Tales of the unexpected shock

Artificial agents prone to anxiety could provide a stepping stone to more effective treatments for anxiety disorders.

Oliver Robinson has spent much of his career being unpleasant to his research participants – but all in a good cause. His aim has been to induce a state of mild anxiety, and to understand how resulting changes in brain activity affect cognition – with the long-term goal of generating a deeper mechanistic understanding of anxiety disorders. Having implicated specific brain networks and neurotransmitters in both experimentally induced and pathological anxiety, he is now developing computational models exploring how anxiety influences learning and behaviour – creating artificial agents with the equivalent of an anxiety disorder.

His first opportunity to mistreat subjects came in his PhD studies with Barbara Sahakian in Cambridge. Here, he was exploring how manipulation of serotonin levels affected cognition (specifically emotional processing biases). Serotonin levels can be lowered by restricting participants’ food intake to a cocktail of amino acids lacking tryptophan, the metabolic precursor of serotonin. “We spent a lot of time forcing people to take these drinks that taste rather disgusting,” he recalls.

Moving on to a postdoc at the National Institutes of Health, he ended up working with Christian Grillon, who was studying anxiety in mouse models and was keen to extend his work to humans. Professor Grillon had developed a method for inducing anxiety – threat of electric shock. The element of uncertainty, says Dr Robinson, is what distinguishes anxiety from fear: “Anxiety is response to some unpredictable threat, fear is response to a predictable threat.”

We are all familiar with the sensation of anxiety, and it can have clear adaptive value – making us more aware of threats in potentially dangerous situations, for example. “The difference for somebody with an anxiety disorder is that it’s not only turned on when there’s potential threats around them, it can be on all the time. It can end up quite debilitating because you’re constantly anxious even if there isn’t an obvious cause of that anxiety.”

In the lab, Dr Robinson induces anxiety by getting participants to complete tasks for periods of time during which they know they will receive an unpleasant electric shock, at some unspecified point. Their performance on these tasks is then compared with that achieved when they are not expecting a shock. Threat of shock has a significant impact on some cognitive tasks, such as recognition of fearful faces, says Dr Robinson. “When you threaten people with electrical shocks, they are just a little bit faster to press the button to tell us that the face is fearful when they’re under the anxious condition.”

Importantly, he adds, this ‘artificial’ anxiety is somewhat analogous to that experienced in pathological conditions: “We think that the anxiety we evoke is actually pretty similar at a mechanistic level to the sort of anxiety you have in an anxiety disorder. The key difference is that normal anxiety turns off and on.”

Using functional imaging, Dr Robinson and colleagues identified a brain network associated with anxiety-induced cognitive biases, linking medial regions of the dorsal prefrontal cortex with the amygdala – a structure with a well-known role in the processing of emotional information. “When you feel anxious this circuit starts talking to itself a bit more,” says Dr Robinson. “And the more anxious you are, the more these regions are coupled.” Crucially, activity in this circuit is also more engaged in people with an anxiety disorder. “It goes on and off and on and off in healthy people, but in people with an anxiety disorder it can get stuck in the ‘on’ phase.”

Returning to his neurochemical roots, Dr Robinson also showed that manipulation of serotonin modulated coupling in this circuit, with increased serotonin levels reducing connectivity. “It looks as if maybe serotonin works by applying
the brakes to this circuitry," he suggests. Such a mechanism, he adds, could explain how selective serotonin reuptake inhibitors such as Prozac exert their anti-anxiolytic effects.

Furthermore, he has also found that psychological as well as pharmacological manipulations can influence activity in this circuit. When participants were presented with more complex stimuli involving shapes as well as faces and told to attend to the shapes, activity in the circuit was reduced: "So telling people what to do, giving them a psychological instruction, can also modulate activity in this circuitry," says Dr Robinson.

**Modelling anxiety**

Dr Robinson is keen to stress that the results do not fully 'explain' anxiety. "I have quite a brain-based attitude, but you can't think about these things totally in isolation. Social situations, economics and everything all play into what makes people anxious." Rather, he suggests, the findings provide insight into one specific aspect of anxiety. Unpicking different aspects of anxiety may help to reveal why some patients respond to drugs, some to psychological treatments and some to neither, so patients could ultimately be matched with the treatment most likely to work for them.

This goal to impact on treatment also underpins his recent move into the emerging field of 'computational psychiatry', following his move to UCL in 2014. "The idea is that we can use computational modelling as a bridge between the symptoms you see in the clinic, such as avoidance, to underlying biology."

His latest studies are drawing upon the techniques of machine learning and artificial intelligence. "They allow us to take a much richer look at the data we collect," he suggests. Conventional studies typical collapse large amounts of data into averages. "What that does is throw away a lot of important information." For learning tasks, for example, it is valuable to understand how responses change over time.

The key theoretical concept informing this work is reinforcement learning, the idea that the brain is constantly making predictions about the world it expects to experience and updates its predictions whenever they prove wrong. Much work on animals and humans supports the idea of such 'prediction errors' and has identified potential neural substrates for them.

Reinforcement can be modelled mathematically, incorporating factors such as the desire to maximise rewards and to minimise punishments. By collecting data from participants, Dr Robinson can develop models that recapitulate the experimental data. "We can then look at what we have to mess with in our models to mimic people with anxiety disorders."

One factor turning out to be significant is a so-called avoidance bias parameter, which captures the degree to which people avoid actions that have the potential to cause harm. Tweaking this factor in his models generates behaviour mimicking that of patients: "We've shown on a decision-making task that people with anxiety disorders show increased reliance on this avoidance bias parameter, so they're more likely to inhibit their behaviour in the face of negative information. And this scales up to avoidance as a symptom."

His models therefore mimic pathological anxiety – something fans of the Hitchhiker’s Guide to the Galaxy might appreciate: "I sometimes flippantly describe this as the 'Marvin the Paranoid Android' branch of research," he jokes.

But his research – and computational psychiatry more generally – has more serious and ambitious aims: "If you can have a model that describes behaviour in these terms ultimately you might be able to map that model onto underlying neurophysiologically plausible neuronal activation," he suggests. "The ultimate goal is to use this bridging model to go right from neuronal firing, cells in the brain, all the way up to observable symptoms. If we can do that we'd be in a position in psychiatry that's closer to other branches of medicine where we understand from the bottom up what the mechanism is that leads to the symptom."

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