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Project Acronym: SEROTONINSLEEP

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SEROTONERGIC REGULATION OF SLEEP RELATED NEURAL CIRCUITS

Marie Curie Actions
Final Report

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Publishable summary

In recent years, remarkable emphasis has been focused on unraveling the mysteries of the brain on large scales. Efforts such as the Obama BRAIN initiative and EU Human Brain Project and channeled billions of dollars into brain research in order to accelerate the understanding of brain function and combat debilitating disease. Much of the progress towards these goals promises to be made in small model organisms, where scale is tractable and technological manipulations are both feasible and ethical. The larval zebrafish is a particularly auspicious model organism because its translucent brain enables analyses that were never before possible. As genetically encoded calcium indicators can be used to image the activity of the entire brain at cellular resolution in a single experiment, researchers now have an unprecedented window into the circuits underlying behavior and behavioral states. Of these behavioral states, sleep and wakefulness are particularly interesting because even though they are so ubiquitous across animals, little is known about their purpose or mechanism.

To investigate how sleep and wakefulness are regulated in the larval zebrafish, we sought to characterize a robust, lab-reproducible behavior that could be used to study the interaction of serotonergic and hypocretin neurotransmitter systems in the brain. We quickly converged on the zebrafish optomotor response (OMR), as it has a strong foundation in the literature and reflects a relatively simple visuomotor transformation poised for modulation by accessory neural circuits. By exploring the relationship between this behavior and its underlying brain-wide circuit dynamics, we reasoned that we could both establish new tools for interpreting large-scale neural data and identify candidate brain regions, based on activity and anatomy, for intersection with neuromodulatory systems.

To investigate the central neural computations of the zebrafish OMR, we recorded swimming behavior in response to monocular and binocular motion. Detailed kinematic analysis and minimal modeling approaches revealed the general algorithms guiding eye- and direction-specific locomotion: swim bout frequency and orientation change were modulated independently, suggesting separate but overlapping information channels for egocentrically defined motion patterns. To chart the complete neural circuit, we used whole-brain and targeted two-photon calcium imaging, cluster analysis of neural response classes, ablations and anatomical tracings. Our observations implicate a specific retino-recipient arborization field (AF6) as the monocular, direction-selective sensory entry site to the circuit. Downstream, the primary information processing occurs in lateralized pretectal nuclei that integrate motion binocularly and provide necessary reciprocal suppression via an interhemispheric connection. Subsequent locomotor instructions are then refined and demixed along behavioral axes in specific premotor areas. Investigation of possible model spaces and architectures, using observed neuronal response classes, identified the

significant dimensions of functional connectivity that were most critical for explaining the behavior. Together, our experiments and modeling provide a whole-brain description of the zebrafish OMR that establishes a framework for studying complementary behaviors and neural systems.

We chose to investigate the OMR because it is an accessible gateway to a fundamental sensorimotor transformation layered with rich complexity. While we address the feed-forward foundation of the OMR with a simple orthogonal stimulus set, the circuit properties revealed here provide a strong basis for future probes of other stimulus-action relationships. Indeed, complementary studies of behaviors that hope to explain sleep and wakefulness on brain-wide scales must necessarily ground themselves in this elementary system controlling a basal behavior. The framework presented here thus provides a strong foundation for future studies of how sleep, wakefulness, and pharmacology can affect neural activity and behavior across a vertebrate brain.

Expected final results and their potential impact and use (including the socio-economic impact and the wider societal implications of the project so far)

A major goal of neuroscience is to link brain-wide activity to behavior. With this project, I have made great strides towards understanding a simple vertebrate behavior. This allowed me to propose theoretical models that will be crucial for understanding more complex behavioral phenomena such as state-dependent behavior, as observed during sleep and wake cycles. I have contributed to multiple studies over the course of the SEROTONINSLEEP project, learned and implemented new technology, and made advances in the theoretical interpretation of large-scale neural data.

Publications and prepared manuscripts during SEROTONINSLEEP project

Whole-brain activity mapping onto a zebrafish brain atlas
Owen Randlett, Caroline L. Wee, **Eva A. Naumann**, Onyeka Nnaemeka, David Schoppik, James E Fitzgerald, Ruben Portugues, Alix M B Lacoste, Clemens Riegler, Florian Engert & Alexander F Schier
Nature Methods (2015) doi:10.1038/nmeth.3581 14 September 2015

Neural circuits underlying visually evoked escapes in larval zebrafish
Timothy W. Dunn, Christoph Gebhardt, **Eva A. Naumann**, Misha B. Ahrens, Florian Engert, & Filippo Del Bene (in press at Neuron)

A neural basis for the modulation of spontaneous behavior in larval zebrafish

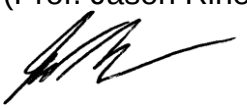
*Timothy W. Dunn, *Yu Mu, Sujatha Narayan, **Eva A. Naumann**, Chao-Tsung Yang, Owen Randlett, Alexander F. Schier, Jeremy Freeman, Florian Engert, & Misha B. Ahrens (submitted to eLife)

Satiation state-dependent regulation of appetite by zebrafish serotonergic circuits"
Caroline Wee, Robert E. Johnson, Erin Song, Owen Randlett, Jimmy Bohnslav, Maxim Nikitchenko, Josua Jordi, Adam D. Douglass, **Eva A. Naumann**, Jared Wortzman, Thomas Panier, Abhinav Grama, Koichi Kawakami, Florian Engert, & Samuel Kunes (in preparation)

Neural architectures for visuomotor transformations in the larval zebrafish
Eva A. Naumann, James E. Fitzgerald, Timothy W. Dunn, Jason Rihel, Haim Sompolinsky, & Florian Engert, (submitted to Cell)

Date: October 25th, 2015

Signature Scientist in Charge:
(Prof. Jason Rihel)



Date: October 25th, 2015

Signature Researcher/ beneficiary:
(Eva A. Naumann)