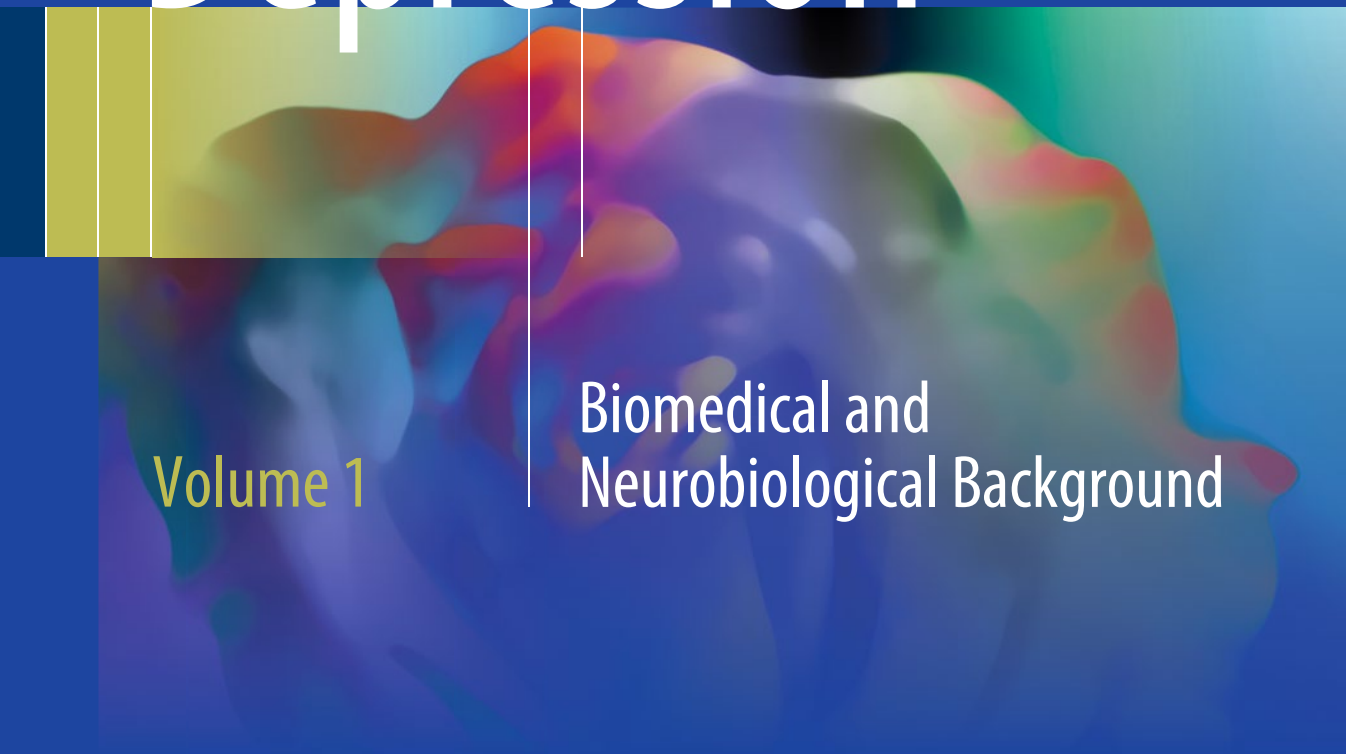
Yong-Ku Kim
Editor

Understanding Depression



Volume 1

Biomedical and Neurobiological Background

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Editor
Yong-Ku Kim
College of Medicine
Korea University
Kyonggi-do
South Korea

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Preface

This book, in two volumes, focuses on contemporary issues and dilemmas in relation to depression. The aim is to equip readers with an up-to-date understanding of the clinical and neurobiological underpinnings of depression and their relationships to clinical manifestations and the development of more effective treatments. This first volume is devoted specifically to biomedical and neurobiological issues. Detailed information is presented on a wide range of topics, including genetics, molecular and cellular biology, and aspects at the neural circuit and multicellular system levels. Readers will gain a deeper appreciation of the factors and interactions underlying individual variation in responsiveness to stress and vulnerability to depression, as well as a clear understanding of potential treatment targets and causes of treatment resistance based on the latest research. A concluding section considers progress toward precision psychiatry and gender and cultural differences in depression. The companion volume is dedicated to clinical and management issues in depression. *Understanding Depression* will be an excellent source of information for both researchers and practitioners in the field.

Part I (Chaps. 1–5) deals with the genetic and epigenetic aspect of depression. Depression is a complex and heterogeneous disorder, at etiological, phenotypical, and biological levels. The gene or series of genes that cause depression have not yet been identified. However, certain genetic variations, called polymorphisms, may increase the risk of depression in a susceptible person. Gene-environment (G × E) interaction in the pathophysiology of depression leads to advances in personalized medicine by means of genotyping for interindividual variability in drug action and metabolism. Such a concept may explain why some individuals become depressed while others remain unaffected.

Chapter 1 highlights a current and available knowledge about the pharmacogenetics and pharmacogenomics of antidepressant drugs and complementary approaches, in particular epigenomics and transcriptomics of antidepressants. Candidate gene studies demonstrate that a number of genes involved in antidepressant pharmacodynamics (such as BDNF, SLC6A4, HTR2A) and pharmacokinetics (CYP450 and ABCB1 genes) are likely modulators of antidepressant efficacy. More appropriate methodological approaches through GWAS, sequencing studies, and multi-marker tests based on whole genome data are expected to improve our knowledge in diagnosis, treatment, and prognosis of depression.

Chapter 2 provides a comprehensive review of currently existing imaging genetics studies on depression susceptibility gene polymorphisms (such as BDNF, COMT, MAOA, HTR1A, TPH2), which have measured effects on gray matter structure, white matter integrity, and functional metabolic activity patterns of the brain. The imaging genetics studies provide an opportunity to identify neural pathways that mediate the vulnerability to depression and identify genes that contribute to changes in relevant brain regions.

Chapter 3 reviews existing research studies with consideration of gene and environment interactions and epigenetics in assessing and understanding depression pathogenesis. The limitations and future perspectives with respect to the studies in G × E interactions and epigenetics are discussed. In light of advances in multi-omics technologies, future research may lead to innovative ideas that are relevant to disease prevention and drug responsiveness for depression.

Chapter 4 introduces the critical role of microRNA (miRNA) in shaping the genetic information processing in disrupted neuromolecular circuitry in depression. A tiny member from the noncoding RNA family, miRNA, has recently emerged as a promising epigenetic modifier of depression. MiRNA has an inherent capacity to influence gene functions and mediate epigenetic influence on synaptic plasticity. MiRNAs have a direct role in the etiopathogenesis of depression and will be used as potential biomarkers or therapeutic targets in depression.

Chapter 5 examines the relationship between stress, hypothalamic-pituitary-adrenal (HPA) axis function, and depression and the role of early life stress as an important risk factor for HPA axis dysregulation. The dysregulation of the HPA axis is partially attributable to an imbalance between glucocorticoid and mineralocorticoid receptors. Evidence demonstrates that glucocorticoid receptor function is impaired in major depression, but few studies assess the activity of mineralocorticoid receptors in cases of depression with early life stress. Thus, more studies are needed to elucidate this issue.

Part II (Chaps. 6–9) focuses on the molecular and cellular-level aspects of depression. Currently, various factors such as neuronal, glial, and synaptic dysfunctions explain the pathophysiological mechanisms of depression and pharmacological approaches. Interactions among stress, glucocorticoids, glutamatergic transmissions, and glial cells are important in the pathophysiology of depression. More recently, the mammalian target of rapamycin (mTOR) pathway's role in the pathophysiology of depression and molecular mechanisms involved in the activity of emerging and classic antidepressant agents has become an object of attention.

Chapter 6 emphasizes the complex role of serotonin receptors in depression and its implications for treatment. Paradoxical antidepressant-like effects of both agonists and antagonists of 5-HT receptors are likely connected to the diverse neurochemical mechanisms they instantiate. Identifying the role of 5-HT receptors in response to antidepressants is an essential step in recognizing their mechanisms of action, thereby potentially producing more effective antidepressants with fewer side effects in patients with major depressive disorder.

Chapter 7 focuses on the emerging role of glutamate receptors in the pathophysiology of depression. Depression is closely associated with disturbances in glutamate receptors as well as complex interactions with neuroinflammatory, neuroendocrine, and neurotrophic factors, although which is a consequence and which is a cause remain unknown. Currently, the resultant overexpression of extrasynaptic *N*-methyl-D-aspartate (NMDA) receptors is considered one of the essential causative stages in the pathophysiology of depression.

Chapter 8 highlights the clinical and experimental evidence of the role of the mammalian target of rapamycin (mTOR) signaling pathway in the pathophysiology and treatment of depression. Activation of the mTOR pathway seems to underlie the rapid antidepressant action of ketamine, an antagonist of *N*-methyl-D-aspartate (NMDA) receptors. Future clinical trials assessing peripheral markers and neuroimaging studies are important to evaluate the role of mTOR in antidepressant responses.

Chapter 9 reviews the candidates of biological markers for depression in general, as well as more specifically for the melancholic and atypical subtypes. Biological markers are objective measures of biological processes and can be found based on blood levels of single molecules, genetic variants, epigenetic changes, or neuroimaging findings. Such biological subtyping of depression into homogeneous clusters based on biological markers would be an inevitable task for the development of personalized treatment regimens for depression.

Part III (Chaps. 10–15) addresses neural circuit-level aspects of depression. Molecular, functional, and structural imaging approaches have been increasingly used to detect neurobiological changes, analyze neurochemical correlates, and parse pathophysiological mechanisms underlying depression. Currently, the diagnosis of depression requires extensive participation from clinical experts. It has drawn much attention to the development of new neuroscience techniques for efficient and reliable diagnosis and treatment of depression.

Chapter 10 addresses the structural, functional, molecular neuroimaging in depression. Depression is associated with both structural and functional abnormalities, as detected by neuroimaging modalities. Dysfunctional networks and monoamine deficiency, particularly 5-HT and dopamine deficiency, have been identified with the applications of radionuclide imaging and MRI techniques. Furthermore, potential imaging biomarkers have been revealed to be associated with depression severity, characteristic symptoms, and even therapeutic effects. Exploring the implications of these molecular, structural, and functional changes for the behavior and cognitions of depression is warranted.

Chapter 11 introduces a novel form of psychopathology that focuses on spatiotemporal rather than cognitive or experiential features, spatiotemporal psychopathology. Spontaneous activity's spatial and temporal features provide the bridge between the brain and cognition. The psychopathological symptoms of depression can be better understood by the spatiotemporal approach. Spatiotemporal psychopathology provides the bridge between biological psychiatry and cognitive psychopathology.

Chapter 12 explores neuroimaging modalities and recent literature regarding treatment prediction of outcomes of depression treatment on an individual basis. Several interesting studies provide evidence for the usefulness of neuroimaging in predicting the treatment outcomes of depression. To approach the goal of specific treatment regimens for individual patients, studies must be designed with integrated neuroimaging methods (e.g., EEG and fMRI), which will confirm clinical diagnoses, and research pretreatment imaging features that may predict outcomes, ideally confirmed with independent datasets.

Chapter 13 refers to the cortical-subcortical interactions in the pathophysiology of depression. Specifically, interactions among the prefrontal cortex, ventral striatum, amygdala, and dorsal raphe nucleus are implicated in the neural circuits of depression. Dysfunction in prefrontal-subcortical circuits comprises an integrative framework for understanding motor, cognitive, and emotional functions in depression.

Chapter 14 describes different pathophysiology and treatment strategies between melancholic depression and atypical depression. Melancholic depression is associated with hyperactivity of the HPA axis, while atypical depression is associated with hypoactivity of the HPA axis. Atypical depression is associated with lesser impairment of the noradrenaline neurotransmitter system. Hypersecretion of corticotropin-releasing hormone (CRH) and the resulting hypercortisolism are not found in patients with atypical depression. Considering the biological mechanisms of depressive subtypes, it is helpful to understand the pathogenesis of each depressive disorder, in order to predict an individual's response to treatment for depression.

Chapter 15 provides an extensive review of the effect and mechanism of neurostimulations, such as ECT, MST, tDCS, VNS, DBS, and TMS in depression. Neurostimulations produce several neurobiological changes in the brain, although it is still not entirely clear which of these mechanisms produce the improvement of depressive symptoms. Both antidepressants and neurostimulation techniques, which are effective in the treatment of depression, play a major role in the modulation of several neurotransmitter systems.

Part IV (Chaps. 16–20) highlights multicellular system-level aspects of depression. Over the years, numerous animal models have been established to elucidate the pathophysiology that underlies depression and to test novel antidepressant treatment strategies. Depression is characterized by a pathological inflammatory process and neurodegeneration. Inflammation in depression is considered as a possible cause of dementia in late life depression (LLD). Recently, glial functions have been investigated, and increasing evidence has suggested that glial cells perform important roles in various brain functions. The gut microbiome plays a crucial role in the bidirectional gut-brain axis that integrates gut and central nervous system activities and is a critical mediator of microbiome-CNS signaling in depression.

Chapter 16 provides a critical view of the usefulness and disappointments of experimental animal models for depression. To avoid such disappointments, we should use more complex animal models that involve species that have better homological validity and try to model subtypes of depression.

Optogenetic models have been applied to investigate the neurobiology of depression, and optogenetic tools may lead to the development of novel treatment strategies for depression.

Chapter 17 sheds light on the relationship between the gut-microbiota-brain axis and depression. Microorganisms affect the brain via the immune system, neuroendocrine system, and nervus vagus. Nutrition, stress, and medication lead to dysbiosis by changing the microbiota composition. Probiotic bacteria have a potential to be used in depression treatment. Fecal microbiota transplantation (FMT) is a hopeful sign for cases of treatment-resistant depression in the future.

Chapter 18 suggests the role of chronic inflammation and neuroprogression in the pathophysiology of depression. The multiple effects of chronic low-grade inflammation initiated by chronic stress and depression on the integrity of the brain's neural network contribute to the neurotoxicity of pro-inflammatory cytokines, the modulation of biogenic amine neurotransmitters, and the activation of the neurotoxic arm of tryptophan-kynurenine pathway. Neuroinflammation and neurodegeneration also affect intermediary metabolism of brain glucose as a result of the dysfunction of insulin and could be the prelude for dementia in some cases of chronic depression.

Chapter 19 focuses on the modulating microglial activation as a possible therapeutic target for depression. Up-to-date knowledge about the effects of psychotic drugs, especially aripiprazole, on microglial modulation and the relationship between microglia and neurotransmitters, such as serotonin and noradrenaline, is addressed. Microglia-like (iMG) cells from human peripheral blood may be useful as a tool for predicting drug responsiveness before actual treatments and in diagnosis, consequently leading to tailored therapies for depression in the future.

Chapter 20 focuses on the use of animal models in defining antidepressant response. Animal models are an important topic of preclinical research on the neurobiology of psychiatric disorders, help in screening putative drugs for treating the disorder, and permit a better comprehension of mechanisms implicated. It appears that the mouse forced swimming test (FST) is the most suitable animal model of depression for predicting antidepressant response, as it is easily and rapidly performed, robust, specific for antidepressant drugs, and reproducible. Moreover, it permits a good correlation with clinical studies in a translational approach.

Part V (Chaps. 21–25) deals with individual-, age-, gender-, and culture-specific aspects of depression. The personalized or precision medicine approach to depression is a very active avenue of investigation. Childhood and adolescent depression and late-onset depression have different features compared with adult depression. The neurobiology and risk factors for age-specific depression are thoroughly discussed. The mechanisms underlying sex differences in disease progression are not well understood; however, a strong link exists between different inflammation states of men and women and their propensity to develop certain diseases. The understanding of cultural differences in depression will help to identify the vulnerability risk factors and preventive resilience factors for depression.

Chapter 21 emphasizes the concept and usefulness of the precision medicine or personalized medicine approach in the clinical practice of treating depression. The development of biosignatures profiling clinical phenotypes; neuroimaging and EEG data; a diverse array of peripheral/serum growth factors, cytokines, hormones, and metabolic markers; genetic makeup; and environmental factors (e.g., childhood early experiences) is clearly an alternative to the single-biomarker approach. The personalized or precision medicine approach to depression has the ultimate goal of identifying predictors that can be used in clinical practice and guides psychiatrists in improving treatment outcomes and reducing side effects.

Chapter 22 focuses on the genetic-environmental and biological risk factors for child and adolescent depression and the existing strategies effective for preventing depression. Child and adolescent depression not only is a current mental health problem but also causes negative long-term consequences in adulthood. Adolescence is a key window for preventive interventions, because the prevalence of depression significantly increases during this developmental period. The need for efficacious preventive interventions for the childhood and adolescent periods is widely recognized.

Chapter 23 highlights important new advances in the understanding of the biological underpinnings of late life depression (LLD). LLD plays an important role in the emergence of neurodegenerative disorders. Treatment paradigms for LLD must address prevention of risk factors that form a common pathway for both depression and dementia. Future models of LLD will examine not just subcortical/hippocampal pathways, genetic polymorphisms, and inflammatory and glial markers but also how these complex systems interact with one another.

Chapter 24 highlights the gender differences in depression. Gender differences in depression are seen in its prevalence, clinical manifestations, and comorbidities. Possible explanations based on psychosocial and biological factors have been suggested. Interactions among gonadal hormones, the HPA axis, and neurotransmitters show how gender differences affect the manifestations of depression and the treatment responses to specific strategies.

Chapter 25 updates the epidemiology of depression across different cultures. Despite the inherent limitations of this primarily cross-sectional epidemiological data, it confirms depression is a major public health concern across cultures, indicating associations of depression with numerous adverse outcomes. Investigating the worldwide prevalence of depression and its associated features may contribute to the proper identification of environmental risk factors for this disorder, which may facilitate the identification of vulnerable individuals who might benefit from targeted preventative strategies.

I wish to give my heartfelt thanks to all chapter authors for their valuable time spent preparing manuscripts. They are leading research scientists with knowledge and expertise in their respective fields. It goes without saying that without their support, this book would not exist. I also wish to thank Dr. Sue Lee at Springer Nature for her assistance in all aspects of this book. I believe that this book will function as a step on the path toward the ultimate goal of understanding and treating depression.

Seoul, South Korea Yong-Ku Kim

Contents

Part I

Genetic and Epigenetic Aspects of Depression

Highlights on Pharmacogenetics and Pharmacogenomics in Depression

1

Chiara Fabbri and Alessandro Serretti

1.1 Introduction

As molecular biology became more and more integrated in all medical fields, in the previous century, genetic polymorphisms were demonstrated to contribute to the pathogenesis of major psychiatric disorders such as mood disorders and schizophrenia (Bertelsen 1985). The following step was to demonstrate that also response to treatments such as antidepressant drugs frequently clusters in families since it has a genetic component. It was estimated that genetics accounts for 20–95% of variability in CNS (central nervous system) drug disposition and pharmacodynamics (Cacabelos et al. 2012).

