Depression as a Systemic Illness

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I would like to dedicate this book to my wife, Dr. Gladys Witt Strain, for her continuing support and loving interest in my efforts for more than half a century, and to my three sons: Drs. Jay, Jeffrey, and Jamie Strain, who have contributed to my academic efforts over the years. Finally, I would like to dedicate this volume to Mrs. Cynthia Green Colin, who has witnessed and fostered my academic growth and accomplishments over the past 35 years, not only through her funds—the Green Fund, the Malcolm Gibbs Fund—but even more importantly, through her intellectual and steadfast support of the concepts and ideas that I have tried to promote.

—JJS

I would like to dedicate this book to my wife, Dr. Susan Blumenfield, and our three children, Jay, Bob, and Sharon, for their support and encouragement in all my various professional endeavors over the years. I would also include my four grandchildren, Lucy, Leo, Nia, and Obi, with the thought that someday one or more of them might be making contributions to this important and fascinating area of study.

—MB

This book is dedicated to our beloved colleague and friend: Dr. Jimmie Holland who passed away December 24, 2017. Jimmie was a person of all seasons: Mother, grandmother, teacher, practitioner, researcher and devoted to the care of patients and staff. She was a remarkable leader at Memorial Sloan Kettering Cancer Center and revolutioned the psychological care of cancer patients not only in the United States but through out the world. Through her continuing effort she influenced cancer hospitals to have psychiatrists on their staff. She came up with a sixth vital sign: "distress" to be asked every patient the staff would encounter. Jimmie began psycho-oncology journals, wrote the first text book in the field, and initiated at least two international societies to address the psychological needs of patients with cancer. And, still she had the capacity to be compassionate, loving, caring, a friend, and thoughtful to all of those she encountered. We will miss you Jimmie and are grateful to have known you, worked with you, and to have seen you excel in bringing psychological care to the cancer community. Your chapter in this volume is another testimony to the gifts you gave the world.

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Foreword

Depression occupies the minds and work of people of diverse disciplines. Prior to the introduction of anti-depressive treatments, depression was widely treated with interventions like electric-convulsive therapy (ECT). In the mid-1900s, the first monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were introduced. For decades subsequently, much research focused on such treatments. Depression was considered a mental disorder. The focus on these antidepressants was followed over the next five or six decades with few new developments.

This book stresses the breadth of the topic, describing depression as a systemic illness, not just a mental illness. The best thinking today is that there are new tools and concepts in research, awareness of multiple causes, multiple kinds of depression, and increasing recognition of the mechanics and physiology that produce them. The book creates an optimistic and innovative approach to understanding and treating depression.

Brain plasticity is remarkable. Much current focus has been on brain action. However, this text uniquely conceives of depression as systemic, resembling other non-psychiatric chronic illnesses such as diabetes, hypertension, asthma, congestive heart failure, etc.

New research techniques have generated a conviction that integrating diverse lines of research enhances the promise for advances in understanding the disorder of depression. Another conviction among depression experts is that clinicians and scientists should focus on earlier stages of the disorder. Early intervention appears to produce better outcomes. Also, there is a greater focus on the continuing effects of depression.

Brain plasticity and recognition of depression's pervasive impact throughout the body—McEwen's "allostatic load"—has induced scientists to examine enduring and long-term effects of depression. More depressive episodes and longer periods of depression appear to be correlated with more serious states of depression.

Contributory causes are multiple—genetics, family history, adverse childhood development, environmental stress, etc. Depression is highly heterogeneous. For example, when youth have persistent anxiety and/or depression as well as mental lability, subclinical mania, accompanied by parents with early-onset bipolar disease, 50% of such children also develop bipolar disease.

The systemic nature of depression with the many interconnections also results in omnipresent comorbidity. This new text explores, e.g., cancer, heart disease, and neurological disorders in this regard.

New treatment approaches being developed make use of neuroimaging, brain stimulation, and substances like ketamine. The latter produces rapid improvement in mood

rating in patients resistant to typical antidepressants, but it may have a minimal lasting effect if not serially repeated; it is not as yet FDA-approved for depressive disorders.

There are five different types of transcranial medical stimulation (TMS). In some, TMS generates brain tissue regrowth over four- to six-week periods. Treatments like cognitive behavioral therapy work on circuits. Interpersonal therapy, too, is being used in creative ways in underdeveloped countries. One emphasis is looking for interventions that may foster synaptic plasticity and connections.

The enthusiasm of many scientists is palpable. Some assert "a scientific revolution in mood disorder research is anticipated." Encouraged by advances in cancer treatment through precision medicine, some foresee possible application of precision medicine to depression. The rich knowledge being developed from neuroimaging has led to "neuroimaging phenotypes," which means an imaging picture shared widely by many depressed patients.

These developments are significant for education. The impact on training, the important role of primary health care professionals, the potential of psychoeducation are pertinent educational issues. Should primary care physicians not be able to diagnose and care for "garden variety" depressive disorders, and then, if necessary, refer refractory patients on to more experienced clinicians? Medical school curricula and residency training will need to be altered for non-psychiatric physicians to have sufficient skills to accomplish this.

Depression deserves recognition as an illness of major proportions. It affects vastly different body systems. The World Health Organization ranks it as exacting the greatest burden of illness on the world population. Innovative treatments and ideas provide optimism.

