biometric analyses of vibrissal tactile discrimination in the rat. J. Neurosci.; 10: 2638-48

23. Chakrabarti S, Schwarz C. 2018. Cortical modulation of sensory flow during active touch in the rat whisker system. Nat. Commun.; 9.10.1038/s41467-018-06200-6

24. Charpier S, Pidoux M, Mahon S. 2020. Converging sensory and motor cortical inputs onto the same striatal neurons: An in vivo intracellular investigation. Plos One; 15.10.1371/journal.pone.0228260

25. Cohen JD, Hirata A, Castro-Alamancos MA. 2008. Vibrissa sensation in superior colliculus: Wide-field sensitivity and state-dependent cortical feedback. J. Neurosci.; 28: 11205-20.10.1523/jneurosci.2999-08.2008

26. Curtis JC, Kleinfeld D. Seeing what the mouse sees with its vibrissae: a matter of behavioral state. Neuron. 2006 May 18;50(4):524-6. doi: 10.1016/j.neuron.2006.05.004. PMID: 16701202; PMCID: PMC2863010.

27. Deschênes M, Timofeeva E, Lavallée P, Dufresne C. The vibrissal system as a model of thalamic operations. Prog Brain Res. 2005;149:31-40. doi: 10.1016/S0079-6123(05)49003-2. PMID: 16226574.

28. Deschenes M, Timofeeva E, Lavallee P. 2003. The relay of high-frequency sensory signals in the whisker-to-barreloid pathway. J. Neurosci.; 23: 6778-87

29. Dörfl J. The innervation of the mystacial region of the white mouse: A topographical study. J Anat. 1985 Oct;142:173-84. PMID: 17103584; PMCID: PMC1166371.

30. Ebara S, Kumamoto K, Matsuura T, Mazurkiewicz JE, Rice FL. 2002. Similarities and differences in the innervation of mystacial vibrissal follicle-sinus complexes in the rat and cat: A confocal microscopic study. Journal of Comparative Neurology; 449: 103-19

31. Ego-Stengel V, Le Cam J, Shulz DE. Coding of apparent motion in the thalamic nucleus of the rat vibrissal somatosensory system. J Neurosci. 2012 Mar 7;32(10):3339-51. doi: 10.1523/JNEUROSCI.3890-11.2012. PMID: 22399756; PMCID: PMC6621038.

32. El-Boustani S, Sermet BS, Foustoukos G, Oram TB, Yizhar O, Petersen CCH. 2020. Anatomically and functionally distinct thalamocortical inputs to primary and secondary mouse whisker somatosensory cortices. Nat. Commun.; 11: 12.10.1038/s41467-020-17087-7

33. Erzurumlu RS, Bates CA, Killackey HP. Differential organization of thalamic projection cells in the brain stem trigeminal complex of the rat. Brain Res. 1980 Oct 6;198(2):427-33. doi: 10.1016/0006-8993(80)90756-8. PMID: 7407607.

34. Estebanez L, Bertherat J, Shulz DE, Bourdieu L, Leger JF. 2016. A radial map of multi-whisker correlation selectivity in the rat barrel cortex. Nat. Commun.; 7.10.1038/ncomms13528

35. Furuta T, Nakamura K, Deschenes M. 2006. Angular tuning bias of vibrissa-responsive cells in the paralemniscal pathway. J. Neurosci.; 26: 10548-57.10.1523/jneurosci.1746-06.2006

36. Furuta T, Urbain N, Kaneko T, Deschenes M. 2010. Corticofugal control of vibrissa-sensitive neurons in the interpolaris nucleus of the trigeminal complex. J. Neurosci.; 30: 1832-8.10.1523/jneurosci.4274-09.2010

37. Goldin MA, Harrell ER, Estebanez L, Shulz DE. 2018. Rich spatio-temporal stimulus dynamics unveil sensory specialization in cortical area s2. Nat. Commun.; 9.10.1038/s41467-018-06585-4

38. Gottschaldt KM, Iggo A, Young DW. Functional characteristics of mechanoreceptors in sinus hair follicles of the cat. J Physiol. 1973 Dec;235(2):287-315. doi: 10.1113/jphysiol.1973.sp010388. PMID: 4763992; PMCID: PMC1350747.