Since these findings, genetics and pharmacogenetics have been considered a powerful tool to develop objective diagnostic markers and provide guidance for tailored treatments in psychiatry. Response to psychotropic drugs shows high variability among individuals, and currently the lack of validated biomarkers of treatment outcomes results in the use of a trial and error principle to identify the most effective and tolerated treatment. This increases the time needed to reach symptom remission or in some cases does not allow remission, with possible evolution in a chronic disease. The prevalence, personal, and social burned of psychiatric disorders stimulated a strong wave of research aimed to identify biomarkers able to personalize treatments in a reproducible and valid way.

Among mental disorders, depressive disorders are responsible for highest burden in terms of disability-adjusted life years (DALYs) (40.5%) (Whiteford et al. 2013) and consequently for the highest health expenditure (direct costs alone amount to 42 billion dollars per year in Europe (Sobocki et al. 2006)). About one third of patients with MDD (major depressive disorder) reaches complete symptom remission after the first antidepressant trial, and about two thirds meets the criteria for treatment-resistant depression (i.e., inadequate response to two or more treatments) (Trivedi and Daly 2008). Since the availability of antidepressants belonging to different classes (i.e., with different mechanisms of action) and non-pharmacological treatments (e.g., psychotherapy) that can be prescribed alone or in combination, the lack of treatment targeting is responsible for part of the unsuccessful outcomes. Biomarkers and particularly genetic polymorphisms have been considered excellent candidates to provide treatment targeted on the individual patient in the last three decades. Human genomes differ for millions of polymorphisms, the most common of which are single nucleotide polymorphisms (SNPs), i.e., replacement of a single DNA base. Less common and

C. Fabbri • A. Serretti (✉)
Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy
e-mail: alessandro.serretti@unibo.it

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larger variations include deletions, insertions, and copy number variations, but genetic studies of complex traits (such as drug response) are usually focused on SNPs.

After the first enthusiastic findings in the 1990s that involved some candidate genes such as the serotonin transporter (see Sect. 1.2.1 for details), the lack of consistent replication in the following studies resulted in a period of uncertainty and disappointment without the possibility to develop any clinical application. In the meantime, advances in genotyping technologies and analysis approaches have been exponential and made possible a new wave of innovation and progress in the last 10 years. Particularly, genome-wide arrays (a technology that allows the genotyping of 500 K–3 million polymorphisms throughout the whole genome) became more and more available in terms of costs, and innovative statistical approaches have been developed, thanks to the generation and growth of genome-wide databases. Indeed, the pharmacogenomics of antidepressants is today known to be a complex trait, i.e., the result of the effect of multiple genetic loci that may have additive or multiplicative effect. Recent approaches have tried to take into account this complexity by using multilocus models that include hundreds or thousands variants at the same time. In the following sections these recent methodologies and their results are described, but first of all candidate gene studies—that were the starting point of antidepressant pharmacogenetics—are briefly summarized.

1.2 Pharmacogenetics of Antidepressants: Are Candidate Gene Studies Useful?

The term "pharmacogenetics" was coined when the first studies that investigated variants possibly associated with drug response were published. Those studies were based on the hypothesis that a small number of polymorphisms in some genes could be responsible for the most part of variance in treatment outcome. Since this was shown not to be the case, the usefulness of this type of study could be considered doubtful. The following sections discuss this issue taking into account previous findings and clinical applications of candidate gene studies.

1.2.1 Main Findings of Candidate Gene Studies

Candidate gene studies are focused on a limited number of polymorphisms in genes which products are known to be involved in drug metabolism (pharmacokinetics) or drug mechanisms of action (pharmacodynamics). The most studied and confirmed genes in the former group are cytochrome P450 (CYP450) genes that are responsible for antidepressant metabolism in the liver and ABCB1, encoding for the P-glycoprotein that is responsible for drug transport through the blood brain barrier (BBB). In the latter group, the serotonin transporter (SLC6A4), serotonin receptors, brain-derived neurotrophic factor (BDNF), and genes related to signal transduction (particularly GNB3 and FKBP5) were the most replicated for association with antidepressant response (Fabbri et al. 2016).

CYP450 genes are highly polymorphic resulting in several groups with different metabolizing activity (from poor metabolizers to ultra-rapid metabolizers, with extensive metabolizers being the group with the normal activity level). CYP2D6 and CYP2C19 isoforms were the most studied as modulators of antidepressant treatment outcomes (both in terms of efficacy and side effects). There is convincing evidence that functional polymorphisms in these CYP450 genes affect plasma levels of target antidepressants and their metabolites, but findings are more contradictory for clinical outcomes. In the latter group, the most replicated result was higher occurrence/severity of side effects in non-extensive CYP2D6 or CYP2C19 metabolizers (Müller et al. 2013). An explanation of these findings may be a non-linear relationship between antidepressant plasma levels and efficacy/side effects that was not possible to clearly define probably because of small sample size of previous studies. Poor

metabolizers are indeed the group that is expected to show the most extreme clinical outcomes, but it is also the rarest group (around 1.5–3% in the Caucasian population), and most part of available studies was performed in samples including few hundreds of subjects or less (Porcelli et al. 2011). A meta-analysis investigating CYP2D6 and CYP2C19 association with antidepressant efficacy and side effects is still lacking, and it would be very helpful in clarifying the value of pharmacogenetic tests including these CYP450 genes in their predictive model (see Sect. 1.2.2).

CYP450 phenotypes affect antidepressant plasma levels, while P-glycoprotein (ABCB1 gene) limits the uptake of many antidepressants into the brain. Some polymorphisms in this gene (rs2032582, rs1045642, rs2032583, rs2235015) were associated with altered P-glycoprotein expression and/or function and with antidepressant efficacy (Fabbri et al. 2016). The distinction between antidepressants that are or not targets of P-glycoprotein and the affinity of P-glycoprotein to each target antidepressant is relevant in this case and was not always considered by pharmacogenetic studies.

Among genes responsible for antidepressant pharmacodynamics, some polymorphisms of the SLC6A4 gene are included in all the pharmacogenetic tests available on the market (see Sect. 1.2.2). SLC6A4 codes for the serotonin transporter that is the main target of the most part of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). In particular, the 5-HTTLPR insertion-deletion variant was investigated by more than 50 studies despite the mean sample size was limited considering current standards (around 150 subjects). The last meta-analysis suggested that the polymorphism is associated with treatment efficacy particularly in some groups (Caucasian subjects treated with SSRIs) (Porcelli et al. 2012), despite the effect size of this variant alone is estimated to be modest (odds ratio between 1.53 and 2.10).

Among serotonin receptors, HTR2A (serotonin receptor 2A) may be pivotal for the final antidepressant effect since it mediates the increase in the firing rate of serotonergic neurons and hippocampal plasticity in animal models (Qesseveur et al. 2016). The effect of rs6313 and rs7997012 on antidepressant efficacy was confirmed at meta-analytic level (odds ratio between 1.33 and 1.92) despite inconsistent findings were reported by individual studies (Lin et al. 2014).

BDNF was the most studied among genes coding for neurotrophins, a family of proteins that control the survival, development, and function of neurons. BDNF is hypothesized to serve as link between antidepressant drugs and the neuroplastic changes that result in the improvement of depressive symptoms. The Valine66Methionine (Val66Met or rs6265) is a BDNF functional polymorphism since the Met allele results in decreased levels of active BDNF in vitro and it may be associated with psychiatric disorders including mood disorders and anxiety (Glatt and Lee 2016). In depressed patients, the cumulative evidence is partially inconsistent with these observations since the heterozygote genotype (Met/Val) was reported to have higher chances of treatment response and remission even if the effect size was again small (odds ratio between 1.26 and 1.74) (Niitsu et al. 2013). This finding may be interpreted as the result of a complex pattern of molecular and behavioral consequences of BDNF levels in different brain areas. For example, higher BDNF levels in the hippocampus were associated with antidepressant effects, but BDNF actions might be different or even opposite in different brain regions. The best example is the ventral tegmental area-nucleus accumbens (NAc) dopaminergic reward circuit, in which chronic stress increases BDNF expression (Yu and Chen 2011). Another relevant issue to consider is the interaction between neurotrophins and glucocorticoids that affects depressive symptoms and antidepressant response. FKBP5 (FK506-binding protein 52) increases the sensitivity of the glucocorticoid receptor (GR) and plays a role in stress response and depressive states. Drugs that reduce FKBP5 gene expression were demonstrated to elicit increase of BDNF levels and antidepressant effects (Xing et al. 2015). rs1360780 has been the most studied polymorphism because carriers of the TT genotype showed FKBP5 levels that were twice as high as C allele carriers in vitro (Binder

et al. 2004). Meta-analytic results confirmed a small advantage of T allele carriers in a stratified analysis of patients of European origin (Niitsu et al. 2013) and the polymorphisms was included in some of the pharmacogenetic tests available on the market (see Sect. 1.2.2).

Another pivotal molecule in signal transduction is the guanine nucleotide-binding protein (G protein) that mediates a broad range of signaling cascades in response to a number of hormones and neurotransmitters. GNB3 encodes for the beta polypeptide 3 of that protein, and the rs5443 (C825T) polymorphism was object of particular interest since the T allele leads to altered activity of the protein (Ruiz-Velasco and Ikeda 2003). The cumulative evidence from pharmacogenetic studies suggests better response in T allele carriers especially in subjects of Asian ancestry despite controversial results were reported (Niitsu et al. 2013).

A number of other candidate genes have been investigated in addition to the ones discussed in this section, particularly other genes which products are involved in mechanisms of antidepressant action such as HTR1A (serotonin receptor 1A), HTR2C (serotonin receptor 2C), COMT (catechol-O-methyltransferase), MAOA (monoamine oxidase A), tryptophan hydroxylase 1 (TPH1), glutamatergic receptors, proteins involved in BDNF signaling or other neurotrophins, and interleukins (Fabbri et al. 2013).

Despite the effect sizes of individual polymorphisms are small as discussed in this section and the candidate gene approach is clearly limited since the complexity of the mechanisms involved in antidepressant response, we suggest that the study of the pharmacogenetics of antidepressants should not be separated by the understanding of the biological mechanisms through which genes affect the phenotype. A hypothesis-free approach (analysis based on genome-wide data) is a powerful tool for exploration, but meaningful clinical applications are unlikely without the clarification of the contribution of individual genes in terms of biological role. Indeed, all the studied clinical applications are currently based on the results of candidate gene studies.

1.2.2 Clinical Applications

The pharmacogenetic tests currently available on the market are based on different combinations of polymorphisms in candidate genes that usually include those discussed in Sect. 1.2.1, particularly SLC6A4, HTR2A, CYP450 genes, and ABCB1. These tests are quite popular, thanks to the Web, and patients may decide by themselves to undergo the test and bring the results to their psychiatrist for interpretation and prescription of the "right" drug. According to the published data of the companies that commercialize these tests, antidepressant treatment guided by genotyping according to their algorithm may improve symptom remission (Hall-Flavin et al. 2013; Singh 2015) and reduce health-care utilization (Winner et al. 2013) and costs compared to treatment as usual (Winner et al. 2015). The main concern is the unavailability of the treatment decision algorithm based on the polymorphisms included in each of these tests, thus replication by independent investigators that do not collaborate with these companies was not performed. A couple of academic studies had similar designs and compared treatment guided by genotype versus treatment as usual, but they took into account polymorphisms in single candidate genes. They suggested that rs2032583 and rs2235015 polymorphisms in the ABCB1 gene may be useful to guide dose adjustments or drug switch (Breitenstein et al. 2014), and genotyping of FKBP5 rs1360780 may improve treatment outcome compared to treatment as usual (Stamm et al. 2016). The cost-effectiveness of these tests is still unclear.

1.3 Pharmacogenomics of Antidepressants

The cost of genotyping has shown more than an exponential decrease in the last decades, and at the same time, genotyping technologies became better and better. According to the US National Human Genome Research Institute (NHGRI), the reductions in DNA sequencing cost exceeded

the Moore's Law (which describes a long-term trend in the computer hardware industry that involves the doubling of "compute power" every 2 years) around 2008, indicating more than excellent technology improvements in the field (https://www.genome.gov/sequencingcostsdata/). Thus, the new standard approach of research became genomics or pharmacogenomics that consists in the study of polymorphisms throughout the whole genome using genome-wide arrays or sequencing.

1.3.1 Genome-Wide Association Studies (GWAS)

Genome-wide arrays allow the genotyping of 300 K–3 millions of common polymorphisms (mainly SNPs) throughout the whole genome, and they are designed to capture especially tag polymorphisms (i.e., polymorphisms that are inherited in conjunction with other polymorphisms), validated polymorphisms, and possibly polymorphisms in functional areas of the genome or in groups of genes that are hypothesized to be relevant for a particular type of study. The genome-wide technology provides high-throughput multiplex processing of samples at reasonable costs and overcomes the need of any a priori hypothesis that represented one of the limitations of candidate gene studies. At least ten GWAS of antidepressant response/side effects have been performed at the time this chapter was written (Uher et al. 2010; Garriock et al. 2010; Ising et al. 2009; Myung et al. 2015; Biernacka et al. 2015; Sasayama et al. 2013; Tansey et al. 2012; Cocchi et al. 2016; Li et al. 2016; Ji et al. 2013) in addition to meta-analyses (GENDEP Investigators, MARS Investigators, and STAR*D Investigators 2013), but no genome-wide convincing result has been reported. The usually accepted genome-wide threshold for significance is 5×10^{-8} since hundreds of thousands of tests are performed by GWAS, and this requires correction for multiple testing.

In samples that were of main Caucasian origin, the best findings were some intergenic SNPs on chromosome 1 (rs2136093, rs6701608, rs2136094) and 10 (rs16920624, rs11598854, rs7081156) (Uher et al. 2010) and SNPs in the UBE3C (rs6966038), BMP7 (rs6127921) and RORA (rs809736) genes (Garriock et al. 2010), RFK (rs11144870), GRK5 (rs915120) (Ji et al. 2013), and rs6989467 in the 5′ flanking region of the CDH17 gene (Ising et al. 2009). The GWAS in the largest Caucasian sample identified one significant variant (the intergenic SNP rs1908557) (Li et al. 2016). In Asian samples, a couple of genome-wide significant SNPs were reported in the AUTS2 gene (rs7785360 and rs12698828) that has been implicated in neurodevelopmental disorders including autism but also schizoaffective and bipolar affective disorders (Myung et al. 2015). This study was carried out in sample of Korean origin, but another GWAS in an independent sample of the same ethnic origin reported different findings that involved the CTNNA3 gene and inorganic cation transmembrane transporter activity pathway (Cocchi et al. 2016). The GWAS on the largest Asian sample (mainly Chinese subjects) did not report any genome-wide significant result, but some SNPs were close to significance in the meta-analysis of this data with a Caucasian sample (in the HPRTP4 pseudogene/VSTM5 region), and one suggestive finding was reported in the 5′ upstream of the NRG1 gene (neuregulin-1 that is involved in brain development and it was associated with mental disorders, particularly schizophrenia) (Biernacka et al. 2015). The last Asian GWAS was performed in a quite small Japanese sample, and it reported nonsignificant signals in the CUX1 gene (rs365836 and rs201522) (Sasayama et al. 2013).

An overview of GWAS results and functions of the genes involved by the top findings is reported in Table 1.1.

This list of non-replicated results may look disappointing and difficult to interpret since GWAS were expected to represent a turning point in antidepressant pharmacogenomics. Different issues are hypothesized to be responsible for the paucity of genome-wide findings and the lack of result replication. In detail, (1) the samples of previous GWAS included hundreds of subjects or

Table 1.1 Summary of genome-wide association studies (GWAS) results

Study	Sample size	Ethnicity	AD	Top results (p value)	Biological role
Ising et al. (2009)	339 + 361 for replication	Caucasian	Mixed ADs	rs6989467 in the 5′ flaking region of CDH17 ($p = 7.6 \times 10^{-7}$)	CDH17 (cadherin 17) codes for a calcium-dependent, membrane-associated glycoprotein that is not expressed in the CNS, a connection to antidepressant response is difficult to hypothesize
Uher et al. (2010)	706	Caucasian	Escitalopram Nortriptyline	rs2136093 (3.82×10^{-7}), rs6701608 (4.66×10^{-7}), rs2136094 (5.86×10^{-7}), s16920624 (7.37×10^{-7}), rs11598854 (7.67×10^{-7}), rs7081156 (1.01×10^{-6})	Intergenic SNPs, a mechanism for involvement in antidepressant effect is difficult to hypothesize
Garriock et al. (2010)	1491	Mainly Caucasian	Citalopram	rs6966038 in UBE3C (4.65×10^{-7}), rs6127921 100 Kbp from BMP7 (3.45×10^{-6}), rs809736 in RORA (8.19×10^{-6})	UBE3C codes for an ubiquitin protein ligase that is expressed in the CNS including prefrontal cortex and hippocampus, specific mechanisms linking it to antidepressant action are unknown. BMP7 codes for bone morphogenetic protein 7 that acts as a secreted ligand of the TGF-beta and it is expressed in the CNS. RORA codes for a member of the NR1 subfamily of nuclear hormone receptors that regulates the expression of some genes involved in circadian rhythm
Ji et al. (2013)	499	Caucasian	Escitalopram Citalopram	rs11144870 in RFK (1.04×10^{-6}), rs915120 in GRK5 (1.15×10^{-5})	RFK codes for an enzyme that catalyzes a critical step of vitamin B2 metabolism. B vitamins were suggested to affect the risk of depressive symptoms (Ji et al. 2013). GRK5 codes for a member of the G protein-coupled receptor kinase subfamily that regulates monoamine receptors such as β1-adrenergic receptor and dopamine D1A receptor (Ji et al. 2013)
Li et al. (2016)	4536	Caucasian	Bupropion	rs1908557 (2.6×10^{-8})	Intergenic SNP within the intron of human spliced expressed sequence tags in chromosome 4

Study	Sample size	Ethnicity	AD	Top results (p value)	Biological role
Myung et al. (2015)	870	Korean	Mixed SSRIs	rs7785360 and rs12698828 in AUTS2 (3.57×10^{-8})	AUTS2 (autism susceptibility candidate 2) has been implicated in neurodevelopment and as a candidate gene for several neuropsychiatric disorders including autism, schizoaffective, and bipolar affective disorders (Myung et al. 2015)
Biernacka et al. (2015)	865	Mainly Chinese	Mixed SSRIs	rs56058016 in VWA5B1 (1.1×10^{-7}), rs4747621 (1.75×10^{-7}), rs7041589 (5.40×10^{-7}), rs113243734 in ZC3HAV1L (5.64×10^{-7}), rs9328202 in RPS25P7 (6.15×10^{-7})	VWA5B1 codes for von Willebrand factor A domain containing 5B1 that is a large multimeric glycoprotein found in blood plasma but expressed also in some brain areas (particularly hypothalamus), but a biological mechanism of connection to antidepressant response is difficult to hypothesize ZC3HAV1L encodes for a protein of unclear function that is lowly expressed in the CNS. RPS25P7 is a pseudogene
Sasayama et al. (2013)	92 + 136 for replication	Japanese	Mixed	rs365836 and rs201522 in CUX1 (2.3×10^{-6} and 4.0×10^{-6}, respectively)	CUX1 (cut-like homeobox 1) codes for a domain of a DNA-binding protein that may regulate gene expression, morphogenesis, differentiation, and cell cycle progression. It may be implicated in disrupt cognition, social behavior, and autism (Doan et al. 2016; Liu et al. 2016)

Only results referred to individual polymorphisms are reported in this table and not findings of multi-marker analyses. For two GWAS (Tansey et al. 2012 ; Cocchi et al. 2016) no relevant top findings were reported in the SNP level analysis. Biological role refers to the function of the coded protein and the putative biological mechanism by which it may be relevant to antidepressant effect. Gene expression in the CNS was checked using GTEx Consortium data (http://www.gtexportal.org/home/). Genome-wide significant findings were underlined. *ADs* antidepressants, *CNS* central nervous system, *SSRIs* selective serotonin reuptake inhibitors

few thousands at maximum, while samples of tens of thousands are probably needed to identify associations with common polymorphisms having small effects (odds ratio of the best GWAS findings are usually 1.1–1.2); (2) very limited covering of genomic polymorphisms were provided by previous GWAS that included around 1 million SNPs or less in most part of cases, while around 40 million of SNPs were mapped in the human genome according to recent data (McCarthy et al. 2016); (3) antidepressant response is known to be a polygenic trait, and statistical tests based on individual polymorphisms are expected to provide less power compared to multi-marker tests (see Sect. 1.3.2), but previous GWAS have been mostly focused on individual polymorphisms.

