Toward a self-wired active reconstruction of the hippocampal trisynaptic loop: DG-CA3

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We know molecular details of many types of synapses in the major regions of the hippocampus important to learning and memory, but we don't know if these regions self-wire into the anatomically accurate network or require external electrical or chemical inputs to create a functional tri-synaptic network from the dentate gyrus (DG) to the CA3 to the CA1. Monitoring activity from each hippocampal region in behaving animals produces specific patterns of activity for each region, but we lack information about the inputs necessary to evoke these patterns and their relationships.

Here we reconstructed paired components of the tri-synaptic pathway, with a focus on the DG to CA3 connection. Questions that we address to validate our model include: 1) Can specific subregions of the hippocampus be reproducibly dissected as evidenced by region-restricted gene expression? 2) Will these regions maintain and establish their original identity in a uniform culture environment removed from external inputs? 3) Further, given that CA3 development precedes DG in vivo, is the natural axon polarity of DG to CA3 inherently controlled or does it require external cues? To answer these questions, we seeded dissociated cells from micro-dissected regions of the rat hippocampus onto a multi-electrode array (MEA) with an attached micro-device (Fig. 1). In this microfabricated device, axons from the each hippocampal subregion extend through the 3 µm high x 10 µm wide x 400 µm long tunnels into the apposing compartment.

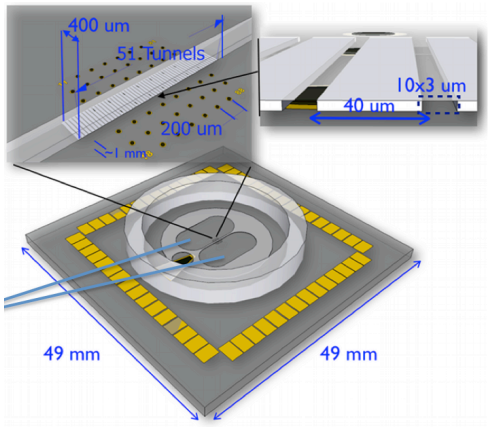

Figure 2. Microfabricated tunnel device on MEA for monitoring communication between chambers of two types of neurons.

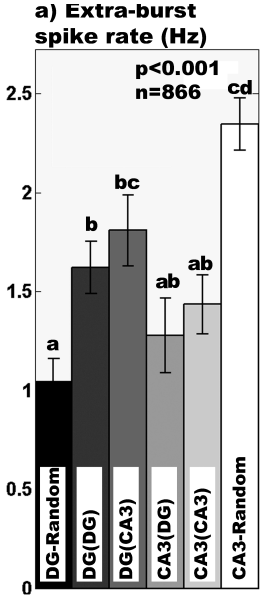

Figure 1. Distinct spike rates for distinct pairs of hippocampal neurons

We addressed the above issues by quantitative PCR of region-restricted gene expression to show the fidelity of neuron phenotype, by evaluation of distinct spike and burst dynamics in each sub-region compartment (Fig. 2) and by establishing the polarity of directional communication between sub-regions, whether random or anatomically accurate from the DG to the CA3 (Fig. 3). Surprisingly, intrinsic capabilities of the DG neurons promote axon extension toward the CA3 neurons, with limited back propagation. This technology will enable determination of the network integration of stimulation-dependent plasticity and how subregion-specific information patterns are reliably transmitted but differentially processed within each hippocampal subregion.

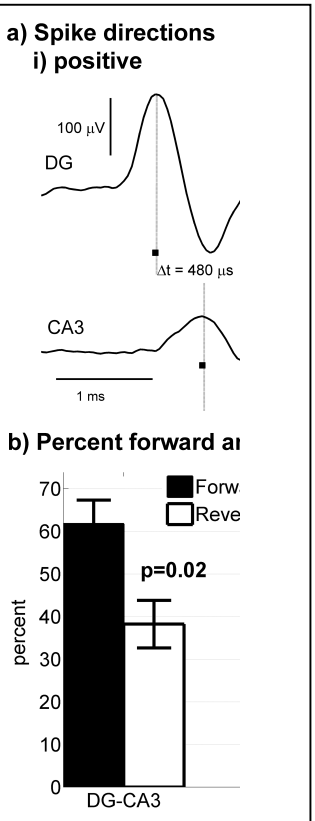

Figure 3. Positive-forward direction of spike propagation prevails in DG-CA3 networks.

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