39. Haidarliu, S., Simony, E., Golomb, D., & Ahissar, E. (2010). Muscle architecture in the mystacial pad of the rat. Anatomical record (Hoboken, N.J. : 2007), 293(7), 1192–1206. https://doi.org/10.1002/ar.21156

40. Harvey, M. A., Bermejo, R., & Zeigler, H. P. (2001). Discriminative whisking in the head-fixed rat: optoelectronic monitoring during tactile detection and discrimination tasks. Somatosensory & motor research, 18(3), 211–222. https://doi.org/10.1080/01421590120072204

41. Hayashi H. (1980). Distributions of vibrissae afferent fiber collaterals in the trigeminal nuclei as revealed by intra-axonal injection of horseradish peroxidase. Brain research, 183(2), 442–446. https://doi.org/10.1016/0006-8993(80)90478-3

42. Hemelt, M. E., Kwegyir-Afful, E. E., Bruno, R. M., Simons, D. J., & Keller, A. (2010). Consistency of angular tuning in the rat vibrissa system. Journal of neurophysiology, 104(6), 3105–3112. https://doi.org/10.1152/jn.00697.2009

43. Herfst, L. J., & Brecht, M. (2008). Whisker movements evoked by stimulation of single motor neurons in the facial nucleus of the rat. Journal of neurophysiology, 99(6), 2821–2832. https://doi.org/10.1152/jn.01014.2007

44. Hires, S. A., Schuyler, A., Sy, J., Huang, V., Wyche, I., Wang, X., & Golomb, D. (2016). Beyond cones: an improved model of whisker bending based on measured mechanics and tapering. Journal of neurophysiology, 116(2), 812–824. https://doi.org/10.1152/jn.00511.2015

45. Hobbs, J. A., Towal, R. B., & Hartmann, M. J. (2016). Spatiotemporal Patterns of Contact Across the Rat Vibrissal Array During Exploratory Behavior. Frontiers in behavioral neuroscience, 9, 356. https://doi.org/10.3389/fnbeh.2015.00356

46. Huet, L. A., Schroeder, C. L., & Hartmann, M. J. (2015). Tactile signals transmitted by the vibrissa during active whisking behavior. Journal of neurophysiology, 113(10), 3511–3518. https://doi.org/10.1152/jn.00011.2015

47. Ito M. 1981. Some quantitative aspects of vibrissa-driven neuronal responses in rat neocortex. J. Neurophysiol.; 46: 705-15

48. Jacob V, Estebanez L, Cam J, Tiercelin JY, Parra P, Paresys G, Shulz DE. 2010. The matrix: A new tool for probing the whisker-to-barrel system with natural stimuli. J. Neurosci. Methods; 189: 65-74.10.1016/j.jneumeth.2010.03.020

49. Jacob V, Le Cam J, Ego-Stengel V, Shulz DE. 2008. Emergent properties of tactile scenes selectively activate barrel cortex neurons. Neuron; 60: 1112-25.10.1016/j.neuron.2008.10.017

50. Jacob V, Mitani A, Toyoizumi T, Fox K. 2017. Whisker row deprivation affects the flow of sensory information through rat barrel cortex. J. Neurophysiol.; 117: 4-17.10.1152/jn.00289.2016

51. Jones LM, Depireux DA, Simons DJ, Keller A. 2004. Robust temporal coding in the trigeminal system. Science; 304: 1986-9.10.1126/science.1097779

52. Jouhanneau, J. S., Ferrarese, L., Estebanez, L., Audette, N. J., Brecht, M., Barth, A. L., & Poulet, J. F. (2014). Cortical fosGFP expression reveals broad receptive field excitatory

neurons targeted by POm. Neuron, 84(5), 1065–1078. https://doi.org/10.1016/j.neuron.2014.10.014

