Whole-brain neuronal dynamics underlying spontaneous behavior in larval zebrafish

Antoine Légaré [1], Vincent Boily [1], Sandrine Poulin [1], Mado Lemieux [1], Patrick Desrosiers [1,3,4], Paul De Koninck [1,2]

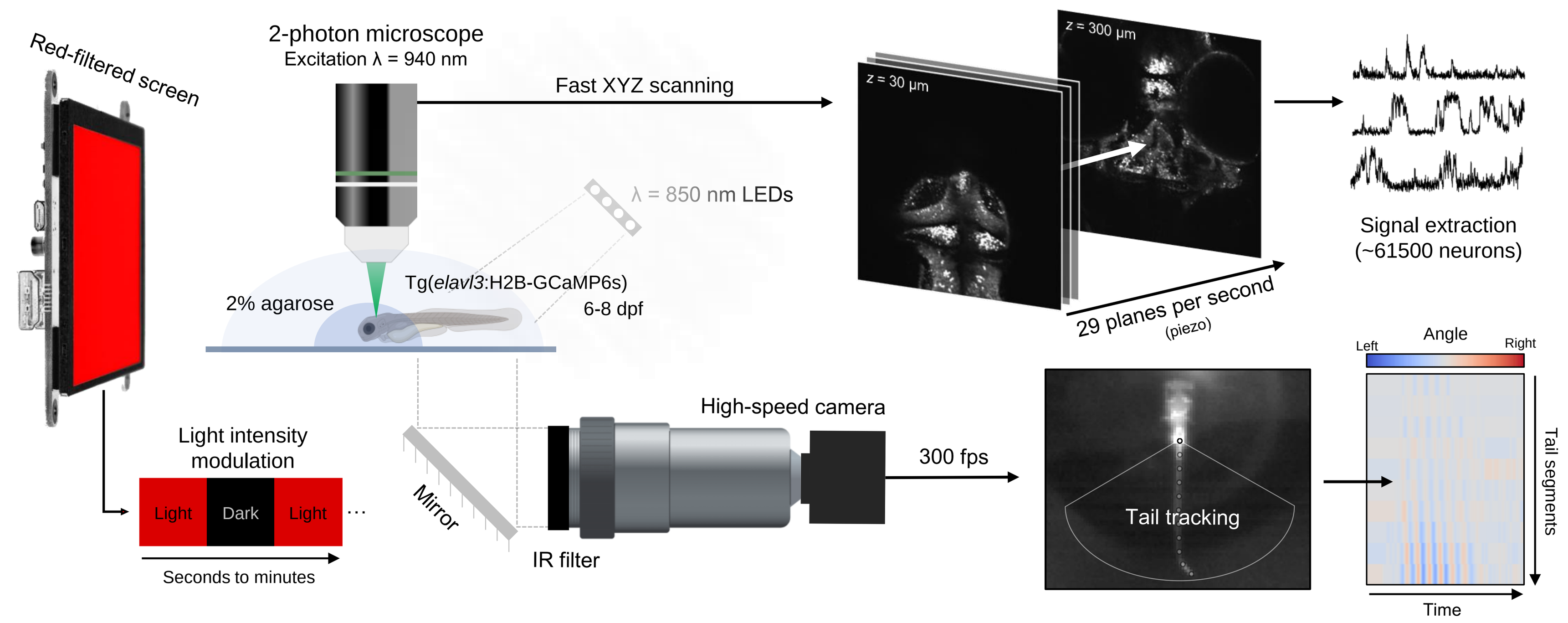
[1] CERVO Brain Research Centre, Québec (QC). Université Laval, Québec (QC) Canada: [2] Département de biochimie, de microbiologie et de bio-informatique [3] Département de physique, de génie physique et d'optique [4] Centre Interdisciplinaire en Modélisation Mathématique de l'Université Laval (CIMMUL)

