

# Is depression caused by a hyperactive habenula?

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**October 31 (Monday), 2016,  
13:00-14:00**

**1F Seminar Room, BSI Central Building**

## **Abstract**

The habenula, a small structure adjacent to the thalamus, plays a central role in the brain's processing of aversive stimuli. Not only does it respond to such stimuli, it also inhibits midbrain dopamine neuron firing and its stimulation can drive conditioned place avoidance. Based on these findings, many investigators have suggested that habenula hyperactivity may play a role in depression, and this hypothesis is supported by work in animal models. However, the habenula hyperactivity hypothesis of depression has yet to be tested directly in humans.

I will present two studies, both of which use a computational approach to examine the role of the habenula in humans. The first study (Lawson et al 2014, PNAS) showed that in healthy volunteers the habenula responds to aversively conditioned stimuli. As initially neutral cues became increasingly associated with painful electric shocks, habenula activation increased significantly. The second study (Lawson et al 2016, Molecular Psychiatry) showed a similar pattern in an independent sample of healthy volunteers. However, in unmedicated depressed patients habenula activation significantly decreased in response to increasing association with shocks, contradicting the hypothesis. These data suggest that the habenula does function abnormally in depression, but that the simple "hyperactivity" hypothesis is probably incorrect.

**Host: Hiro. Nakahara** Lab for Integrated Theoretical Neuroscience