Considering it a systemic illness represents a change from the former perspective that brought patients with depression brief interludes of relief with ECT, psychotherapy, and/or drugs while ignoring the long-term course and its biological accompaniments. We deal with a longstanding illness that needs enduring attention. If treated early, and if one can modify the number, intensity, and length of episodes, we will be likely to produce improved outcomes.

This formulation of depression as a systemic illness, not just a mental illness, may also be welcomed, recognizing the many decades in which psychiatric illness and treatment suffered from stigma. Outstanding innovative leaders from many fields grasping the breadth of depression's impact are working together, accumulating vast data and manifesting enthusiasm about possible major strides going forward.

This rich book brings experts together and covers extensively the biological, psychological, endocrinological, genetic, and imaging aspects of depression. This collaboration by outstanding scientists and clinicians represents probably our greatest hope for real improvement in the management of depression. It is well described here. While not minimizing how much has to be done, this is an uplifting book, given the excellence of

its contributors and their laboratories, and the proliferation of new and imaginative tools and concepts to advance the effort to bring depression under control.

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Acknowledgments

First, I would like to acknowledge the colleagues who have contributed to this volume and the exploration of a unique concept: *depression is a systemic illness, and not just a mental disorder*. Their focus to bring this concept to the front and center is the hallmark of this book, and our hope is that we may influence the global community to examine unique ways to not only understand the phenomenon of depression, but explore models to enhance its detection and treatment. With the knowledge from the World Health Organization that depression is the illness with the greatest burdens of health in the world—it is incumbent that we move from the halls of academia to the real world where people suffer and sometimes end their lives because of this ubiquitous illness. New ways must be found to determine its presence, new models for physicians to execute evidence-based care, and the incorporation of the patient as a key resource in actualizing advanced methods to identify, screen, be present for care, and follow through with recommendations. As said earlier, my wife and sons have been steadfast supporters of these efforts, and Jay, my eldest son, has worked with me on these projects since he was 14 years old and even now that he is a trained trauma surgeon. And I hasten to mention again Cynthia Green Colin, Emeritus Trustee of the Mount Sinai Medical School and Hospital, without whose unwavering support this book, the countless studies, the hundreds of lectures given at home and abroad, and the development of an electronic medical record—when such documentation was virtually unknown—would not have been possible to accomplish.

Finally, I want to acknowledge the natural laboratory that the Icahn School of Medicine at Mount Sinai has afforded to me; the opportunity to develop and test methods to enhance the knowledge base of countless physicians of all specialties, nurses, residents, and students with regard to promoting the psychological care of the medically ill. The patients, the students, doctors in training, nurses, social workers, and ethicists have all supported the creation of a *center of excellence* for encouraging better care. My hope is this book will continue to promote that effort.

—James J. Strain

I would like to acknowledge my colleague and friend Dr. Jim Strain, who originated the concept of this book and not only gave birth to it while we were co-editing an earlier book on psychosomatic medicine, but nurtured and brought it to fruition with his unique creativity and energy. It has been an honor and privilege to work with him. I also want to acknowledge all my many teachers, colleagues, and students over the years, who, along with our patients, have taught me about the mind, emotions, physical functioning, and illness. We have learned so much over the past 50 years, and yet there is so much more on the horizon.

—Michael Blumenfield

Prologue

James J. Strain, MD

DEPRESSION AS A SYSTEMIC DISEASE

This book is intended to make two major points. One of them is the increasing accumulation of evidence that depression should be thought of as a systemic disease and not simply as an "emotional" or "mental" disorder. The second point is that, because of this evidence, medical education needs to change so that wider arrays of physicians are trained to recognize and treat this systemic illness, especially the non refractory depressions, which increasingly presents in their practices.

Chapters in this book, presenting data supporting the hypothesis that depression is a systemic disease, describe the biological parameters of depression and its effects on cortisol, the hypothalamic-pituitary-adrenal axis, cytokines, glucose metabolism, platelet activity, etc., and how they affect physiological systems, promoting an allostatic load that can exacerbate somatic morbidity. Inflammation has been recently implicated as a possible mechanism or accompaniment of major depressive disorders and is an important focus of contemporary research.

"Neuropsychiatric research has pivoted from investigation of monoaminergic mechanisms to novel mediators, including the role of inflammatory processes. Subsets of mood disorder patients exhibit immune-related abnormalities, including elevated levels of proinflammatory cytokines, monocytes, and neutrophils in the peripheral circulation; dysregulation of neuroglia and blood-brain barrier function; and disruption of gut microbiota. The field of psychoneuroimmunology is one of great therapeutic opportunity . . . such as peripheral cytokine targeting antibodies, microglia and astrocyte targeting therapies . . . producing findings that identify therapeutic targets for future development"[1] (p. 1–14). Furthermore, disruptions may occur in a neuroimmune axis that interfaces the immune system and the central nervous system that controls behavior. Evidence has been found in patients and animal models of depression that demonstrates how the peripheral immune system acts on the brain to alter responses to stress and vulnerability to mood disorders.[2] It follows that this ubiquitous disorder could and should be initially screened for, diagnosed, and treated by the primary care physician (PCP). Another important reason for the necessary and essential move to PCPs for care of depression is that in most countries, even developed ones, there are not enough psychiatrists to participate in collaborative care—and now there is a strong *headwind* in the United States to address effective mental health care via the medical doctors available—most often the PCP.

