The Cutting Edge

NEUROBIOLOGY OF ANXIETY: FROM NEURAL CIRCUITS TO NOVEL SOLUTIONS?

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We are currently at an important juncture in the research and clinical care of anxiety-related disorders. On the one hand, anxiety disorders are highly prevalent, very frequently chronic in their course, and associated with a host of negative outcomes, such as greater risk of suicide, medical and psychiatric comorbidities, and lower remission rates when comorbid with depression.[1–4] Medications are effective in treating anxiety, but only help a portion of patients. Psychosocial interventions, which themselves are also only effective in a portion of patients, are often difficult to find in the community. As such, there is a pressing clinical need for improvements in the treatment of anxiety disorders—a fact that is strikingly highlighted for example by the toll posttraumatic stress disorder (PTSD) has taken on soldiers who have served in Iraq or Afghanistan. On the other hand, of the range of psychopathology studies in humans using tools such as neuroimaging, and modeled in animals, anxiety has enjoyed some of the deepest neuroscientific study and most ready translation between human patients and animal models. This work has been especially successful in the translation of a neural circuit-level formulation between humans and animal models, but has only sparsely examined neural correlates of existing clinical treatments for anxiety.

Neuroscientific advances, using both human and experimental animal levels of study, offer the greatest promise for advancing and improving treatment. In this piece, I will outline a core set of findings that together inform a systems level, or neural circuit view of anxiety, and explore ways in which this understanding may result in a diverse set of novel interventions.

NEURAL CIRCUITRY OF ANXIETY

An important distinction to make within anxiety is between "fear" disorders, which are characterized primarily by exaggerated reactivity to fear cues (e.g. social anxiety disorder (SAD), agoraphobia), and "anxious/misery" disorders, which feature a wide-ranging anticipatory anxiety that is not contingent on cue reactivity (e.g. generalized anxiety disorder (GAD)). Disorders such as PTSD have both fear and anxious/misery components, and disorders such as major depression (MDD) share many anxious/misery features despite being expressed more as a mood disturbance. Obsessive compulsive disorder has been left out of this discussion since neuroimaging studies have shown that it involves circuits distinct from those implicated in the other anxiety disorders, and as such likely will be reclassified in a different category in the next diagnostic manual.[5]

We conducted a meta-analysis of negative emotional processing in the three anxiety disorders with sufficient data (PTSD, SAD, and specific phobia).[6] In order to relate neural abnormalities in these disorders to fear

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processing, we also meta-analyzed imaging studies of healthy subjects undergoing fear conditioning. Strikingly, all three disorders, despite differing levels of severity and generalization, resulted in hyperactivation of the amygdala and insula in patients, a pattern also observed during fear conditioning in healthy subjects. As such, the "fear" component of these disorders appears to be mapped to excessive amygdala and insula reactivity, consistent with a central implication of the amygdala in animal work on anxiety.[7,8] Others have shown that the insula is important in interoception, and thus mediates the brain's monitoring of arousal and aversive states—which are core areas of dysfunction in anxiety.[9]

A large body of neuroimaging work on fear conditioning and fear extinction in healthy subjects also implicates dorsal anterior cingulate and medial prefrontal (ACC/mPFC) regions in the monitoring and expression of fear responses (e.g. autonomic responses), and the ventral ACC/mPFC in the inhibition or extinction of these responses.[10] Likewise, we have shown using an emotional conflict task, that dorsal ACC/mPFC activity tracks the disruptive effects of emotional conflict, whereas ventral ACC/mPFC regulates it.[11–14] This similarity in neural circuitry between fear conditioning/extinction and emotional conflict regulation suggests that both may tap into the same broader emotion regulatory network in the brain.[10] These findings also accord well with work in rodents, wherein prelimbic cortex (homologous to human dorsal ACC/mPFC) is involved in expression of conditioned fear, whereas the infralimbic cortex (homologous to ventral ACC/mPFC) is required for fear extinction.[15]

