CHAPTER 1.1

Introduction to the handbook on fear and anxiety

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Any volume that seeks to analyze two concepts – here fear and anxiety – needs to start by differentiating them. This volume will bring up this distinction in a number of contexts, and it will become clear that different authors may have somewhat different conceptions of what the distinction may be (e.g., chapter by McNaughton and Zangrossi). For current purposes, and because the editors have a robust position on this topic, we will start with this distinction: fear is the motivation associated with a number of behaviors that normally occur on exposure to clearly threatening stimuli. Anxiety is the motivation associated with behaviors that occur to potential, signaled, or ambiguous threat. Both anxiety and fear are often measured through the intensity or persistence of the behaviors with which they are associated, and may further be assessed by their ability to be conditioned to stimuli associated with these threats. These characterizations make it clear that fear and anxiety may intergrade or overlap, just as the stimuli that elicit them represent extremes of continua of clarity and immediacy of threat, such that a particular threat might appear at various points along these continua.

From an ethological perspective, both fear and anxiety are highly adaptive responses. Both are persistent and intense under appropriate conditions, in all vertebrate species in which they have been examined. However, the behaviors associated with fear and anxiety are time- and labor intensive; they may have to be, in order to be successful in meeting the array of dangers that every living organism faces. Failures of intensity or persistence are some of, but certainly not all, the ways that fear and anxiety systems may be insufficient. The simple fact that each of us is alive to read these words indicates that every one of our direct ancestors, human or prehuman, displayed fear and anxiety patterns that were at least adequate to keep them alive through successful reproduction. It is not a negligible legacy.

The problem with all such intense and persistent reactions is that they take effort and time. The evolutionary history of all species has included a world of threatening events. Left unchecked, the motivations and behavioral expression of fear and anxiety might easily consume a disproportionate portion of the energy and time budgets of individual animals, to the detriment of other crucial behaviors like obtaining food, sex, reproduction, and self-care. The major mechanisms limiting fear and anxiety, such as habituation and extinction, and behaviors facilitating these limitation processes, for example, risk assessment, are

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described in several chapters in this volume (Fanselow and Ponnusamy; Myers and Davis; Blanchard et al.). The Myers and Davis chapter, in particular, highlights some of the potential therapeutic values of promoting factors that limit the duration of conditioned fear or anxiety reactions.

Fear and anxiety are both complex reactions. The range of ways in which they can be maladaptive reflects this complexity. In addition to being too intense or too persistent, they may be elicited by incorrect stimuli, that is, those that are not genuinely threatening. In turn, the perceived threat qualities of a given stimulus may depend on many factors, including innate or preprogrammed tendencies, specific learning by direct experience or by observation of the experiences of others, nonspecific stressors past or present, etc. This multiplicity of factors contributing to the threatening qualities of stimuli that elicit fear and anxiety has led to parallel variation in the stimuli used as models of anxiety (see chapters by Fanselow and Ponnusamy for conditioned, and by Litvin et al. for unconditioned models of anxiety).

The behavioral expression of these emotions is another area where fear, anxiety, and, in particular, anxiety disorders, show great variability. A foundation for this, in terms of normal mammalian response to threat, is outlined in the chapter by Blanchard and Blanchard, potentially providing a counterpart to the later chapter by Nutt, describing, in part, behavioral aspects of current classifications of anxiety disorders. Other focal behaviors commonly used in animal models relevant to fear or anxiety are described in Myers and Davis, as well as in Cain and LeDoux: both chapters additionally provide information on neural systems and neurotransmitters involved in these behaviors and their conditioning. Canteras outlines brain systems that are activated in response to a particularly high intensity, unconditioned, threat stimulus, a predator; and Canteras and Blanchard compare the brain systems engaged in particular unconditioned and conditioned paradigms, as well as trends in use of these paradigms.

The use of animal models is described in greater detail in the third section of the text, which deals with the pharmacology of fear and anxiety. It would perhaps be more precise to say the pharmacology of anxiety, as the goal of discovering new mechanisms in the pharmacological treatment of anxiety disorders is a major driving force behind research in this area. These chapters are organized in terms of major neurotransmitter systems, including peptide receptor ligands (Steckler); $GABA_A$/benzodiazepine receptor ligands (Rowlett); 5-HT interacting drugs (Guimarães et al.); glutamatergic compounds (J. Cryan and K. Dev); and the endocannabinoid system (D. Piomelli and M. Bortolato). Andrew Holmes provides an overview of the pharmacology of anxiolysis, and Catherine Belzung et al. provide a meta-analysis of rodent studies of targeted mutations of neurotransmission genes related to anxiety.