Introduction

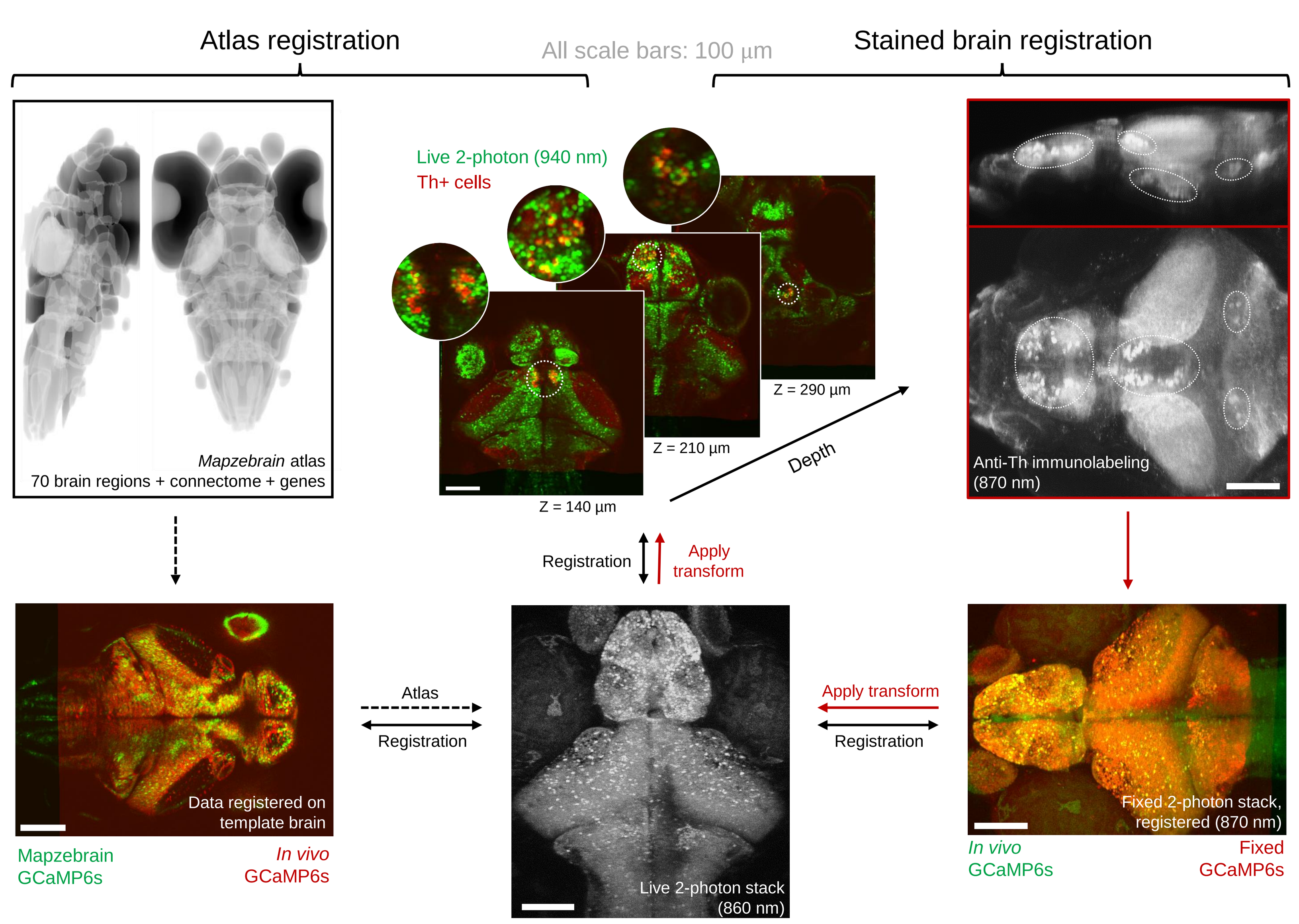
- Simultaneous large-scale neuronal activity recordings and behavioral measurements in multiple animal models are revealing widely distributed neuronal populations associated with behavior.
- Using simultaneous calcium imaging and behavioral monitoring in transgenic larval zebrafish[1], our goal is to characterize how neuronal populations distributed across the brain interact to generate behavior.
- Using immunolabeling and atlas registration, we are studying neuromodulators as prime candidates in orchestrating the slow fluctuations associated with behavior and arousal states.

