Cerebellum at a junction, now there's a function

This article provides new evidence that the cerebellum, a structure located in the rear of the brain, has a larger role in controlling reward circuitry and social behavior than previously thought.

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In a paper recently published in *Science,* Ilaria Carta and associates investigate the cerebellum's function beyond its known role. This research broadens the understanding of mental disorders. It provides an explanation for why functional imaging experiments indicate a connection between the cerebellum and addiction. The primary finding being that the cerebellum sends direct excitatory projections to the ventral tegmental area (VTA) which is associated with reward. The implications of this finding are important. This shows that the cerebellum's functions are broader than the motor movements (including posture, balance, and speech) previously associated with it.[3] Additionally, this finding can later be used to possibly help treat mental disorders associated with addiction and reward. This research shows that there is still a lot to learn about the cerebellum and the brain as a whole.

Background

It was long known that the cerebellum played a role in motor coordination, and this experiment attempted to look beyond that.[8] Previous studies by Van Overwalle and colleagues have examined the connection between the cerebellum and social-cognitive processes. This research gave background information on connections that the cerebellum makes.[6] Additionally, the ventral tegmental area was focused on during this experiment because of its known connection to addiction. Research by Eric Nestler informed this knowledge and provided background data to support the idea of a VTA connection being significant and linked to reward circuitry related to the cerebellum.[5] In a study by Tiffany Rogers and colleagues, the neuronal circuitry by which the cerebellum modulates the medial prefrontal cortex dopamine release was investigated. Their findings give credence to the idea of cerebellar involvement in autism, schizophrenia, and other cognitive disorders in addition to dopamine reward circuitry. Some researchers hypothesize that the cerebellum may refine higher-order functions.[9,4]

Methods

A variety of methods was used during this experiment, including *in vivo* and in vitro electrophysiology, herpes viral tracing, self-stimulation, and histology. Three to four-month-old adult mice of both genders were used as the subject to determine the relationship between the cerebellum and reward circuitry/social behavior. The parallel rod floor test, behavior tests, and the three-chamber test were some of the main experimental procedures used. All behavioral experiments were analyzed by doing statistical comparisons in GraphPad and Matlab for electrophysiological experiments.

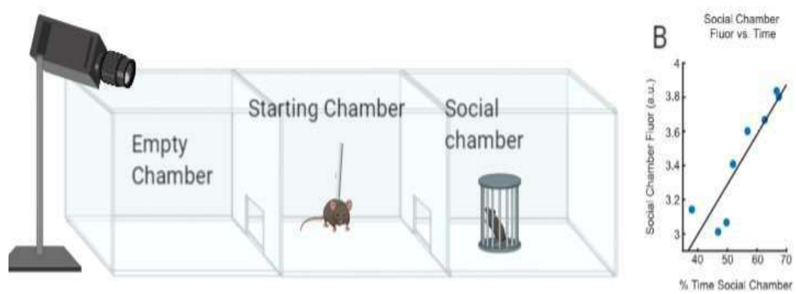
The three-chamber test used adult mice that were bilaterally implanted with a 200µm fiber-optic that targeted the VTA and was coated with molecular probes. After 2 weeks post-surgery, the mice were recorded in a clear 3 chamber plastic box (24x13in) where one side was a "social" side with another mouse, and the other side was empty. The quantity of social behavior between mice was recorded on video and timed by a computer and an individual who was unaware of the experiment. This experiment was based off a similar one done by Anton Ilango and colleagues.[1] Fiber photometry was used to monitor changes in calcium in cerebellar axons located in the VTA as a method of determining neuronal activity.

Results

Using the behavioral tests, it was determined that stimulation of cerebellum-VTA projections was able to cause both short and long-term preference proving that the pathway was rewarding. Optogenetic inhibition during the 3-chamber test removed social preferencewhich indicates that the connection between the cerebellum and VTA is required for normal social behavior. Additionally, when undergoing optogenetic stimulation the cerebello-VTA projections increased the activity of VTA both *in vivo* and in vitro. Nevertheless, optogenetic activation of the cerebello-VTA inputs did not cause an increase in sociability. It was found that the monosynaptic excitatory projections from the cerebellar nuclei to the VTA activate reward circuitry and contribute to social tendencies.

These findings are significant. The new knowledge about the cerebello-VTA connections will open the doors for future research connecting the cerebellum to social behavior and reward. This research can help inform and add to the present role and understanding of the cerebellum. Additionally, the findings from this experiment connect to cognitive illnesses which researchers are attempting to address. This new research will inform further studies into the cerebellum and show that the cerebellum plays a larger role in mental illness than previously anticipated.

Figure 1: Results of Three-Chamber Test (2,7)



This figure shows the results of the study completed with adult mice, ranging in age from 3-4 months. The testing environment of the three-chamber test is shown (A). The three-chambered test results showed that fluorescence increased over time in the social chamber indicating that the VTA and cerebellum are connected to social behavior(B).

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