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NEUROSCIENCE

Anxiety is the sum of its parts

Anxiety does not arise from a single neural circuit. An interplay between neighbouring, yet opposing, circuits produces anxiety, and outputs from these circuits regulate specific anxiety responses.

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We all know anxiety. We might have experienced it while waiting to hear about a promotion at work, or on our way to see the doctor because she wants to talk about test results in person. A diffuse uneasiness, sometimes accompanied by perspiration and subtle changes in breathing, anxiety ebbs and flows depending on life's circumstances, and can even occur for no apparent reason. The condition can be healthy and adaptive, but research in the United States[1] shows that, for roughly one-third of people, anxiety is a debilitating disorder at some point in their lives. Nevertheless, answers to important questions — such as how different neuronal populations represent anxiety, and how the various components of the anxious state are constructed and represented in neural circuits — remain elusive. In two papers published on *Nature*'s website today, Jennings *et al.*[2] and Kim *et al.*[3] address these questions using optogenetics to manipulate distinct neuronal subpopulations in mice and so dissect out the contribution of intermixed but functionally distinct cell groups.

Both teams analysed a large, diffuse brain region called the bed nucleus of the stria terminalis (BNST). Previous studies[4–7] have found that lesions of the BNST reduce anxiety and fear of specific environments. Other work has discovered[8,9] distinct subregions and subpopulations of BNST neurons, and has found that the region has connections with several other brain areas that are involved in motivated behaviour and stress responses. However, the functions of the various BNST subpopulations and subregions, as well as the significance of these connections, have remained unclear.

Jennings and colleagues focused on the role of the ventral BNST (vBNST) in mediating anxiety and regulating motivated behaviour, which, along with several other behaviours, may be modulated by anxiety. Consistent with the idea that the vBNST contains functionally distinct cell populations, the authors found that learned anxiety that is associated with specific environments leads to increased activity of some vBNST neurons and decreased activity of others.

Both of these cell populations made specific synaptic connections with neurons of another brain region called the ventral tegmental area (VTA), which is known to guide motivated behaviour. Specifically, cells that were excited by anxiety-inducing environments in turn excited their VTA partner, and stimulating these excitatory vBNST–VTA connections increased anxiety and decreased reward-seeking behaviour. By contrast, vBNST neurons that were inhibited by anxiety-inducing environments also inhibited their downstream VTA neurons, and stimulating these inhibitory connections promoted reward-seeking behaviour and reduced anxiety.

A caveat of this work is that the authors did not inhibit vBNST–VTA connections during natural anxiety states, but rather stimulated the neurons to regulate anxiety and motivated behaviours. Thus, it is possible that engagement of these circuits by anxiety does not produce the same behavioural effects naturally as those seen with artificial stimulation. However, the fact that during anxious states the vBNST–VTA neurons, which are known to promote anxiety, were activated and those that reduce anxiety were inhibited provides strong correlative evidence that learned anxiety naturally engages these neuronal subpopulations. The interplay between these two opposing 'push–pull' circuits may set an adaptive, or even a maladaptive, level of anxiety, and allow for bidirectional regulation of reward-motivated behaviour during anxiety.