Methods

During live imaging, the fish is head-restrained in agarose. Whole-brain imaging is performed using resonant scanning 2-photon microscopy while tail movements are monitored using a high-speed camera.



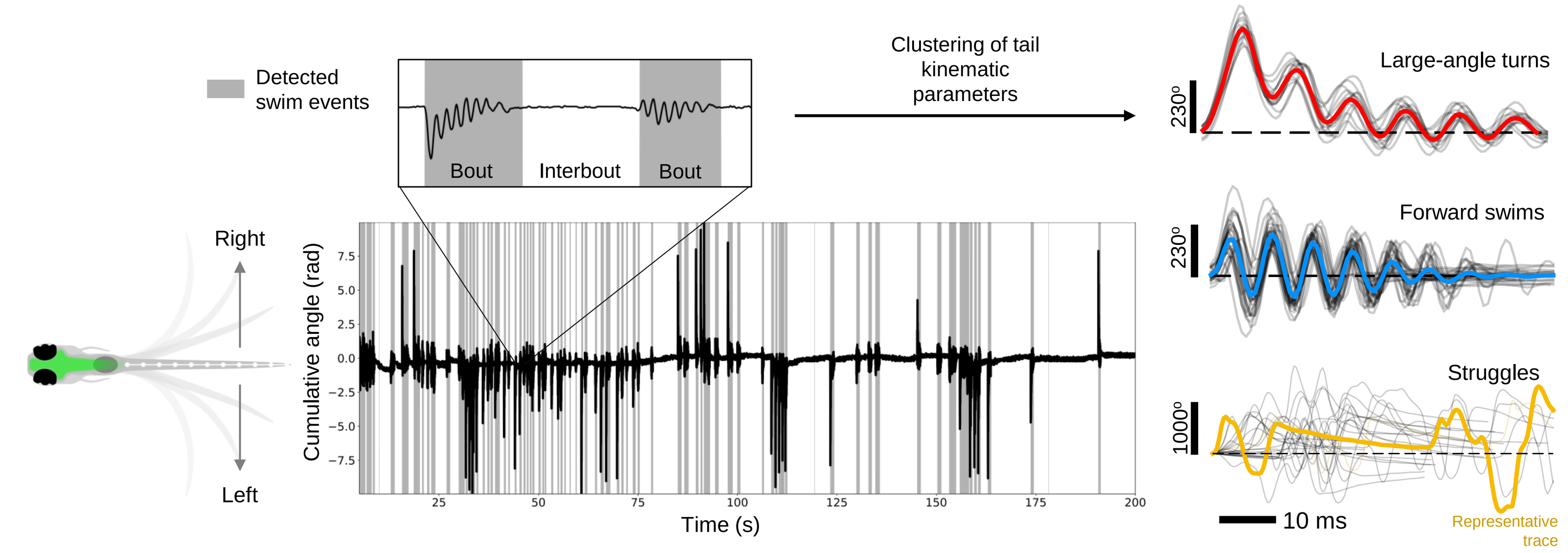
After experiments, fish are fixed and different neuronal subpopulations are stained using whole-mount immunolabeling. Stainings are warped onto *in vivo* data using image registration at single-cell precision[2]. Anatomical stacks are also aligned to a brain atlas[3] to map neurons in brain regions.



