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Motivation to bully is regulated by brain reward circuits

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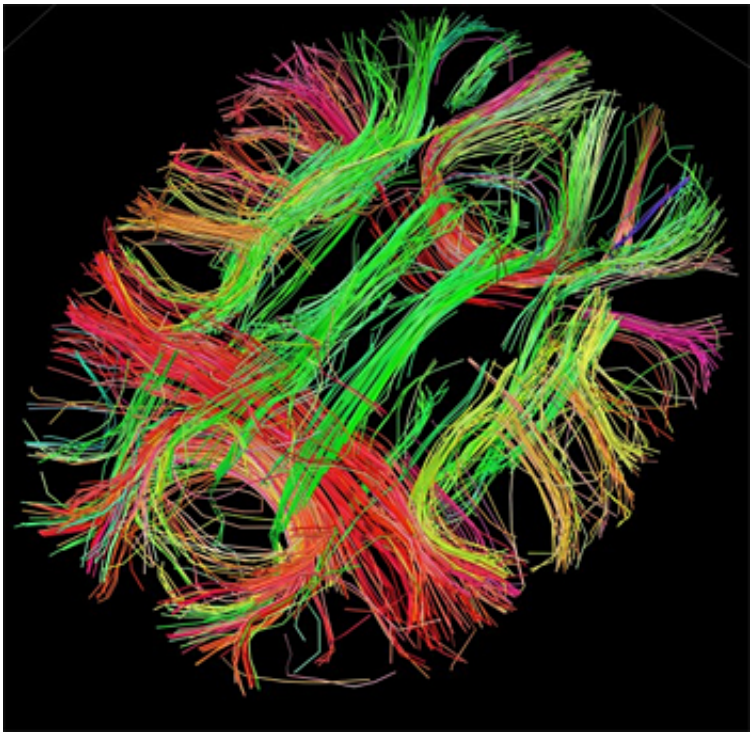

White matter fiber architecture of the brain. Credit: Human Connectome Project.

Individual differences in the motivation to engage in or to avoid aggressive social interaction (bullying) are mediated by the basal forebrain, lateral habenula circuit in the brain, according to a study conducted at the Icahn School of Medicine at Mount Sinai and published June 30 in the journal *Nature*.

The Mount Sinai study focuses on identifying the mechanisms by which specific brain reward regions interact to modulate the motivational or rewarding component of aggressive behavior using a mouse model.

Maladaptive aggressive behavior is associated with a number of psychiatric disorders and is thought to partly result from inappropriate activation of brain reward systems in response to aggressive or violent social stimuli. While previous research has implicated the basal forebrain as a potentially important brain reward region for aggression-related behaviors, there had been limited functional evidence that the basal forebrain, or its projections to other brain regions, directly controls the rewarding aspects of aggression.

"Our study is the first to demonstrate that bullying behavior activates a primary brain reward circuit that makes it pleasurable to a subset of individuals," says Scott Russo, PhD, Associate Professor of Neuroscience at the Icahn School of Medicine at Mount Sinai. "Furthermore, we show that manipulating activity in this circuit alters the activity of brain cells and ultimately, aggression behavior."

To study individual differences in aggressive behavior, the current team established a mouse behavioral model that exposed adult males to a younger subordinate mouse for three minutes each day for three consecutive days, and found that 70 percent of mice exhibited aggressive behavior (AGGs) while 30 percent of mice show no aggression at all (NONs).

Using conditioned place preference, a technique commonly used in animal studies to evaluate preferences for environmental stimuli that have been associated with a positive or negative reward, study investigators research found that AGGs mice bullied/attacked the subordinate mouse and subsequently developed a conditioned place preference for the intruder-paired context, suggesting that the aggressive

mice found the ability to subordinate another mouse rewarding. Conversely, NONs mice did not bully/attack the intruder mouse and subsequently developed a conditioned place aversion.

All sensations, movements, thoughts, memories and feelings are the result of signals that pass through nerve cells (neurons), the primary functional unit of the brain and central nervous system. When a signal passes from the cell body to the end of the cell axon that stretches away from the cell body, chemicals known as neurotransmitters are released into the synapse, the place where signals are exchanged between cells. The neurotransmitters then cross the synapse and attach to receptors on the neighboring cell, which can change the properties of the receiving cell. Found throughout the brain and produced by neurons, gamma aminobutyric acid (GABA) is an inhibitory neurotransmitter that binds to GABA receptors, making the neighboring neuron less excitable.

The current study team investigated GABA projection neurons that can send long-range connections to inhibit neurons in other brain regions. Specifically, using electrophysiological and histological techniques, the research team found that when exposed to the opportunity to bully another individual, AGGs mice exhibit increased activity of the basal forebrain GABA projection neurons that reduce activity in the lateral habenula, an area of the brain that would normally encode an aversion to aggressive stimuli. Conversely, they found NONs exhibit reduced basal forebrain activation and a subsequent increase in lateral habenula neuronal firing, which makes the aggression stimuli aversive.

While previous research has found the lateral habenula to play a role in negative moods states and aversion across a broad range of species, including mice and humans, little was previously known about the neural mechanisms that directly regulate the motivational component of aggressive behavior.

Researchers then used optogenetic tools to directly manipulate the activity of GABA between the basal forebrain and the lateral habenula, demonstrating that stimulation or inhibition of BF-lHb projections is both sufficient and necessary to alter the inclination to engage in or avoid the opportunity to bully.

"When we artificially induced the rapid GABA neuron activation between the basal forebrain and lateral habenula, we watched in real time as the aggressive mice became docile and no longer showed bullying behavior," says Dr. Russo. "Our study is unique in that we took information about the basal forebrain, lateral habenula projections and then actually went back and manipulated these connections within animals to conclusively show that the circuits bi-directionally control aggression behavior."

The study findings demonstrate a previously unidentified functional role for the lateral habenula and its inputs from the basal forebrain in mediating the rewarding component of aggression and suggest that targeting shared underlying deficits in motivational circuitry may provide useful information for the development of novel therapeutic drugs for treating aggression-related neuropsychiatric disorders.

More information: Basal forebrain projections to the lateral habenula modulate aggression reward, *Nature*, DOI: 10.1038/nature18601

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