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				19b. TELEPHONE NUMBER 574-631-7488	

RPPR Final Report
as of 24-Jan-2019

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INVESTIGATOR(S):

Name: Lei Li
Email: Li.78@nd.edu
Phone Number: 5746317488
Principal: Y

Organization: **University of Notre Dame**

Address: ND Research, Notre Dame, IN 465565708

Country: USA

DUNS Number: 824910376

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Final Report for Period Beginning 01-Aug-2016 and Ending 30-Apr-2017

Title: Melatonin modulation of the olfacto-retinal centrifugal visual pathway

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Submitted By: Lei Li

Email: Li.78@nd.edu

Phone: (574) 631-7488

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STEM Participants: 3

Major Goals: The objective of the proposed research is to elucidate the mechanisms and roles of cross-modal sensory information integration in the regulation of vertebrate visual system functions. In previous studies, we demonstrated that in zebrafish, olfactory signals propagate to the retina via the olfacto-retinal centrifugal pathway, and that the input from the olfactory bulb increases visual sensitivity through dopaminergic and GnRH mediated retinal pathways. In this research, we will study the role of endocrine hormones (such as melatonin) on the process of centrifugal visual modulation. In Aim-1, we will determine the expression of melatonin receptors in the centrifugal visual pathway and examine the role of melatonin released from the pineal gland on the olfacto-retinal pathway. In Aim-2, based on the results obtained from animal studies, we will create neural computational models that represent multi-organ sensory integration and predict the consequence of sensory integration in visual modulation.

Accomplishments: During the funding period, we conducted research using zebrafish models (behavioral visual test, retinal ganglion cell recording, etc) and based on findings from wet-lab research, we created computer models that can interpret the outcome of multi-sensory integration between different organs (e.g., retina, olfactory bulb, and to some extent, the pineal gland). The results from this research has accepted by Frontiers In Computational Neuroscience for publication. In summary, we accomplished all the goals proposed in the research plan.

Training Opportunities: During the finding period, we trained two undergraduate students (John Malin, Jennifer Wojtowicz) and one graduate student (Sreya Banerjee). All of them were from the University of Notre Dame. The undergraduate students have graduated from Notre Dame and they are now in medical schools to pursue MD degrees. The graduate student is still in the Ph.D. program at Notre Dame.

Results Dissemination: Nothing to Report

Honors and Awards: Jennifer Wojtowicz received University of Notre Dame Dean's Research Award for her research conducted in my laboratory. Her research was support by this grant.

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Technology Transfer: Nothing to Report

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Article Title: An Extreme Value Theory Model of Cross-Modal Sensory Information Integration in Modulation of Vertebrate Visual System Functions

Authors: Sreya Banerjee, Walter J Scheirer, Lei Li

Keywords: cross-modal sensory integration, statistical extreme value theory, classification, olfaction, vision, zebrafish

Abstract: We propose a computational model of vision that describes the relationship between olfactory input and visual sensitivity of zebrafish based on the principles of the statistical extreme value theory. This relationship is mediated through centrifugal input which makes possible the physical connections between the neural retina and olfactory bulb. Motivation for using extreme value theory stems from physiological evidence suggesting that extremes and not the mean of the cell responses direct cellular activity in the vertebrate brain. We argue that the visual system, as measured by retinal ganglion cell responses in spikes/sec, follows an extreme value process for sensory integration and the increase in visual sensitivity from the olfactory input can be better modeled using extreme value distributions. As zebrafish maintains high evolutionary proximity to mammals, our model can be extended to other vertebrates as well.

Distribution Statement: 1-Approved for public release; distribution is unlimited.

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RESEARCH SUMMARY

The goal of the proposed research is to characterize the roles of multi-sensory inputs in retinal function using zebrafish models and creates computer models that predict and analyze the roles of sensory integration in retinal sensitivity. Based on our previous works of zebrafish olfacto-retinal centrifugal (ORC) modulation, we proposed to create computational models that describe the relationship between olfactory input and visual sensitivity based on the principles of the statistical extreme value theory (EVT). We hypothesized that this type of relationship is mediated through centrifugal input which makes possible the physical connections between the neural retina and olfactory bulb. Motivation for using EVT stems from physiological evidence suggesting that extremes and not the mean of the cell responses direct cellular activity in the vertebrate brain. We felt that it is likely that the visual system, as measured by retinal ganglion cell responses in spikes/sec, follows an extreme value process for sensory integration and the increase in visual sensitivity from the olfactory input can be better modeled using extreme value distributions. Some of the research results have been published.