53. Kaloti AS, Johnson EC, Bresee CS, Naufel SN, Perich MG, Jones DL, Hartmann MJZ. 2016. Representation of stimulus speed and direction in vibrissal-sensitive regions of the trigeminal nuclei: A comparison of single unit and population responses. Plos One; 11.10.1371/journal.pone.0158399
54. Kerr FW & Lysak, WR (1964). Somatotopic organization of trigeminal-ganglion neurones. Archives of neurology, 11, 593–602. https://doi.org/10.1001/archneur.1964.00460240025003
55. Kheradpezhouh E, Adibi M, Arabzadeh E. 2017. Response dynamics of rat barrel cortex neurons to repeated sensory stimulation. Scientific Reports; 7.10.1038/s41598-017-11477-6
56. Klein, B. G., Rhoades, R. W. (1985). Representation of whisker follicle intrinsic musculature in the facial motor nucleus of the rat. The Journal of comparative neurology, 232(1), 55–69. https://doi.org/10.1002/cne.902320106
57. Kleinfeld D, Deschenes M. 2011. Neuronal basis for object location in the vibrissa scanning sensorimotor system. Neuron; 72: 455-68.10.1016/j.neuron.2011.10.009
58. Knutsen P. M., Pietr M., Ahissar E. (2006). Haptic object localization in the vibrissal system: behavior and performance. J. Neurosci. 26 8451–8464. 10.1523/JNEUROSCI.1516-06.2006

59. Krupa DJ, Brisben AJ, Nicolelis MAL. 2001a. A multi-channel whisker stimulator for producing spatiotemporally complex tactile stimuli. J. Neurosci. Methods; 104: 199-208.10.1016/s0165-0270(00)00345-9

60. Krupa, D. J., Matell, M. S., Brisben, A. J., Oliveira, L. M., & Nicolelis, M. A. (2001b). Behavioral properties of the trigeminal somatosensory system in rats performing whisker-dependent tactile discriminations. The Journal of neuroscience: the official journal of the Society for Neuroscience, 21(15), 5752–5763. https://doi.org/10.1523/JNEUROSCI.21-15-05752.2001

61. Krupa, D. J., Wiest, M. C., Shuler, M. G., Laubach, M., & Nicolelis, M. A. (2004). Layer-specific somatosensory cortical activation during active tactile discrimination. Science (New York, N.Y.), 304(5679), 1989–1992. https://doi.org/10.1126/science.1093318

62. Laturnus S, Hoffmann A, Chakrabarti S, Schwarz C. 2021. Functional analysis of information rates conveyed by rat whisker-related trigeminal nuclei neurons. J. Neurophysiol.; 125: 1517-31.10.1152/jn.00350.2020

63. Le Cam J, Estebanez L, Jacob V, Shulz DE. 2011. Spatial structure of multiwhisker receptive fields in the barrel cortex is stimulus dependent. J. Neurophysiol.; 106: 986-98.10.1152/jn.00044.2011

64. Leiser SC, Moxon KA. 2007. Responses of trigeminal ganglion neurons during natural whisking behaviors in the awake rat. Neuron; 53: 117-33.10.1016/j.neuron.2006.10.036

65. Lichtenstein SH, Carvell GE, Simons DJ. 1990. Responses of rat trigeminal ganglion neurons to movements of vibrissae in different directions. Somatosensory and Motor Research; 7: 47-65

66. Lyall, E. H., Mossing, D. P., Pluta, S. R., Chu, Y. W., Dudai, A., & Adesnik, H. (2021). Synthesis of a comprehensive population code for contextual features in the awake sensory cortex. eLife, 10, e62687. https://doi.org/10.7554/eLife.62687

67. Mazurek M, Kager M, Van Hooser SD. 2014. Robust quantification of orientation selectivity and direction selectivity. Frontiers in neural circuits; 8: 92-.10.3389/fncir.2014.00092