The clinical section of the book was designed to clarify and focus on the key issues that often complicate and confuse individuals researching translational approaches to fear and anxiety disorders. The chapter by Young et al. offers a powerful fusion of animal and human research approaches to the neuroendocrinology and related brain mechanisms of fear and anxiety. The chapter on diagnostics (Nutt et al.) provides an approach to the issues of diagnostic specificities and overlaps, to give a clear and succinct overview of this complex field that animal model researchers will find of benefit in understanding their current models and developing new ones. The drug treatment chapter (Baldwin and Garner) presents an overview of the current clinical treatments of anxiety disorders, based on recent high-level consensus meetings.

The chapter on imaging by Malizia and Nutt looks at the achievements of this approach in anxiety and fear, and the ways in which current and future developments may – or may not – help in drug discovery and possibly in future animal research. Similarly, the section on challenge tests (Esquivel et al.) offers a current state of the art in this complex arena that has only little been translated to the human drug discovery

field despite its clear potential; it also presents a real challenge – or opportunity – to those working in the animal study field as a way of improving translational models. Finally the genetics section (Maron et al.) will provide a useful framework for those working on both human disorders and those exploring related issues in rodents, especially transgenics and trait loci approaches.

As these brief descriptions of the chapters indicate, the scope of the phenomena encompassed by the concepts of fear and anxiety is very wide, reaching from an analysis of animal behavior through neural systems and pharmacology to human psychopathologies. Many readers of this volume, perhaps the majority, are likely to be interested primarily because of the latter, which brings up the question of how firm is the relationship between these anxiety psychopathologies, and the procedures designed to model them, using animal subjects. It is a question that also speaks directly to the value of both neural system and pharmacological research that is based largely on such models, but aimed at intervention and treatment of the human disorders. Some trends in the use of these models are presented in the Canteras and Blanchard chapter.

Our basic goal for this handbook was simply to present this multiplicity of facets to fear and anxiety, describing particular aspects of relevant animal models and their physiological mechanisms, as well as research and analysis on anxiety psychopathologies. This material speaks to great progress on both ''pure science'' and ''applied'' fronts during the past couple of decades.

Nonetheless, it is tempting to try to go one step further, to attempt to integrate this material in such a way as to point out a systematic future direction to research on anxiety. A useful corrective for such dramatic effort is that the editors are by no means in total agreement about a core premise for much of this work, that there is a substantial relationship between at least some, or some components of, animal models of anxiety and clinical anxiety. On this topic, our views range from ''animal models say little about human anxiety disorders'' to ''animal models tell more about the biology of the systems than do current classifications of human anxiety disorders.'' However, what we can and do agree on is the importance of understanding fear and anxiety, and we expect that some of the disagreements as well as the convergences may clarify views of where refinements are needed or may be particularly useful, in research approaches to fear and anxiety. The perceived strength of this relationship has clear implications for the relevance of neural systems based on such models, as well as the adequacy of preclinical research to identify new treatment mechanisms, with regard to anxiety disorders.

The problem driving the need for this relationship can be illustrated by examination of a very recent phenomenon in research: the increasing development and use of a concept of the endophenotype, as applied to psychiatric conditions. Endophenotypes are very broadly defined as components along the pathway between genotype and disease state (Gottesman and Gould, 2003) or as ''heritable, quantitative traits hypothesized to more closely represent genetic risk for complex polygenic mental disorders than overt symptoms and behaviors'' (Fineberg et al., 2007). What they represent are strategies for deconstruction and simplification of the elements that may be associated with psychiatric diagnostic categories, by focusing on a coherent, usually heritable, biological process that may be involved in a disorder. Ideally, identification and characterization of such an endophenotype (e.g., reduced predictive pursuit response in schizophrenics and their unaffected first-degree relatives; Hong et al., 2007) may enable tracking backward, to the genome and to experiential and epigenetic factors that modulate the endophenotype; and forward to endophenotype-related aspects of behavior that comprise components of the psychopathological condition.