It is interesting to note that family practice residencies include training for the screening, diagnosis, treatment, and assessment of outcome for depression, while standard internal medicine residencies—the source of most of our PCPs—do not have similar pedagogical expectations.[3] It is stunning that of the 8 million annual ambulatory care visits for depression, PCPs see more than one half.[4] And, equally stunning, PCPs prescribed more than 70% of the antidepressants in the United States[5]—even though they may not have had the training of the family practitioner, let alone the more intensive focus of residencies in psychiatry.

Possibly reflecting that fact, although PCP practices have established care-management processes for such common diseases as asthma, diabetes, hypertension, and congestive heart failure, they have not done so for depression. This is despite the fact that today, screening, diagnostic, and treatment phases for depressive illness, and also assessment of meaningful outcomes, can be assisted by teams, such as social workers and nurse physician assistants; and new technologies, e.g., screening devices, algorithms, electronic health records (EHR), telemedicine and SKYPE interviews for consultative review (second opinions).

The World Health Organization (WHO) in March 2017 stated that depression is the illness causing the greatest burden of health in the world. Heart disease is the greatest burden for mortality.[6,7] There is an increased recognition of the important relationship between depression and heart disease: it is now widely understood that depression is a risk factor for worsening heart disease greater than smoking. The unsurprising adverse effects that depression can have on many illnesses will be described in detail in this volume.

Because patients are reluctant to go to psychiatrists as a result of the stigma of mental health disorders, and because there are too few psychiatrists in the world anyway, many patients will not be diagnosed, and many, even if identified, are under-treated if treated at all. This is a crisis in health care worldwide that should—indeed, must—lead to important changes in how medicine is practiced, how doctors are trained, and how systems of care need to be transformed. In order to provide assistance for this hugely burdensome illness in developed as well as developing countries, major changes are required in the education of physicians, in particular the primary care physician (PCP). They are the *gateway* for the patient's access to diagnosis and treatment. The training of PCPs to recognize and treat these illnesses should be a major academic focus. We need to move from a *collaborative care model* (the current framework for mental health care in the medical setting)—to the *medical model* where the PCP is an autonomous physician working with his/her team for the care of depression, although, as for other illnesses, occasionally referring to a specialist.

There are three helpful ways to understand depressive disorders in the medically ill:

1. The first is outside the focus of this book: namely, as psychologically depressive reactions to the stressors of medical illness (possibly leading to non-compliance, giving up, feelings of guilt and shame, and even to self-harm);
2. The second way is to understand how depressive disorders can biologically adversely affect physical disease and processes—that they may have a significant and negative

effect on the body and on bodily function because of their effects on allostatic load and consequent biological stresses on body functions. Most of the arguments in in the early chapters emphasize this aspect of understanding.

3. The third way of understanding shows how some somatic-dysfunctions and medical treatments, including pharmacological agents, can lead biologically to the occurrence of depression and somatic physiological changes (e.g., interferon, medications utilized for HIV) (see Chapter 10 on drug–drug interactions). These reactions are not "psychological" in that they are not the patient's psychological response to a medical illness or physical limitation, e.g., demoralization or stresses from having cancer or having coronary artery disease; reactive depressive disorders; adjustment disorders, major depressive disorders from the stressors of physical illness. They are direct effects of body dysfunction and medications on the structure of the brain.

Though less stressed in the supportive chapters, the third way demonstrates the *bidirectionality* of depressive disorders, and it deserves emphasis, since it supports the two major points of this volume: that major depressive disorders are *systemic diseases* and that the PCP needs to be trained to understand why this common systemic disorder could and should be within their domain of competence. Several examples of this bidirectionality of depression will be presented in the chapters that follow. However, these chapters will not be an *all*-inclusive inventory of the innumerable somatically or pharmacologically induced affective disorders that may occur.

Finally, a new model to approach the identification and management of depression is sorely needed, as has been uniquely developed with comprehensive guidelines for such illnesses as stroke, sepsis, delirium, and decubitus ulcers—illustrated in the concluding chapter. A possible approach with an innovative electronic health record and currently available technology, such as the smartphone, the health kiosk, newly developed apps, telemedicine, SKYPE, etc., illustrate how the PCPs and their staff can be assisted to access essential information and guidelines, which, at the same time, will lessen the demands on the physicians' time.

It is my hope that this book may save lives, or at the least make some lives better.

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Depression as a Systemic Illness

1

The Biological Basis of Depression
Insights from Animal Models

Eric J. Nestler

INTRODUCTION

Depression, like all psychiatric syndromes, is defined solely on the basis of behavioral abnormalities. We still lack today any biological measure—e.g., brain imaging, genetic, peripheral blood finding—that forms part of the diagnosis of depression. Depression is a highly heterogeneous syndrome, probably comprising numerous disease states and pathophysiological mechanisms. It also exhibits broad overlap with several other psychiatric syndromes, including anxiety disorders and post-traumatic stress disorder (PTSD). There is no clear biological distinction across these several diagnoses, and they are highly comorbid. In fact, in war-torn regions of the world, roughly one-third of individuals who seek psychiatric treatment are diagnosed with depression, another third with PTSD, and the final third with anxiety disorders.[1] Roughly 35% of the risk for depression is genetic, yet it has been extremely difficult to identify individual genes that pose that risk, with few genes reaching genome-wide significance in studies to date.[2] Finally, virtually all of today's antidepressant medications are based on discoveries made through serendipity over six decades ago and target the brain's monoamine pathways.[3] Sixty years later, we have arguably not introduced a single antidepressant medication with a novel mechanism of action, although ketamine (which targets glutamatergic pathways) is now undergoing clinical evaluation and shows considerable promise.[4]