Taking into account the reported limitations of available GWAS of antidepressant response, there are two main possible strategies to improve them

(in addition to provide better covering of genome variants): recruit new larger MDD samples characterized for antidepressant response and/or develop analysis approaches to maximize the power of detecting associations in the available samples. Some examples of the latter are provided by multi-marker tests discussed in Sect. 1.3.3.

1.3.2 Sequencing Studies

As reported at the beginning of Sect. 1.3, the cost of sequencing dropped down more than exponentially in the last 15 years. In 2001 the first draft of the human sequence was published, thanks to the Human Genome Project (HGP), one of the world's largest collaborative biological projects (International Human Genome Sequencing Consortium 2004). The HGP had a cost of about 2.7 billion dollars; now the cost of sequencing is about 1.000 dollars per genome providing the benchmark for routine, affordable personal genome sequencing.

Unfortunately, only one sequencing study focused on the genomics of antidepressant response and only exons (the coding segments of the genome) were sequenced. rs41271330 in the bone morphogenetic protein (BMP5) gene was found as promising marker of response by this study (Tammiste et al. 2013), suggesting a link with one of the top findings of a previous GWAS (rs6127921 in the BMP7 gene (Garriock et al. 2010)). Another study was limited to a functional exome array, and it revealed an exome-wide significant finding in a methylated DNA immunoprecipitation sequencing site. It also reported that a combination of this and other two exome variants predicted antidepressant response with area under the receiver operating characteristic (ROC) curve of 0.95 (Wong et al. 2014). This study was performed in a Mexican-American sample, and the attempt to replicate the three-locus model in three Caucasian GWAS failed (Uher et al. 2015); thus the result could be interpreted as highly influenced by ethnicity or other specific characteristics of the sample or as a false positive.

The generation of sequencing data is growing fast, and it is expected to accelerate in the next few years, also in the context of a number of national projects involving the creation of biobanks (e.g., the US Precision Medicine Initiative; see https://www.nih.gov/research-training/allofus-research-program). Thus, the use of sequencing data is expected to become the standard genomic data used for all genomic and pharmacogenomic studies in the relatively near future. Sequencing allows the identification of rare variants that are not included in GWAS arrays and the application of multi-marker tests that is based on the burden of rare variants in a specific gene or pathway of the genome.

1.3.3 Multi-Marker Tests Based on Whole Genome Data

The generation of genome-wide data and more recently sequencing data provided the opportunity to develop analysis approaches that combine the effect of a number of variants at the same time. This type of approach started from taking into account that the functional units of the genome can be identified in genes and that genes can be grouped according to the biological processes their products play a role in. The latter is called pathway analysis, and it consists of the analysis of all the polymorphisms in the genes that are part of the same biological pathway. This method is expected to reduce the confounding effects of heterogeneity within and across samples (i.e., heterogeneity is expected to impact more on individual polymorphisms than pathways), thus increasing power and chances to replicate findings in independent samples. Available pathway analysis supported the involvement of neuroplasticity and inflammation pathways in antidepressant response (Uher et al. 2015; Ising et al. 2009; Fabbri et al. 2014; Fabbri et al. 2015; O'Dushlaine et al. 2014; Hunter et al. 2013; Cocchi et al. 2016). Particularly, the long-term potentiation (LTP) pathway (Hunter et al. 2013), the inorganic cation transmembrane transporter activity pathway (Cocchi et al. 2016), and the GAP43 pathway (Fabbri et al. 2015) are involved in hippocampal plasticity and neurogenesis that are mechanisms known to mediate the antidepressant effect (Tanti and Belzung 2013). These

pathways included a number of genes coding for glutamate receptors (GRM1, GRM5, GRIA1, GRIN2A, GRIN2B, GRIN2C), postsynaptic L-type voltage-dependent Ca2+ channels (CACNA1C, CACNA1C, CACNB1, CACNB2), regulators of GABA and glutamatergic neurotransmission (e.g., ZDHHC7, NRG1, and HOMER1), and cell adhesion processes (e.g., FN1, EFNA5, and EPHA5). Abnormalities in inflammatory cytokine production and immune cell activation represent another key pathogenetic process in MDD, and antidepressants were demonstrated to restore these abnormalities. In particular the KEGG B cell receptor signaling pathway (Fabbri et al. 2014), the antigen processing and presentation pathway, and the tumor necrosis factor pathway (Hunter et al. 2013) were suggested to affect antidepressant response. Finally, genes involved in extracellular matrix remodeling (e.g., ADAMTSL1, CD36, PON2, APOB, and PIK3R1) and thus modulating the release of inflammatory factors were associated with antidepressant efficacy (Ising et al. 2009).

Polygenic risk scores (PRS) are another relatively recent multi-marker approach that was developed to analyze genome-wide data. PRS capture in a single variable the additive effect of SNP alleles across the whole genome. In contrast to the analysis of single SNPs (that requires stringent level of statistical significance), PRS are constructed from multiple SNPs with lower evidence of association, with the assumption that genetic markers that do not meet the genome-wide significance threshold might have good predictive power when they are considered collectively. The typical approach of studies using PRS is to estimate the polygenic score in a training sample and then test it in a validation or target sample in order to replicate the predictive value of the PRS. Unfortunately, the available studies investigating antidepressant response showed very unsatisfying or absent predictive value of PRS across independent samples. The best finding suggested that a PRS associated with symptom remission may account for approximately 1.2% of the variance in remission in the validation sample (GENDEP Investigators, MARS Investigators, and STAR*D Investigators 2013) that was statistically significant but clearly not enough for future translation in any possible clinical application. The PRS approach was a recent attempt to overcome the limitations of single marker analysis and move toward the identification of the complex polygenic contribution of polymorphisms to antidepressant response, but we suggest that it still needs methodological improvements. This observation is based on the fact that PRS had results below the expectations also for traits with a demonstrated high genetic contribution such as schizophrenia, since twin studies suggested heritability around 80% and PRS were able to explain 1.4–4.7% of phenotype variance in case-control samples (Derks et al. 2012). Some of the issues limiting the potential of PRS may be the use of broad clinical definitions or diagnosis for heterogeneous traits and the use of addictive models of the SNPs included in the score that could be an oversimplification of the reality (other types of interactions are possible such as multiplicative). Further, as stated above, not all variants are covered in present PRS studies.

To conclude this section, more sophisticated statistical methods are expected to be used in the future. An example is the application of approaches based on machine learning to antidepressant pharmacogenomics that has been carried out in animals models treated with antidepressants (Malki et al. 2016), but it still lacks meaningful application to humans.

1.4 Complementary Approaches

Genetic polymorphisms represent somehow a first level of biomarker considering that gene expression depends on several regulatory mechanisms and the final protein levels are affected by gene expression level but also by protein metabolism. Thus, there are categories of biomarkers that are complementary to genomic ones, particularly those studied by epigenomics, transcriptomics, and proteomics.

Epigenomics is the study of epigenetic modifications that are reversible modifications on DNA or histones that affect gene expression without altering the DNA sequence. Epigenomic

maintenance is a continuous process that is pivotal for adaptation to the environment and biological mechanisms like DNA repair (Alabert and Groth 2012). Exposure to pharmaceuticals, nutrition, and stress are capable of producing epigenetic modifications with possible lasting effects on human development, metabolism, and health. The most characterized epigenetic modifications are DNA methylation and histone modification, and the former was particularly studied in relation to antidepressant response. The classic type of DNA methylation refers to the addition of a methyl group to the cytosine pyrimidine ring located in CpG dinucleotide sites within genes that affect gene expression. Epigenetic modifications in a number of genes have been linked to childhood trauma and MDD, such as FKBP5 and BDNF, and antidepressants were demonstrated to have epigenetic effects (Lisoway et al. 2017). Studies investigating gene methylation in association with antidepressant response are currently limited in number, and whether increased or decreased DNA methylation is related to response differs across studies and by genetic loci. Other issues are that the most part of studies focused on baseline levels of DNA methylation rather than the reversal of probable pathological epigenetic patterns through effective treatment and almost all studies had a candidate gene approach. Taking into account these limitations, epigenetic modifications of SLC6A4, BDNF, and IL11 genes showed promising results as biomarkers for prediction of antidepressant response (Lisoway et al. 2017).

Transcriptomics is the study of gene expression levels that are usually determined in blood. Blood as a target tissue is easily accessible, and gene expression levels in blood have shown to be comparable with those obtained in prefrontal cortex, thanks to MDD-related transcriptomic research (Lin and Tsai 2016). Candidate gene studies mainly investigated the expression of genes involved in inflammation [interleukin 1 beta (IL-1B), macrophage migration inhibitory factor (MIF), tumor necrosis factor alpha (TNFα)] and neurotrophins [BDNF and nerve growth factor (VGF)], and they reported that these biomarkers may be baseline predictors of treatment outcome or show different variations at follow-up depending on treatment outcome (Fabbri et al. 2016). Several genome-wide gene expression studies have investigated antidepressant response. One of those proposed RORA as peripheral marker of antidepressant response (Lin and Tsai 2016) and interestingly this gene was among the top findings of a previous GWAS (Garriock et al. 2010). The other available transcriptomic studies reported several genes involved in inflammatory processes among significant results, particularly IRF7, IRF2, IL1B, TNF, CD3D, CD97, IFITM3, and GZMA. Two transcriptomics studies investigated also which combination of markers showed the best predictive properties. The first model included the expression of four genes (PPT1, TNF, IL1B, and HIST1H1E) that was reported to predict antidepressant efficacy with area under the ROC curve of 0.94, but no independent replication was carried out. Another 13-genes model was also proposed, including genes associated with immune/inflammatory activation (CD3D, CD97, IFITM3, and GZMA) and mediation of cell proliferation (GZMA and TIMP1). The model showed sensitivity of 66.7 to predict non-remission in the original sample and of 86.1 in an independent sample including six genes of the original set of 13 (Lin and Tsai 2016). These findings are the first attempts to translate transcriptomics in clinical applications for predicting antidepressant response, but clearly they still lack of the required validation and reproducibility and more research is needed.

Fewer studies investigated proteomics biomarkers of antidepressant response, indeed the most part of studies focused on single proteins, particularly neurotrophins [BDNF and glial cell line-derived neurotrophic factor (GDNF)] and inflammatory markers [C reactive protein (CRP), IL-1, IL-6 and TNF-α] (Fabbri et al. 2017).

Conclusion

This chapter summarized the available knowledge in the field of antidepressant pharmacogenetics and pharmacogenomics and provided some information about complementary approaches, in particular epigenomics and transcriptomics.

The existing literature focused on the candidate gene approach for more than a decade, and current clinical applications are based on the results of this type of studies. Candidate gene studies demonstrated that a number of genes involved in antidepressant mechanisms of action (such as BDNF, SLC6A4, HTR2A) and antidepressant pharmacokinetics (CYP450 and ABCB1 genes) are probably modulators of antidepressant efficacy with small individual effect sizes. Despite these results provided useful information about the role of a limited number of genes, the complexity of antidepressant pharmacogenomics cannot be identified by the candidate approach. GWAS have become a quite spread methodology only in the last 7–8 years in psychiatric research, and analysis approaches based on genome-wide data probably still need improvement, as suggested by the recent development of multi-marker tests. The evolution of analysis methods is a pivotal issue for the progress of research in pharmacogenomics since the recent rapid improvement of genotyping technologies that is not limited to GWAS, but it is quickly moving to whole genome sequencing. As reported previously in this chapter, the cost of whole human genome sequencing dropped from 100 million dollars in 2001 to 1000 dollars today, encouraging the creation of national biobanks in a number of countries. As examples, the US Precision Medicine Initiative (https://www.nih.gov/research-training/allofus-research-program) coordinated by the National Institutes of Health (NIH) and the UK Biobank (https://www.ukbiobank.ac.uk/about-biobank-uk/) established by UK Health Government authorities and supported by the National Health Service (NHS). Both projects aim to collect health-related measures through medical health records and biological specimens for biomarkers determination (including genome sequencing) on a large part of the general population (500,000–1 million or more subjects). UK Biobank recruited 500,000 people aged between 40 and 69 years in 2006–2010, and the US Precision Medicine Initiative is going to start recruitment in 2017. These projects are expected to improve the prevention, diagnosis, and treatment of a wide range of serious illness including psychiatric disorders through the development of measures of disease risk, predictors of individual disease evolution, and treatment response. Further desirable outcomes are the improvement of our knowledge in disease pathogenesis and identification of new drug targets.

Figure 1.1 provides a representation of the different methodological approaches to antidepressant pharmacogenetics/pharmacogenomics. The recent acceleration of progress in the field suggests that innovative and more robust findings will be obtained in the near future.

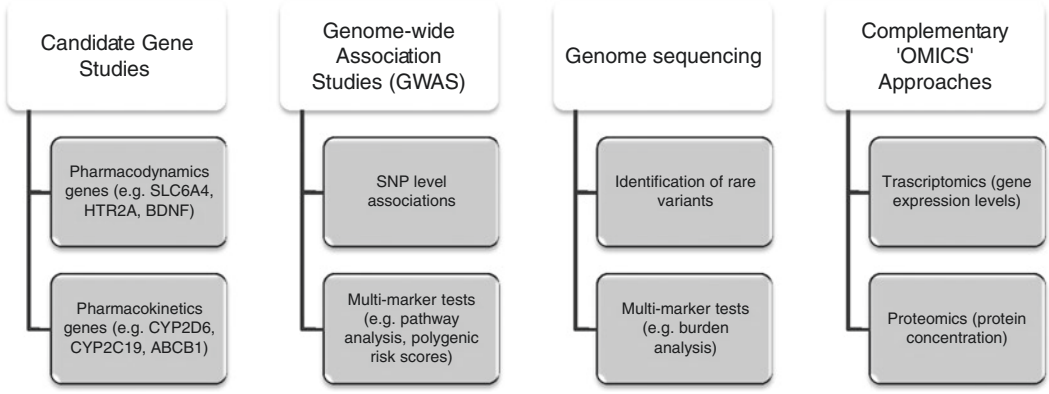

Fig. 1.1 Overview of methodological approaches in the study of antidepressant pharmacogenetics and pharmacogenomics

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2 Imaging Genetics Studies on Susceptibility Genes for Major Depressive Disorder, the Present and the Future

Eunsoo Won, Byung Joo Ham, and Yong-Ku Kim

2.1 Introduction

The genetic risk component for major depressive disorder (MDD) is considered to be substantial (Sullivan et al. 2000), with an estimated heritability of over 40% and more than a twofold increase in lifetime risk among first-degree relatives (Lohoff 2010). As genes do not directly encode for psychiatric symptoms and genetic effects do not directly translate into psychiatric phenotypes (Pezawas and Meyer-Lindenberg 2010), the concept of intermediate phenotype has been applied in psychiatric genetics (Meyer-Lindenberg and Weinberger 2006). Intermediate phenotypes are measurable components along the pathway between disease and distal genotype (Gottesman and Gould 2003), and neuroimaging techniques have visualized intermediate phenotypes of neuroanatomical nature in MDD. Genetic variants may influence neural circuits through molecular and cellular mechanisms (Meyer-Lindenberg 2010). In order to evaluate the impact of genetic variation on behavior-related psychiatric symptoms, imaging genetics has been applied in various psychiatric disorders (Hariri and Weinberger 2003). Therefore, anatomical or physiological imaging technologies have been used as phenotypic assays to map neural phenotypes as a function of genotype (Scharinger et al. 2010).

Numerous imaging genetics studies have been carried out over the past years (Scharinger et al. 2010), and as imaging genetics studies evolved from association studies in order to overcome the limitations inherent to clinical phenotypes, the strategy has been dominated by the candidate gene approach (Meyer-Lindenberg 2010). Although currently considered insufficient to explain the etiology of depression in its current form, the two most prominent hypotheses on MDD were the monoamine hypothesis and neurotrophin hypothesis, which assumed that depression is caused by a deficiency in monoamines and neurotrophins at functionally important receptor sites in the brain (Castren 2005). Therefore, various association studies have been conducted on monoaminergic and neurotrophic genes which have been considered to be susceptibility genes for MDD, such as the brain-derived neurotrophic factor (BDNF) gene, catechol-O-methyltransferase (COMT) gene, monoamine oxidase A (MAOA) gene, serotonin receptor 1A (HTR1A) gene, serotonin transporter gene, and tryptophan hydroxylase-2 (TPH2) gene; hence, numerous imaging genetics studies have been also carried on these genes accordingly (Won and Ham 2016).

E. Won • B.J. Ham
Department of Psychiatry, College of Medicine, Korea University, Seoul, South Korea

Y.-K. Kim (✉)
Department of Psychiatry, College of Medicine, Korea University, Seoul, South Korea

Department of Psychiatry, Korea University Ansan Hospital, College of Medicine, Ansan, South Korea
e-mail: yongku@korea.edu

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These studies have reported MDD susceptibility genes to influence brain circuits involved in mood regulation (Canli et al. 2009), which may eventually lead to individual differences in behavior (Hariri et al. 2006).

Various neuroimaging techniques have been applied in the field of imaging genetics. Among the many techniques, magnetic resonance imaging (MRI) has been used to measure gray matter (GM) structure, white matter (WM) integrity and density, and functional metabolic activity patterns (Dunlop and Mayberg 2014). Neuroimaging techniques that measure morphological GM changes in the brain include the whole-brain voxel-based morphometry (VBM) method, which involves a voxel-wise comparison of the local concentration of gray matter between two groups of subjects (Ashburner and Friston 2000), and the automated procedure of FreeSurfer which can estimate both GM volume and cortical thickness (Han et al. 2006). WM integrity can be estimated using diffusion tensor imaging (DTI) which detects WM abnormalities in a sensitive and accurate manner (Choi et al. 2014). Functional metabolic activity patterns are measured by functional magnetic resonance imaging (fMRI) which reflects brain metabolic activity (Dunlop and Mayberg 2014).

