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.

JOSHUA P. JOHANSEN

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 States1 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 studies4–7 have found that lesions of the BNST reduce anxiety and fear of specific environments. Other work has discovered8,9 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
so how, cells in the two subregions of the dor-
sal 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 anx-
xiety, 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 sub-
region’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 neu-
rons connecting to the adBNST encode
anxiety-related information and what types
of experience recruit this anxiety-reducing
circuit.

Kim et al. also examined specific connec-
tions 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 respira-
tion; and stimulating connections with VTA
neurons resulted in place preference (Fig.
1).

The two studies give us a richer understand-
ing of how anxiety is represented by oppos-
ing but complementary neural circuits in the
BNST. They highlight the modular nature of
anxiety circuits and suggest a concerted mech-
anism for bidirectional regulation of anxiety-
related responses. This type of bidirectional
coding has been seen in other parts of the
anxiety circuit10,11, particularly in the brain’s
medial prefrontal cortex, in which single neu-
rons 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 evidence12,13 that
partially distinct neuronal subpopulations
mediate fear and safety-from-fear learn-
ing. 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. ■

Joshua P. Johansen is at the RIKEN Brain
Science Institute, Saitama 351-0198, Japan.
e-mail: jjohans@brain.riken.jp

org/10.1038/nature12041 (2013).
3. Kim, S.-Y. et al. Nature http://dx.doi.org/10.1038/
nature12018 (2013).
(2004).
Fanselow, M. S. Proc. Natl Acad. Sci. USA 107,
14881–14886 (2010).
(2012).
10. Adhikari, A., Topiwala, M. A. & Gordon, J. A. Neuron