Kim and co-workers asked whether, and if

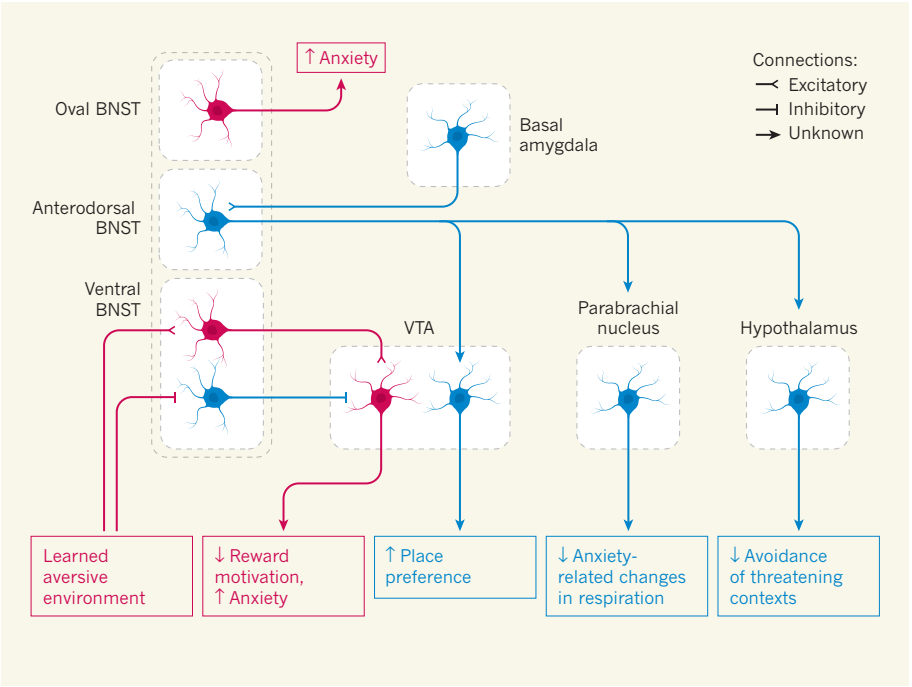

Figure 1 | Multiple personalities of an anxiety circuit. Two studies[2,3] show that various subregions in the bed nucleus of the stria terminalis (BNST) of the mouse brain contain intermixed cell populations that can produce (red) or ameliorate (blue) anxiety in a modular manner. Within the dorsal BNST, outputs from the oval nucleus promote anxiety, whereas outputs from the anterodorsal BNST — driven by activity in the amygdala — reduce anxiety. Anterodorsal BNST neurons also make specific connections to other brain regions, such as the hypothalamus, parabrachial nucleus and ventral tegmental area (VTA), to ameliorate specific features of anxiety. The ventral BNST contains intermixed but functionally distinct subpopulations of neurons. When the mice are exposed to a known anxiety-causing environment, some of these neurons are excited, stimulating their connections in the VTA to produce anxiety and reduce reward motivation. Other ventral BNST neurons that reduce anxiety and enhance reward motivation are inhibited, facilitating the production of anxiety.

so how, cells in the two subregions of the dorsal BNST, the oval nucleus (ovBNST) and the anterodorsal BNST (adBNST), differentially regulate anxiety. They found that the activity of ovBNST neurons promoted anxiety. Moreover, inputs from the amygdala, a brain region that has been implicated in fear, reward and anxiety, activated adBNST neurons and reduced anxiety, and inhibition of these inputs increased anxiety. Consistent with a role in reducing anxiety, adBNST neurons fired more when the animals were in a safe environment than when they were in an anxiety-producing one, thus distinguishing between the two places (Fig. 1).

Intriguingly, inhibiting amygdala inputs to the adBNST reduced the ability of this subregion's neurons to distinguish between safe and anxiety-producing places, which suggests that adBNST cells reduce anxiety in response to a 'safety' signal from the amygdala. Future work should determine how amygdala neurons connecting to the adBNST encode anxiety-related information and what types of experience recruit this anxiety-reducing circuit.

Kim *et al*. also examined specific connections between the adBNST and other brain regions and found that, depending on the connections involved, the adBNST reduced specific aspects of the anxiety response. For instance, stimulating the connections between the adBNST and the hypothalamus reduced the tendency of mice to avoid anxiety-producing places; stimulating connections to neurons of the parabrachial nucleus led to reduced anxiety-induced changes in respiration; and stimulating connections with VTA neurons resulted in place preference (Fig. 1).

The two studies give us a richer understanding of how anxiety is represented by opposing but complementary neural circuits in the BNST. They highlight the modular nature of anxiety circuits and suggest a concerted mechanism for bidirectional regulation of anxiety-related responses. This type of bidirectional coding has been seen in other parts of the anxiety circuit[10,11], particularly in the brain's medial prefrontal cortex, in which single neurons differentially represent safe and anxiety-producing environments.

In fact, this type of circuit design may be a general feature of both fear and anxiety systems. There is strong evidence[12,13] that partially distinct neuronal subpopulations mediate fear and safety-from-fear learning. Moreover, fear and anxiety are closely related conceptually, and brain regions such as the amygdala, medial prefrontal cortex, hippocampus and BNST are involved in both. Understanding the principles shared by the two systems, and how their respective neural circuits interact, will be research areas of great interest for the future. ■

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