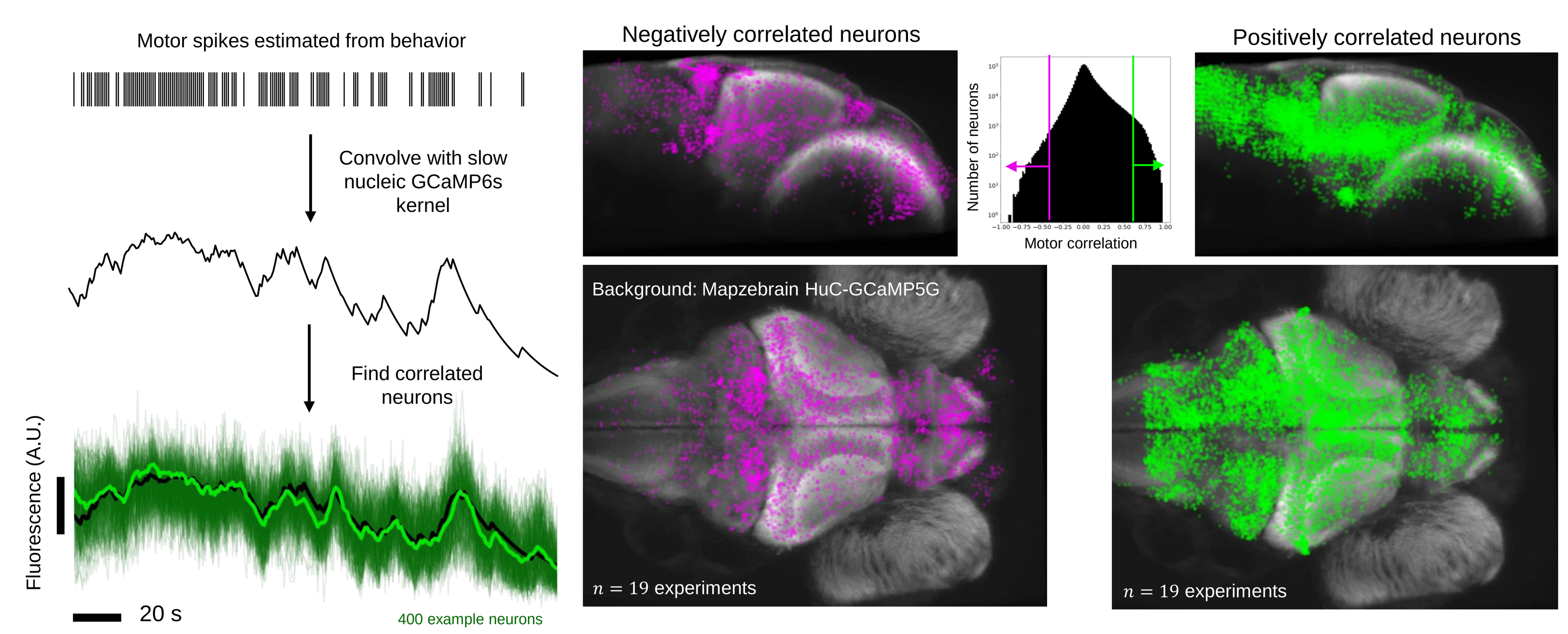
Results

Neuronal representation of behavior

Larval zebrafish swim in discrete bouts followed by glides. Clustering of tail angles[4] during swim bouts reveals different spontaneous swim types. We aim to determine their relationship with brain states and neuromodulation.