How do we overcome these fundamental obstacles in depression research to better understand its biological underpinnings and to develop more effective treatments? By analogy with all other fields of medicine, animal models are an essential component of this effort. However, there are several fundamental limitations for animal models of depression (and for all psychiatric disorders, for that matter) that have dramatically hindered progress.[5] Many of the core symptoms of depression (e.g., guilt, ruminations, suicidality) are inherently inaccessible in animals. The absence of known strong genetic factors with high penetrance means that studies are performed on genetically normal animals that lack the heritable component seen in humans. Consequently, the field has focused on stress responses, with the rationale that adverse life events are a strong risk factor for depression.[6] Over the past several decades, we have learned a great deal about

how rodents respond to acute or chronic stress. However, we still have a very limited understanding of which of those mechanisms, or other mechanisms, mediate the many forms of depression—and related syndromic outcomes of stress; namely, anxiety and PTSD—seen in humans.

Here we briefly summarize the range of animal models used in the depression field and what has been learned about depression from them. We highlight new experimental approaches that have dramatically advanced efforts to use animal models to delineate the neural circuits and molecular abnormalities that control depression-related behavioral abnormalities in animals.

ANIMAL MODELS OF DEPRESSION

Animal studies in depression can be divided into acute assays versus chronic stress models (Table 1.1). The former are seen as useful screens of the behavioral state of an animal, while the latter might replicate aspects of adaptive or maladaptive responses to stress in humans. An important consideration is the evaluation of the behavioral state of an animal, not only by whether it replicates the human syndrome of depression (or anxiety or PTSD), but also by whether it recapitulates domains of behavioral abnormalities seen across these diagnoses. This latter approach fits well with the RDoC (research domain criteria) approach to evaluating human syndromes, which looks beyond syndromes to specific behavioral impairments that track onto an established neural circuitry.[7]

The validity of an animal model is often described in three ways.[5] *Construct* or *etiological validity* refers to the degree to which the animal model recapitulates the causes of the human syndrome. *Face validity* refers to the degree to which the animal model recapitulates the core symptoms of the human syndrome. *Pharmacological validity* refers to the degree to which drugs that are effective in treating the animal model prove to be efficacious in humans. As our introduction indicated, all three levels of validity are a challenge for depression. We do not yet know what causes human depression (causative genetic or non-genetic factors), hence, complete construct validity is impossible. We know that chronic stress can increase the risk for depression in some individuals, although most individuals maintain normal functioning in the face of such stress. Thus, most chronic stress models in rodents are limited because they cannot perfectly distinguish adaptive vs. maladaptive responses to the stress. Face validity of animal depression models is limited by the focus on only the symptoms (e.g., anhedonia, sleep

Table 1.1 Examples of Behavioral Procedures in Rodents Used to Study Depression[a]

Chronic Stress Models	*Acute Stress Assays*	*Phenotypic Screens*
Chronic social defeat stress	Forced swim test	Sucrose preference
Maternal separation	Tail suspension test	Intracranial self-stimulation
Chronic variable stress	Novelty-suppressed feeding	Fear conditioning
Social isolation	Learned helplessness	Other cognitive tests
Chronic restraint stress		Other tests of natural reward

[a]The table does not list a large range of assays used to study anxiety-like behavior in rodents.

disturbances, social impairments, metabolic disturbances, etc.) that can be measured in animals. Pharmacological validation has almost completely failed, since it has not been possible—despite 60 years of research—to validate a non–monoamine-based antidepressant medication in humans. Finally, all chronic stress models in rodents produce mixed symptoms of depression- and anxiety-related behavioral abnormalities. Of course this reflects the mixed patterns seen in humans as well. Ultimately, a better understanding of which human syndrome is modeled by a given animal procedure will require a better delineation of that human syndrome.

Acute Stress and Phenotypic Assays

Acute stress and phenotypic assays are the most widely used in the field. Most, such as the forced swim test, tail suspension test, learned helplessness, and novelty-suppressed feeding, assess an animal's response to an acute stress. Other acute assays, such as the sucrose preference test and fear conditioning, are useful in assessing aspects of an animal's behavioral state. While these assays are very useful as screens, they cannot be viewed as animal models of depression since they lack construct and face validity. Another assay used to assess an animal's behavioral state is intracranial self-stimulation, which measures the degree to which an animal will work (e.g., press a lever) to deliver electrical current into the brain's reward circuitry.[8]