Functional single nucleotide polymorphisms (SNPs), which have direct effects on gene biology, are attractive substrates for imaging genetics studies (Bigos and Weinberger 2010). Therefore, imaging genetics studies on MDD that have applied the imaging techniques stated above have reported brain areas involved in emotion processing to be under the influence of MDD susceptibility gene SNPs (Price and Drevets 2010), represented as changes in volume or thickness of GM, decrease in WM integrity, or hypo-/hyperfunctional metabolic activity of certain brain areas (Won and Ham 2016). This paper provides a comprehensive review of currently existing imaging genetics studies on MDD susceptibility gene polymorphisms, which have measured changes in GM structure, WM integrity, and functional metabolic activity patterns of the brain (Table 2.1).

2.2 Susceptibility Genes for Major Depressive Disorder

2.2.1 Brain-Derived Neurotrophic Factor Gene

BDNF is considered to play an important role in activity-dependent neuroplasticity, by promoting neurotrophic and anti-apoptotic effects such as neuronal survival, axonal growth, dendritic differentiation, and long-term potentiation (Lu et al. 2005). The BDNF gene is located on chromosome 11p13 (Maisonpierre et al. 1990), and BDNF is highly expressed in the central nervous system, especially in the hippocampus (Martinowich et al. 2007). Reduction in BDNF expression is suggested to be associated the pathophysiology of MDD (Duman 2004). Among the many genetic variations within the BDNF gene, rs6265 in exon 11 is a functional nonsynonymous single nucleotide polymorphism (SNP) that leads to an amino acid substitution from valine to methionine at codon 66 (Val66Met), which subsequently alters intracellular trafficking and activity-dependent secretion of BDNF (Egan et al. 2003). The Met allele of the *BDNF* rs6265 (Val66Met) has been associated with poorer episodic memory performance (Egan et al. 2003), and a meta-analysis reported significant associations of the Met allele with MDD in the male gender (Verhagen et al. 2010). The Val allele has been associated with higher trait anxiety (Lang et al. 2005), neuroticism (Sen et al. 2003), and childhood-onset mood disorders (Strauss et al. 2005). However, negative findings on the association of the Val66Met polymorphism with MDD have also been reported (Oswald et al. 2005; Surtees et al. 2007).

2.2.2 Catechol-O-Methyltransferase Gene

COMT is the principal enzyme influencing monoamine degradation (Garris and Wightman 1994), and as COMT is known to have a marked

Table 2.1 Available imaging genetics studies on major depressive disorder susceptibility gene polymorphisms, which have measured changes in gray matter structure, white matter integrity, and functional metabolic activity patterns of the brain

Method	Gene polymorphism	Region	Finding	Subject	References
Volumetric analyses	*BDNF* rs6265 (Val66Met)	Hippocampus	Met carrier < Val/Val	HC	Pezawas et al. (2004)
		Hippocampus	Val/Met < Val/Val	HC	Szeszko et al. (2005)
		Hippocampus	Met carrier < Val/Val	HC	Bueller et al. (2006)
		DLPFC	Age-related volume reduction in Met carrier	HC	Nemoto et al. (2006)
		Hippocampus	Met carrier < Val/Val	MDD patient, HC	Frodl et al. (2007)
		Hippocampus	Met carrier < Val/Val	HC	Chepenik et al. (2009)
		ACC, DLPFC, hippocampus	Val/Met < Val/Val	HC	Matsuo et al. (2009)
		Amygdala, hippocampus	Met carrier < Val/Val	HC	Montag et al. (2009)
		Hippocampus	Met carrier < Val/Val	HC	Schofield et al. (2009)
	COMT rs4680 (Val158Met)	Hippocampus, temporal lobe	Met carrier > Val/Val	HC	Taylor et al. (2007)
		PFC (inferior frontal cortex, superior frontal gyrus, OFC)	Met carrier < Val/Val	HC	Cerasa et al. (2008a)
		Hippocampus	Met/Met > Val carrier	HC	Honea et al. (2009)
		Amygdala, hippocampus	↑ Met allele ➔ ↑ volume	HC	Ehrlich et al. (2010)
		Hippocampus	↑ Val allele ➔ ↑ volume	HC	Wang et al. (2013)
	MAOA-uVNTR	ACC, amygdala, cingulate gyrus, hypothalamus, insula	*MAOA*-L < *MAOA*-H	HC	Meyer-Lindenberg et al. (2006)
		OFC	*MAOA*-L > *MAOA*-H	HC (male)	Meyer-Lindenberg et al. (2006)
		OFC	*MAOA*-L > *MAOA*-H	HC (male)	Cerasa et al. (2008b)

(continued)

Table 2.1 (continued)

Method	Gene polymorphism	Region	Finding	Subject	References
	5-HTTLPR	Cerebellum	l/l < s carrier	HC	Canli et al. (2005a)
		ACC, frontal gyrus	l/l > s carrier	HC	Canli et al. (2005b)
		Amygdala, ACC	l/l > s carrier	HC	Pezawas et al. (2005)
		Amygdala, ACC, DLPFC, DMPFC, hippocampus	l/l > s/s	HC	Frodl et al. (2008)
		Hippocampus	l/l < s/s	MDD patient	Frodl et al. (2008)
		Hippocampus	s carrier + history for emotional neglect < s carrier or history for emotional neglect	MDD patient	Frodl et al. (2010)
		Hippocampus	l/l < s carrier	HC (female)	Price et al. (2013)
		Hippocampus	l/l > s carrier	HC (male)	Price et al. (2013)
		Hippocampus	↑ s allele → ↓ volume → increased risk for MDD onset	HC	Little et al. (2014)
		OFC	↑ s allele → ↓ volume	HC	Little et al. (2014)
		Hippocampus	s carrier → ↑ negative impact of life event	HC	Rabl et al. (2014)
	TPH2 rs4570625 (G-703T)	Amygdala, hippocampus	G/G > T carrier	HC	Inoue et al. (2010)
		OFC	G/G < T carrier	HC (female)	Yoon et al. (2012)
Cortical thickness analyses	*COMT* rs4680 (Val158Met)	Inferior frontal gyrus, temporal gyrus	↑ Met allele ➔ ↑ thickness	HC (children, adolescent)	Shaw et al. (2009)
		Inferior prefrontal sulcus, superior temporal sulcus	Met carrier > Val/Val	HC	Cerasa et al. (2010)
	MAOA-uVNTR	OFC	*MAOA*-L < *MAOA*-H	HC (male)	Cerasa et al. (2010)
	MAOA-uVNTR	OFC	No difference between *MAOA*-L and *MAOA*-H	MDD patient, HC	Won et al. (2016a)
White matter integrity analyses	*BDNF* rs6265 (Val66Met)	CC (splenium), inferior fronto-occipital fasciculus, optic radiation, superior CR	↑ Val allele ➔ ↓ FA	HC (twin, non-twin sibling)	Chiang et al. (2011)
		CC, posterior CR	Met carrier > Val/Val	HC	Tost et al. (2013)
	COMT rs4680 (Val158Met)	CC (genu)	Met/Val < Val/Val	HC (children, adolescent)	Thomason et al. (2010)
		Anterior thalamic radiation	Met/Met < Val/Val	HC (children, adolescent)	Thomason et al. (2010)

Functional analyses	*BDNF* rs6265 (Val66Met)	Hippocampus	Val/Met > Val/Val, while performing the N-back working memory task	HC	Egan et al. (2003)
		Hippocampus	Met carrier < Val/Val, during memory encoding and retrieval	HC	Hariri et al. (2003)
		Hippocampus, parahippocampal gyrus	↑ Met allele ➔ ↓ activity, during memory encoding	HC (Asian)	Hashimoto et al. (2008)
		Amygdala	Met carrier > Val/Val, in response to emotional stimuli	HC (female)	Montag et al. (2008)
		Fusiform gyrus, hippocampus	Met carrier > Val/Val, in response to oddball target stimuli	HC	Schofield et al. (2009)
		DLPFC	Met carrier < Val/Val, in response to oddball target stimuli	HC	Schofield et al. (2009)
		Amygdala, hippocampus	Met carrier > Val/Val, in response to emotional faces	MDD patient (adolescent)	Lau et al. (2010)
	COMT rs4680 (Val158Met)	Amygdala, DLPFC, fusiform gyrus, hippocampus, inferior parietal lobule thalamus, VLPFC	↑ metallele ➔ ↑ activation, in response to unpleasant stimuli compared with neutral stimuli	HC	Smolka et al. (2005)
		OFC	↑ Val allele ➔ ↑ activation, during house-matching task	HC	Bishop et al. (2006)
		Hippocampus, VLPFC	Met/Met > Met/Val > Val/Val, during perceptual task matching fearful and angry facial expressions	HC	Drabant et al. (2006)
		DLPFC, superior prefrontal gyrus, ventral striatum	Met/Met > Met/Val > Val/Val, during anticipation of uncertain rewards	HC	Dreher et al. (2009)
		OFC	Met/Met > Met/Val > Val/Val, in the reward anticipation phase	HC	Dreher et al. (2009)
		Amygdala, temporal polar region	Met/Met < Val/Val, during fearful affect facial recognition tasks	HC (female)	Kempton et al. (2009)
		Amygdala, temporal polar region	Deactivation of Met/Met > Val/Val, during fearful affect facial recognition tasks	HC (male)	Kempton et al. (2009)
		Precentral gyrus	Deactivation of Met/Met > Val/Val, during fearful affect facial recognition tasks	HC (female)	Kempton et al. (2009)

(continued)

Table 2.1 (continued)

Method	Gene polymorphism	Region	Finding	Subject	References
		Superior occipital gyrus	Deactivation of Met/Met > Val/Val, during fearful affect facial recognition tasks	HC (male)	Kempton et al. (2009)
		Cerebellum, hippocampus, insula	↑ met allele ➔ ↑ activation, during memory encoding task	HC	Krach et al. (2010)
		Parahippocampal gyrus	↑ met allele ➔ ↑ activation, during memory retrieval task	HC	Krach et al. (2010)
		Amygdala	Met/Met > Val carrier, during processing of unpleasant stimuli	HC	Rasch et al. (2010)
		Fusiform gyrus, inferior temporal gyrus, medial frontal gyrus, postcentral gyrus	↑ met allele ➔ ↑ activation, during processing of unpleasant stimuli	HC	Rasch et al. (2010)
		Occipital cortex	↓ met allele ➔ ↑ activation, during processing of unpleasant stimuli	HC	Rasch et al. (2010)
		Insula, middle temporal gyrus, postcentral gyrus, superior temporal gyrus	↑ met allele ➔ ↑ activation, during processing of positive stimuli	HC	Rasch et al. (2010)
		Amygdala, basal ganglia, brainstem, medial prefrontal region	↑ met allele ➔ ↑ activation, for conscious fear during facial emotion perception task	HC	Williams et al. (2010)
		Amygdala	Met/Met < Val/Met < Val/Val, in response to fearful/angry faces	HC	Domschke et al. (2012)
		Fusiform gyrus, inferior temporal gyrus, lateral PFC, occipital area, striatum, thalamus	↑ Val allele ➔ ↑ activation, in response to fearful/angry faces	HC	Domschke et al. (2012)
		Inferior frontal gyrus	↑ met allele ➔ ↑ activation, during emotional processing	HC	Opmeer et al. (2013)

		Amygdala, hippocampus	↑ met allele ➔ ↑ activation, during emotional processing	MDD patient, HC	Opmeer et al. (2013)
		Middle frontal gyrus	↓ met allele ➔ ↑ activation, during working memory task	MDD patient, HC	Opmeer et al. (2013)
	MAOA-uVNTR	ACC	*MAOA*-L < *MAOA*-H, during response inhibition	HC (male)	Meyer-Lindenberg et al. (2006)
		Amygdala	*MAOA*-L > *MAOA*-H, during perceptual matching of angry and fearful faces	HC	Meyer-Lindenberg et al. (2006)
		Amygdala, hippocampus	*MAOA*-L > *MAOA*-H, during retrieval of negatively valenced emotional material	HC (male)	Meyer-Lindenberg et al. (2006)
		Cingulate cortex, insular cortex, OFC	*MAOA*-L < *MAOA*-H, during perceptual matching of angry and fearful faces	HC	Meyer-Lindenberg et al. (2006)
		Amygdala	3R/3R > 3R/4R > 4R/4R, in response to sad versus neutral facial expressions	HC (Asian, female)	Lee and Ham (2008a)
		Hippocampus	3R/3R > 3R/4R > 4R/4R, in response to angry versus neutral facial expressions	HC (Asian, female)	Lee and Ham (2008b)
		Amygdala, ACC	*MAOA*-L > *MAOA*-H, in response to a rude insult	HC (male)	Denson et al. (2014)
	HTR1A rs6295 C(−1019)G	Amygdala	C/C < G carrier, in response to sad, angry, happy, and neutral facial stimuli	MDD patient	Dannlowski et al. (2007)
		Amygdala	C/C > G carrier, during face processing tasks of angry and fearful facial expressions	HC	Fakra et al. (2009)

(continued)

Table 2.1 (continued)

Method	Gene polymorphism	Region	Finding	Subject	References
	5-HTTLPR	Amygdala	l/l < s carrier, in response to fearful stimuli	HC	Hariri et al. (2002)
		Amygdala	Number of s allele predicts amygdala response, during performance of a perceptual task of threatening stimuli	HC	Bertolino et al. (2005)
		Amygdala	l/l < s carrier, in response to negative words relative to neutral words	HC	Canli et al. (2005a)
		Amygdala	l/l < s carrier, during perceptual tasks involving the matching of fearful and angry facial expression	HC	Hariri et al. (2005)
		Amygdala	l/l < s carrier, during the presentation of aversive pictures	HC (male)	Heinz et al. (2005)
		Amygdala	l/l < s carrier, in response to emotional facial stimuli	MDD patient	Dannlowski et al. (2007)
		Amygdala	l/l < s carrier, in response to emotional facial stimuli	MDD patient, HC	Dannlowski et al. (2008)
		Amygdala	l carrier>s/s, in response to angry facial stimuli	HC (Asian, female)	Lee and Ham (2008a)
		Amygdala	l/l < s carrier, in response to sad faces	HC	Dannlowski et al. (2010)
		Amygdala	l/l < s/s, during recovery from sad mood	HC	Gillihan et al. (2010)
		Amygdala	l/l < s carrier, in sad mood state	HC (female, adolescent)	Furman et al. (2011)
		Amygdala	l/l < s carrier, in response to a series of facial expressions of sadness	MDD patient, HC	Costafreda et al. (2013)
	TPH2 rs4570625 (G-703T)	Amygdala	G/G < T carrier, during face processing tasks	HC	Brown et al. (2005)
		Amygdala	G/G < T carrier, in response to fearful/sad/happy relative to neutral faces	HC (female)	Canli et al. (2005b)
		Amygdala	G/G > G/T > T/T, in response to sad facial stimuli	HC (Asian, female)	Lee and Ham (2008b)

BDNF brain-derived neurotrophic factor, *HC* healthy control, *DLPFC* dorsolateral prefrontal cortex, *MDD* major depressive disorder, *ACC* anterior cingulate cortex, *COMT* catechol-O-methyltransferase, *PFC* prefrontal cortex, *OFC* orbitofrontal cortex, *MAOA-uVNTR* monoamine oxidase A upstream variable number of tandem repeats, *5-HTTLPR* serotonin transporter-linked polymorphic region, *DMPFC* dorsomedial prefrontal cortex, *TPH2* tryptophan hydroxylase-2, *CC* corpus callosum, *CR* corona radiata, *VLPFC* ventrolateral prefrontal cortex, *HTR1A* serotonin receptor 1A gene

effect on the amount of available dopamine in the prefrontal cortex, previous studies have focused on COMT and its association with various psychiatric disorders (Seok et al. 2013). A functional SNP of the COMT gene results in a valine to methionine mutation at position 158, *COMT* rs4680 (Val158Met) (Lotta et al. 1995). The Met allele is associated with increased synaptic dopamine, due to Met allele possessing enzymes being only one-third to one-fourth as active as the enzyme containing the Val allele (Lotta et al. 1995). Therefore, individuals with the Met allele have been suggested to show enhanced executive functioning (Egan et al. 2001). However, the Val allele has been reported to have a compensatory advantage in adapting to stressful situations (Zubieta et al. 2003); therefore the Met allele has been associated with an increased risk for MDD development (Ohara et al. 1998).

2.2.3 Monoamine Oxidase A (MAOA) Gene

MAOA degrades monoaminergic neurotransmitters such as norepinephrine, dopamine, and serotonin in the brain (Weyler et al. 1990). An upstream variable number of tandem repeats (uVNTR) polymorphism in the promoter region of the *MAOA* gene consists of a 30-bp repeat sequence present in 2, 3, 3.5, 4, or 5 repeats (R) (Zhang et al. 2010). *MAOA*-uVNTR influences enzymatic activity as the 3.5R or 4R alleles are transcribed two to ten times more efficiently than 3R or 5R alleles (Sabol et al. 1998). Therefore, *MAOA*-uVNTR polymorphism produces genotypes with low activity (2R, 3R, 5R alleles, *MAOA*-L) and high activity (3.5R, 4R, *MAOA*-H) (Williams et al. 2009). Although *MAOA*-H has been implicated in depression in various studies (Yu et al. 2005), others have failed to find this association (Huang et al. 2009; Serretti et al. 2002; Melas et al. 2013).

2.2.4 Serotonin Receptor 1A Gene

Serotonin 1A receptors are located both at a postsynaptic and at a presynaptic level, and mediate the firing of serotonin neurons, and regulate serotonin signaling on cortical and limbic neurons (Blier 2010). Therefore, serotonin 1A receptors are thought to play an important role in the pathogenesis of depressive symptomatology (Serretti et al. 2004). The serotonin 1A receptor gene (*HTR1A*) was mapped on the long arm of chromosome five (5q11.2-13) (Kobilka et al. 1987), and a functional polymorphism in the promoter region of the gene was reported, which consisted of a G to C substitution (Wu and Comings 1999). This C(-1019)G polymorphism was reported to modulate the rate of transcription of *HTR1A*, with the presence of the G allele leading to an increase of serotonin 1A autoreceptors and a reduction of serotonergic neurotransmission (Stahl 1994). C(−1019)G (rs6295) has been associated with numerous psychiatric disorders (Rothe et al. 2004; Strobel et al. 2003), with homozygous G(−1019) genotype being implicated in depression (Lemonde et al. 2003).

2.2.5 Serotonin Transporter Gene

Selective serotonin reuptake inhibitors (SSRIs) primarily target the serotonin transporter, due to the major role of the transporter in the reuptake of serotonin (Blakely et al. 1998). The serotonin transporter gene is located on chromosome 17q11.1–17q12 (Serretti et al. 2007), and one of the polymorphic sites is an insertion/deletion in the 5′-flanking promoter region (serotonin transporter-linked polymorphic region, 5-HTTLPR), which results in a short (s) versus long (l) polymorphism (Michaelovsky et al. 1999). The l and s variants are known to have functional differences in modulating gene transcription and ultimately serotonin reuptake availability (Heils et al. 1996). The l allele has been associated with more efficient transcription (Lesch et al. 1994), whereas the s allele is shown to have a three- to fourfold lower 5-HT uptake function in lymphoblasts due to reduced transcriptional efficiency (Lesch et al. 1996). Although a majority of studies have reported an association between the s/s genotype and MDD (Cervilla et al. 2006; Ramasubbu et al. 2006), a number of studies have

also reported otherwise (Collier et al. 1996; Furlong et al. 1998; Stober et al. 1996).