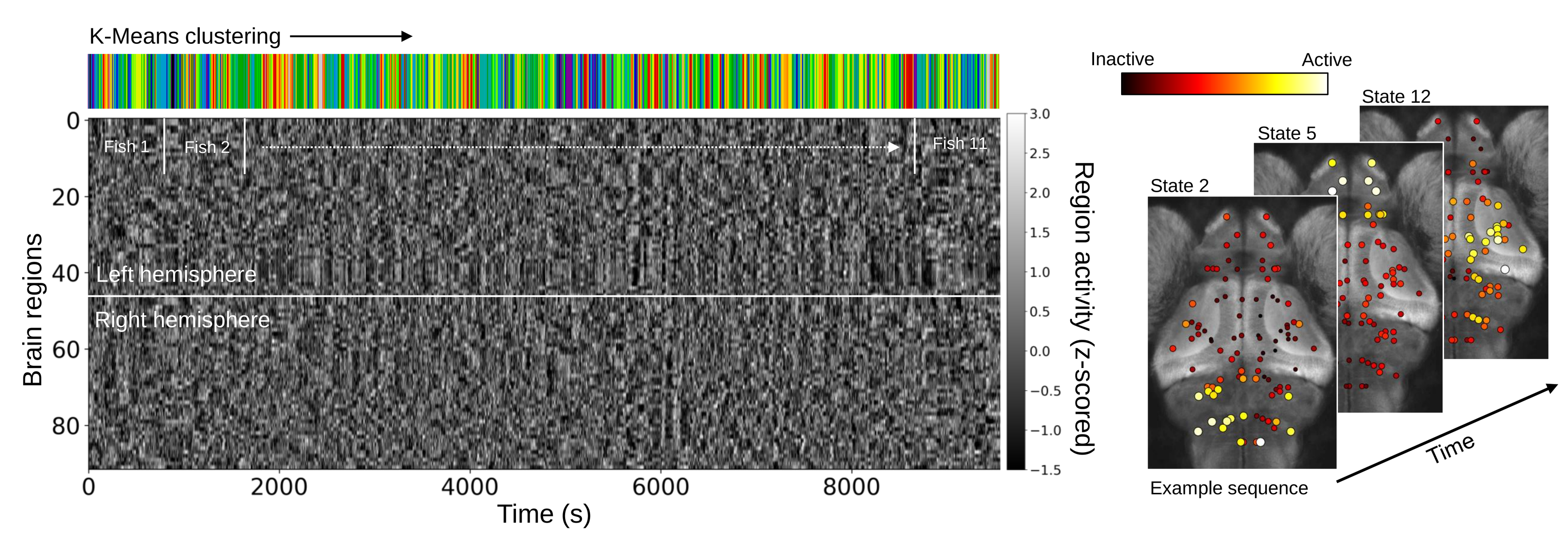


Regression analysis is used to correlate neuronal activity with the observed tail movements, revealing widespread neuronal representations of behavior across the brain. We observe a smaller fraction of negatively correlated neurons distributed in more focal locations, notably in the cerebellum.