The three anxiety disorders we examined in our meta-analysis differed with respect to severity and generalized nature of their symptoms, which was in turn reflected by their neurobiological correlates. In particular, PTSD was characterized by a lower frequency of amygdala/insula hyperactivation than the other disorders, but was uniquely associated with hypoactivation in the ACC/mPFC.[6] Consistent with this finding and the functional parcellation of dorsal and ventral ACC/mFPC, Milad and colleagues [16] have shown that PTSD patients have impairments in the recall of extinction memories, and that this is associated with hyperactivation in the dorsal ACC/mPFC (exaggerated resultant fear expression) and hypoactivation in the ventral ACC/mPFC (disturbed fear regulation). Likewise, in the emotional conflict task, we have shown impairments in dorsal and ventral ACC/mPFC in GAD and MDD, along with behavioral evidence of impaired emotional conflict regulation. Collectively, these data implicate ACC/mPFC dysfunction in anxious/misery-type symptoms in anxiety disorders (as well as the related condition of MDD), and may better explain real-world impairment in these conditions than in isolated "fear" disorders, despite a lower frequency of amygdala/insula hyperactivity.

A final region implicated in anxiety through animal work, but which has not been investigated in great depth

in humans, is the hippocampus. In animals, the ventral hippocampus (human anterior hippocampus) mediates endogenous anxiety, whereas the dorsal hippocampus (human posterior hippocampus) is involved in memory, including fear- or extinction-related memory. Although Milad and colleagues [16] also found hippocampal hypoactivity during extinction recall in PTSD, few other neuroimaging studies of anxiety disorders report similar hippocampal dysfunction. It is unclear what accounts for the discrepancy between neural circuitry of anxiety in animals and of anxiety disorders in humans in this case, as would the rest of the circuitry appears well conserved. One possibility is that tasks used in animal work that best tap into the contribution of the hippocampus to human anxiety are different from those that are typically used to examine amygdala or ACC/mPFC activity.

Despite these major advances in understanding the neural circuitry of anxiety, many important questions remain unanswered. For example, though ACC/mPFC dysfunction is broadly implicated in neural abnormalities associated with anxious/misery-type symptoms, it is unclear how this maps onto specific constellations of symptoms across different disorders (e.g. GAD versus PTSD), the heterogeneity within a single disorder (e.g. the diversity of symptoms possible in PTSD), or the ways patients cope with or compensate for emotional dysfunction over time. Equally, little is currently known about the brain mechanisms of established treatments for anxiety disorders, both pharmacological and psychosocial. As a consequence, animal models of treatment for anxiety are simplistic and generally revolve around fear extinction paradigms. This degree of simplification may, in fact, present a barrier to finding new approaches for modulating these circuits that have the best chance for crossing the translational divide between rodents and humans.

IMPROVING BIASED THREAT REACTIVITY THROUGH TRAINING

Using neuroscience tasks in humans to assess the function and behavioral consequences of a specific neural circuit (such as those outlined above), opens up the potential that repetitive and adaptive training in that task can improve functioning in the relevant neural circuit. This once-controversial proposition has recently been proven possible by a growing body of work, across various forms of psychopathology. Adult brains, even those dysfunctional because of mental illness, still retain a surprising degree of plasticity.[17–19]

In the context of anxiety, this approach has been used to leverage a method for measuring attentional capture by threat stimuli, which is elevated in many forms of anxiety, into a way to modify that attentional bias.[20] Repetitive training of subjects that helps them avert their attention from threat stimuli appears to improve both the attentional bias, and clinical symptoms in several

anxiety disorders.[21,22] Though a subsequent meta-analysis suggests that the effect size of attention bias modification approaches may be smaller than originally thought,[21] this type of training provides a proof of concept that by understanding threat-processing circuitry and having a meaningful behavioral readout for its function, one can design a novel intervention for anxiety.

By extension, it may be possible to enhance emotion regulation through targeted training aimed at patients with deficits in general emotion regulatory module (as in anxious/misery-type disorders), and to target the training at the neuroscientifically informed defective circuitry. Although this approach is still in its infancy compared to attentional bias modification, insights into how this may be possible come from examining the circuitry outlined above. Exaggerated emotional reactivity (i.e. amygdala, insula) may be diminished by instilling a bias toward positive or rewarding stimuli, and away from negative or threat stimuli. The ability to monitor environmental demands, orient to salient events, and properly contextualize negative emotional responses (i.e. dorsal ACC/mPFC), and the ability to inhibit excessive negative emotional reactivity (i.e. ventral ACC/mPFC) may be trained through tasks that require subjects to appropriately modulate their emotional responses in order to successfully perform the task.