68. Mehta S. B., Whitmer D., Figueroa R., Williams B. A., Kleinfeld D. (2007). Active spatial perception in the vibrissa scanning sensorimotor system. PLoS Biol. 5:e15 10.1371/journal.pbio.0050015

69. Melzer P, Vanderloos H, Dorfl J, Welker E, Robert P, Emery D, Berrini JC. 1985. A magnetic device to stimulate selected whiskers of freely moving or restrained small rodents - its application in a deoxyglucose study. Brain Research; 348: 229-40.10.1016/0006-8993(85)90441-x

70. Minnery, B. S., & Simons, D. J. (2003). Response properties of whisker-associated trigeminothalamic neurons in rat nucleus principalis. Journal of neurophysiology, 89(1), 40–56. https://doi.org/10.1152/jn.00272.2002

71. Moore J. D., Lindsay N. M., Deschenes M., Kleinfeld D. (2015). Vibrissa self-motion and touch are reliably encoded along the same somatosensory pathway from brainstem through thalamus. PLoS Biol. 13:e1002253 10.1371/journal.pbio.1002253

72. O'Connor D. H., Clack N. G., Huber D., Komiyama T., Myers E. W., Svoboda K. (2010). Vibrissa-based object localization in head-fixed mice. J. Neurosci. 30 1947–1967. 10.1523/jneurosci.3762-09.2010

73. Pierret, T., Lavallée, P., & Deschênes, M. (2000). Parallel streams for the relay of vibrissal information through thalamic barreloids. The Journal of neuroscience: the official journal of the Society for Neuroscience, 20(19), 7455–7462. https://doi.org/10.1523/JNEUROSCI.20-19-07455.2000

74. Pluta SR, Lyall EH, Telian GI, Ryapolova-Webb E, Adesnik H. 2017. Surround integration organizes a spatial map during active sensation. Neuron; 94: 1220-33.e5.10.1016/j.neuron.2017.04.026

75. Ramirez A, Pnevmatikakis EA, Merel J, Paninski L, Miller KD, Bruno RM. 2014. Spatiotemporal receptive fields of barrel cortex revealed by reverse correlation of synaptic input. Nat. Neurosci.; 17: 866-75.10.1038/nn.3720

76. Rice F. L. (1993). Structure, vascularization, and innervation of the mystacial pad of the rat as revealed by the lectin Griffonia simplicifolia. The Journal of comparative neurology, 337(3), 386–399. https://doi.org/10.1002/cne.903370304

77. Rice FL, Fundin BT, Arvidsson J, Aldskogius H, Johansson O. 1997. Comprehensive immunofluorescence and lectin binding analysis of vibrissal follicle sinus complex innervation in the mystacial pad of the rat. Journal of Comparative Neurology; 385: 149-84

78. Rice FL, Mance A, Munger BL. 1986. A comparative light microscopic analysis of the sensory innervation of the mystacial pad .1. Innervation of vibrissal follicle-sinus complexes. Journal of Comparative Neurology; 252: 154-74

79. Rodgers KM, Benison AM, Barth DS. 2006. Two-dimensional coincidence detection in the vibrissa/barrel field. J. Neurophysiol.; 96: 1981-90.10.1152/jn.00404.2006

80. Sachdev, R. N., Sellien, H., & Ebner, F. (2001). Temporal organization of multi-whisker contact in rats. Somatosensory & motor research, 18(2), 91–100. https://doi.org/10.1080/135578501012006192

81. Severson KS, Xu D, Van de Loo M, Bai L, Ginty DD, O'Connor DH. 2017. Active touch and self-motion encoding by merkel cell-associated afferents. Neuron; 94: 666-+.10.1016/j.neuron.2017.03.045

82. Shipley MT. 1974. Response characteristics of single units in rats trigeminal nuclei to vibrissa displacements. J. Neurophysiol.; 37: 73-90.10.1152/jn.1974.37.1.73

