Neuronal Ensembles 2024

On May 2, 2024, we hosted an international symposium on Neuronal Ensembles. The meeting took place online, with over 900 registrants from over the world. This was the third instance of a meeting focused on ensembles, again organized by Rafael Yuste from Columbia University, Rosa Cossart, from INMED, France, and Emre Yaksi, from the University of Trondheim Norway. This year’s edition focused on the comparison between human data and results from animal experiments. The meeting started with a welcome from the organizers, who defined ensembles as coactive groups of neurons that can happen in response to sensory stimulation or motor action, but also occur spontaneously. Thus, the focus phenomenology is on the existence of an endogenous circuit motif that can be engaged in different functional conditions.

The first speaker was Madeleine Lancaster from the Medical Research Council’s Laboratory of Molecular Biology in Cambridge, UK. Lancaster is the researcher that first pioneered human organoids and explained how they are layered, like the developing brain. She argued that what distinguishes human versus other primates is the fact that we have a protracted neurogenic period. But instead of 3D organoids, she presented her results from air-liquid interphase cultures, which have a denser neuropil without cell death, or holes which are the sign of damage. These neurons have dendritic spines, action, potentials, long-ranged connectivity, which can be functional, as demonstrated with microelectrode array recordings. Moreover, in mouse co-cultures of spinal cord and muscle, spine cord activity can generate and mouse contractions. She addressed the differences between human and mouse cultures, arguing, that the later neurogenesis of humans leads to the slower maturation of the culture. She also spoke about cell replacement therapy for disease and the limitation of human organoids. She discussed briefly the work of the Pasca lab at Stanford that has maintained up to 270 days and observe a GABA switch which happens in human development. But she argued that interphase cultures a greater prospect since they can be cultured in the long term and show maturation of NMDA. All neuronal cell types were apparently generated in these cultures, with the exception of microglia.

The second speaker will Syd Cash, from the Massachusetts General Hospital in Harvard Medical School. He reported it on neuronal ensembles, measured in recordings from human patients using high density electrical arrays. Cash discussed the Braingate project, now ongoing for 20 years with 18 patient participants in five sites, which has traditionally used the Utah array, composed of 100 electrodes. The language decoding using this method is evidence for the replay of ensembles after learning and during slow wave sleep. He presented data from epileptic seizures, and argued that they display heterogeneous dynamics, that depends on the type of the seizure. Cash then discussed the recent results with newer Neuropixel probes, with many more electrodes that can record up to 200 units. One can categorized the units as axonal or dendritic recordings, and record simultaneously from different layers. Recording from the prefrontal cortex of patients display a concordance between neural activity and the phonetics of language. In these recordings, ensembles involve tens of neurons.

The third speaker of the session was Kevin Kelley from Stanford University, who had been previously associated with the Pasca lab. He showed data from 3-D organoids diversity. Using different combinations of transcription factors, one can generate up to 2/3rds of all cell types in the human cortex. This speaks to the power of the transcription factor code of morphogenesis. Kelley show spoke about the discovery of a new type of interneuron in the human stratum, which he called TAC3. The possibility of generate new cell types is exciting. He then talked about transplantation exponents of human organoids into rat brains. These hybrid systems can last for up to two years, receive inputs and
form functional networks. These circuits display molecular maturation, normal function on morphology including dendritic spines, and can also modulate the behavior of the rat.

The second session focused on hippocampal ensembles using animal models. The first speaker was Soledad Gonzalez-Cogno from the University of Trondheim in Norway. She described the discovery of ultra slow oscillations in the hippocampus of mice, defined as having a frequency of lower than 0.1 Hz, with intervals that can be as long as 500 seconds. She recorded these oscillations using calcium imaging in the medial entorhinal cortex. The average frequency was 0.0066 Hz, and the average period of 151 seconds. Using principal component analysis, she found manifold activity and discovered sequences of firing that can be represented as ring attractors. These attractors are periodic and are modulator by running, although they do not display waves, but repeating activity structures. She did not find oscillations in the parasubiculum or primary visual cortex. The mechanisms and function of these oscillations remain mysterious. Using Neuropixel probes she also found the ultraslow sequences, although they were hard to detect due to the noise of the recordings. She finished arguing that these sequences conforming scaffold for computations, as a basis function that can be used for a slow behaviors.

