

Fear and Anxiety: The Benefits of Translational Research

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Jack Gorman, after many years on the faculty at Columbia and the New York State Psychiatric Institute, is currently Professor in the Department of Psychiatry at Mount Sinai School of Medicine in New York City. He is also the Scientific Director of the Phobia, Anxiety, and Stress Disorders Clinic at Long Island Jewish Medical Center and an international authority on the neuropsychopharmacology of mood and anxiety disorders. In 2002, Gorman served as the President of the American Psychopathological Association. During his tenure, he organized the annual conference of the APPA on the topic of translational research focused on fear and anxiety. With this publication of the proceedings, we can all benefit from the unique opportunity that this conference provides for mental health specialists to learn about, discuss, and debate cutting-edge issues.

Containing chapters by many of the acknowledged leaders in the field, this volume, by focusing on the fundamentals of fear and anxiety, addresses key aspects of the emotional life of psychiatrists as well as their patients. Indeed, dysregulation of fear and anxiety plays a role in many, if not most, of the diagnoses in DSM-IV.

The opening chapter by Sullivan and LeDoux revisits the neural circuitry of fear and anxiety and the key role of the amygdala. Animal models of amygdala function have provided fundamental insights into how the neural systems devoted to emotional states can influence perception, learning, and memory as well as modulate our behavior in social settings. Although I have my doubts as to whether subjective conscious experience can be reduced to "simply one component of a vast network of processes that occur between stimulus perception and behavioral response," I am certain that we share much in common with the animals that have been the focus of the work in LeDoux's laboratory.

The penultimate chapter (13) by Johnson and LeDoux breaks new ground by examining the electrical activity of various cell types found in the lateral nucleus of the amygdala. The lateral nucleus is a key intermediate structure that likely provides a rapid yet crude representation of the environment, allowing for a "fast response to potential danger." Particularly intriguing are the presumed fast-spiking GABAergic interneurons of the lateral nucleus that can fire at incredible speed (up to 100 times per second) and that likely serve to integrate the activity of what have come to be called "principal" projection glutamatergic neurons that project their axons from the lateral nucleus.

In this regard, it will be fascinating to follow the story of stathmin, an inhibitor of microtubule formation, that is highly expressed in the lateral nucleus of the amygdala as well as in the thalamic and cortical structures that send information to the lateral nucleus about the conditioned (learned fear) and unconditioned (innate fear) stimuli. Shumyatsky and colleagues¹ recently reported that mice lacking the gene that encodes stathmin show (1) deficits in spike-timing-dependent long-term potentiation; and (2) decreased memory in amygdala-dependent fear conditioning as well as failure to recognize danger in innately aversive environments.

Another high point of this volume is the chapter by Bruce S. McEwen and Ana Magarinos entitled, "Does Stress Damage the

Brain?" Although for some reason they avoid the use of the terms *allostasis* and *allostatic load* (terms popularized by McEwen that usefully describe the balance between factors that can result either in resilience to stress or in compounding its negative effects), they do focus on the concept of balance between complex networks of feedback and feedforward interactions that characterize "every mediator from excitatory amino acids to glucocorticoids to the inflammatory-oxidative stress cascade" and emphasize the fact that these networks have many ways to maintain their delicate balance. They also emphasize (in this and other reviews) the balance between the mind and the body, reminding us that the subjective realities of the mind include not only what goes on in the brain but visceral sensations as well, including pain and the effects of inflammatory states. These components influence fear and anxiety as well as affect mood, attention, and arousal. Examples of allostatic overload include abdominal obesity, the acceleration of atherosclerosis, hypertension, and increased risk for cardiovascular disease and stroke, all conditions that involve both the brain and the body. Many of these medical conditions are seen in patients with chronic mood and anxiety disorders, as they are part of the same whole and do not involve just the body or the brain in isolation.

Although studies in humans cannot examine these neural systems with the same specificity as animal studies, identifying links in the neural representation of behavior across species will likely lead to a deeper understanding of some of the biological determinants of a number of psychiatric disorders over the lifespan. Functional brain imaging studies are at the forefront of this area of translational research, a trend that is amply reflected in this volume with chapters by Danny Pine and Michael D. De Bellis, among others.

For example, Pine and his colleagues have adapted a threat paradigm for adolescents using functional magnetic resonance imaging. Their aim is to examine amygdala activation under conditions designed to induce fear. The threat was a mildly aversive air blast directed to the throat. Participants were told that they might receive the air blast when viewing one stimulus (threat condition) and would not receive the blast when viewing the other stimulus (safe condition). Participants were asked to complete fear ratings immediately after each trial. On the basis of the relatively mild nature of the air blast, they expected participants to report varying degrees of fear. Those who reported increased fear showed right amygdala activation during the threat condition and left amygdala activation in the safe condition. These procedures offer a promising tool for studying youth with anxiety disorders.

This group is also pioneering the use of reward-receipt and reward-omission procedures as well as more classical tests of an individual's ability to recall facial photographs depicting "happy," "fearful," or "angry" emotions followed by a memory recall test,²⁻³ all in preparation for functional brain imaging studies that are doubtless underway at present.

Three years ago, Jack Gorman presided over the annual conference of the American Psychopathological Association. In retrospect, we must affirm the view he announces in the preface to this volume:

Never before in the history of psychiatry and psychology have we been able to call on a basic science relevant to the clinical illnesses we are charged with treating.

We also can look forward to the integration of genetics, gene-environment interactions, and the clarification of epige-

netic mechanisms during critical periods of brain development at some future meeting of the APPA.⁴

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