83. Simons DJ. 1983. Multi-whisker stimulation and its effects on vibrissa units in rat sml barrel cortex. Brain Research; 276: 178-82.10.1016/0006-8993(83)90561-9

84. Sosnik R, Haidarliu S, Ahissar E. 2001. Temporal frequency of whisker movement. I. Representations in brain stem and thalamus. J. Neurophysiol.; 86: 339-53.10.1152/jn.2001.86.1.339

85. Szwed M, Bagdasarian K, Blumenfeld B, Barak O, Derdikman D, Ahissar E. 2006. Responses of trigeminal ganglion neurons to the radial distance of contact during active vibrissal touch. J. Neurophysiol.; 95: 791-802

86. Timofeeva E, Lavallee P, Arsenault D, Deschenes M. 2004. Synthesis of multiwhisker-receptive fields in subcortical stations of the vibrissa system. J. Neurophysiol.; 91: 1510-5.10.1152/jn.01109.2003

87. Timofeeva E, Mérette C, Emond C, Lavallée P, Deschênes M. A map of angular tuning preference in thalamic barreloids. J Neurosci. 2003 Nov 19;23(33):10717-23. doi: 10.1523/JNEUROSCI.23-33-10717.2003. PMID: 14627657; PMCID: PMC6740914.

88. Towal RB, Quist BW, Gopal V, Solomon JH, Hartmann MJZ. 2011. The morphology of the rat vibrissal array: A model for quantifying spatiotemporal patterns of whisker-object contact. Plos Computational Biology; 7.10.1371/journal.pcbi.1001120

89. Tsur, O., Khrapunsky, Y., & Azouz, R. (2019). Sensorimotor integration in the whisker somatosensory brain stem trigeminal loop. Journal of neurophysiology, 122(5), 2061–2075. https://doi.org/10.1152/jn.00116.2019

90. Urbain N, Deschenes M. 2007. Motor cortex gates vibrissal responses in a thalamocortical projection pathway. Neuron; 56: 714-25.10.1016/j.neuron.2007.10.023

91. Veinante P, Deschenes M. 1999. Single- and multi-whisker channels in the ascending projections from the principal trigeminal nucleus in the rat. J. Neurosci.; 19: 5085-95

92. Vilarchao ME, Estebanez L, Shulz DE, Ferezou I. 2018. Supra-barrel distribution of directional tuning for global motion in the mouse somatosensory cortex. Cell Reports; 22: 3534-47.10.1016/j.celrep.2018.03.006

93. Welker E, Rao SB, Dorfl J, Melzer P, Vanderloos H. 1992. Plasticity in the barrel cortex of the adult-mouse - effects of chronic stimulation upon deoxyglucose uptake in the behaving animal. J. Neurosci.; 12: 153-70

94. Welker WI. 1964. Analysis of sniffing of the albino rat. Behavioural Brain Research; 22: 223-44

95. Whiteley, S. J., Knutsen, P. M., Matthews, D. W., & Kleinfeld, D. (2015). Deflection of a vibrissa leads to a gradient of strain across mechanoreceptors in a mystacial follicle. Journal of neurophysiology, 114(1), 138–145. https://doi.org/10.1152/jn.00179.2015

96. Whitmire CJ, Liew YJ, Stanley GB. 2021. Thalamic state influences timing precision in the thalamocortical circuit. J. Neurophysiol.; 125: 1833-50.10.1152/jn.00261.2020

97. Woolsey, T. A., & Van der Loos, H. (1970). The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. Brain research, 17(2), 205–242. https://doi.org/10.1016/0006-8993(70)90079-x

98. Yu YSW, Bush NE, Hartmann MJZ. 2019. Whisker vibrations and the activity of trigeminal primary afferents in response to airflow. J. Neurosci.; 39: 5881-96.10.1523/jneurosci.2971-18.2019

99. Zucker, E., & Welker, W. I. (1969). Coding of somatic sensory input by vibrissae neurons in the rat's trigeminal ganglion. Brain research, 12(1), 138–156. https://doi.org/10.1016/0006-8993(69)90061-4