2.2.6 Tryptophan Hydroxylase-2 Gene

TPH2 is the rate-limiting enzyme in the synthetic pathway for brain serotonin and therefore is considered important in the maintenance of normal serotonin transmission (Torgersen 1986). The human *TPH2* gene spans approximately 100 kb, consists of 11 exons, and is located on chromosome 12q21.1 (Gutknecht et al. 2007). The T allele of the common G to T base substitution G(−703)T (rs4570625) in the promoter region of the *TPH2* gene has been associated with altered *TPH2* mRNA expression which may result in low functional expression of *TPH2*. A previous meta-analysis reported significant evidence for *TPH2* G(−703)T (rs4570625) as a MDD susceptibility SNP (Gao et al. 2012), with the T allele being considered the risk allele.

2.3 Imaging Genetics Studies on Polymorphisms of MDD Susceptibility Genes

2.3.1 Volumetric Analyses of Brain Areas Influenced by MDD Susceptibility Genes

Previous imaging genetics studies have measured brain volume as an intermediate phenotype of neuroanatomical nature in MDD. Although various methods are available to closely measure morphological volumetric changes in the brain, the manual volumetric region-of-interest (ROI) method has evolved into the fully automated, whole-brain VBM method (Ashburner and Friston 2000). VBM is an unbiased whole-brain approach for detecting structural differences in gray matter between different clinical populations and provides a systematic estimate of regional gray matter based on voxel-by-voxel comparison through the whole brain (Jung et al. 2014). Previous volumetric studies on MDD have reported loss of gray matter volumes in the prefrontal cortex (PFC) (Taki et al. 2005; Vasic et al. 2008; Grieve et al. 2013), orbitofrontal cortex (OFC) (Vasic et al. 2008; Grieve et al. 2013), temporal lobe (Shah et al. 1998; Grieve et al. 2013), hippocampus (Vasic et al. 2008; Bergouignan et al. 2009), cingulate gyrus (Vasic et al. 2008), anterior cingulate cortex (ACC) (Tang et al. 2007; Lai 2013), thalamus (Vasic et al. 2008), and insular (Lai and Wu 2014; Stratmann et al. 2014).

Imaging genetics studies have reported changes in volumes of brain areas involved in emotion processing, influenced by MDD susceptibility genes (Won and Ham 2016). For the *BDNF* rs6265 (Val66Met), significantly smaller hippocampal volumes were reported for patients and healthy controls (HCs) carrying the Met allele compared with subjects homozygous for the Val allele (Frodl et al. 2007; Pezawas et al. 2004; Schofield et al. 2009; Montag et al. 2009; Chepenik et al. 2009). Val/Met healthy subjects were also reported to show smaller hippocampus (Szeszko et al. 2005; Matsuo et al. 2009) and dorsolateral prefrontal cortex volumes compared to subjects homozygous for the Val allele (Matsuo et al. 2009). Significantly smaller amygdala volume was reported for Met allele carrier HCs compared to Val allele homozygous subjects (Montag et al. 2009). Val/Met carrier healthy subjects also showed significantly smaller anterior cingulate cortex (ACC) volume compared to Val allele homozygotes (Matsuo et al. 2009).

Val allele homozygous HCs of the *COMT* rs4680 (Val158Met) have been reported to show smaller volumes of the temporal lobe (Taylor et al. 2007) and hippocampus (Taylor et al. 2007; Cerasa et al. 2008b), but larger volumes of the prefrontal cortex, such as the inferior frontal cortex, superior frontal gyrus, and OFC (Cerasa et al. 2008b). Significant decreases in hippocampal volume were also reported in HCs carrying the Val allele compared to Met allele homozygotes (Honea et al. 2009). It was suggested that the number of Met alleles was positively associated with increases in hippocampal (Cerasa et al. 2008b; Ehrlich et al. 2010) and amygdala volumes (Ehrlich et al. 2010) and that the number of

Val alleles predicted an increase of prefrontal cortex volume (Cerasa et al. 2008b). However, opposite results were reported, with the Val allele being linked to larger hippocampal volume in healthy Chinese subjects, which has been suggested to be due to ethnic differences in genetic effects (Wang et al. 2013).

MAOA-L healthy individuals of the *MAOA*-uVNTR have been reported to show volume reductions in the amygdala, hypothalamus, insula, and cingulate gyrus, with prominent reductions in the ACC (Meyer-Lindenberg et al. 2006). In the same study, a sex-specific increase in OFC volume in *MAOA*-L males compared to *MAOA*-H males was also reported, whereas no genotype-associated structural changes were detected in females.(Meyer-Lindenberg et al. 2006) An increase in OFC volume in *MAOA*-L healthy male individuals was replicated in a following study (Cerasa et al. 2008a).

Healthy s allele carriers of the 5-HTTLPR were shown to have increased volume in the cerebellum, and l allele homozygotes were shown to have increased volume in the superior and medial frontal gyri, inferior frontal gyrus, and anterior cingulate (Canli et al. 2005b). Whereas l allele homozygous patients with MDD showed significantly decreased hippocampal volume compared to s allele homozygous patients, s allele homozygosity was associated with decreased hippocampal volume in HCs (Frodl et al. 2008). Homozygous l allele carrier healthy subjects also had significantly larger volumes in the amygdala, ACC, DLPFC, and dorsomedial prefrontal cortex (DMPFC) compared to homozygous s allele carriers (Frodl et al. 2008). Also, reduced gray matter volume was observed in the ACC and the amygdala, in healthy subjects carrying the s allele (Pezawas et al. 2005). Patients with MDD carrying the s allele along with a history of emotional neglect were reported to have decreased hippocampal volume, compared to patients who possessed one risk factor, either being environmental or genetic (Frodl et al. 2010). In HCs, the negative impact of life events on hippocampal volume was reported to be increased in s allele carriers (Rabl et al. 2014). The 5-HTTLPR genotype was also reported to significantly interact with gender in predicting larger hippocampal volumes in s allele carrying females and smaller hippocampal volumes in s allele carrying males (Price et al. 2013). Regarding risk for MDD onset in adolescents, increasing copies of s alleles predicted smaller hippocampal and orbitofrontal cortex volumes, but only smaller hippocampal volume predicted increased risk for depression onset during adolescence (Little et al. 2014).

Healthy T allele carriers of the *TPH2* G(-703) T (rs4570625) showed reduced amygdala and hippocampal volumes compared to homozygous G allele carriers (Inoue et al. 2010). Healthy Asian females homozygous for the G allele showed reduced OFC volume relative to T allele carriers (Yoon et al. 2012).

2.3.2 Cortical Thickness Analyses of Brain Areas Influenced by MDD Susceptibility Genes

Cortical thickness refers to the GM of the cortex, and a decrease in neurons and synapses may be responsible for the reduction in GM (Fjell and Walhovd 2010), which may lead to the decline in function of the thinned areas. Cortical thinning has also been reported to be involved with disturbances in arousal, attention, and memory for social stimuli, which in turn may increase the risk of developing depressive illness (Hilgetag and Barbas 2006), and has been assumed to reflect neurodevelopmental mechanisms. Whereas it has been suggested that measurement of cerebral volume may give insufficient information about the dimensions of structure, measurement of cortical thickness enables a continuous measurement across the cortical surface (Scott et al. 2009) and might be more sensitive to detect structural abnormalities (Wagner et al. 2012). It has also been suggested that cortical thickness measurements should be preferred over GM volume for imaging genetics studies (Winkler et al. 2010). FreeSurfer has been reported previously to be a highly reliable method for automated cortical thickness measurement (Han et al. 2006) and therefore may be a useful tool for the investigation of longitudinal brain development and pathophysiological

brain changes. Recent analyses of cortical thickness in MDD patients have reported reduced cortical thickness in areas such as ACC, posterior cingulate cortex (PCC), OFC, DLPFC, and temporal cortex (Lim et al. 2012; Tu et al. 2012; Grieve et al. 2013).

Fewer imaging genetics studies have been conducted on cortical thickness compared to brain volume. In a study conducted on children and adolescents, the Met allele of the *COMT* rs4680 (Val158Met) was associated with a linear increase in cortical thickness in the inferior frontal gyrus and temporal gyrus (Shaw et al. 2009). Cerasa et al. reported healthy individuals carrying the Met allele to have a thicker cortex in the superior temporal sulcus and inferior prefrontal sulcus compared to Val allele homozygotes and suggested that higher synaptic dopamine levels associated with the presence of the Met allele may influence neuronal architecture in brain structures important for executive and emotional processing. For the *MAOA*-uVNTR, an increase in OFC thickness in *MAOA*-H healthy male subjects was reported (Cerasa et al. 2010). However, negative results on the association between decreased OFC thickness in patients with depression and *MAOA*-uVNTR have also recently been reported (Won et al. 2016b).

2.3.3 Analyses on the Integrity of White Matter Regions Influenced by MDD Susceptibility Genes

Neuroimaging studies on depression have consistently identified neuroanatomical abnormalities in gray matter (GM) regions that participate in affect regulation (Konarski et al. 2008). Given that WM tracts connect various GM areas of the brain, many studies have also investigated possible abnormalities in WM architecture and integrity in patients with MDD. Novel techniques using DTI and tract-based spatial statistics (TBSS) have made it possible to detect such abnormalities in a more sensitive and accurate manner (Choi et al. 2014). DTI measures microscopic movements of water in axon fibers and expresses the character of the axon fiber using FA and other diffusivity values. The FA index is the most widely used parameter of DTI, because it is sensitive to the presence and integrity of WM fibers (Roberts et al. 2013). Previous DTI studies have found strong correlations between depression and impaired integrity of WM tracts that contribute to emotional regulation (Kieseppa et al. 2010), such as the superior longitudinal fasciculus, corpus callosum (CC), uncinate fasciculus, internal and external capsule, cingulum, and anterior corona radiata (Murphy and Frodl 2011).

Compared to imaging genetics studies on the influence of MDD susceptibility genes on GM structure, fewer studies have been conducted on white matter integrity. For the *BDNF* rs6265 (Val66Met), the Val allele was associated with reduced FA values of the splenium of the CC, left optic radiation, inferior fronto-occipital fasciculus, and superior corona radiata in healthy adult twins and their non-twin siblings (Chiang et al. 2011). Tost et al. reported Val allele homozygous HCs to have lower FA values compared with Met allele carriers in white matter tracts such as the CC and the posterior corona radiate (Tost et al. 2013). For the COMT rs4680 Val158Met, Met/Val heterozygotes had significantly lower FA values of the genu of the CC, compared to Val allele homozygotes in healthy children and adolescents (Thomason et al. 2010). In the same group, Val allele homozygotes had significantly higher FA values of the anterior thalamic radiation compared to Met-allele homozygotes.

2.3.4 Functional Analyses of Brain Areas Influenced by MDD Susceptibility Genes

FMRI is a functional neuroimaging procedure that measures brain activity by detecting changes associated with blood flow (Huettel et al. 2005), as cerebral blood flow and neuronal activation are coupled. It was suggested that fMRI has a unique potential in studying psychiatric patients, particularly in characterizing individual variations (Weinberger et al. 1996). The first fMRI-based imaging genetics study was on the association

between the apolipoprotein E (APOE) gene and risk for Alzheimer's disease (Bookheimer et al. 2000). Thereafter, numerous fMRI-based imaging genetics studies were performed on psychiatric disorders including depression.

Egan et al. reported healthy Val/Met heterozygotes of the BDNF rs6265 (Val66Met) to show abnormal patterns of increased hippocampal activation compared to baseline while performing the N-back working memory task, when Val/Val subjects showed deactivation (Egan et al. 2003). Hariri et al. reported memory-related hippocampal activity to be greater, during both encoding and retrieval, in subjects homozygous for the Val allele (Hariri et al. 2003). Hashimoto et al. reported inverse correlations between the dose of Met allele and hippocampal and parahippocampal gyrus activity during memory encoding, in Asian HCs (Hashimoto et al. 2008). Montag et al. reported Met allele carriers to show stronger amygdala activation in response to emotional stimuli compared to neutral stimuli, in healthy female subjects (Montag et al. 2008). Schofield et al. reported enhanced fusiform gyrus and hippocampal activity in Met allele carrier HCs compared to Val allele homozygotes in response to oddball target stimuli. However, Met allele carriers showed reduced activity in the dorsolateral prefrontal cortex (Schofield et al. 2009). Lau et al. reported Met carriers to show greater amygdala and anterior hippocampal region responses to emotional faces than Val/Val homozygotes in MDD adolescent patients only compared to HCs (Lau et al. 2010).

Reactivity to unpleasant stimuli compared with neutral stimuli was positively correlated with the number of Met alleles of the *COMT* rs4680 (Val158Met), in the hippocampus, amygdala, thalamus, ventrolateral prefrontal cortex, dorsolateral prefrontal cortex, fusiform gyrus, and inferior parietal lobule of HCs. However, *COMT* rs4680 (Val158Met) had no significant impact on brain activation by pleasant stimuli in the same subjects (Smolka et al. 2005). Bishop et al. reported Val allele load to positively correlate with OFC activity in HCs, during a house-matching task with affectively negative versus neutral distractors (Bishop et al. 2006). Also, Met allele homozygous HCs showed greater hippocampal formation and ventrolateral prefrontal cortex activity compared to Val allele homozygotes, with Val/Met heterozygotes exhibiting an intermediate response (Drabant et al. 2006) while completing a simple perceptual task which involved matching fearful and angry facial expressions. Dreher et al. reported Met/Met HCs to have increased activation of the ventral striatum, dorsolateral PFC, and superior prefrontal gyrus compared to Val/Val carriers, with heterozygous individuals presenting an intermediate response during anticipation of uncertain rewards. In the reward anticipation phase, Met/Met carrier individuals showed increased OFC activation compared to Val homozygous individuals, with heterozygous subjects presenting an intermediate response (Dreher et al. 2009). A gene dose effect in HCs was replicated in a subsequent study, with a linear increase in activation of the cerebellum, hippocampus, and insula as the number of Met alleles increased, during memory encoding tasks. In the same subjects, posterior parahippocampal gyrus activation increased as the number of Met alleles increased, during memory retrieval tasks (Krach et al. 2010). Williams et al. also reported a greater number of Met alleles predicted increased activation in brainstem, amygdala, basal ganglia, and medial prefrontal regions for conscious fear during facial emotion perception tasks, but reduced activation regarding conscious happiness (Williams et al. 2010). Kempton et al. reported *COMT* rs4680 (Val158Met) to have impact on gender-related patterns of activation in limbic and paralimbic regions, as female Val/Val homozygotes showed increased amygdala and temporal polar region activation compared to female Met/Met homozygotes during fearful affect facial recognition tasks. In contrast, males showed deactivation in both these regions, with Met/Met carriers showing greater deactivation than Val/Val carriers. The superior occipital gyrus revealed females showing little change from baseline and male Met/Met carriers showing greater deactivation than male Val/Val carriers. In the precentral gyrus, deactivation was observed in females, while males showed little change from baseline

(Kempton et al. 2009). Rasch et al. reported higher activation of the amygdala of Met/Met homozygous HCs during processing of unpleasant stimuli, compared to Val/Val homozygotes and Val/Met heterozygotes. Also, activations of the fusiform gyrus, postcentral gyrus, medial frontal gyrus, and inferior temporal gyrus were positively related to the number of Met alleles. However, activity of the occipital cortex was negatively associated with the number of Met alleles. For pleasant pictures, positive associations with the number of Met alleles in the postcentral gyrus, middle temporal gyrus, insula, and superior temporal gyrus were observed (Rasch et al. 2010). Domschke et al. reported an allele dose effect in response to fearful/angry faces in HCs, as Val/Val carriers showed greater amygdala responsiveness compared to carriers of one or two Met alleles and Met/Met carriers showed less amygdala responsiveness compared to carriers of one or two Val alleles. Also activations of the inferior temporal gyrus, fusiform gyrus, lateral prefrontal cortex, occipital area, thalamus, and striatum were positively associated with the Val allele (Domschke et al. 2012). Opmeer et al. conducted a study on MDD patients and HCs, which reported positive correlations only in HCs, between the Met allele and activity of the inferior frontal gyrus during the processing of emotion. Also, negative correlations between the Met allele and activity of the middle frontal gyrus were observed in patients and controls as a whole, during working memory tasks. In addition, positive correlations between the Met allele and amygdala and hippocampus activity were observed during the processing of emotion in the same individuals (Opmeer et al. 2013).

MAOA-L healthy individuals were reported to show increased activity in the amygdala but decreased response of the cingulate cortex, insular cortex, and OFC during the matching of emotional faces (Meyer-Lindenberg et al. 2006). For brain activation during emotional memory, *MAOA*-L male healthy individuals showed increased reactivity of the amygdala and hippocampus during retrieval of negatively valenced emotional material. The same individuals also showed deficient activation of the dorsal anterior cingulate during response inhibition (Meyer-Lindenberg et al. 2006). In healthy Asian female individuals, a linear trend was shown for hippocampal activation in response to angry versus neutral facial expressions, with greater activation in participants with 3R/3R compared to subjects with 3R/4R and 4R/4R. The same group also showed a linear trend in amygdala activation, with greatest activation in participants with the 3R/3R genotype and the lowest activation in participants with the 4R/4R genotype, in response to sad versus neutral facial expressions (Lee and Ham 2008a). A recent study reported *MAOA*-L male healthy subjects to show increases in activity of the dorsal ACC and amygdala in response to an insult by a rude experimenter, while the *MAOA*-H group did not (Denson et al. 2014).

For the C(-1019)G (rs6295), MDD patients carrying the G allele showed an increase in amygdala activation in response to facial stimuli that consisted of sad, angry, happy, and neutral expressions, compared with C allele homozygous MDD patients (Dannlowski et al. 2007). In a study including healthy individuals, C/C genotype carriers showed increased threat-related amygdala activation compared to G allele carriers, during face processing tasks of angry and fearful facial expressions (Fakra et al. 2009).

