Boosting glutamate reduces anxiety in monkeys

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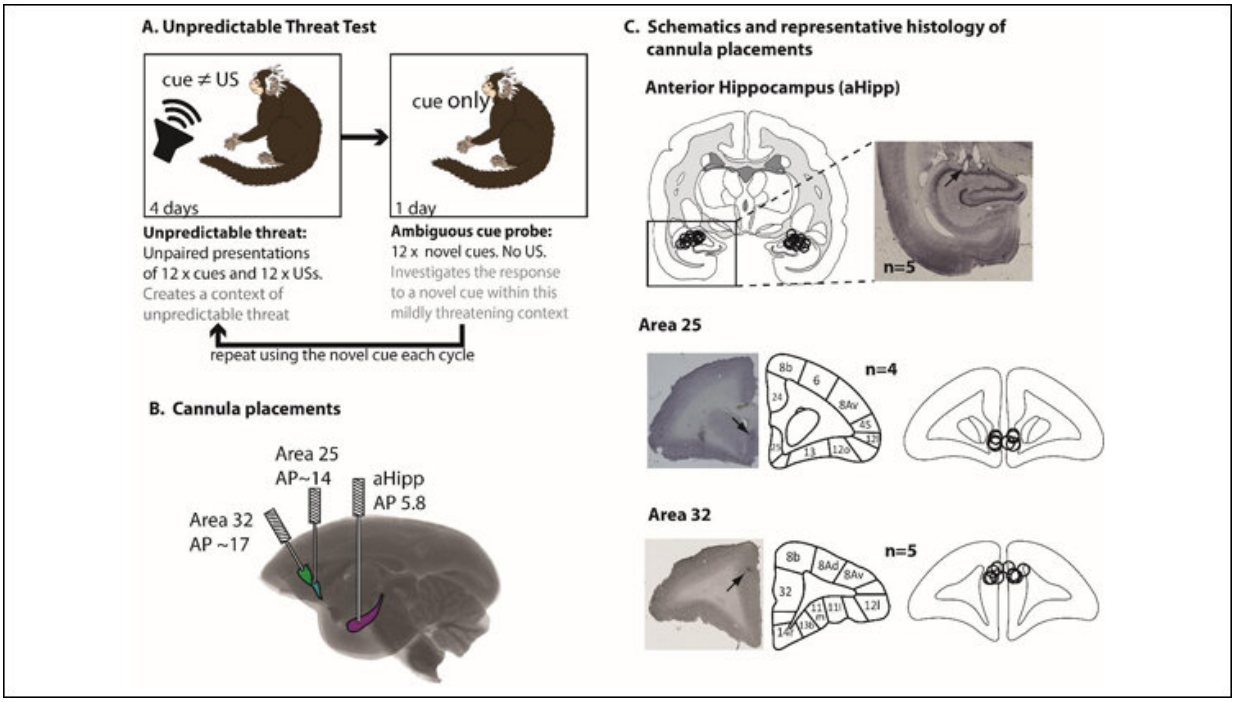

Unpredictable threat test and cannulae schematics A. In the unpredictable threat test (n = 6), animals were placed in a familiar environment for 25 mins and played two types of auditory stimuli, a novel auditory cue and an unconditioned stimulus (US) for the 4 unpredictable threat days. Each cue was 20 sec long, 75dB and was presented 12 times with an intertrial interval (ITI) of 40-80 sec. Each mildly aversive US was 0.4 sec long, 117dB and presented 12 times with an ITI of 40-80 sec. The threat of the aversive US was unpredictable as there was no relationship between the order of the cues and USs. On the ambiguous cue probe (5th day), monkeys were presented with a novel, ambiguous 20 sec, 75dB cue presented 12 times with an ITI of 100-180 sec in the same context. No USs were presented. All drug manipulations occur on ambiguous cue probes. The

cycle then repeated with the novel cue incorporated into the unpredictable threat training. Credit: Zeredo *et al*., *JNeurosci* (2019)

Researchers studying male and female marmosets have homed in on the primate brain circuitry responsible for individual differences in overall anxiety. Their findings, published in *JNeurosci*, show that increasing levels of the neurotransmitter glutamate in the hippocampus normalizes anxious monkeys' "fight or flight" response.

Previous human and animal studies suggest roles for glutamate, the hippocampus, and two prefrontal brain regions—known as area 25 and area 32—in the behavioral and physiological response to threat. However, the contribution and interaction of these neural components in highly anxious primates is unclear.

Hannah Clarke and colleagues were able to make anxious monkeys more comfortable with an unfamiliar human, who wore different masks to conceal his or her identity, by increasing glutamate release in the anterior hippocampus. In response to an unexpected loud sound, increased hippocampal glutamate was associated with increased blood pressure, heart rate, and scanning of the environment—all of which are part of a typical threat response and reduced in anxious individuals.

These effects depended on functioning of area 25, implicating this brain region and its connection to the hippocampus as a promising target for reducing anxiety.

More information: Glutamate within the marmoset anterior hippocampus interacts with area 25 to regulate the behavioral and cardiovascular correlates of high-trait anxiety, *JNeurosci* (2019). DOI: 10.1523/JNEUROSCI.2451-18.2018

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