# Artificially speeding up a mouse's heart rate found to increase anxiety symptoms

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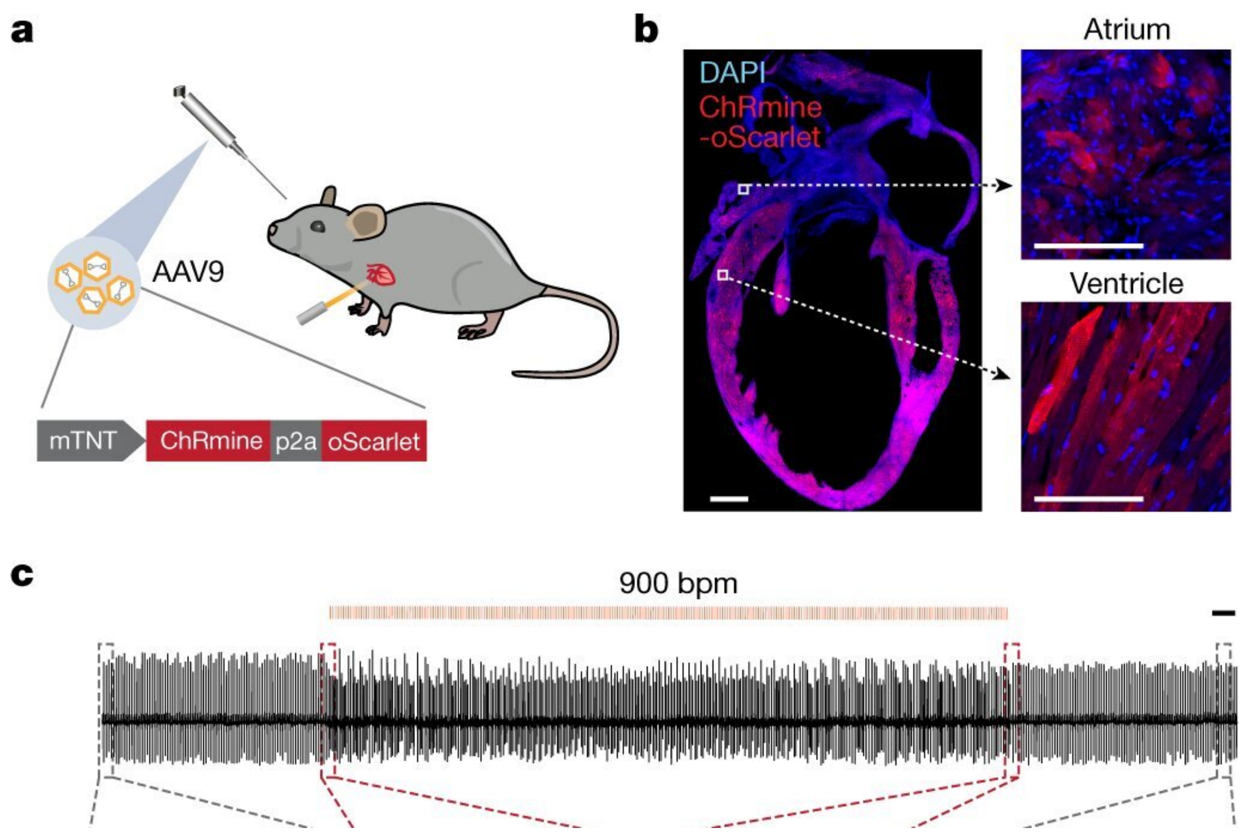


Development of a noninvasive optical pacemaker. a, Schematic showing the optical control of cardiac rhythm with an external light source enabled by retro-orbital injection of AAV9-mTNT::ChRmine-p2A-oScarlet. b, Confocal cross-section images indicating homogeneous transgene expression of ChRmine-p2A-oScarlet (red) with DAPI staining (blue) in atria and ventricles. Scale bars, 1 mm (main); 100 µm (inset). c, Example electrocardiogram (ECG) trace with optical pacing using 589 nm light delivered at 15 Hz (at 900 bpm) with a pulse width of 10 ms and irradiance of 160 mW $mm^{-2}$. Scale bar, 500 ms. Inset traces: ECG signal before and after light delivery (gray) and at light onset and cessation (red). Scale bar, 50 ms, 0.5 mV. d, Reliability of photoactivated QRS complexes at 900 bpm as a function of cutaneous optical irradiance (n = 6 mice). e, Example ECG traces of individual 10-ms optical pulses. Gray arrowheads indicate P waves associated with sinus rhythm, which are overridden (red arrowheads) during optical pacing. Scale bar, 25 ms, 0.25 mV. f, Example ECG traces of pacing at 600, 800 and 1,000 bpm. Scale bar, 50 ms, 0.5 mV. The shaded area indicates the period of illumination at the specified frequency at 100% duty cycle. g, Characterization of optical pacing fidelity, showing stimulation frequency versus ECG-measured heart rate (n = 6 mice). All ECG measurements were performed in anasthetized mice. Credit: *Nature* (2023). DOI: 10.1038/s41586-023-05748-8

A team of psychiatrists and bioengineers at Stanford University has found that artificially speeding up a mouse's heart rate leads to increases in symptoms of anxiety. In their study, published in the journal *Nature*, the group found a way to speed up the heart rate of lab mice without impacting other parts of its body and used that method to learn more about what happens in the brain when the heart speeds up. Yoni Couderc and Anna Beyeler with Bordeaux University, have published a News and Views piece in the same journal issue outlining the work done by the team in California.

Prior research and anecdotal evidence have shown that in conditions of fear or anxiety, the heart responds by beating faster. For many years, medical scientists have wondered if the reverse is true—is it possible that something other than the brain speeding up the heart rate could lead to an increase in fear or anxiety? To find out, the researchers had to find a way to speed up the heart without impacting other parts of the body.

Speeding up the heart rate artificially is easy; there are many drugs, such as caffeine, that influence heart rate. But they also impact other parts of the body, such as the brain. To find out what happens when the heart speeds up absent any other side effects, the researchers looked to a protein made by algae, called ChRmine. When exposed to light, a reaction occurs that allows charged particles to pass through—without the light, such particles are blocked.

The team applied ChRmine to the outside layer of hearts in living mice and then closed up their chests. They then placed vests with lights sewn in them on the mice. Turning on the lights opened the gates, allowing already present charged particles to move into the heart, resulting in an increase in heart rate.

The researchers then placed the mice in a test stress box and found that speeding up their heart rates induced the mice to behave as they normally do when anxious or scared. Further testing showed that when their heart rates were artificially sped up, parts of their insular cortex lit up, a physical sign of anxiety. Blocking such activity allowed the mice to relax when subjected once again to the box stress test.

**More information:** Brian Hsueh et al, Cardiogenic control of affective behavioural state, *Nature* (2023). DOI: 10.1038/s41586-023-05748-8

Yoni Couderc et al, How an anxious heart talks to the brain, *Nature* (2023). DOI: 10.1038/d41586-023-00502-6