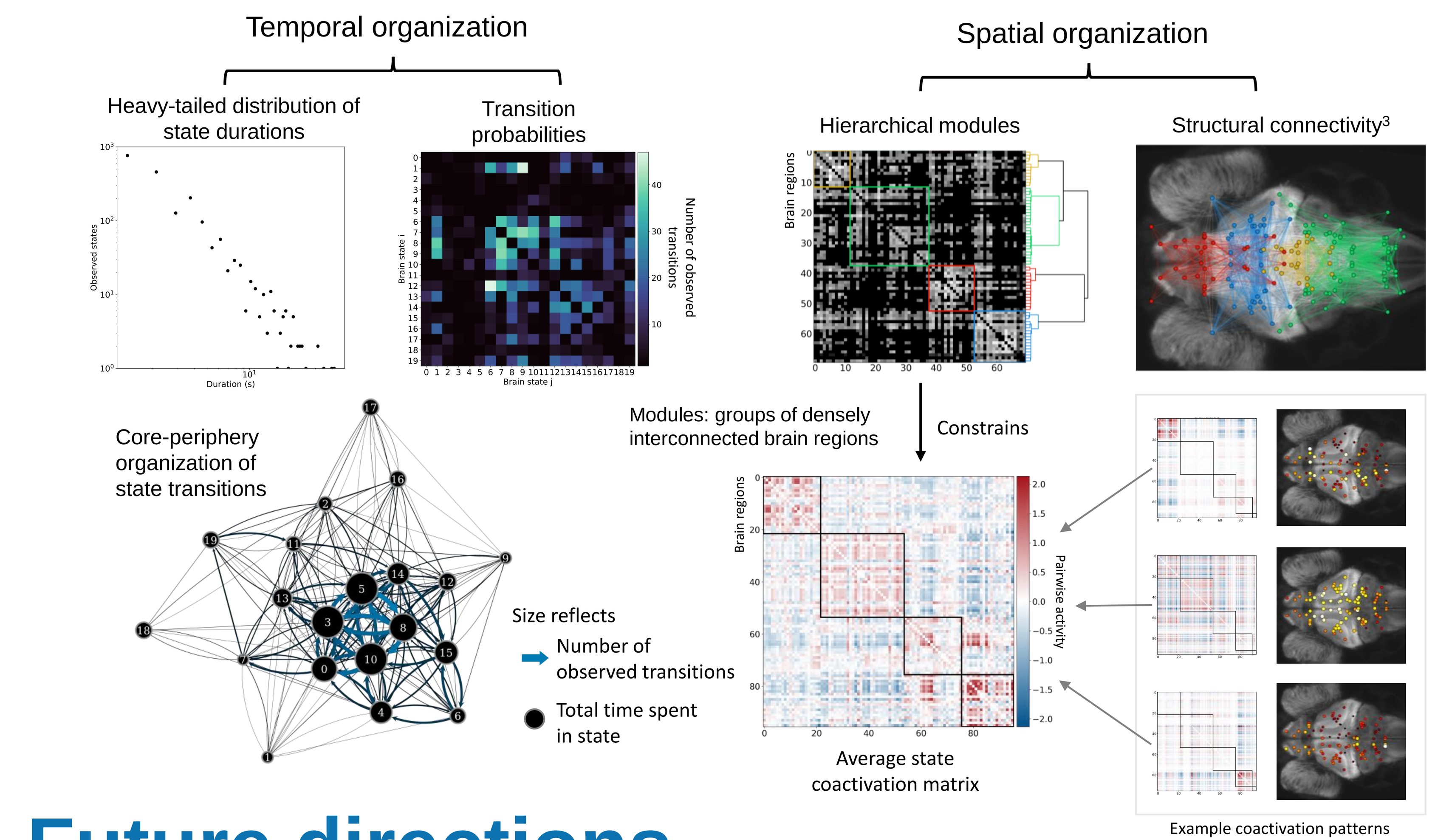


Spontaneous brain states

To investigate the brain's functional background unfolding during behavior, we begin by regressing out motor-correlated activity. Then, we apply clustering along the temporal axis of the fish-concatenated region activity matrix to find recurrent states of brain activity throughout the population.



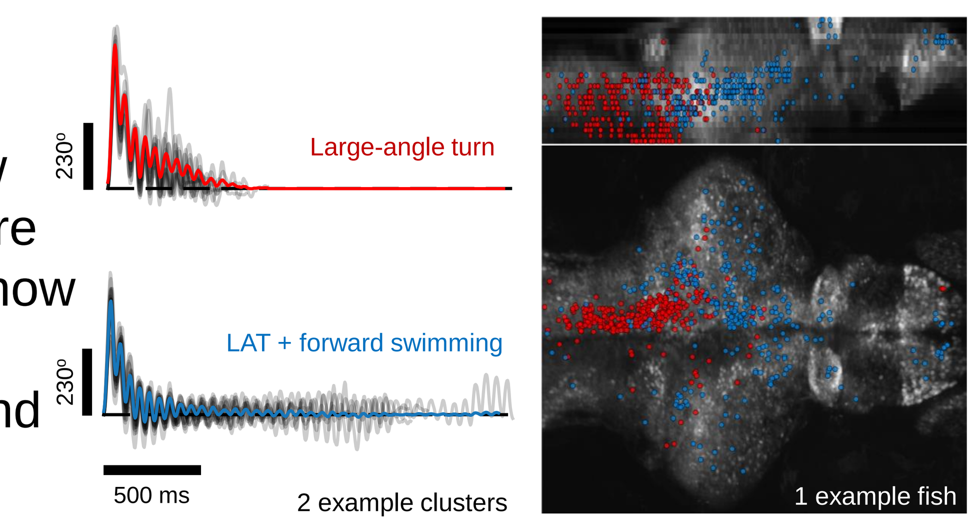
These brain states unfold over many time scales, exhibiting recurrent transitions where some states occur more frequently than others. The spatial organization of coactivation patterns is constrained by the modular structure of the connectome across brain regions.