Healthy individuals with one or two copies of the s allele of the 5-HTTLPR were reported to exhibit greater amygdala neuronal activity, in response to fearful stimuli compared to individuals homozygous for the l allele (Hariri et al. 2002). Bertolino et al. reported that the number of s alleles predicted amygdala response during performance of perceptual tasks of threatening stimuli (Bertolino et al. 2005). Canli et al. reported 5-HTTLPR to be linked to the differential activation toward positive/negative/neutral stimuli, with significantly greater activation of the amygdala in s allele carriers compared to l allele homozygotes, in response to negative words relative to neutral words (Canli et al. 2005b). Amygdala activity was reported to be significantly greater in healthy s allele carriers in comparison with l allele homozygotes during perceptual tasks involving the matching of fearful and angry facial expressions (Hariri et al. 2005). During the presentation of

aversive, but not pleasant pictures, healthy male s allele carriers showed stronger activation of the amygdala (Heinz et al. 2005). In patients with major depression, s allele carriers showed increased amygdala activity elicited by facial stimuli that consisted of sad, angry, happy, and neutral expressions, compared with l allele carriers (Dannlowski et al. 2007). A subsequent study was carried out on MDD patients and HCs, with results showing MDD patients carrying the s allele to have increased amygdala activity to facial stimuli, and this was also the case when MDD patients were grouped together with HCs (Dannlowski et al. 2008). A study conducted on healthy Asian females reported opposite results from a majority of studies conducted on Caucasian populations, with increased activations in response to angry facial stimuli in the amygdala of subjects with the l allele compared with those who were homozygous for the s allele (Lee and Ham 2008b). The authors suggested a regulatory function of genetic background in the association between 5-HTTLPR and amygdala activity elicited by negative emotional stimuli was suggested. Dannlowski et al. suggested 5-HTTLPR genotype to impact the central processing predominantly of negative environmental cues but not of emotionally salient stimuli in a study conducted on HCs, as s allele carriers showed similar amygdala responses to happy faces compared to homozygous l allele carriers, but increased amygdala responses to sad faces (Dannlowski et al. 2010). One of the mechanisms by which the s allele confers depression risk was then suggested as the hyperactivity of the amygdala during recovery from a sad mood, due to results showing homozygous s allele carrier HCs to have greater amygdala activity compared to homozygous l allele carriers, during the mood recovery stage but not during the induced sad mood stage (Gillihan et al. 2010). In a study conducted on healthy adolescent females, it was suggested that s allele carriers possess a neural "readiness" to engage in negative affect, as participants with at least one copy of the s allele showed stronger and earlier activation in the amygdala as a sad mood state was increased (Gillihan et al. 2010). Costafreda et al. recently conducted a study on MDD patients and HCs and reported s allele carriers to have a greater increase of amygdala reactivity in response to a series of facial expressions of sadness; however, no significant interaction effects of genotype and diagnosis were revealed (Costafreda et al. 2013).

T allele carriers of the *TPH2* G(-703)T (rs4570625) showed greater activity of the amygdala in comparison with G allele homozygotes during face processing tasks (Brown et al. 2005). Canli et al. reported T allele carriers to show greater amygdala activation in response to fearful and sad, relative to neutral faces, with activation not limited to emotional expressions of negative valence, as the presence of the T allele was also associated with increased amygdala responsiveness to happy relative to neutral faces (Canli et al. 2005a). A study conducted on Asian female healthy subjects reported amygdala activation toward sad facial stimuli, with G/G genotype individuals showing the most intense response and the T/T genotype individuals showing the least intense response to the same stimuli; hence moderating effects of genetic background was again suggested (Lee and Ham 2008b).

Conclusion

Currently available imaging genetics studies on MDD susceptibility gene polymorphisms support the notion that genetic variations influence GM structure, WM integrity, and functional metabolic activity of the brain. The Met allele of *BDNF* rs6265 (Val66Met) has been associated with decreased volume of brain areas such as the amygdala, ACC, DLPFC, and hippocampus. Results on the effect of COMT rs4680 (Val158Met) on brain volume have not been consistent and appear to differ depending on the brain area; however, the Val allele seems to be associated with decreased hippocampal volume, with evidence existing on ethnic differences in genetic effects. The s allele of the 5-HTTLPR seems to be associated with decreased volume of the amygdala and ACC; however, its effect on hippocampal volume is still controversial. For cortical thickness, the Met allele of COMT rs4680 (Val158Met) has been linked to increased thickness of various

brain areas, but only a few imaging genetics studies on MDD susceptibility genes that have measured cortical thickness exist. The Val allele of *BDNF* rs6265 (Val66Met) has been linked to decreased integrity of various WM regions, the CC in particular. FMRI studies on BDNF rs6265 (Val66Met) have reported inconsistent results; however, the Met allele seems to be associated with decreased hippocampal activation during memory-related tasks and increased amygdala activation in response to emotional stimuli. A gene dose effect has repeatedly been reported for the Met allele of the *COMT* rs4680 (Val158Met), with activation of various brain regions to be enhanced with the number of Met alleles. Although conflicting results exist on the effect of *MAOA*-uVNTR, *MAOA*-L seems to be associated with increased activation of the hippocampus and amygdala in response to emotional stimuli. The s allele of 5-HTTLPR has constantly been associated with increased activation of the amygdala in response to negative emotional stimuli, with ethnicity suggested to moderate the relationship between 5-HTTLPR and amygdala function. The T allele of *TPH2* G(-703)T (rs4570625) has been associated with increased activation of the amygdala, with moderating effects of genetic background again being suggested.

Imaging genetics has evolved to a frequently employed strategy that has advanced our understanding of how genes shape behavior (Bigos and Weinberger 2010); however, certain limitations exist. Although candidate gene studies provide valuable insights into pathogenetic pathways, genome-wide association (GWA) studies provide little support for traditional candidate gene approaches (Bosker et al. 2011). Also, although neuroimaging techniques have offered valuable insights into brain regions of interest (Phelps and LeDoux 2005), simple changes in regional brain structure and activity are not sufficient to reveal the complex mechanism underlying depression (Krishnan and Nestler 2008). Therefore, a holistic approach that integrates a GWA method that provides a means to explore the genome for causative factors (Psychiatric et al. 2009) and advanced multimodal neuroimaging methods that investigate in depth the related brain pathways will aid our comprehension of the etiology of depression.

Recently, GWA methods have been conducted on various psychiatric disorders, and imaging genetics studies have begun to adopt GWA methods as well (Scharinger et al. 2010). For instance, an intergenic SNP (rs7294919) involved in tescalcin (TESC) gene regulation has been associated with hippocampal volume in two large genome-wide association studies (Dannlowski et al. 2015). The SNP of the neutral amino acid transporter gene (SLC6A15), rs1545843 has been linked to an increased risk for MDD in a GWA study, with a genotype by diagnosis interactive effect on the volume of the hippocampus (Kohli et al. 2011). Also, the use of multimodal imaging is currently being recommended in investigating brain circuities involved in psychiatric disorders (Bigos and Weinberger 2010). An example is a study which combined positron emission tomography (PET) with fMRI to determine the contribution of serotonin 1A autoreceptors to amygdala reactivity, which reported serotonin 1A autoreceptor density to predict 30–44% of the variability in amygdala reactivity (Fisher et al. 2006). The authors suggested that decreased capacity for negative feedback regulation of serotonin release may be linked to increased reactivity of the amygdala.

The other important factor to consider in depression is the interaction between gene and the environment. Epigenetic regulation is currently considered to have an essential role in which gene-environment interactions contribute to MDD (Boulle et al. 2012). Imaging genetics studies on the relationship between DNA methylation status and GM and WM alterations are accumulating. Dannlowski et al. reported a positive association between serotonin transporter gene promoter DNA methylation rates and hippocampus, amygdala, insula, and caudate nucleus volumes

(Dannlowski et al. 2014). Nikolova et al. reported that increased serotonin transporter gene promoter methylation predicted increased threat-related amygdala reactivity (Nikolova et al. 2014). Ziegler et al. reported decreased oxytocin receptor gene (OXTR) methylation to be associated with increased amygdala responsiveness during social phobia-related word processing (Ziegler et al. 2015). Na et al. included MDD patients and HCs in their study, reporting a positive correlation between the methylation of the glucocorticoid receptor gene (NR3C1) promoter and subfield volumes of the hippocampus in both groups (Na et al. 2014). Choi et al. reported a significant inverse correlation between BDNF promoter methylation and FA of the anterior corona radiata in MDD patients (Choi et al. 2014). Won et al. reported an association between reduced white matter integrity in the corpus callosum and the serotonin transporter gene DNA methylation in medication-naïve patients with MDD (Won et al. 2016a).

Imaging genetics studies provide an opportunity to identify neural pathways that mediate the vulnerability to the disorder and identify genes that contribute to changes in relevant brain regions (Bigos and Weinberger 2010). If the current shortcomings of imaging genetics studies are compensated accordingly, the future of imaging genetics holds great promise for research on psychiatric disorders, such as depression.

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Gene-Environment Interactions and Role of Epigenetics in Depression

3

Eugene Lin and Shih-Jen Tsai

3.1 Introduction

Depression, one of the most prevalent and complicated mental illnesses worldwide, is envisioned to be the second prominent cause of disability by 2030 (Mathers and Loncar 2006; Lin and Chen 2008). Present approaches such as gene-environment (G × E) interactions and epigenetics have been utilized to weigh the involvement of genes to pathogenesis of depression in clinical applications of genomic association studies. Consequently, accumulating evidence indicates that patients with depression clearly reflected an interplay between environmental factors and applicable genes when compared with healthy controls (Lopizzo et al. 2015; Lin and Tsai 2016a). Even though further discoveries in support of this hypothesis are warranted, a mammoth amount of probable biomarkers in G × E interactions and epigenetics have been discovered to be associated with depression. In this chapter, we briefly looked over a variety of existing research studies with consideration of G × E interactions and epigenetics in assessing and understanding depression pathogenesis.

First, we reviewed the candidate genes that were pinpointed as potential biomarkers and were associated with depression in the G × E interactions studies. Furthermore, we assessed some probable genes that were investigated in epigenetic studies and were discovered to be associated with depression. Finally, we showed the limitations and future perspectives with respect to the studies in G × E interactions and epigenetics. In future work, replication studies with extensive and independent cohorts will be warranted to verify the role of the potential biomarkers addressed in the previous studies in terms of G × E interactions and epigenetics for depression (Lin 2012; Lin and Tsai 2012).

3.2 Environmental and Genetic Factors and G × E Interactions on Depression

3.2.1 Environmental Factors on Depression

Environmental risk factors for depression encompass stress, early adverse childhood experiences (including child maltreatment, neglect, emotional abuse, physical abuse, and sexual abuse), and stressful life events (including perinatal condi-

E. Lin
Institute of Biomedical Sciences, China Medical University, Taichung, Taiwan

Vita Genomics, Inc., Taipei, Taiwan

TickleFish Systems Corporation, Seattle, WA, USA

S.-J. Tsai (✉)
Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

Division of Psychiatry, National Yang-Ming University, Taipei, Taiwan
e-mail: tsai610913@gmail.com

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tions, family and marriage conflicts, legal and crime matters, disrupted interpersonal relationships, loss events, financial difficulties, job problems, and events related to adverse physical health) (Yen et al. 2005; Riordan et al. 2006; Joiner et al. 2007; Shapero et al. 2014).

3.2.2 Genetic Factors on Depression

It has long been noted that more and more risk loci for depression have been identified (Flint and Kendler 2014). However, it is difficult to replicate the findings tracked down by multiple research groups (Bosker et al. 2011). To resolve conflicting results, it is usually attempted by leveraging meta-analysis studies (Flint and Kendler 2014). A meta-analysis study based on candidate gene data indicated that there were seven significant genes in depression including the apolipoprotein E (*APOE*), dopamine receptor D4 (*DRD4*), G protein subunit beta 3 (*GNB3*), 5-hydroxytryptamine receptor 1A (*HTR1A*), methylenetetrahydrofolate reductase (*MTHFR*), solute carrier family 6 member 3 (*SLC6A3*), and solute carrier family 6 member 4 (*SLC6A4*; serotonin neurotransmitter transporter) genes (Flint and Kendler 2014).

Genetic association studies have pointed out that genes may contribute to suicidal risk. Up to the present time, most of the genetic and clinical association studies targeted the serotonergic pathway as the foundation of elected biological correlates of suicidal risk; and therefore, the probable genes were mainly relevant to the serotonergic system (Bondy et al. 2006). Furthermore, the genetic contributions of additive factors are predicted to be 30–50% for suicidal risk including plans, ideation, and attempts (Voracek and Loibl 2007). It has been suggested that numerous candidate genes such as the serotonin neurotransmitter transporter, tryptophan hydroxylase 1 (*TPH1*), tryptophan hydroxylase 2 (*TPH2*), and brain-derived neurotrophic factor (*BDNF*) genes were linked to suicidal risk, but not all studies supported these discoveries (Brezo et al. 2008; Bondy et al. 2006; Tsai et al. 2011). In addition, twin and family studies reported a greater concordance rate for suicidal risk in monozygotic than dizygotic twins (24.1% vs. 2.8%) and approximately fivefold higher relative suicidal risk in the relatives of patients who died of suicidal acts, even after adjustment for psychiatric disorders (Baldessarini and Hennen 2004; Voracek and Loibl 2007). Finally, evidence from various study designs (including adoption concerns, family matters, geographical factors, immigrant issues, surname problems, and twin studies of suicide) points to genetic contributions to suicidal behavior suicide risk (Baldessarini and Hennen 2004; Voracek and Loibl 2007).

3.2.3 G × E Interactions on Depression

Here we targeted several association studies that assessed both single-locus effects and multilocus interactions to verify the hypothesis that the proposed candidate genes could contribute to depression and suicidal behaviors individually and via complicated G × E interactions. This review is not intended as a comprehensive survey of all possible reports studied in the literature.

3.2.3.1 Serotonin Transporter Gene-Linked Polymorphic Region (5-HTTLPR)

The 5-HTTLPR variant in the *SLC6A4* (serotonin neurotransmitter transporter) gene is commonly reported with short and long alleles, and the short allele is associated with lower *SLC6A4* gene expression activity (Gibb et al. 2006; Lin and Tsai 2016b). The short allele in 5-HTTLPR has 14 repeats of a sequence, while the long allele has 16 repeats.

The report by Caspi et al. (2003) was the first to assess G × E interactions between stressful life events and the 5-HTTLPR variant in the *SLC6A4* gene. Caspi et al. (2003) conducted a prospective longitudinal study of 1037 Dunedin children who were evaluated at regular intervals about their stressful life events occurring from the age of 21 to 26 years. Caspi et al. (2003) pinpointed a compelling G × E interaction between the 5-HTTLPR variant and stressful life events to predict suicide

ideation or suicide attempts among individuals carrying one or both short alleles of 5-HTTLPR. Their analysis also indicated that individuals with a short allele who had stressful life events between 21 and 26 years of age showed an increase in depressive symptoms, while individuals with long/long homozygotes did not.

Furthermore, Roy et al. (2007) examined both the 5-HTTLPR variant alone and G × E interactions to verify the hypothesis that the 5-HTTLPR variant may contribute to suicidal behaviors individually and via complicated interactions with childhood trauma among substance-dependent patients. The sample population consisted of 306 male African-American patients with substance dependence and 132 male African-American controls. In their study, patients completed the 34-item Childhood Trauma Questionnaire (CTQ) which generates scores based on childhood physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. Roy et al. (2007) found G × E interactions between the 5-HTTLPR variant and childhood trauma toward the arousing tendency of suicidal behaviors for individuals with a low-expressing 5-HTTLPR genotype, but not for individuals with intermediate-expressing and high-expressing genotypes. However, no substantial difference was found between patients with suicidal risk and controls for the distribution of 5-HTTLPR genotypes.

In addition, Cicchetti et al. (2010) examined G × E interactions between the 5-HTTLPR variant and environmental factors (maltreatment vs. non-maltreatment) in suicidal risk with preadolescent maltreated and non-maltreated children. In their study, maltreatment was examined by combining the number of various subtypes of maltreatment (such as emotional maltreatment, neglect, physical abuse, and sexual abuse) each child had experienced. Cicchetti et al. (2010) reported evidence for G × E interactions between the 5-HTTLPR variant and the number of various subtypes of maltreatment such that children with short/short or short/long genotypes in the 5-HTTLPR variant expressed greater suicidal risk than those with a long/long genotype among children who experienced one or two forms of maltreatment. However, children who experienced three to four forms of maltreatment had greater levels of suicidal risk, regardless of different genotypes in the 5-HTTLPR variant.

3.2.3.2 Neurotrophic Tyrosine Kinase Receptor 2 (*NTRK2*)

The *NTRK2* gene, a receptor for the *BDNF* gene, has been implicated in major depressive disorder, geriatric depression, and cognitive function (Lin et al. 2009). In an Ireland population, Murphy et al. (2011) investigated both single-locus effects and G × E interactions to verify the hypothesis that 18 candidate genes might be linked to the risk of suicide attempts individually and via complicated gene-gene and G × E interactions among 159 psychiatric patients. Murphy et al. (2011) genotyped 28 single nucleotide polymorphisms (SNPs) in the 5-hydroxytryptamine receptor 1B (*HTR1B*), *BDNF*, solute carrier family 1 member 2 (*SLC1A2*), solute carrier family 1 member 3 (*SLC1A3*), *NTRK2*, and 13 other candidate genes. In their analysis, Murphy et al. (2011) identified a putative G × E interaction ($P = 0.056$ for the complete sample; $P = 0.054$ for females only) between the rs1659400 SNP in the *NTRK2* gene and history of childhood abuse in influencing the risk of subsequent suicidal acts. However, the *NTRK2* rs1659400 SNP was not associated with suicide attempts in single-marker-based analysis. They also revealed that there were significant associations between three SNPs (such as the *SLC1A2* rs4755404, *SLC1A3* rs2269272, and *HTR1B* rs6296 SNPs) and suicide attempts in single-marker-based analysis. In addition, by using the logistic regression model, they reported a significant 3-locus gene-gene interaction involving the *SLC1A2* rs4755404, *HTR1B* rs6296, and *NTRK2* rs1659400 SNPs.

3.2.3.3 Hypothalamic-Pituitary-Adrenal (HPA) Axis Regulatory Genes

The HPA axis regulatory genes including the corticotropin-releasing hormone (*CRH*), corticotropin-releasing hormone-binding protein (*CRHBP*), corticotropin-releasing hormone receptor 1 (*CRHR1*), corticotropin-releasing

hormone receptor 2 (*CRHR2*), and FK506-binding protein 5 (*FKBP5*) genes have received much attention in the studies of G × E interactions in depression and suicidal behaviors.

Appel et al. (2011) reported a significant G × E interaction between the *FKBP5* rs1360780 SNP and physical abuse on depression development in a German sample. Likewise, Zimmermann et al. (2011) confirmed that G × E interactions between the *FKBP5* rs1360780 SNP and traumatic life events predicted the onset of major depression in a UK study. Similarly, a recent study by Kohrt et al. (2015) found that G × E interactions between the *FKBP5* rs9296158 SNP and childhood maltreatment influenced depressive symptoms among adults in a South Asia population. The protein encoded by the *FKBP5* gene might play a key role in immunoregulation, and SNPs in the *FKBP5* gene have been linked to depression (Szczepankiewicz et al. 2014).