Determine the expression of melatonin receptors in the retina and the role of melatonin on zebrafish visual sensitivity

During the funding period, most of the wet-lab researches have been focused on the characterization of the expression of melatonin receptors in the retina. Based on public NCBI information, we designed melatonin receptor primers (for RT-PCR) and probes (for in situ hybridization) and tested the expression of melatonin receptors using single-cell and whole-mount preparations. We obtained positive results but they were preliminary. We will be confirmed our findings with more experiments.

Create computational frameworks for multi-sensory integration

There are different types of extreme value theorems one can make use of, and we limited ourselves to Pareto distribution, which is derived from the Pickands-Balkema-de Haam Theorem. Several sets of experiments were performed to create the computer models based on the firing patterns from the zebrafish works.

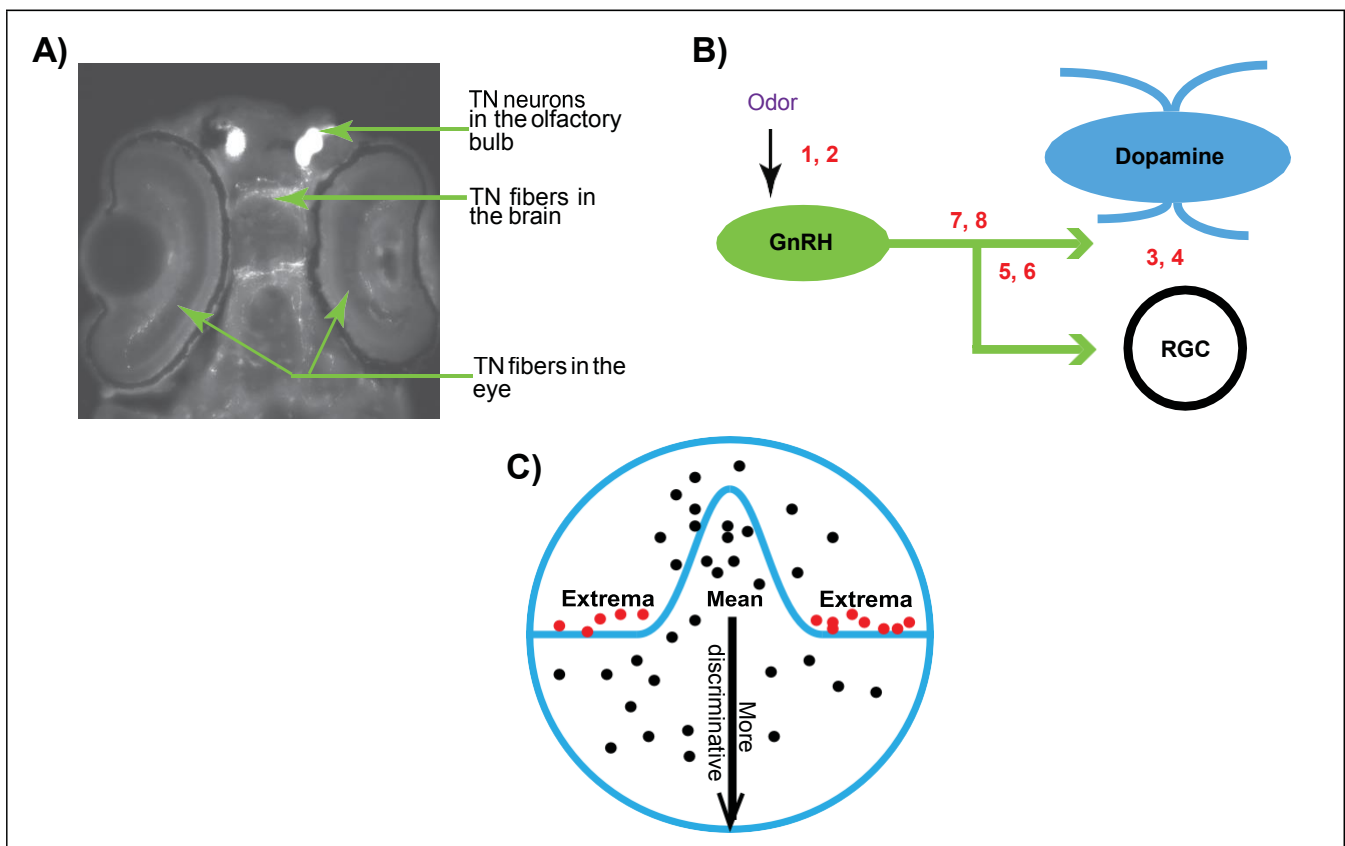
Experiment 1: One of our initial experiments was to check whether the raw data we collected from the experiments confirms our hypothesis that the EVT can be applied to build an accurate model. We posited that since the retinal ganglion cell (RGC) responses with olfactory stimulation represent extreme aberration from the baseline and are non-negative integers, the Weibull distribution could be a perfect candidate for modeling our data. But how differently does our data fit with the Weibull distribution versus a central tendency model like the Gaussian distribution? We explored this in our first experiment by comparing our data with the Weibull and Gaussian distributions. Using the data collected from experiments as a basis, we simulated an expansive data space by fitting distributions over the original data. Initially, we assumed that the distribution of RGC responses in zebrafish through its entire lifecycle would be Gaussian. To confirm our assumption, we performed two tests of normality: a Kolmogorov Smirnov test and a Lilliefors test. Based on the results of the normality tests, we fitted Gaussian distribution to our data with olfactory stimulus. However, the distribution of data without olfactory stimulus was found out to be non-Gaussian. Then, we used Bayesian Information criteria to find the best fit. We conclude that the distribution for the data was found out to be Generalized Pareto. Afterwards, we generated 100,000 non-negative samples of RGC responses from the respective distributions for further analysis.