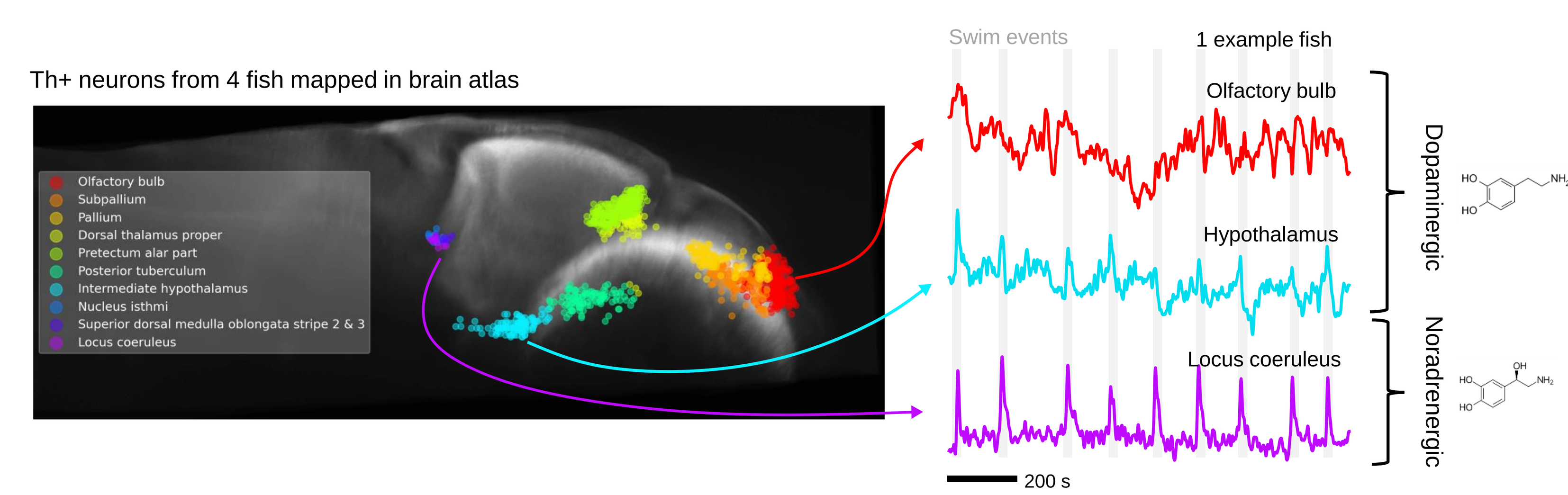
Future directions

Spatial organization of motor circuits

Using a multiple regressor approach based on swimming clusters, we want to study how different movement patterns are represented in the brain, and how these representations are associated with brain states and neuromodulation.



Neuromodulators



By introducing neuromodulatory subpopulations into our integrated study, we seek to characterize how their activity influences spatial (ie. module activation) and temporal (i.e. state transitions) dynamics of the brain, while modulating kinematic properties of the swimming patterns. This framework will be applied to study the impact of the exposome on the development of brain circuits.

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Ref: [1] Vladimirov *et al.* (2014) *Nat Methods* 11 [2] Lovett-Baron *et al.* (2017) *Cell 171* [3] Kunst *et al.* (2019) *Neuron 103* [4] Marques *et al.* (2018) *Current Biology 28.*