An African-American study by Roy et al. (2010) examined both single-locus effects and G × E interactions to verify the hypothesis that the *FKBP5* gene, an HPA axis regulatory gene, might be associated with the etiology of suicide risk individually and via complicated G × E interactions with the impact of childhood trauma. In their study, single-locus analysis showed considerable effects of the *FKBP5* rs3777747, rs4713902, and rs9470080 SNPs with suicidal risk among the analyzed 16 SNPs. Further, G × E interactions involving the *FKBP5* gene (including the rs3800373, rs9296158, and rs1360780 SNPs) and childhood trauma on suicide attempt were suggested using the CTQ score. In addition, the haplotype block including the rs3800373, rs9296158, rs1360780, and rs9470080 SNPs of the *FKBP5* gene was found to be strongly associated with suicidal risk only in persons who experienced high levels of childhood trauma. Their results indicated that the *FKBP5* gene was linked to suicidal risk individually and interactively with childhood trauma.

Moreover, in a cohort of a family-based design of offspring who attempted suicide and both parents, Ben-Efraim et al. (2011) investigated whether there are G × E interactions between the *CRHR1* gene and stressful life events in influencing suicidal behaviors. They assessed the impacts of combinations between the *CRHR1* gene and stressful life events by using sex differences. Ben-Efraim et al. (2011) observed three G × E interactions for three subsets of distinct male patients, whereas one G × E interaction was associated with female patients only. For both male and female patients with suicide attempts, there were significant G × E interactions involving the *CRHR1* rs7209436 SNP and childhood/adolescence physical assault or attack. Additionally, there was a significant G × E interaction between the *CRHR1* rs16940665 SNP and adulthood physical assault or attack for male patients with suicide attempts only. Furthermore, G × E interactions involving the *CRHR1* rs4792887 SNP and cumulative stressful life events were suggested to confirm the previous findings in male patients with suicide attempts.

Further, a study by Roy et al. (2012) examined both single-locus effects and G × E interactions to verify the hypothesis that the HPA axis regulatory candidate genes may contribute to suicidal behaviors individually and via complicated interactions among African-Americans. Roy et al. (2012) administered the CTQ for a total of 474 participants (including 112 suicide attempters and 362 controls) and genotyped five candidate genes including the *CRHBP*, *CRH*, *CRHR1*, *CRHR2*, and *FKBP5* genes. By using the continuous CTQ score, they reported a potential G × E interaction involving three SNPs (including the rs6453267, rs7728378, and rs10474485 SNPs) in the *CRHBP* gene and childhood trauma to predict suicide attempts. In their study, single-locus analysis demonstrated significant single-locus effects of the *CRHBP* rs6453267 SNP and *CRHR1* rs9900679 SNP on the risk of suicidal behaviors. Further, there was a probable gene-gene interaction between the rs3800373 SNP in the *FKBP5* gene and the rs7728378 SNP in the *CRHBP* gene, indicating an additive effect between the *FKBP5* and *CRHBP* genes.

3.2.3.4 Serotonin 2A Receptor (*HTR2A*)

One of the serotonin receptors is encoded by the *HTR2A* gene, which has been suggested as a biomarker for antidepressant treatment and psychi-

atric illnesses including major depressive disorders, anxiety disorders, obsessive-compulsive disorders, attention deficit hyperactivity disorders, eating disorders, schizophrenia, and Alzheimer's disease (Lin and Chen 2008; Lane et al. 2012).

In a family-based study design of 660 offspring who have made a suicide attempt and both parents, Ben-Efraim et al. (2013) aimed to explore both single-locus effects and G × E interactions to verify the hypothesis that the *HTR2A* gene might be associated with the etiology of suicide attempts individually and via complicated interactions. Their data demonstrated significant single-locus effects of the *HTR2A* rs6310 and rs6305 SNPs on the risk of suicide attempts. In addition, they reported a potential G × E interaction involving the *HTR2A* rs6313 SNP and cumulative types of lifetime stressful life events. Ben-Efraim et al. (2013) also identified a significant G × E interaction between the *HTR2A* rs7322347 SNP and physical assault in childhood/adolescence among female subjects. Their results implicated that the SNPs from the HTR2A gene were linked to the risk of suicide attempts individually and interactively with stressful life events.

3.3 Epigenetic Mechanisms and Depression

Recent advances in scientific research indicate that epigenetic mechanisms such as DNA methylation, microRNAs, and histone modifications may play a pivotal role in psychiatric disorders including depression (Bagot et al. 2014). DNA methylation is a process involving the addition of a methyl group to the DNA molecule, in particular when a cytosine is followed by a guanine (CpG dinucleotide) (Klose and Bird 2006). The emerging picture is that DNA methylation, a major epigenetic actor, is globally linked with decreased transcriptional activity, where DNA methylation is activated by a family of DNA methyltransferase proteins (Jones 2012). Most studies on DNA methylation have focused on CpG islands, 1 kb CpG-rich regions, in promoter regions; however, DNA methylation in other genomic regions (such as gene bodies and intergenic regions) remains less understood (Jones 2012).

Another new arena in epigenetics is served by small noncoding RNAs, in particular microRNAs. Noncoding RNAs contain the sequence of nucleotides that does not generate proteins. MicroRNAs are smaller than 200 nucleotides in length (Nagano and Fraser 2011; Lin and Tsai 2016a). Furthermore, a histone modification is a covalent posttranslational modification to histone proteins, which stably interact with DNA to form nucleosomes (Bagot et al. 2014).

This section focuses on the latest developments in the field of epigenetics with respect to depression. This review is not intended as a comprehensive survey of all possible epigenetic reports studied in the literature. A growing amount of research studies have been conducted when investigators remain to pay much attention to epigenetics research.

3.3.1 DNA Methylation

Both animal and human studies indicated that the epigenetic mechanism of DNA methylation is linked to childhood maltreatment (Lutz and Turecki 2014). Evidence also indicates that stressful events during adulthood influence the risk for psychiatric disorders, including depression. In the context of animal models, it has been implicated that stressful early life events can change the DNA methylation level of genes, including the arginine vasopressin (*Avp*), estrogen receptor 1 (*Esr1*), glutamate decarboxylase 1 (*Gad1*), glial cell-derived neurotrophic factor (*Gdnf*), nuclear receptor subfamily 3 group C member 1 (*Nr3c1*), and *Slc6a4* (serotonin neurotransmitter transporter) genes (Champagne et al. 2006; Weaver et al. 2006; Murgatroyd et al. 2009; Kinnally et al. 2010; Zhang et al. 2010; Uchida et al. 2011).

By using an animal model of childhood maltreatment, Roth et al. (2009) reported that stressful early life events increased DNA methylation in the *Bdnf* gene for rats. Similarly, subsequent

studies confirmed that alterations in DNA methylation were associated with the *Bdnf* gene (Blaze et al. 2015; Doherty et al. 2016).

The *BDNF* gene is a well-known biomarker for the pathophysiology of depression (Hashimoto 2010). To identify an epigenetic biomarker for determining depression, Fuchikami et al. (2011) tested the methylation profile of 2 CpG islands at the promoters of exon I and IV of the *BDNF* gene by comparing 20 Japanese patients with major depression to 18 healthy controls. Their findings indicated that the methylation levels of CpG units within CpG I, but not CpG IV, of the *BDNF* gene could differentiate patients with major depression from healthy controls (Fuchikami et al. 2011).

It has been shown that decreased hippocampal glucocorticoid receptor expression was associated with depression and suicide, where the *NR3C1* gene encodes glucocorticoid receptor (Webster et al. 2002). McGowan et al. (2009) investigated whether there are epigenetic differences in a promoter of the *NR3C1* gene from postmortem hippocampus by comparing 12 suicide victims with a history of childhood abuse to 12 controls. Their data indicated that increased cytosine methylation was detected in abused suicide completers at two discrete CpG sites in the promoter region of the *NR3C1* gene, speculating that DNA methylation might persist into adulthood (McGowan et al. 2009). Their data were consistent with observations from animal studies on epigenetic regulation of the Nr3c1 gene, suggesting epigenetic alterations in relevant genomic regions by early life events (Weaver et al. 2007).

It has been observed that a truncated variant of the *NTRK2* gene is expressed in astrocytes. Given that *BDNF-NTRK2* signaling has been associated to depression and suicide, Ernst et al. (2009) hypothesize that *NTRK2* expression is significantly decreased in the suicide group as compared to controls and that methylation is associated with this downregulation. To test the hypothesis, they analyzed microarray data in a postmortem case-control study using HG-U133 chips (Affymetrix, High Wycombe, England) (Ernst et al. 2009). Ernst et al. (2009) found that the expression of the *NTRK2* gene was downregulated in suicide completers, and this downregulation was mediated by the methylation state at two specific CpG dinucleotides of the promoter region in the *NTRK2* gene in the frontal cortex of suicide completers.

By comparing 39 postmortem frontal cortex samples of major depressive disorder to 26 controls, Sabunciyan et al. (2012) investigated the genome-wide DNA methylation scan with a microarray platform, which is a methylation-sensitive restriction enzyme-based approach using 3.5 million CpGs. Although their observations did not persist significantly after correction for multiple testing, the greatest difference was in the proline-rich membrane anchor 1 (*PRIMA1*) gene with 12–15% increased DNA methylation in major depression (Sabunciyan et al. 2012). While it is unlikely that DNA methylation alterations exist in the frontal cortex of patients with major depression, the critical target may be in other brain areas such as hippocampus and amygdala (Sabunciyan et al. 2012).

3.3.2 MicroRNAs

With a genome-wide gene expression method, Garbett et al. (2015) studied whether transcriptome-based profiles can be utilized as peripheral biomarkers for major depression by using dermal fibroblasts from patients with major depression. Dermal fibroblast samples (n = 32) from both patients with major depression and matched controls were assayed by leveraging a genome-wide mRNA expression method with GeneChip HT HG-U133+PM Array Plate (Affymetrix, USA) (Garbett et al. 2015). Quantitative polymerase chain reaction-based analysis for microRNA species was conducted to weigh an interplay between the mRNA and microRNA expression alterations (Garbett et al. 2015). They found a robust mRNA gene expression alteration in various molecular pathways, including cell-to-cell communication (such as the MET proto-oncogene receptor tyrosine kinase (*MET*), protocadherin 10 (*PCDH10*), periplakin (*PPL*), and tenascin XB (*TNXB*) genes) by comparing the fibroblasts of major depression to

matched controls. In addition, it was found that the most influential microRNA candidate was hsa-miR-122, which was significantly expressed in the hippocampus (Garbett et al. 2015). It was also revealed that the microRNA and mRNA expression alterations significantly interacted with each other.

Likewise, Li et al. (2013) explored the characteristics of the BDNF protein and BDNF-related microRNAs in the etiology of depression. Their analysis revealed that 40 patients with depression had decreased serum BDNF levels and greater serum miR-132 and miR-182 levels when comparing with 40 healthy controls.

3.3.3 Histone Modifications

In an animal model, Covington et al. (2009) reported that histone acetylation was transiently reduced and then persistently gained in the nucleus accumbens, a key limbic brain region, after chronic social defeat stress, indicating that histone acetylation may play an adaptive role in stress and depression. Similarly, several investigations have pinpointed that histone acetylation in the hippocampus may play an overall adaptive role in stress and antidepressant responses (Covington et al. 2011; Hollis et al. 2011; Sun et al. 2013). Hunter et al. (2009) also examined regulation of histone methylation with regard to chronic stress in the hippocampus.

3.4 Perspectives

It should be noted that the aforementioned studies are faced with several limitations. Firstly, the small-scale size of the cohort warrants no well-defined conclusions (Lin and Lane 2015). Secondly, numerous biomarkers did not replicate well across independent studies, making us to question whether the novel associations were well founded (Lin and Tsai 2016c). It is also essential to look over probable biomarkers between various ethnic groups owing to the fact that diversified populations might result in different findings (Lin and Tsai 2016a).

To assess G × E interactions, future studies may take advantage of leveraging novel machine learning techniques such as generalized multifactor dimensionality reduction (Lou et al. 2007; Lin et al. 2009; Liou et al. 2012). In order to weigh G × E interactions, a variety of favorable machine learning methods also encompass artificial neural network algorithms, Bayesian approaches, multifactor dimensionality reduction, generalized multifactor dimensionality reduction, and regression models (Lin et al. 2006; Lin and Tsai 2011; Lane et al. 2012). Moreover, future research can look over the contributions of genetic biomarkers by whole genome sequencing (Ng and Kirkness 2010) or exome sequencing (Bamshad et al. 2011). Whole genome sequencing represents a comprehensive strategy of genomic research and generates a wide spectrum of genetic variation in a single person because of the cost-cutting and maximized throughput of next-generation sequencing technologies (Tucker et al. 2009). Exome sequencing, which selectively sequences the nucleotides of protein-coding exons in a single person, has been utilized as an efficient and alternative method for Mendelian disorders and common diseases (Bamshad et al. 2011). In sum, integrating whole genome sequencing approaches with novel machine learning tools may potentially build up an in-depth understanding of G × E interactions on depression and suicide.

In future work, a bioinformatics pipeline can be used to provide a thorough evaluation and validate whether the findings are replicated in diagnostic prediction studies. Additionally, we could investigate potential biomarkers by using a custom data mining pipeline so that genetic networks would be illustrated at the genome level. Ultimately, future work will need to come up with an integration of varied biomarkers, including clinical data, genetics, transcriptomics, metabolomics, proteomics, epigenetics, and imaging data, in order to accurately grasp depression pathogenesis as well as antidepressant therapy (Breitenstein et al. 2014). Additionally, machine learning modeling plays a key role in wiping out the false positive candidate genes that were found in the current association studies with meta-analysis, epistasis analysis, and pathway

models (Lin and Lane 2015). Machine learning modeling combined with multi-omics data not only could take care of missing information from any single data source but also could bridge the gap between phenotypes and biological regulation models (Leung et al. 2016). While predictive tests are currently unavailable for disease states and antidepressant treatment remission in depression ahead of time, machine learning modeling in future research will be explored to forecast the likelihood of drug efficacy and provide guidance on choosing medications for clinicians (Lin and Chen 2008; Lin and Lane 2017).

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4 miRNAs As Critical Epigenetic Players in Determining Neurobiological Correlates of Major Depressive Disorder

Bhaskar Roy and Yogesh Dwivedi

4.1 Introduction

Early or late-life adversities most often lead to the development of depressive symptoms in individuals with variability in coping the stressful conditions (Shapero et al. 2014). This is associated with an overall manifestation of the poor quality of life, significant disability, morbidity, and mortality in affected individuals (Milanovic et al. 2015). Posing a serious threat to the psychosocial abilities, about 300 million people were found to be under serious bereavement of major depressive disorder (MDD) with a constant increase in prevalence worldwide (Waters et al. 2015). The severity of this disorder was found to be further alarming due to nonresponsiveness of patients to antidepressant medications (Levinstein and Samuels 2014) and high-risk factor associated with committing suicide or suicidal ideation (Welton 2007). Based on the present understanding, MDD is described as a mental disorder which has shown vulnerability to environmental stimuli (aan het Rot et al. 2009; Lopizzo et al. 2015). Primarily driven by the psychopathological status of the central nervous system, this debilitating disorder itself represents several complex neuromolecular coordinates (Otte et al. 2016) that needs to be apprehended in greater detail. Dissecting out the role of those coordinates by analyzing biochemical involvement at the molecular level may help in understanding the etiopathology of this psychiatric illness.

Over the past decades, mounting reports have shown the compromised adaptive response against stress-induced situation as a primary contributing factor in the pathogenesis of MDD (Monroe et al. 2014; Lueboonthavatchai 2009; Kessler 1997). In this relation, numerous biochemical and neuroimaging studies have further pointed out the involvement of altered neuroplasticity and aberrant information processing in neural circuits of depressed brain (Pittenger and Duman 2008). Collectively, these structural and functional abnormalities in the neurocognitive system may lie at the core of maladaptive stress responsiveness and found to be governed by several genetic and epigenetic factors (Mann and Currier 2010; Tafet and Nemeroff 2016). Although the multitudes of genetic factors including variable number of tandem repeats (VNTR) and single nucleotide polymorphism (SNP) have shown strong association in predisposing susceptibility to depressive illness (Flint and Kendler 2014; Cohen-Woods et al. 2013), they have shown deficits in establishing a functional role to this affective disorder. However, recent advancement in understanding the epigenetic contribution in answering the neuropatho-

B. Roy • Y. Dwivedi (✉)
UAB Mood Disorder Program, Department of Psychiatry and Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL, USA
e-mail: ydwivedi@uab.edu

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logical complexities associated with mental disorders seems to be more convincing (Tsankova et al. 2007). Due to the nature of epigenetic regulations on mental disorders like MDD, which stems from the core of gene x environment interaction (Klengel and Binder 2013), it represents a broader scope to link up the underlying molecular role with this illness. In this context, a tiny member from noncoding RNA family, known as microRNA (miRNA), has recently emerged as a promising epigenetic modifier of MDD-related genetic landscape in both preclinical and clinical studies (Dwivedi 2014; Wan et al. 2015; Dwivedi et al. 2015). miRNA has an inherent capacity to influence gene function in a repressive manner either individually or by participating in a coordinated network (Azevedo et al. 2016; Smalheiser et al. 2012; Dwivedi et al. 2015). The overall antagonizing effect of miRNAs in modulating gene function or instrumenting gene regulatory network has been overt with a wide range of physiology to pathophysiological conditions (Issler and Chen 2015; Geaghan and Cairns 2015). Supported by human postmortem brain, patient peripheral blood monocyte, and rodent model of depression, miRNAs have been found to be an interesting molecular interface between environmental stimuli and intracellular information processing circuits behind complex MDD neurobiology (Ma et al. 2016; Lopez et al. 2014; Roy et al. 2017; Smalheiser et al. 2012; Gururajan et al. 2016). A comprehensive list of all miRNAs discussed in this chapter has been presented in Table 4.1.

