# Abstracts

## B.R.A.I.N. Research Group

### The role of endogenous cellular prion protein in brain synaptic function

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α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are the major neurotransmitter receptors in the brain that are involved in glutamate-based neuronal communication. Increases and decreases in AMPAR number, distribution, and efficacy represent some of the mechanisms that neurons employ to modulate their communication strength, which is known as synaptic plasticity. Defects in synaptic plasticity may be responsible for many brain disorders including Alzheimer’s disease (AD). It has been shown that beta-amyloid oligomers bind the cellular prion protein (PrPC), a cell-surface glycoprotein with many physiological functions such as cellular differentiation, adhesion and control of cell morphology. However, the role of PrPC in synaptic plasticity and learning and memory remains obscure. We used electrophysiological techniques to explore the function of PrPC at CA1 synapses in the hippocampus, a region critical for learning and memory and preferentially affected in AD. Preliminary data suggest that C57BL/6J-Prnp knockout mice have enhanced long-term potentiation. The input/output function of synaptic transmission and paired-pulse potentiation were unaffected. Ongoing investigations will confirm these initial findings and examine the role of glutamate receptors in PrPC–dependent modulation of synaptic plasticity. We conclude that PrPC may serve to limit synaptic potentiation.

### How an asymmetric L1 motor circuit generates symmetrical motor output

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Motor behavior is essential in almost all aspects of animal life. Neural circuits that govern motor output, or motor circuits, are evolutionarily conserved for the core structures and functions. During animal development, motor circuits could experience significant changes; yet, for animals that do not undergo metamorphosis, they might largely maintain their stereotypical locomotor patterns throughout development. How distinct motor circuits generate similar motor output during development is poorly understood. We describe studies here to begin addressing this question using the simple nervous system of C. elegans. C. elegans maintains serpentine-like dorsal/ventral bending waves for locomotion in all developmental stages post hatching. In adult, cholinergic A- and B-type motor neurons innervate and stimulate dorsal and ventral body wall muscles, whereas GABAergic D-type motor neurons innervate and inhibit muscles on both sides. Together, they constitute symmetric motor circuit input onto dorsal and ventral body wall muscles that generates balanced muscle activity in adult worms. The cellular components of motor circuit differ drastically in younger C. elegans. All ventral-innervating cholinergic motor neurons are not born until the end of first larval (L1) stage. A partial electron microscopy (EM) reconstruction study suggests that, A- and B-type motor neurons only innervate dorsal muscle, and D-type motor neurons only innervate ventral muscle in L1 stage. With this layout, L1 motor circuit should generate asymmetric input to muscles, biasing towards dorsal excitation and ventral inhibition. However, L1 larva outputs balanced dorsal/ventral bending waves. How does an asymmetric circuit produce symmetric output? To answer this question, we have analyzed the structure and function of L1 motor circuit. We fully reconstructed the connectivity of a complete L1 larva by EM, and identified previously uncharacterized candidate cellular components for muscle activity in addition to A-, B-, and D-type motor neurons. To elucidate the functional contribution of candidate cells to L1 muscle activity, we developed a novel all-optical manipulation scheme that allows non-invasive systematic probing of neural circuits with a simple setup and unrestricted opsin/calcium-indicator combinations. We then combined calcium imaging, cell ablation, and all-optical manipulation to identify cellular substrates for symmetric L1 muscle output. We unraveled a non-canonical circuit mechanism that drives ventral excitation and dorsal inhibition, hence balancing the asymmetry of A-B-D motor neurons. By utilizing cutting-edge techniques for anatomical and functional studies, our work sheds light on the adaptability of a developing motor circuit, and addresses the basis for functional resemblance of different circuit assemblies, which could be extrapolated to other organisms.

### Modelling the impact of new learning and neurogenesis on memory stability in the hippocampus.

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In neural networks, the stability of stored information may be compromised by a) changing the neural architecture, and b) adding new memories. We tested these ideas in a three layer feed-forward neural network. In this network the input, middle and output layers represent the entorhinal cortex, DG and CA3 regions, respectively. We presented the network with input patterns, drawn from two partially overlapping distributions A and B. The network was trained to transform these A and B input patterns into one of two discrete output patterns. The ability of the network to generalize was assessed by presenting novel input patterns that were either drawn from the A and B distributions, and asking whether it could correctly categorize them. Following initial training, we either a) added new neurons to the middle layer, or b) trained the network on two new distributions, C and D. Changes in neural architecture induced by either a) new neuron addition or b) new learning impaired AB categorization performance, consistent with previous modeling and experimental data. Moreover, increasing excitability and connectivity (input and output) of the new neurons exacerbated these forgetting effects. We next examined how these factors interact. In this experiment, we trained the network on distributions A and B and then added new neurons, as above. We then retrained the network on the new distributions C and D. In this case, the addition of new neurons weakened memory for the original AB categorization, but, at the same time, enhanced learning of the new CD categorization. By exploring how new neuron addition impacts stored memories, and new memory storage, our results begin to help us understand how adult neurogenesis in the hippocampus influences cognition. ## Cardiovascular and Respiratory Research Group ## Endocrine and Diabetes Research Group

### FIP abstract submission

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