This is clearly a complex and difficult business, and moreover one that is likely to be relatively fruitless in many cases. There is no guarantee that a particular endophenotype selected for analysis

will eventually prove to have an integral relationship to the disorder of interest. As Keck and Strohle (2005) acknowledge: "…identification of reliable endophenotypes is currently one of the major rate-limiting steps in psychiatric genetic studies." Nonetheless, the endophenotype approach appears to represent a valuable new strategy in research on biological contributions to psychiatric disorders, precisely because contemporary diagnoses and classification of these disorders currently pay so little attention to their biological underpinnings (Gottesman and Gould, 2003).

The concept of animal modeling as it applies to anxiety has at least two major sources: first, a desire to understand basic emotional processes. This has been a consistent thread throughout most of the history of psychology, and it has resulted in research that typically had no specific conceptual connection to psychopathology. Second, a more recent trend has been development of models specifically to evaluate the effects of pharmacological and other potential treatments for anxiety disorders in general, or for particular categories of anxiety disorder. What both of these have in common is the use of subject species that are a great deal more amenable to both genetic and physiological/pharmacological interventions and analyses than are people. The result, as various chapters in this handbook illustrate, is that a good deal is known about the neural and biochemical systems involved in animal models of anxiety, along with a much more recent but rapidly expanding knowledge base on genetic factors relevant to some of these models.

The point is that this information is available, and that it is currently informing and being informed by findings from new technologies that provide some information on brain processes without possible damage to human subjects. In particular, imaging studies have tended to verify the basic "emotional brain" findings based on animal models, while adding some additional sites that appear to be more important in humans than in nonhuman mammals (Malizia and Nutt). However, as yet imaging studies are far from capable of determining which structures or systems are integral to a process, as opposed to merely active during that process. Human genetic analyses of anxiety are also capable of providing important information, but the likely combination of polygenic regulation (Lesch, 2001) with a strong influence of both experiential and epigenetic factors (e.g., Korte, 2001; Barr et al., 2004; Diorio and Meaney, 2007) in anxiety suggests that an adequate analysis of the role of genetics would require disproportionate effort and expense in investigations using only human populations. Indeed, even for a condition such as autism spectrum disorder (ASD), which has much higher twin concordance rates than do anxiety disorders, the genetics component has proved resistant to analysis: Although many individual genes have been evaluated for association with ASD, replication of positive results has been rare (Gupta and State, 2007).

Such considerations suggest that the study of anxiety, although largely fueled by the desire to understand and ameliorate human anxiety-linked psychopathologies, will continue to rely heavily on animal models. This being the case, the optimal strategy would appear to be to improve both the animal models, and the clarity of our conceptions of human anxiety. Building bridges requires an adequate foundation on both sides of the river. We hope this volume contributes to this effort.

References

Barr, C.S., Newman, T.K., Shannon, C., Parker, C., Dvoskin, R.L., Becker, M.L., Schwandt, M., Champoux, M., Lesch, K.P., Goldman, D., Suomi, S.J. and Higley, J.D. (2004) Rearing condition and rh5-HTTLPR interact to influence limbic-hypothalamic-pituitary-adrenal axis response to stress in infant macaques. Biol. Psychiatry, 55: 733–738.

Diorio, J. and Meaney, M.J. (2007) Maternal programming of defensive responses through sustained effects on gene expression. J. Psychiatry Neurosci., 32: 275–284.

Fineberg, N.A., Saxena, S., Zohar, J. and Craig, K.J. (2007) Obsessive-compulsive disorder: boundary issues. CNS Spectr., 12: 359–364. 367–375.

Gottesman, I.I. and Gould, T.D. (2003) The endophenotype concept in psychiatry: etymology and strategic intentions. Am. J. Psychiatry, 160: 636–645.

Gupta, A.R. and State, M.W. (2007) Recent advances in the genetics of autism. Biol. Psychiatry, 61: 429–437.

Hong, L.E., Turano, K.A., O'Neill, H., Hao, L., Wonodi, I., McMahon, R.P., Elliott, A. and Thaker, G.K. (2007) Refining the predictive pursuit endophenotype in schizophrenia. *Biol. Psychiatry* (In press).

Keck, M.E. and Strohle, A. (2005) Challenge studies in anxiety disorders. Handb. Exp. Pharmacol., 169: 449–468.

Korte, S.M. (2001) Corticosteroids in relation to fear, anxiety and psychopathology. Neurosci. Biobehav. Rev., 25: 117–142.

Lesch, K.P. (2001) Molecular foundation of anxiety disorders. J. Neural Transm., 108: 717–746.