Chronic Stress Assays

The two best-validated chronic stress models are chronic social defeat stress and maternal separation. In the former model, a mouse is exposed repeatedly to a more aggressive, dominant mouse, typically over a course of 10 days. This induces a range of depression- and anxiety-related behavioral abnormalities.[9,10] Social defeat is unique, compared to other chronic stress models in adult rodents, in several respects. First, only about two-thirds of mice subjected to the stress develop this range of symptoms and are referred to as "susceptible." The remaining one-third avoid the depression-like symptoms and are referred to as "resilient."[11] Thus, social defeat stress makes it possible to distinguish between maladaptive responses to stress (seen in susceptible mice) and adaptive responses to stress (seen in resilient mice). Moreover, because the resilient mice display equal levels of anxiety-like behaviors, the models also make it possible to differentiate "depression" from "anxiety," as best as can be inferred from rodents. Additionally, unlike all other chronic stress models in adult rodents, where the behavioral abnormalities rapidly revert to normal within days after the last stress, a subset of the behavioral abnormalities induced by social defeat stress is permanent.[9,11,12] This makes it possible to establish pharmacological validity for social defeat stress: standard antidepressants reverse the long-lasting behavioral abnormalities only after repeated (weeks) administration.[8,12] The model also shows responses to ketamine, but not anxiolytic agents.[8,13,14] An original weakness of the social defeat model was that it was developed in male mice only, although recent advances have extended the approach to females as well.[15]

Maternal separation also shows considerable validation. We know that early life stress is a strong risk factor for depression in humans.[6] Mice and rats removed from their mothers

during early life show lifelong increases in susceptibility to subsequent stressful events later in life.[16–19] Again, the paradigm produces a mixture of depression- and anxiety-like behavioral features. Chronic variable stress, also referred to as "chronic mild stress" or "chronic unpredictable stress," exposes rodents to different physical stresses each day (e.g., restraint, foot shock, cold temperatures, forced swimming, etc.). After repeated exposures, rats and mice succumb and display a range of depression- and anxiety-like symptoms.[20–22] A useful feature of chronic variable stress is that females are more susceptible than males,[21] which recapitulates the roughly twofold greater incidence of depression in woman and girls. A weakness of the procedure—as with repeated restraint or foot-shock stress as well—is that only physical stresses are employed, in contrast to the fact that the stress diathesis in human depression usually involves psychological and social forms of stress. Another weakness of the model is that the behavioral symptoms only persist a few days after the last stress, which means that antidepressant drugs can be studied for their ability to prevent deleterious outcomes but not reverse them post-stress.

NEUROBIOLOGY OF DEPRESSION

Over the past several decades, animal models of depression and acute behavioral assays have revealed a substantial amount of information about how the brain responds to stress. This work has defined brain regions and their circuits that control mood under normal conditions as well as responses to acute or chronic stress. The work has also defined numerous theories for cellular and molecular mechanisms of depression, which define clear steps forward in the development of improved treatments for the syndrome. While the molecular and cellular abnormalities defined in animal models have been replicated to an increasing degree in depressed humans examined at autopsy, the major gap in the field remains the lack of clinical validation of the therapeutic potential of these approaches. Following are brief summaries of some of the major advances in understanding depression, with a focus on the novel experimental approaches used.

Neural Circuitry

Work in rodents has largely confirmed decades-old hypotheses from studies of humans sustaining traumatic brain injury or stroke, and since confirmed by brain imaging approaches, that broad circuits in forebrain are in important in mood regulation (Figure 1.1).[23–25] These regions include several areas of prefrontal cortex, hippocampus, amygdala, nucleus accumbens, septal nuclei, and thalamus, among others. These regions display many reciprocal connections and function as a highly integrated circuit. Nevertheless, each region appears to mediate partly distinct functions: the prefrontal cortex regions are important for executive control, behavioral flexibility, impulsivity, and compulsivity; the hippocampus mediates declarative memory but functions more broadly in controlling emotions; the amygdala is important for associative memories for rewarding and aversive stimuli; the nucleus accumbens controls motor and probably emotional responses to rewarding and aversive stimuli; the septal nuclei also regulate responses to rewarding and aversive stimuli; and the thalamus integrates sensory information with cortical and subcortical regions.[26] Each of these regions is innervated

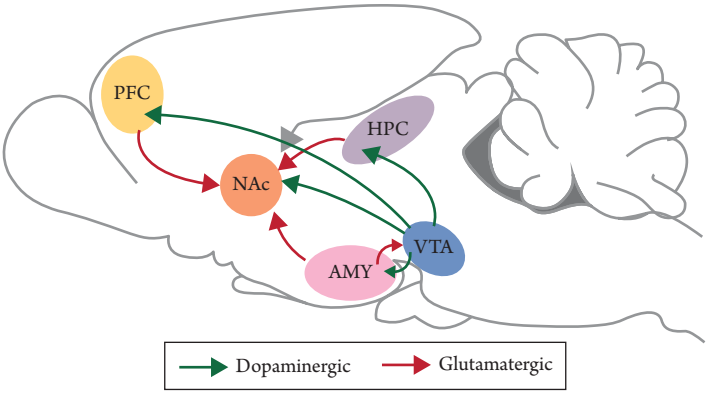

Figure 1.1 Brain regions involved in regulating mood. Depicted are the major components of the limbic-reward circuitry: dopaminergic neurons (*green*) project from the ventral tegmental area (VTA) to nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala (AMY), and hippocampus (HPC), among several other regions. The NAc receives excitatory glutamatergic innervation (*red*) from the HPC, PFC, and AMY. From Bagot RC, Labonté B, Peña CJ, Nestler EJ (2014) Epigenetic signaling in psychiatric disorders: stress and depression. Dialogues Clin Neurosci 16:281-295.

