

## Virtual DANDRITE Lecture

**Friday 7 May 2021**

**16.00 – 17.00**

### Online via Zoom

Please find Zoom link via the Outlook calendar invitation. If you have not received this, please write an e-mail to Kathrine: [kh@dandrite.au.dk](mailto:kh@dandrite.au.dk)



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## Brain Circuit Reset: Principle of Cognitive Enhancement in Health and Disease

Flexibly adapting to novel challenging situations is critical for survival, as we are experiencing during the pandemic. Notably, this flexibility is impaired in many neuropsychiatric disorders including autism and schizophrenia. Thus, understanding whether and how novel experience impacts brain circuitry to facilitate cognitive flexibility has important translational relevance. Here we show that novel experience resets the neural circuits that link the ventral hippocampus (vHPC) and the medial prefrontal cortex (mPFC), facilitating the ability to overcome an established strategy. Exposing mice to novelty disrupted a previously encoded strategy by reorganizing vHPC activity to local theta (4-12 Hz) oscillations and weakening existing vHPC-mPFC connectivity. As mice subsequently adapted to a new task, vHPC neurons developed new task-associated activity, vHPC-mPFC connectivity was strengthened, and mPFC neurons updated encoding with new rules. Without novelty, however, mice adhered to their established strategy. Blocking dopamine D1-receptors (D1Rs) or inhibiting novelty-tagged cells expressing D1Rs in the vHPC prevented these behavioral and physiological effects of novelty. Furthermore, activation of D1Rs mimicked the effects of novelty. These results suggest that novelty promotes adaptive learning by D1R-mediated resetting of vHPC-mPFC circuitry, thereby enabling subsequent learning-associated circuit plasticity. Because many neuropsychiatric disorders are associated with rigid vHPC-mPFC circuit plasticity, our study provides new mechanistic insights for potential therapeutic interventions.