Wired To Be Afraid

Aadyaa Mehrotra

Fear is one of the six fundamental emotions alongside happiness, sadness, ect. (Ekman, 1992), fear in my opinion is one of the most important for survival. It is basically the boy's survival response to a threat, as soon as it reads it as an immediate threat, such as a sudden sound that turns out to be an ice machine or a shadow that turns out to be nothing. What makes it worth knowing is that fear is not only a feeling, it's actually a coordinated chain of reactions and structural events, around the amygdala, that can be traced to specific neurotransmitters and receptor subtypes. On a regular basis when a system works, it keeps people alive. When it misfires or makes a mistake, the circuity produces phobias, PTSD, or even panic disorder.

The Neurotransmitter Systems Involved In Fear

The Glutamate, which is like the "on switch", is where the chemical that makes neurons fire builds on that fear memory. When a neutral cue or in other words a threat that you anticipate that's coming; the NMDA receptors in the amygdala detect overlap and the synapse strengthens, which links to what scares you to that danger (LeDoux, 2000). The AMPA receptors are added to the membrane to make those fires stronger next time. Blocking those NMDA receptors during that window then the fear is never learned at all. The GABA is known as the "off switch", where the inhibitory neurons inside the amygdala act like a brake. The prefrontal cortex then keeps the response to keep firing at everything. In fact people with anxiety have a weaker version of that brake. Norepinephrine is like the alarm, which is released by the Locus Coeruleus during a threat, it makes your heart race and that hyper-alert feeling while simultaneously making sure that memory is stamped harder. Moving on to Serotonin which does not create as much sensitivity, it kind of tries to see how reactive the amygdala is and how well the prefrontal cortex can regulate it, which in turn is the target of most anxiety medications. The CRF is what connects the circuit to the body's hormones. The CRF (corticotropin-releasing factor) neurons is in the central amygdala, also the BNST (bed nucleus of the stria terminalis) is what drives the behavioral side of fear and push that hypothalamus, as well where CRF from the paraventricular nucleus triggers that ACTH (adrenocorticotropic hormone) from that pituitary and then the cortisol to the adrenal glands. The cortisol then feeds back onto the hippocampus and the prefrontal cortex to shut off that response, through chronic stress that makes the shutoff less effective.

Receptor Subtypes and Where They Reside

The Amygdala then splits the jobs across the regions: the lateral amygdala absorbs that sensory information, the basolateral complex (BLA) stores the link between the cue and the danger, then the central amygdala triggers that reaction (LeDoux, 2000). The Gulatmate then acts on the NMDA receptors in the BLA, especially when it contains the GluN2B subunit, which is where two things happen at once. The Benzodiazepines such as Xanax bind to the GABA-A receptors broadly, but the a2 and the a3 subunits carry the anti-anxiety effect while the a1 is more responsible for sedation. Norepinephrine acts on the beta-adrenergic receptors (B1 and B2) in the BLA. The CRF then binds to that CRF 1 receptors packed in the central amygdala and the BNST, a region that is tied to draw out that anxiety rather than a quick scare. Outside the amygdala, the hippocampus supplies the cortex, then the ventromedial prefrontal cortex (vmPFC) calms that response back down, and the periaqueductal gray produces that freeze or flight behavior.

Genetic and Environmental Influences in Fear

Surprisingly Fear is shaped by both inherited genes and lived experience, and neither alone can decide the outcome. Twin studies show that about 30 to 40 percent of the risk for anxiety and phobias actually generate from genes (Hettema et al., 2001). Whatever that inheritance is is not a specific fear, it's sort of a threshold: some people's threat system may react more easily than others. BDNF Val66Met affects a protein which is used in learning, and people with this Met version have a harder time unlearning a fear one it has already formed (Soliman et al., 2010). COMT Val158Met changes how fast dopamine is cleared from the prefrontal cortex, which in turn, affects how well someone can regulate back down. FKBP5 controls the cortisol stress response and how these two forces work together: when one of the forces is combined with a difficult childhood it is linked to a much higher PTSD risk (Binder et al., 2008). The environment also carries a big part. Fear can be learned directly, like shown in Watson and Rayner's study, where an infant came to fear a white rat with a loud noise (Watson and Rayner, 1920). However, the study could never be run today and only involve one participant, but the study shows how quickly experience can instill fear. Fear can also be picked up by watching parents react fearfully, or through early or long term stress that actually leaves the stress system more sensitive. Some of these effects are epigenetic, which means experience changes how strongly certain genes get used without changing the DNA itself.