by brainstem monoaminergic neurons, including dopamine, serotonin, and norepinephrine. Presumably, innervation by the latter two explains the actions of today's antidepressants, virtually all of which act via serotonergic and/or noradrenergic mechanisms.[3]

Recent work in animal models has taken advantage of optogenetic and DREADD (designer receptors activated by designer drug) tools, which make it possible to control the activity of specific circuits in the brain in awake-behaving animals. In optogenetics, a bacterial ion channel or pump that is activated by light is expressed—either with a viral vector or transgenically—in a given neuronal cell type. Light is then directed into a targeted brain region via an implanted optic fiber. By delivering light pulses at precise frequencies, it is possible to control the frequency (e.g., low frequency vs. high frequency) and pattern (e.g., tonic firing vs. phasic firing) of activity of the targeted circuit.[27] DREADDs are synthetic G protein-coupled receptors that link to an excitatory effector (e.g., Gq) or an inhibitory one (e.g., Gi). They can be activated upon systemic delivery of clozapine-N-oxide, which has minimal effects on endogenously expressed receptors.[28] Both approaches have strengths and weaknesses.

With these tools, it has been possible, for example, to demonstrate a crucial role for dopaminergic neurons in the midbrain ventral tegmental area in controlling responses to acute and to different types of chronic stress.[29,30] Interestingly, projections of these neurons to nucleus accumbens have a very different effect compared to projections to prefrontal cortex. Likewise, stimulation of the two different subtypes of projection neurons from nucleus accumbens, termed *D1-type* and *D2-type medium spiny neurons* based on the predominant type of dopamine receptor expressed, exert opposite effects on stress responses,[31] as do inputs to nucleus accumbens neurons from prefrontal cortex vs. hippocampus.[32] Related approaches have confirmed the importance of serotoninergic neurons in the midbrain dorsal raphe, and their reciprocal connections to prefrontal cortex, in

mediating antidepressant-like responses,[33] as well as defined the neural circuitry involved in fear- and anxiety-related behaviors.[34,35]

These approaches are providing transformationally greater delineation of the neural circuits in the brain that control depression-related behavioral abnormalities than was possible in earlier research. This work is thereby essential for RDoC-oriented studies of diverse stress- and mood-related syndromes in humans. These advances are also informing the mechanism of action and identification of novel sites for deep brain stimulation, an experimental treatment for severe depression.[36] As well, given that ketamine is thought to produce its rapid antidepressant effects via glutamatergic mechanisms,[4,22,37–39] optogenetics and DREADDs should help define the mechanism of action of this novel therapeutic.

Transcriptomics

Technical innovations in our ability to map genome-wide changes in gene expression in the brain have provided further advances in our understanding of the pathophysiology of depression. RNA-sequencing (RNA-seq) makes it possible to quantify all RNA products expressed by the genome within a given brain region or even within a single cell type within that brain region. Since a majority of all RNAs expressed in a cell are non-coding (i.e., they serve regulatory functions), earlier microarray studies missed a substantial portion of expressed genes. Likewise, RNA-seq provides quantification of all splice variants encoded in a given gene, something not possible with microarrays.

We are now seeing for the first time large scale RNA-seq studies of several brain regions implicated in depression from a wide range of animal models.[40–43] It is likely that the coming years will bring still further RNA-seq characterization of animal models focused on individual cell types (neuronal as well as non-neuronal—astroglia, microglia, oligodendrocytes, endothelial cells), as well as RNA-seq of single cells in depression models. Early work in the latter area is revealing far greater heterogeneity within a given cell type thought to be largely homogeneous with earlier methods.[e.g., 44,45]

Work to date is already defining several interesting principles of stress responses in animal models. Each chronic stress model seems to regulate a largely distinct set of genes associated with the induction of similar depression-related behavioral abnormalities.[21 vs. 43] By overlaying such data on RNA-seq findings of depressed vs. control human brain—work that is now beginning to appear—it should be possible to provide a molecular validation of animal models, something heretofore not possible. Our early impression is that each chronic stress model in a rodent recapitulates a largely different subset of gene expression abnormalities seen in human depression, which is consistent with the notion that each model recapitulates a different aspect or subset of the very broad pathology subsumed under depression and related syndromes. In a related vein, RNA-seq profiling of animal models and depressed human brain will help guide efforts aimed at identifying specific genetic variations that contribute to the heritable risk for depression.

Studies of chronic social defeat stress, which enables the distinction between animals that are susceptible to chronic stress from those that are resilient (see the preceding

discussion), have demonstrated that, to a great extent, resilience is the more plastic state, associated with regulation of far more genes across multiple brain regions compared with susceptibility.[11,43] These findings have raised the interesting perspective that, in addition to developing ways to prevent the deleterious effects of stress, another approach in antidepressant drug discovery is to induce mechanisms of natural resilience in individuals who are inherently more susceptible. An interesting observation is the prominence of regulated genes that control gene transcription, including transcription factors and a host of proteins that control the epigenetic state of a gene and thereby its transcription.[46] As just some examples, the transcription factors ΔFosB and ß-catenin have been shown to promote resilience when acting within the nucleus accumbens.[13,47,48] Similar pro-resilience effects are seen upon inhibition of HDACs (histone deacetylases) or activation of certain histone methyltransferases (e.g., G9a) in this and certain other brain regions.[49–51]