100. Zweifel NO, Bush NE, Abraham I, Murphey TD, Hartmann MJZ. 2021. A dynamical model for generating synthetic data to active tactile behavior in the rat. Proceedings of the National Academy of Sciences of the United States of America; 118.10.1073/pnas.2011905118

Vita

Schnaude Dorizan

RESEARCH OBJECTIVE

My long-term research interests involve understanding the neural mechanisms that underlie behavior. My ongoing research is focused on using the rodent vibrissa (whisker) system as a model to investigate the neurobiological mechanisms of sensorimotor integration in the rodent brainstem. My goal is to build an inclusive scientific community by creating opportunities for students from disadvantaged backgrounds and increasing access through mentorship and advocacy.

EDUCATION

Northwestern University, Evanston, IL
PhD in Systems Neuroscience February 2022
Dissertation: "Sensory Representation of Stimulus Features in the Rodent Whisker-Responsive Trigeminal Brainstem."

Kellogg School of Management at Northwestern University, Evanston, IL
Certificate in Management for Scientists and Engineers August 2021

University of Maryland Baltimore County, Baltimore, MD
BS in Biology & BS in Psychology May 2013

RESEARCH EXPERIENCE

Northwestern University, Interdepartmental Neuroscience Program (NUIN) June 2019 - Present
PhD Candidate
Mentor: Mitra Hartmann, PhD
Project: "Representation of Stimulus Velocity and Direction in the Rodent Spinal Trigeminal Nucleus Interpolaris."
Skills: Electrophysiology (*in vivo*), animal handling and surgery, animal behavior and behavioral analysis, histology

Northwestern University, NUIN Sept. 2015 - April 2019
PhD Candidate
Mentors: John F. Disterhoft, PhD & Joel L. Voss, PhD
Project: "Developing a Model of Memory Facilitation by Stimulating Cortical-Hippocampal Networks in Rats."
Skills: Electrophysiology (*in vivo*), animal handling and surgery, animal behavior and behavioral analysis

Albert Einstein College of Medicine, Department of Neuroscience Aug. 2013 - July 2015
Post-baccalaureate Research Education Program (PREP) Scholar
Mentor: Kamran Khodakhah, PhD
Project: "A Monosynaptic Pathway from the Cerebellum to the Ventral Tegmental Area May Modulate Sociability in Mice."
Skills: Electrophysiology, animal surgery, statistical analyses, animal behavior, optogenetics

Northwestern University, Department of Physiology June 2012 - Aug. 2012
Research Intern, Summer Research Opportunity Program
Mentor: John F. Disterhoft, PhD
Project: "Neuroanatomical Projections of the Perirhinal Cortex and Examination of Prefrontal Cortex in Trace Eyeblink Conditioning in Rabbits."
Skills: Animal handling and surgery, neuroanatomy, animal behavior, optogenetics

PUBLICATIONS

♦ Carta, I., Chen, C., Schott, A. L., **Dorizan, S.**, Khodakhah, K. (2019). "Cerebellar modulation of the reward circuitry and social behavior." Science 363(6424).
♦ **Dorizan, S.**, Kleczka, K. J., Resulaj, A., Alston, T., Bresee, C. S., Hartmann, M. J. (2022). "A novel stimulator to investigate the tuning of multi-whisker responsive neurons for speed and the direction of global motion." J. Neurosci. Accepted with revisions.

PROFESSIONAL & LEADERSHIP POSITIONS

♦ Leadership Coaching
Center for Leadership, Northwestern University 2021
- Executive leadership coaching designed to significantly build on leadership strengths, explore potential, and advance personal leadership goals. Participants work through leadership challenges, such as developing collaborative teamwork strategies, improving team communication, accountability, and impact, and raising the overall effectiveness of one's mission.

