NEUROSCIENCE

Brain maps of fear and anxiety

Anxiety, 'the disease of the 21st century', is a clinical enigma. Using virtual predators to create real-world threat scenarios, two new studies build on prior rodent-based anxiety theory to map effects of personality and decision complexity in human prefrontal cortex. We may soon have coherent neural maps of these disabling and costly psychiatric disorders.

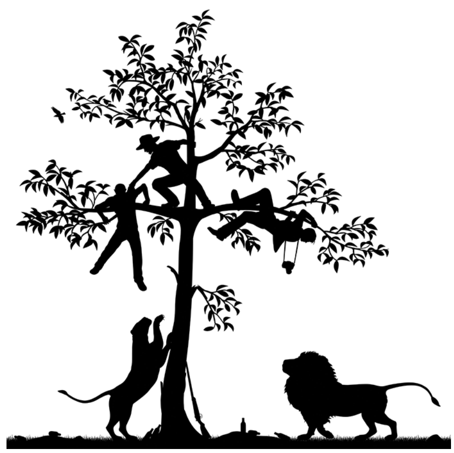
Neil McNaughton

What is anxiety? How does it vary with personality and circumstance? One way to answer these questions is to springboard off detailed rodent research and image the brain during simple real threats created by virtual predators. By varying levels of threat, we then expect to uncover hierarchical neural control[1,2]. In new studies published in *Nature Human Behaviour*, when looking at the amygdala and hippocampus, Fung et al.[3] show effects of anxious personality only when threat is not extremely urgent; and, consistently, Korn & Bach[4] show effects with relatively urgent, heuristic decision-making, but not with slower, optimised decision-making. Different aspects of threat processing, across the studies, engaged different parts of prefrontal cortex in a pattern consistent with hierarchical control. Involvement of both subcortical and prefrontal structures (and the shifts between them) merges elements of prior theories of anxiety[5,6]. We appear to be on the verge of a detailed, systematic picture of the neural control of anxiety, from the most primitive subcortical mechanisms to sophisticated human cortical processes.

Why is this important? Anxiety disorders are a major cause of human distress and create huge costs for modern health systems. But diagnosis uses symptoms (akin to fever); there are no known fundamental causes (akin to measles virus), and so treatments are poorly targeted. We need a better understanding of neural processing of threat.

There is hope. Decades of rodent work have given us a detailed picture of the subcortical and frontal circuits that may be involved in anxiety and fear[5,6]. But rats are not miniature humans any more than mice are miniature rats, so we need to be cautious not to over-generalise.

How can we test whether humans are like rodents when responding to threats? The clearest view of the nature of, and distinctions between, fear and anxiety in both rats and mice comes from 'ethoexperimental'[7] exposure to predators, the effects of which we can subject to challenge with anxiolytic and panicolytic drugs[8] and translate to people[9].



Credit: Robert Adrian Hillman / Alamy Stock Vector

How do we expose people to a real predator in an experiment? Doing so, especially while asking them to remain still in a scanner, sounds tricky. This problem has been solved using virtual worlds that contain 'predators' that deliver real-world pain. Fung et al.[3] used virtual predators that, when contacting the player's avatar, delivered shock. Korn & Bach[4] used predators that destroyed previous gains in a complex foraging situation, which pitted starvation against predation. (The 'fear = frustration' hypothesis in rodent work[10] would see the predators in the two studies as functionally equivalent.)

Both studies found that semi-urgent or heuristic responding to a predator engaged the amygdala and the part of the hippocampus (variously termed temporal, ventral or anterior) close to the amygdala. Fung et al. showed that this activation varied with anxious personality[3] (assessed with the Spielberger State–Trait Anxiety Inventory). Although participants were stationary in a functional MRI scanner, there is every reason to think the amygdala and hippocampus would be engaged when a person (or a rodent) is uncertain as to how to respond to any truly threatening situation, such as the presence of a predator. In contrast, urgent or reactive responses to virtual predators engage subcortical 'survival circuits'[11], such as the periaqueductal grey[12]. This hierarchy seen in humans is consistent with prior rodent data[1,2,6].