Studies of chronic variable stress, which captures the greater susceptibility of females to chronic stress compared with males, are defining some of the molecular determinants of that greater susceptibility. As just one example, female mice express higher levels of DNMT3a (DNA methyltransferase 3a) in nucleus accumbens at baseline and show a greater induction of the enzyme in response to chronic stress.[21] Depressed humans likewise show higher levels of DNMT3a in nucleus accumbens at autopsy, an abnormality partially reversed with antidepressant medication. DNMT3a is an example of an epigenetic enzyme that controls gene activity via methylating cytosine nucleosides within the gene's sequence. Overexpressing DNMT3a in this brain region, by use of viral vectors, makes males as susceptible as females, while knocking out DNMT3a in nucleus accumbens makes females as resilient as males. Knocking out DNMT3a also shifts the pattern of gene expression—assessed by RNA-seq—in female nucleus accumbens closer to that seen in males.[21]

Related approaches are providing insight into the mechanisms of action of antidepressant treatments. This is important because, while we know the acute actions of most antidepressants (e.g., an SSRI [selective serotonin reuptake inhibitor] antagonizes the serotonin transporter), the changes that these sustained acute actions induce in brain with chronic treatment, and are required for the drugs' therapeutic efficacy, are not definitively known. Recent RNA-seq studies have demonstrated largely different gene expression changes induced across the range of forebrain regions implicated in depression.[14] They have also demonstrated that chronic antidepressant treatment is associated—in all brain regions—with the reversal of a subset of gene expression changes associated with susceptibility, induction of a subset of gene expression changes associated with resilience, as well as the regulation of a distinct cohort of genes not affected by chronic stress per se. Comparisons of these effects between chronic imipramine (a standard antidepressant that acts by antagonizing serotonin and norepinephrine transporters) and acute ketamine (an experimental rapidly acting antidepressant that is thought to act on glutamatergic synapses) shows largely distinct gene expression changes across several forebrain regions (Figure 1.2). The induction of genes affected in natural resilience is also seen at the chromatin level.[52] This type of work is providing an ever more comprehensive template of genes that could be targeted for novel therapeutics.

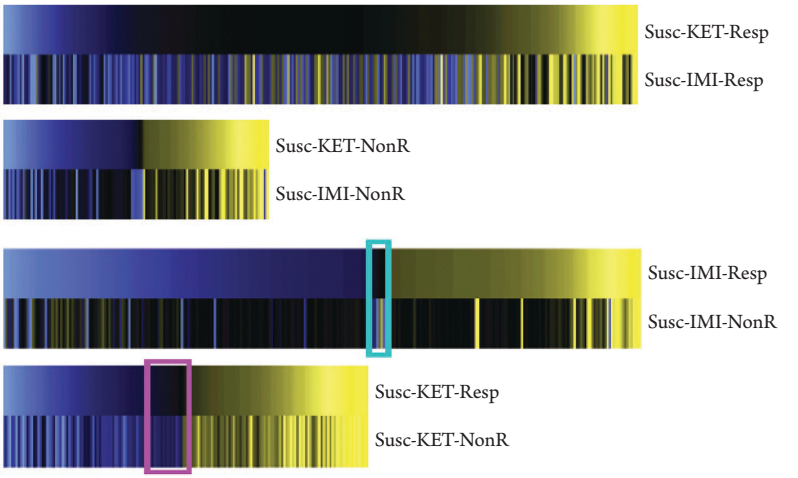

Figure 1.2 Transcriptomic profiles of imipramine (IMI) vs. ketamine (KET) responders (Resp) vs. non-responders (NonR) in nucleus accumbens. Male mice were subjected to chronic social defeat stress. Susceptible (Susc) mice were treated for 2 wk with saline or IMI or 13 d saline + 1 d KET. Roughly 50% of mice treated with IMI or KET responded behaviorally; the other half were treatment resistant. Top two heatmaps: note the largely different sets of genes affected in IMI vs. KET Resp (top) and NonR (bottom). Bottom two heatmaps: note IMI NonR generally fail to show regulation of genes seen in IMI Resp. This was less apparent in KET NonR vs. Resp. Interestingly, NonR is characterized by a small number of gene expression changes not seen in Resp (turquoise and purpose rectangles); these changes might actively oppose Resp. Several other interesting patterns were observed in this large dataset. From Bagot et al. (2016b).

Of course, transcriptional regulation is one of several ways in which cells and circuits respond to acute and chronic stress. Regulation of RNA processing, stability, and translation into protein, and of protein processing, stability, and intracellular trafficking, also play crucial roles in cellular adaptations. As tools are developed to allow the comprehensive analysis of these post-transcriptional mechanisms, it will be important to apply them to depression models.

Cellular and Molecular Mechanisms

The combination of the advanced circuit and molecular approaches just described is refining earlier hypotheses of the molecular and cellular basis of depression, as well as revealing fundamentally novel hypotheses. The reviewer is referred to recent reviews for more detailed descriptions of these mechanisms; a brief overview only is provided here.