♦ Graduate Intern for the Inclusive Teaching in STEM Education Project
Searle Center for Advancing Learning & Teaching, Northwestern University 2020 - Present
- Is a multi-institutional, five-year, NSF-funded program that engages in deep reflection and discussions around topics of equity and inclusion in learning environments across a variety of institutional contexts. Interns facilitate the improvement of awareness, self-efficacy, and ability of graduate students, postdocs, and faculty to create inclusive STEM learning environments for their students by creating prompts and facilitating discussion on affinity groups discussion board and on local and distributed (virtual) learning communities

♦ Summer Research Opportunity Program (SROP) Group Leader
Office of Diversity and Inclusion, Northwestern University 2019, 2020
- SROP is a seven-week research experience at Northwestern University for sophomores and juniors from colleges and universities across the United States. Group Leaders support the planning and execution of SROP, lead and mentor a cohort of five SROP participants, provide weekly guidance and detailed feedback on participant assignments and presentations, serve as a liaison between the Office of Diversity and Inclusion and the SROP program, work collaboratively with fellow SROP Group Leaders to organize and facilitate seminars, plan 2-3 professional development workshops during SROP, and serve as an event manager for SROP social, academic, and professional events

♦ Graduate Intern for the Office of Diversity and Inclusion
Office of Diversity and Inclusion, Northwestern University 2018 - 2019
- Organize and execute the Summer Research Opportunity Program, recruit diverse students at local and regional conferences, and provide valuable feedback on the diversity and retention initiatives carried out by The Graduate School

♦ Skills & Careers in Science Writing
Medill School of Journalism, Northwestern University 2018
- Course focuses on storytelling techniques and best practices for science writing/communication. Students gain exposure to career possibilities and hone their writing skills through authentic writing and editorial assignments. The course will help STEM PhD trainees write clearly and speak confidently about their own research, providing a solid foundation for future pursuits in science writing and communication

♦ Founder and Leader of the Graduate Women of Color Association
Student Organization, Northwestern University 2019 - Present
- Lead monthly meetings that specifically addresses the need of graduate women of color in higher education; create a space where women across disciplines come together to build community, exchange resources, and engage in peer mentorship

♦ President of the Black Graduate Student Association
Student Organization, Northwestern University 2018 - Present
- Retain the growing diverse group at Northwestern by cultivating events and programs that are relevant to the Black graduate population including the Annual Graduate Research Conference; support the mental, physical, social, and emotional well-being of these students

♦ Research Communication Training Program: Participant
Office of STEM Education, Northwestern University 2016, 2019
- Increase the awareness for the urgent need of excellent science communication and to coach graduate and post-doc researchers to improve their own presentation skills. The program focuses

on three important components of communication: building confidence in all communication roles, enhancing the clarity of the message, and forming a connection with any audience

♦ **Mentored Discussions of Teaching**
Searle Center for Advancing Learning & Teaching, Northwestern University 2016
- Course is designed to engage STEM graduate students and postdoctoral fellows in discussions with faculty about teaching and learning. Students are invited to observe faculty teaching undergraduate or early graduate courses and meet with faculty to discuss their perspectives and methods. Participants also engage in group discussions on selected readings that address key topics in teaching.

♦ **NUIN Student Advisory Council**
Interdepartmental Neuroscience, Northwestern University 2015 - Present
- Advocate for and communicate the needs of fellow graduate students to faculty and administration; also aid in organizing student participation in NUIN activities such as the annual retreat and recruitment events

GRANTS & FELLOWSHIPS

♦ The General Motor Control and Mechanisms of Disease T32 Training Grant 2020 - Present
♦ The Neuroscience of Human Cognition T32 Training Grant 2017 - 2019
♦ Collaborative Learning and Integrate Mentoring in the Biosciences Fellowship 2015 – 2017