These types of computer-based interventions have the advantage that they can be readily standardized and well controlled for in randomized trials, do not require involvement of a therapist or even particular treatment expertise in provider, and are not associated with the side effects possible with a medication. Much more work, however, will be needed to optimize this training approach (e.g. dose, duration, type of stimuli, ideal target populations) from where it currently is.

REAL-TIME fMRI AND NEUROFEEDBACK

In a further step toward direct modulation of relevant neural circuitry, techniques have proliferated over the past few years for real-time monitoring of brain activity using fMRI.[23] Though real-time monitoring of neural activity has long been easily possible with EEG, doing so with fMRI provides a major advantage for anxiety-related neural circuitry, which centrally involves deep subcortical and midline cortical structures that are not well assessed with EEG. In these experiments, subject generally adapt a strategy to up- or down-regulate activity in a targeted brain region, based on real-time feedback of activity in that region, or sham feedback. Multiple studies have shown that real-time fMRI neurofeedback can allow subjects to voluntarily modulate amygdala, insula, dorsal ACC, and subgenual ACC activity.[24–28] Learning to modulate amygdala and insula activity, moreover, also resulted in enhanced connectivity with prefrontal cortex.[24,25] Although real-

time fMRI neurofeedback is far from being ready as an intervention, it would certainly provide a novel, albeit technically cumbersome, treatment modality that is borne out of an understanding of neural circuit-level deficits in anxiety.

DIRECT CIRCUIT MODULATION THROUGH TRANSCRANIAL MAGNETIC STIMULATION AND DEEP BRAIN STIMULATION

Furthest along the continuum of neural circuit interventions is direct modulation of anxiety-related circuitry through noninvasive brain stimulation with repetitive transcranial magnetic stimulation (rTMS) or deep brain stimulation (DBS). DBS treatment has generated new excitement for treatment in particular of MDD.[29] Based on well-established DBS methods for disorders such as Parkinson's, chronic stimulation at several sites––the subgenual anterior cingulate, nucleus accumbens, and anterior limb of the internal capsule[30]—all have shown evidence in small open-label studies of efficacy in treatment resistant MDD (including for anxiety symptoms). Larger-scale multisite studies of DBS are currently ongoing. Drawing on these successes, it will be important to further develop DBS approaches for anxiety that are guided by a neural circuit formulation of anxiety, which may involve targeting brain regions not normally the focus of DBS for MDD.

rTMS has been used for over two decades for the treatment of MDD, for which it received FDA approval in 2008. Although very few controlled studies exist for use of rTMS in anxiety disorders, several small-scale studies support the potential utility of rTMS, primarily with PTSD.[31–33] One limitation of current rTMS approaches is that they are not guided by an understanding of specific structural or functional anatomy based on the individual or on specific patient groups parcellated along our emerging neural circuit based understanding. That is, current prefrontal targeting of rTMS is achieved by stimulation at a site referenced as a fixed distance (e.g. 5 cm) anterior to the motor strip. Thus, it is understandable why treatment response to rTMS performed this way may be suboptimal and highly variable. In fact, using the conventional "5 cm rule," stimulation in roughly one third of patients is not even over prefrontal cortex.[34] Development of techniques for simultaneous fMRI imaging while applying TMS stimulation to a variety of brain regions [35] may greatly increase the spatial and temporal specificity of rTMS. For example, stimulation in regions that most robustly evoke activation in the ACC/mPFC may result in the greatest clinical efficacy in treating anxiety. Additional TMS coil development may also further improve direct targeting of deeper brain structures [36].

CONCLUSION

In summary, neuroimaging in humans with anxiety disorders and parallel studies in animal models of anxiety have provided a consistent and coherent view of the neural circuitry involved in anxiety. As a field, we are now in a position to see whether these neural circuit insights can be translated into the novel solutions long sought by our patients.

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