Frontal cortex activation also appeared to depend on the hierarchical level of threat. Fung et al. show that, with semi-urgent threat, activation of the ventromedial prefrontal cortex (and information flow from the hippocampus to it) increases with trait anxiety[3]. Similarly, Korn & Bach show that responses based on predator probability (a simple heuristic) activated dorsolateral prefrontal cortex[4] (as well as amygdala and hippocampus). Their ingenious analysis, taking advantage of Markov-chain decision processes, showed similar increases when the nature of events became relatively certain at high or low predator probability. However, responses based on less-heuristic, and so even more computationally intensive, optimal policies activated posterior dorsomedial prefrontal cortex but not amygdala or hippocampus. Across the studies, then, increasing depth of processing (linked to decreasing urgency of decision) appears to produce a progressive shift in the main locus of processing, from anterior ventromedial via more central dorsolateral to more posterior dorsomedial prefrontal cortex.

Taken together, these results extend to prefrontal cortex the picture of hierarchical neural systems controlling fear and anxiety in which decision urgency (from reactive through heuristic to predictive) determines the level of the hierarchy engaged[1,2]. But they also suggest that at the highest levels of processing—in which simple heuristics give way to complex optimising policies and the amygdala and hippocampus cease to be engaged—there may be a functional change from tactical (how) to strategic (why) processing that means were are no longer dealing with hot emotion but only cold cognition. It may be significant, here, that hippocampal projections are strong in ventromedial and absent in posterior dorsomedial regions (which do not show accompanying hippocampal activation).

Both studies use complex analyses that give a much more nuanced picture than I present here. (Activations include areas like the insula, right inferior frontal gyrus, anterior and posterior cingulate, and thalamus.) However, their radically different paradigms and analyses give very similar pictures of our brain's responses to threat—and of the variation in circuits engaged by different tasks—that are consistent with prior rodent-based theory. Despite their superficial complexity, the circuits that keep us safe (and cause some of our worst experiences) appear to be built on a simple hierarchical pattern in which, with more available time, processing shifts to more rostral and more complex processing circuits. As we go from panic through to worry, our processing shifts from reactive survival, through tactical heuristics, to strategic optimisation. All are potential sources of different types of anxiety disorder for which neuroscience appears, at last, to be providing a coherent, systematic map. ❐

Neil McNaughton
Dept. Psychology, University of Otago, Dunedin, New Zealand.
e-mail: neil.mcnaughton@otago.ac.nz

Published online: 20 May 2019
https://doi.org/10.1038/s41562-019-0621-7

References

1. McNaughton, N. & Corr, P. J. *Neurosci. Biobehav. Rev.* **28**, 285–305 (2004).
2. Graeff, F. G. *Braz. J. Med. Biol. Res.* **27**, 811–829 (1994).
3. Fung, B. et al. *Nat. Hum. Behav.* https://doi.org/10.1038/s41562-019-0595-5 (2019).
4. Korn, C. W. & Bach, D. *Nat. Hum. Behav.* https://doi.org/10.1038/s41562-019-0603-9 (2019).
5. Gray, J.A. & McNaughton, N. *The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-hippocampal System*. 2nd ed. (Oxford University Press, 2000).
6. LeDoux, J. *Anxious: The Modern Mind in the Age of Anxiety*. (Oneworld Publications, 2015).
7. Blanchard, D.C. & Blanchard, R.J. in *Annu. Rev. Psychol.* (eds. Rosenzweig, M. K. & Porter, L. W.) 43–68 (Palo Alto, 1988).
8. Blanchard, R. J., Griebel, G., Henrie, J. A. & Blanchard, D. C. *Neurosci. Biobehav. Rev.* **21**, 783–789 (1997).
9. Blanchard, D. C. *Neurosci. Biobehav. Rev.* **76 Pt A**, 22–28 (2017).
10. Gray, J.A. *The Psychology of Fear and Stress*. (Weidenfeld and Nicolson, 1971).
11. LeDoux, J. *Neuron* **73**, 653–676 (2012).
12. Mobbs, D. et al. *Science* **317**, 1079–1083 (2007).

Competing interests

The author declares no competing interests.