It has long been known that a subset of patients with depression display hyperactivity of the *hypothalamic-pituitary-adrenal (HPA) axis.*[53–55] This knowledge led to the consideration of corticotropin releasing factor-1 (CRF1) antagonists as antidepressants. There is evidence that glucocorticoid receptor antagonists might show some efficacy in treatment, particularly of severe depression. However, more recent research has demonstrated the complexity of the HPA axis's role in depression and related syndromes. First, a subset of

depressed patients display hypoactivity of the HPA axis, and a majority show no detectable derangement at all. Second, it is likely that activation of the HPA axis is a normal, adaptive part of the stress response that helps individual cope positively with stress. By contrast, sustained activation of the HPA axis, as occurs with chronic stress, has deleterious consequences in certain individuals, but this means that far more precise ways of intervening with the HPA axis are required to mine therapeutic activity in subsets of patients that show distinct abnormalities in axis function.

The neurotrophic hypothesis of depression proposes that prolonged exposure to stress, in vulnerable individuals, induces deleterious changes in neuronal morphology and function, effects mediated in part via alterations in several neurotrophic (nerve growth) factors.[56] A corollary of this hypothesis is that prolonged treatment with monoamine-based antidepressants is required in order to reverse such trophic effects. The neurotrophic factor best implicated in depression and antidepressant action is BDNF (brain-derived neurotrophic factor), the expression of which is suppressed in hippocampus and prefrontal cortex by chronic stress, effects reversed with chronic monoamine-based antidepressants or with acute ketamine. However, BDNF's role in depression is complicated by the fact that, while induction of BDNF exerts antidepressant-like effects in hippocampus and prefrontal cortex, it exerts depression-like effects in nucleus accumbens.[26] BDNF is just one of a large number of neurotrophic factors that has been shown to control chronic stress responses in laboratory animals. A key challenge in this line of research has been to develop ways of advancing these discoveries into the clinic. Thus, growth factors are proteins and do not cross the blood–brain barrier, and it has been difficult to generate small-molecule agonists or antagonists of growth factors to test their antidepressant potential in humans.

There is growing evidence for the involvement of immune mechanisms in depression.[57] First, a subset of depressed humans shows evidence of an inflammatory state based on elevated levels of certain pro-inflammatory cytokines (e.g., interleukin-6 [IL6], tumor necrosis factor-α) in their peripheral blood. Similar findings have been reported for susceptible mice after exposure to chronic stress.[58] Moreover, blockade of IL6 peripherally exerts a pro-resilient effect in mice, while transplantation of bone marrow from susceptible mice makes recipient mice more inherently susceptible, an effect not seen with IL6 knockout donor mice.[57] Findings such as these immediately raise the possibility of testing whether antibodies directed against IL6 or other cytokines, now used clinically in the treatment of a range of rheumatological diseases, show antidepressant efficacy in the depressed patients who display a hyperinflammatory state. An important related question is, how do peripheral cytokines influence depression-related behavioral outcomes? Presumably, peripheral cytokines enter the brain to control neuronal responses to act on areas of brain largely outside the blood–brain barrier to generate signals that then influence the rest of the brain. A related question is the extent to which the actions of the cytokines, and their centrally generated signals, act directly on neurons or indirectly by first influencing the host of non-neuronal cells present within the brain. As just one example, there has been increasing interest in resident microglial cells in the brain in controlling stress responses.[57] As additional information is obtained delineating the cellular and molecular circuitry controlled by cytokines, it should be possible to generate increasingly precise treatments to target abnormalities documented in subsets of depressed patients.

FUTURE DIRECTIONS

We have learned a vast amount about the brain over the past several decades. We have also learned a great deal about how the brain adapts vs. maladapts to chronic stress, in many cases validating such molecular and cellular adaptations in the brains of depressed humans at autopsy. Despite these advances, however, we have not significantly advanced the treatment of depression, which today relies on the same mechanisms of action of antidepressants that were discovered by serendipity sixty years ago. We believe that key challenges in clinical research, beyond the limitations inherent in animal research, are also among the major determinants for this failure in drug discovery efforts. It is far more difficult to perform small, exploratory clinical studies than it was a few decades ago. Due largely to regulatory burdens, pharmaceutical companies are far less willing today to share molecules with novel mechanisms of action with academic colleagues to explore their potential antidepressant efficacy. Likewise, the vast majority of academic centers do not have the funding or know-how to generate tool compounds—with novel mechanisms—and gain regulatory clearance to study their activity in humans. This is a gap that the National Institutes of Health has tried to overcome, but it has not yet succeeded. The failure of many antidepressant clinical studies also relates to difficulties with such trials. Unlike decades ago, when such clinical studies tested patients with uncomplicated depression, today's trials by necessity focus on individuals who do not adequately respond to any of the broad range of monoamine-based treatments currently available. Consequently, many patients who participate in antidepressant trials today have more severe cases of depression that are complicated with many comorbid pathologies.

Advances in the basic neurobiology of depression are providing a rich range of potential molecular targets for antidepressant therapeutics. We need to find a way to fund medicinal chemistry efforts through which tool compounds against these targets can be developed and then tested in small, exploratory clinical studies. The success of such studies is likely to be enhanced by focusing on subsets of the broad depression syndrome based on biological measurements, whether genetic risk factors, brain imaging findings, and a range of abnormalities (e.g., cytokines, RNA or protein expression profiles) in peripheral blood or cerebrospinal fluid (CSF). We believe that such capabilities will at long last jump-start drug discovery efforts in depression and bring much-needed relief to the roughly half of all depressed patients who do not respond fully to today's treatments.

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