The second speaker in the hippocampus session was Albert Lee from Harvard Medical School, and he spoke about mental stimulation and imagination in rodent preparations. He argued that the hippocampus has a place cell code that can be in principle used for non-local, imagined representations. To record these, he used a brain machine interface and a virtual reality arena, manipulating the environment of the animal, to force the animal to do navigation tasks, with or without a treadmill present. This way they could compare the data when they are actually navigating the maze as when they are imagining the navigation. Confirming this, in some trials, there were no movement of the animals. The results show that the activity in this imagined navigation sessions was not random, but recapitulated the real navigation. Rats can mentally hold on to the same place for a long time, and they can display repeated activation. A comparison between activity and the running conditions of brain machine interface shows the same multi normal vectors. He argued that the hippocampus uses absolute coordinates to encode space, and that animals can mentally move in that space both by progressing sequentially through it, or by jumping to particular spot. This fits nicely with the idea that the hippocampus in quotes episodic memories that are than projected to the brain, but also originate from the inputs from the entire breath of the hippocampus.

The third speaker of the hippocampus session was Lisa Giacomo, from Stanford University, and she reported data from the medial entorhinal cortex’s grid cells. These neurons have different spatial phase, size or resolution, depending where they are located. Interestingly, they show remapping when the rat moves to a new environment. There are two types of remapping: slow remapping, which leads to the combination of maps between the initial and final position, and fast remapping which is instantaneous. She used a neural network model with excitatory and inhibitory connections to argue that this can be explained by attractors in a neural sheet. Using Neuropixel recordings of animals in the dark, she found increases in the activity of attractors after introductions particular landmarks. The mechanism of this remapping could be due to updating the synaptic weights, like results from Drosophila. But she argued for a mechanism where the synaptic weights have fixed network connectivity. This is consistent with learning by a downstream decoder, rather than by the entorhinal cortex.

The first talk of the cortex session was by Ken Harris from University College, London. He spoke about linking neuronal activity to transcriptomics cell types in primary visual cortex of the mouse. They
combined calcium imaging with transcriptomic mapping from brain slices of the same territories using a method called copa-FISH. He validated these results with patch-Seq. He described how somatostatin neurons increased their activity during running and also compared spontaneous activity with visually evoked one. Although the analysis of interneurons was clear, with differences in their responses to strong visual stimulation and spontaneous activity, excitatory cells showed a continuum of clusters in both synchronicity and running conditions. There was no clear difference between clusters but there was an overall correlation between their responses and their transcriptomics, perhaps due to activity dependent genes.

The second speaker of the cortex session was Natalia DiMarco from Cornell university Medical School. She reported on her studies on the development of cortical somatostatin interneurons. She performed longitudinal recordings from post natal day six to adults mice and found these interneurons were spontaneously active early, but ended up with a massive apoptosis cell death from 30 to 40% which was activity dependent. Interneurons were synchronized with pyramidal cells. Genetic silencing of interneurons increased the same synchrony and decreased the apoptosis. She also reported on her studies of calcium voltage sensitive channel which is responsible for the Timothy syndrome. The interneurons show decrees correlation, consistent with their role of the synchrony of the circuit in the survival of interneurons. Finally, she spoke up on the long branch connectivity layer to three cells, through the corpus callosum.

The last speaker of the meeting with Karl Deisseroth from Stanford University. He reviewed optogenetics, speaking about newer opsins, including ChRmin, and reported on a transgenic mouse line that combines ChRmin with GCAMP 6/8. He also reported about the red-shifted ChRmin RS, and potassium channel rhodopsin KALI, which inhibits neural activity. Finally, he spoke about the combination of a genetically-encoded voltage sensor and its combination with a blue-shifted rhodopsin.

The symposium ended with a summary of the lessons learned by Rafael Yuste, who thanked the TCCI Foundation for its continuous support.