AWARDS & HONORS

♦ McBride Student Award at Northwestern University 2021
♦ Edward Bouchet Graduate Honor Society Inductee at Yale University 2019
♦ Summer Research Opportunity Program Group Leader 2019, 2020
♦ Neuroscience Roadmap Scholar 2017 - Present
♦ National Enhancement of Underrepresented Academic Leaders (NEURAL) Conference 2017
1st Place Oral Presentation Recipient
♦ The Black Graduate Student Association (BGSA) Annual Research Conference 2017
1st Place Poster Presentation Recipient
♦ The National GEM Consortium: GEM Associate Fellow 2015 - Present
♦ Annual Biomedical Research Conference for Minority Students FASEB-MARC Travel Award Recipient 2013
♦ Ronald E. McNair Program: McNair Scholar 2010 - 2013
♦ Meyerhoff Scholars Program: Meyerhoff Scholar 2009 - 2013

SELECT CONFERENCE PRESENTATIONS

♦ "Developing a Model of Memory Facilitation by Stimulating Cortical-Hippocampal Networks in Rats."

- Poster presentation at the Cognitive Neuroscience Society Annual Meeting in San Francisco, March 2019
- Oral presentation at the Annual NEURAL Conference at the University of Alabama-Birmingham, June 2017
- Poster presentation at the BGSA Annual Research Conference in Chicago, IL, April 2017
- Seven Minutes of Science Symposium at Northwestern University in Chicago, IL , Sept. 2016

TEACHING EXPERIENCE

♦ Instructor, "Graduate Student Led Qualifying Exam Prep", (graduate, developed course to prepare pre-candidate graduate students for their qualifying exams). Schnaude Dorizan, Interdepartmental Neuroscience Program, Spring 2019 - Fall 2019

♦ Teaching Assistant, "Neuroscience of Brain Disorders" (undergraduate). Dr. Valarie Kilman, Department of Neurobiology, Northwestern University, Fall 2016

♦ Teaching Assistant, "Neurobiology of Learning and Memory" (undergraduate). Dr. Catherine Woolley, Department of Neurobiology, Northwestern University, Spring 2017

♦ Tutor, N'CAT Tutors: Student-athlete Tutoring (undergraduate), Athletics Department, Northwestern University, Fall 2017 - Fall 2018

♦ Instructor, "Brain-boozled! Misinformation and Your Brain" (high school). Schnaude Dorizan, Splash!, April 2017

PROFESSIONAL SOCIETY MEMBERSHIPS

♦ Society for Neuroscience 2009 - Present
♦ Barrels: Rodent Whisker-to-Barrels Society 2019 - Present
♦ Cognitive Neuroscience Society 2018
♦ Golden Key International Honour Society 2009 - 2013

COMMUNITY OUTREACH & VOLUNTEER SERVICE

♦ Northwestern University Brain Awareness Outreach 2015 - Present
♦ Black Creativity Jr. Science Café Series at the Museum of Science and Industry Feb. 2017, 2018, 2019, 2020
♦ Family Matters: Mentoring, Tutoring, and Leadership 2016 - Present
♦ Alder Planetarium: Invited Guest Speaker at Youth Council Event 2018
♦ Mentor Matching Engine: Online Mentoring for High School Students 2016 - 2018
♦ Introduction to Graduate Education at Northwestern University 2017 - Present

LANGUAGES AND SKILLS

♦ Haitian-Creole Native/bilingual

♦ Software Skills:
- Microsoft Office - Word, Outlook, Excel, PowerPoint, Skype
- Google - Calendar, Docs, Gmail, Drive, Hangouts
- Adobe - Acrobat DC, Illustrator
- Canvas: Instructure Tools for Online Learning
- Neuralynx Neural Acquisition Systems, Neuroexplorer
- MATLAB

♦ Administrative Skills:
- Refined Organizational Abilities
- Multi-Calendar Management
- Answering and Routing Calls
- Office Supply Purchases/Inventory
- Facilities Management
- Liaison with Vendors
- Greeting Clients/Guests

EXTRACURRICULAR ACTIVITIES

♦ Alliance of Chicago Minority Students Organization
♦ Diversity in Biological Sciences Council
♦ Chicago Graduate Student Association
♦ Rainbow Children Dance Collective
♦ Kung Fu