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Freeze or run? Not that simple: Scientists discover neural switch that controls fear

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Fear can make you run, it can make you fight, and it can glue you to the spot. Scientists at the European Molecular Biology Laboratory (EMBL) in Monterotondo, Italy and GlaxoSmithKline in Verona, Italy, have identified not only the part of the brain but the specific type of neurons that determine how mice react to a frightening stimulus. In a study published today in *Neuron*, they combined pharmaceutical and genetic approaches with functional magnetic resonance imaging (fMRI) in mice. Their findings show that deciding whether or not to freeze to fear is a more complex task for our brains than we realised.

The scientists used an innovative technique to control the activity of specific cells in the brain of mice that were experiencing fear. The mice were genetically engineered so that only these cells contain a chemical receptor for a specific drug. When the scientists inject the mouse with that drug it acts on the receptor and blocks the electrical activity of those cells allowing the researchers to find out how these cells are involved in controlling fear. In this case, they used this pharmaco-genetic technique to turn off a set of neurons, called type I cells, in a region of the brain called the amygdala, which was known to be involved in responses to fear. To measure fear in mice, the EMBL scientists trained the mice to associate a sound with an unpleasant shock: when the mice heard the sound, they would freeze in fear.

"When we inhibited these neurons, I was not surprised to see that the mice stopped freezing because that is what the amygdala was thought to do. But we were very surprised when they did a lot of other things

instead, like rearing and other risk-assessment behaviours," says Cornelius Gross, who led the research at EMBL, "it seemed that we were not blocking the fear, but just changing their responses from a passive to an active coping strategy. That is not at all what this part of the amygdala was thought to do."

To find out what other parts of the brain were involved in these responses, the scientists used a magnetic resonance brain scanning technique developed for use in mice by Angelo Bifone's team at GlaxoSmithKline. Much to their surprise, they found that the switch from passive to active fear was accompanied by the activation of large parts of the outer layer of the brain - the cortex - and blocking this activation with the drug atropine could reinstate freezing behaviour and flip back the fear switch. This will give scientists interested in fear circuitry some thinking to do, as the amygdala was thought to control fear via the brain stem, not the cortex.

"This is a powerful demonstration of the ability of functional MRI to resolve brain circuits involved in complex tasks, like processing of emotions and control of behavioural responses," says Bifone, now at the Italian Institute of Technology.

We humans, too, show freezing and risk-assessment behaviours in response to fear. Understanding how to switch from passive to more active fear coping strategies might be helpful for us in adapting to the stress and unpredictability of modern life, the scientists say.

More information: Gozzi, A., Jain, A., Giovanelli, A., Bertollini, C., Crestan, V., Schwarz, A.J., Tsetsenis, T., Ragozzino, D., Gross, C.T., & Bifone, A. A neural switch for active and passive fear. *Neuron*, 26 August 2010.