Experiment 2: The second set of experiments were conducted to verify whether or not the samples generated after fitting distributions to data with or without olfactory stimulus conform to our hypothesis of EVT and how olfactory signals affect visual sensitivity in fishes throughout its' entire lifecycle. To this end, we fitted a Weibull distribution to the top n RGC responses in order to understand how the curves varied when olfactory input was present as opposed to when it was not. The value n was selected via empirical observation. Sampling methods used were random sampling and sampling using Markov Chain Monte Carlo method. Because EVTs applied to samples at the tails of distributions,

independent of the underlying distribution of the data was expected. We expected the Weibull cumulative distributions for data with and without olfaction to be widely separated, giving some probability to RGC responses below the threshold which was practically improbable under normal situations (without olfaction).

Experiment 3: Additionally, we wanted to corroborate whether we could define a deterministic indicator function such that given some RGC response. It is possible that we identify the function of final sensory function as if olfactory stimuli were present or not. In this experiment, we used a linear perceptron and a multi-layer perceptron as binary classifiers. We assumed that each RGC response could be represented as a vector of points. At the end, the model was created after we retrieved 22 data points from wet-bench experiments. We used 100,000 samples for each dataset (with olfactory stimulus and without olfactory stimulus) by dividing the data into two sets: 80-percent as training and 20-percent as testing partition.

Research strategies are outlined below:



Diagrams of proposed research: from animals to computer models. (A) A fluorescent image of a zebrafish (dorsal view, anterior is up) showing the terminalis neurons and axons in the olfactory bulb and retina. (B) A schematic drawing of the experimental setup for RGC recordings in response to olfactory and TN stimulation. The numbers correspond with the following conditions: 1,2 - sham or odor stimulation; 3,4 - activation or inhibition of dopamine receptors; 5,6 - activation or inhibition of GnRH receptors; 7,8 - manipulation of dopamine and GnRH receptors. (C) An overview of EVT modeling. Prior work suggested that it is the extremes (red dots), not the mean (black dots near the center of the circle), that produces strong responses in the brain.