Neurological and Psychiatric Conditions with Fear

So when the Fear systems stop matching real threats, it becomes a disorder, and the same individuals' differences help explain who ends up there. In specific phobias the response is aimed at something harmless, and in panic disorders it fires with no trigger at all. Generalized anxiety is constant and stays a certain low level instead of spiking, which fits the NST and its role at drawing out worry. Now here is the breakdown for PTSD: When you are have an image in your head the amygdala reacts too strongly and the prefrontal cortex is less able to shut that reaction off, so the fear keeps returning even when the person knows that they are safe (Raunch et al., 2006). Also, the hippocampus stops tagging the memory with a time and place, which is why the threat might feel like it's happening now. Most people exposed to trauma might never develop PTSD, it lies how sensitive their stress system already is. The opposite extreme makes the same point. A patient known as S.M. has Urbach Wiethe disease, which destroyed both of her amygdalae, and she showed almost no fear response to snakes, haunted houses, or direct threats (Feinstein et al., 2011).

Treatment

Did you know that most treatments target the same systems that produce fear. Exposure therapy is the go to approach and works through extinction, meaning that people learn new safety associations rather than erasing the old fear (Milad & Quirk, 2012). That relies on the same glutamate machinery that is built on fear, which is why researchers have tested the D-cycloserine, which is a partial agonist at NMDA receptors, to strengthen what exposure accomplishes (Ressler et al., 2004). SSRIs and SNRIs are a go to for anxiety and PTSD despite taking weeks to work, SSRIs block the uptake of serotonin only and SNRIs block both serotonin and norepinephrine. Benzodiazepines act on the GABA-A receptors and work quickly, the tolerance and dependence limit them to short term use. Norepinephrine drugs are used for specific systems, such as prazosin for PTSD nightmares, where trial results have been mixed with propranolol, which has been studied for waking traumatic memories when they are recalled

(Kindt et a., 2009). MDMA assisted therapy has drawn attention, but the FDA declined approval in August 2024 and it remains investigational (cANADY, 2025). Every one of these works by reaching back into the circuit that is produced by fear. The fear circuit is universal, but the settings are personal, and that is what ultimately decides who walks away fine and who doesn't.

References

Binder, E. B., Bradley, R. G., Liu, W., Epstein, M. P., Deveau, T. C., Mercer, K. B., . . . Ressler, K. J. (2008). Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. *JAMA, 299*(11), 1291–1305. https://doi.org/10.1001/jama.299.11.1291

Canady, V. A. (2025). FDA publicly releases MDMA rejection letter; MAPS vows to press forward. *Mental Health Weekly, 35*(35), 1–6. https://doi.org/10.1002/mhw.34582

Ekman, P. (1992). An argument for basic emotions. *Cognition and Emotion, 6*(3–4), 169–200. https://doi.org/10.1080/02699939208411068

Feinstein, J. S., Adolphs, R., Damasio, A., & Tranel, D. (2011). The human amygdala and the induction and experience of fear. *Current Biology, 21*(1), 34–38. https://doi.org/10.1016/j.cub.2010.11.042

Hettema, J. M., Neale, M. C., & Kendler, K. S. (2001). A review and meta-analysis of the genetic epidemiology of anxiety disorders. *American Journal of Psychiatry, 158*(10), 1568–1578. https://doi.org/10.1176/appi.ajp.158.10.1568

Kindt, M., Soeter, M., & Vervliet, B. (2009). Beyond extinction: Erasing human fear responses and preventing the return of fear. *Nature Neuroscience, 12*(3), 256–258. https://doi.org/10.1038/nn.2271

LeDoux, J. E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience, 23*(1), 155–184. https://doi.org/10.1146/annurev.neuro.23.1.155

Milad, M. R., & Quirk, G. J. (2012). Fear extinction as a model for translational neuroscience: Ten years of progress. *Annual Review of Psychology, 63*(1), 129–151. https://doi.org/10.1146/annurev.psych.121208.131631

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research—past, present, and future. *Biological Psychiatry, 60*(4), 376–382. https://doi.org/10.1016/j.biopsych.2006.06.004

Ressler, K. J., Rothbaum, B. O., Tannenbaum, L., Anderson, P., Graap, K., Zimand, E., . . . Davis, M. (2004). Cognitive enhancers as adjuncts to psychotherapy: Use of D-cycloserine in phobic individuals to facilitate extinction of fear. *Archives of General Psychiatry, 61*(11), 1136–1144. https://doi.org/10.1001/archpsyc.61.11.1136

Soliman, F., Glatt, C. E., Bath, K. G., Levita, L., Jones, R. M., Pattwell, S. S., . . . Casey, B. J. (2010). A genetic variant BDNF polymorphism alters extinction learning in both mouse and human. *Science, 327*(5967), 863–866. https://doi.org/10.1126/science.1181886

Watson, J. B., & Rayner, R. (1920). Conditioned emotional reactions. *Journal of Experimental Psychology, 3*(1), 1–14. https://doi.org/10.1037/h0069608