Table 4.1 Comprehensive list of miRNAs involved in stress and major depression

miRNA	Affected function	Reference
miR-132-3p, miR-125b-5p, miR-138-5p, and miR-124-3p	Synaptic plasticity, spine morphogenesis, memory acquisition, fear conditioning, dendritic spine density	Edbauer et al. (2010), Aten et al. (2016), Yi et al. (2014), Wang et al. (2013), Wayman et al. (2008), Impey et al. (2010), Hansen et al. (2010)
miR-134, pre-miR-134	Dendritic spine formation, excitatory synaptic transmission, dendritic transportation, synaptic plasticity, LTP and memory formation, neuronal sprouting, dendritic spine density	Schratt et al. (2006), Bicker et al. (2013), Gao et al. (2010)
miR-138	Palmitoylation-mediated change in G protein α activity, synaptic plasticity, axonal regeneration	Siegel et al. (2009), Schroder et al. (2014), Liu et al. (2013)
miR-9, miR-125a/b and miR-188	Synaptic plasticity, axonal elongation, synaptic connectivity, synaptic strength, and dendritic spine stabilization	Ye et al. (2016)
miR-124	Synaptic plasticity, major depression, dendritic arborization, homeostatic synaptic plasticity (HSP); facilitation of sensory-motor neurons, 5HT-dependent long-term facilitation of sensory-motor neurons	Roy et al. (2017), Xu et al. (2008), Hou et al. (2015), Rajasethupathy et al. (2009)
let-7i, miR-19b, miR-29c, miR-101a, miR-124, miR-137, miR-153, miR-181a, miR-181c, miR-203, miR-218, miR-324-5p, miR-365, miR-409-5p, miR-582-5p, miR-155, miR-29a, miR-30e, miR-721, miR-699, miR-146a, miR-200c, miR-351, miR-155, miR-678, miR-764-5p, miR-135a*	Compromised HPA axis functionality, inflammation, synaptic plasticity, cell differentiation, cell survival, cell adhesion, and epigenetic modifications	Dwivedi et al. (2015)

miRNA	Affected function	Reference
miR-96, miR-141, miR-182, miR-183, miR-183*, miR-198, miR-200a, miR-200a*, miR-200b, miR-200b*, miR-200c, and miR-429	Associated with stress-induced depression phenotype in learned helplessness rat	Smalheiser et al. (2011)
miR-709, miR-186	Stress-induced motor function impairment	Babenko et al. (2012)
miR-134, miR-17-5p and miR-124	Altered dendritic spine morphology of neurons in central nucleus of amygdala	Beveridge et al. (2009), Schratt et al. (2006), Yu et al. (2008)
miR-134 and miR-183	Changes associated with alternative splicing and cholinergic neurotransmission in the stressed brain	Meerson et al. (2010)
miR-298, miR-130b, miR-135a, miR-323, miR-503, miR-15b, miR-532, and miR-125a, miR7a, miR-212, miR-124, miR-139, and miR-182	Depression-related change in miRNA and response to antidepressant in hippocampus	Cao et al. (2013)
miR-34c	Anxiety-like behavioral changes in amygdala of stress-induced mice	Haramati et al. (2011), Heinrichs and Koob (2004)
miR-16	Maternal deprivation-associated changes in mice hippocampus inducing anxiety like phenotype	Bai et al. (2012)
let-7a	Anxiety-like behavioral changes in amygdala of stress-induced mice	Bai et al. (2014)
miR-124 and miR-18a	Glucocorticoid receptor regulation under stress suceptibility	Vreugdenhil et al. (2009), Herman et al. (2012)
miR-504	D1 and D2 dopamine receptor modulation in nucleus accumbens of adult rats due to maternally deprivation	Zhang et al. (2013)
miR-135	Regulating anxiety-like behavior by modulating 5HT system	Issler et al. (2014)
miR-29c, miR-30a, miR-30c, miR-32, miR-193-5p, miR-204, miR-375, miR-5323p, and miR-698	Transgenerational transmission of paternal lifetime experiences via sperm miRNAs	Rodgers et al. (2015)
miR-20a and 20b; miR301a and 130a; and miR-424 and 497	Associated with depressive symptoms in suicide dlPFC	Smalheiser et al. (2012)
Of miR-185*	Impaired neurotrophin signaling pathway in depressed suicide brain	Maussion et al. (2012)
miR-139-5p, miR-195, miR-320c and miR-34c-5p	Involved in disrupting polyamine biosynthesis pathway of depressed suicide brain	Lopez et al. (2014)
miR-1202	Associated with metabotrophic glutamate receptor modulation in depressed suicide brain	Lopez et al. (2014)
miR-511	GDNF-mediated signaling cascade in glial population of depressed brain	Maheu et al. (2015)
miR-218	Modulating depression susceptibility by increasing resiliency against stress-induced depression	Torres-Berrio et al. (2017)

(continued)

Table 4.1 (continued)

miRNA	Affected function	Reference
miR-184 and miR-34a	Glucocorticoid receptor pathway modulation	Azevedo et al. (2016)
miR-107, miR-133a, miR-148a, mir-200c, miR-381, miR-425-3p, miR-494, miR-517b, miR-579, miR589, miR-636, miR-652, miR-941, miR-1243	MDD-associated transcriptome-wide change in miRNA in patient PBMC	Belzeaux et al. (2012)
miR-132 and miR-182	Serum-based expression study reflecting high depression score in MDD patients	Li et al. (2013)
miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743	miRNA-based marker analysis in PBMC of MDD patients	Fan et al. (2014)
miR-221-3p, miR-34a-5p, and let-7d-3p, miR-451a	Serum and CSF sample-based change in miRNAs from MDD patients	Wan et al. (2015)
miR-144-5p, miR-320a, miR-451a, miR-17-5p, miR-223-3p, miR-335, let-7a-5p, let-7d-5p, let-7f-5p, miR-24-3p, miR-425-3p, miR-330-3p, miR-345-5p, let-7b and let-7c	Wide-spread association of miRNAs with etiopathology of MDD in peripheral tissue of depressed patients	Dwivedi (2016)
miR-16	Modulation of 5HT system under MDD environment and counterinfluence by antidepressant fluoxetine	Baudry et al. (2010)

4.2 miRNA Biogeny Following Canonical Pathway

MicroRNA is one of the candidates from the non-coding RNA family with a precise epigenetic role to modulate the coding potential of transcribed mRNA pool based on characteristic sequence complementarity (Bartel 2004; Kim 2005; Holoch and Moazed 2015). In human, so far more than 2500 mature miRNAs have been annotated. Since its first report as an epigenetic modifier in neuropsychiatric illness, miRNAs have shown a thriving trend of being a modulator of single protein-coding gene to act as potential regulatory hub to control a wide array of complex gene network either through direct association or by indirect intermediates (Bracken et al. 2016; Pasquinelli 2012). Despite the restricted size (~22 nucleotides) and limited potential to go through exon splicing procedure for generating more structural variations, this small form factor exhibits a functional diversity in targeting diverse range of RNA molecules spanning from protein-coding (mRNA) (Flynt and Lai 2008) to long noncoding RNAs (lncRNA) (Tan et al. 2015). As elaborated in Fig. 4.1 mammalian miRNA biogenesis follows a programmed pathway to produce the mature effector molecule which starts right after their transcription into a primary transcript (pri-miRNA) by RNA polymerase II or III in nuclei. miRNAs are primarily synthesized as precursor transcripts from primary miRNAs by Drosha, a nuclear RNase III enzyme, which are then exported to the cytosol and processed by the RNase III Dicer to generate mature miRNAs. Mature miRNAs are incorporated into the RNA-induced silencing complex (RISC), which regulates gene expression by pairing primarily to the 3′UTR of protein-coding mRNAs to repress target mRNA translation and/or induce target degradation (Winter et al. 2009; Dwivedi 2014). Once available in mature form, miRNAs start participating in the posttranscriptional regulation of target transcripts by either depleting their endogenous level with the help of RNA-induced

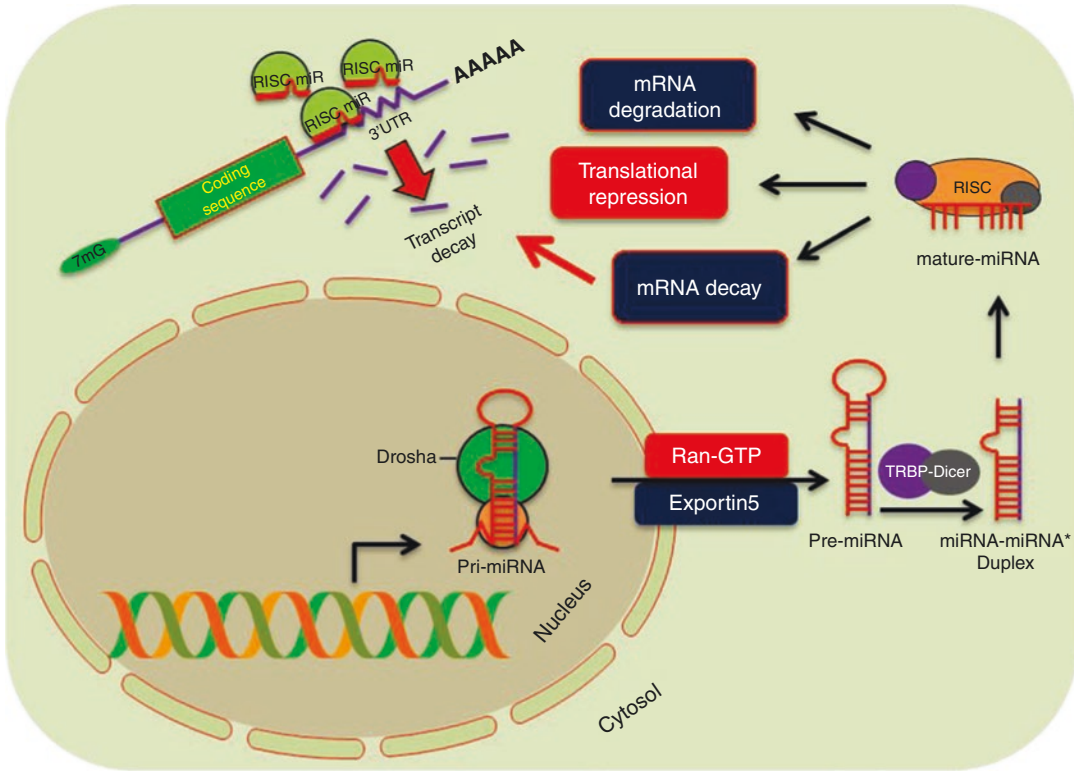

Fig. 4.1 MicroRNA biogenesis and functions. miRNA is transcribed by RNA polymerase II to synthesize primary miRNA (pri-miRNA) in the nucleus. Within nucleus, the pri-miRNA is processed by nuclear RNase III enzyme Drosha to produce precursor miRNA (pre-miRNA). pre-miRNA is transported to cytosolic environment with the help of Ran-GTP and exportin 5 transporter complex. In the cytosol, the pre-miRNA is processed by the RNase III enzyme Dicer to generate mature miRNAs. Mature miRNAs are incorporated into the RNA-induced silencing (RISC) complex, which regulates gene expression by pairing primarily to the 3′untranslated region (UTR) of protein-coding mRNAs. This is achieved via a combination of translational repression, mRNA decay and mRNA degradation

silencing complex (RISC) or by modulating translation machinery recruited on the coding transcript. miRNA functions as master regulator of gene expression at posttranscriptional level either by modulating the mRNA translation or transcript degradation by targeting the 3′untranslated region (3′UTR) (Jonas and Izaurralde 2015). Because of this feature, miRNAs are able to regulate entire genetic circuitries and thereby play a critical role in maintaining biological homeostasis. Considering the fundamental role of miRNAs in mediating biological events, any perturbations in the expression of miRNAs may result in the imbalance of homeostasis, which are often reflected as imbalance in the regulatory network that can distinguish normal vs disease states (Bracken et al. 2016; Miller and Wahlestedt 2010; Luoni and Riva 2016).

4.3 Signature miRNA Expression in Brain

Spatiotemporally regulated miRNA expression can be seen in a diverse array of tissue types present in the mammalian body (Landgraf et al. 2007; Davis and Hata 2009). The brain is also not an exception to this rule where neuron- vs glia-specific and developmental stage-specific miRNA expression determines the physiological and pathophysiological fate of CNS activity (Bian et al. 2013; Kosik 2006). Furthermore, a discrete compartmentalization within the intraneuronal spaces of the human brain has been found to be conserved in humans and across other vertebrate species. For example, miR-128, miR-134, and miR-132 could be made accountable for

their relatively enriched distribution in synaptic neuronal spaces than perinuclear soma (Siegel et al. 2011). This kind of localized distribution of miRNAs in synaptic and/or dendritic areas mostly denotes their activity-dependent requirement to perform exclusive functions highly regulated by intra- and extrasynaptic environmental signals. Similar distributions in miRNAs encoding genetic loci have been found for brain-enriched miRNAs like mir-124, miR-7, miR-9, miR-128, miR-129, miR-133a, miR-138, miR-153, and miR-218 on different arms of the same chromosome or found to be localized on different chromosomes (O'Carroll and Schaefer 2013). This genetic redundancy in coding same miRNA from two or more genetic loci makes more sense for those miRNAs which need to be precisely regulated under complex neuronal inputs received from various neuromodulatory circuits participating in CNS function (O'Carroll and Schaefer 2013). As a matter of fact, a similar observation has been noted for miR-124-3p expression in the prefrontal cortex of stress-induced rodent depression model. Under the investigational parameters, the miR-124 transcript was found to be overrepresented from chromosome 3 despite its presence in two other chromosomal loci from chromosome 2 and 15. Moreover, the transcriptionally active genetic locus for miR-124 on chromosome 3 showed a discernable change in promoter methylation associated with depression phenotype, clearly demonstrating an epigenetic influence on underlying neural circuits (Roy et al. 2017). Collectively, the above evidences make a pressing need to understand the relative involvement of miRNAs in regulating the functions of neurogenesis, synaptic development, axon guidance, and neuronal plasticity under strict neuronal influence (Cao et al. 2016). Keeping this in mind, the following sections in this chapter are primarily focused on elaborating the role of miRNAs in synaptic plasticity with direct relation to depressive illness.

4.4 miRNA-Mediated Epigenetic Influence on Synaptic Plasticity

As mentioned earlier, altered synaptic plasticity is a hallmark of major depression (Duman et al. 2016). Plasticity-related dysregulation represents an overall disability of CNS to properly integrate various neuronal inputs and make changes accordingly to raise appropriate responses to stimuli (Pittenger and Duman 2008). Under depression pathophysiology, similar functional disruption due to compromised plasticity has been highlighted in the hippocampus and corticolimbic axis (Liu et al. 2017). In this connection, striking evidences from recent studies have demonstrated a serious intervention of miRNAs in disintegrating the plasticity-related functions involving MDD brain (Dwivedi 2014; Ma et al. 2016; Roy et al. 2017). According to a growing body of evidences, a complete set of miRNA synthesizing repertoire has been found to be functional in the synaptic compartment of neurons (Lugli et al. 2008; Lugli et al. 2005). Experimental evidences have documented the isolation of two miRNA processing factors Drosha and DGCR8 associated with primary miRNA fraction from the cytosolic environment of synaptosomal compartments (Lugli et al. 2008; Lugli et al. 2012). Careful interpretation of this finding unveils a contrasting fact about canonical biogenesis of miRNA which has been discussed earlier. Identification of miRNA processing machinery along with primary miRNAs at the synaptic compartment clearly indicates the directional targeting to a specialized environment after getting synthesized from nucleus. This has been seen as epigenetic fine-tuning to deliver more customized supply of specific miRNA pool at the synaptic end which is often found to orchestrate the proteomic output to modulate the local protein expression, synapse maturation, and/or function on a activity-dependent manner (Schratt et al.

2006; Martin and Kosik 2002). Carrying the discussion further, requirement of precursor miRNA-processing enzyme Dicer in reconciling synaptic plasticity-related changes has been shown in a forebrain neuron of Dicer knockout mice (Konopka et al. 2010). Morphological changes associated with reduced dendritic branch elaboration and a large increase in dendritic spine length with no concomitant change in spine density was significantly noticed under Dicer deficiency. To put it differently, a possible connection could be drawn to support the miRNA involvement in this case which resulted in improper regulation of plasticity-related genes due to Dicer deficit. This was found to be true for DGCR8 which is an essential factor in microprocessing complex in synthesizing precursor miRNA from primary hairpin like transcripts. Causing a haploinsufficiency in DGCR8 with a microdeletion of chromosome 22q11.2 locus in the heterozygous mouse has shown to be effectively repressing dendritic tree and dendritic spine development (Devaraju et al. 2016; Fenelon et al. 2011). This was the first report to show a directed relationship of impaired miRNA biogenesis pathway with behavioral deficits. The haploinsufficient DGCR8 in Df (16)A± mice demonstrated a cognitive defect with improper acquisition of spatial working memory-dependent task, as well as impaired sensorimotor gating (Devaraju et al. 2016). The linkage between synaptic plasticity, behavioral deficits, and abnormality in miRNA processing was further supported with an elevated level of miRNA expression in CA1 region of mice hippocampus due to chemically induced changes in LTP and LTD (Lee et al. 2012). At the end, additional support could be harnessed from the studies representing cooperating role of RNA-binding protein FMRP with specific sets of miRNA (miR-132-3p, miR-125b-5p, miR-138-5p, and miR-124-3p) in mouse brain to augment translational repression on plasticity-related genes Arc and CaMKIIα (Edbauer et al. 2010). Interestingly, the drosophila homologue of FMRP (dFMR1) was found to be interactive with miR-124-3p in preventing dendritic arborization (Xu et al. 2008).

Short listing of brain-enriched miRNAs based on their functional involvement in reorganizing the behavioral response by modulating plasticity-related gene expression is mostly centered on cognitive dysfunctionality (Xu et al. 2012). Resolving the issues at individual miRNA level inarguably brings the delicate interference of miR-134 in plasticity-related function (Aksoy-Aksel et al. 2014). Biochemical screening identified Lim Kinase (LimK) 1 as a downstream target of miR-134 in the hippocampal synapto-dendritic compartment. The antagonizing effect of miR-134 on LimK1 was found to cause morphological changes in dendritic spines as well as physiological impairment in postsynaptic sites of excitatory synaptic transmission (Schratt et al. 2006). Further, the dendritic localization of miR-134 in hippocampal neurons was made possible by the active participation of DEAH-box helicase DHX36 which helps in miR-134-mediated dendritic spine modification (Bicker et al. 2013). An inverse relationship was found between miR-134 expression and Sirt1 protein expression in CA1 neuron of the hippocampus primarily determined by the interaction of YY1 (Yin Yang 1) transcription factor (Gao et al. 2010). Causing a deficit in Sirt1expression in the same hippocampal neuron was further able to induce the level of miR-134 at synaptosomal compartment with a concomitant decline in BDNF and CREB protein expression. This reciprocal change in participating gene expression was found to take part in LTP-related memory impairment (Gao et al. 2010). Activity-dependent miRNA, miR-132, has been known for its neurotrophin-regulated role in synaptic plasticity (Aten et al. 2016). CREB was identified as upstream regulator of miR-132 expression and shown to have functional impact on hippocampal spine morphogenesis (Yi et al. 2014). Failure to

induce the expression of miR-132 in hippocampal neurons impairs memory acquisition of trace fear conditioning (Wang et al. 2013). The plasticity-related dysfunctionality in spinogenesis of hippocampal neurons was further evidenced due to an attenuated expression of miR-132. The attenuated expression status of miR-132 might be responsible for bringing up the expression level of target protein p250GAP with an inhibitory role in neuronal outgrowth and sprouting (Wayman et al. 2008; Impey et al. 2010). In an attempt to tease out the responsible factors in regulating miR-132 expression, a strong interference of BDNF was further noted which clearly demonstrates the involvement of MAPK/ERK1/2 pathway to influence synthesis of postsynaptic protein (Yoshimura et al. 2016). Additional support on miR-132-mediated plasticity modulation can be exemplified in an overexpression mouse model. In this model, hippocampal MeCP2 was found to be under negative influence of overexpressed miR-132 gene, which significantly increased the dendritic spine density (Hansen et al. 2010). Homeostatic synaptic plasticity (HSP) has a positive impact in enduring synaptic strength (Turrigiano 2012) by increasing the synaptic AMPARs and enhanced synaptic transmission (Henley and Wilkinson 2016). miR-124 has been recently demonstrated to control HSP by tightly regulating the GluA2 expression from AMPA receptor family (Hou et al. 2015). As miR-124 expression is activity dependent, selective repression of neuronal activity at synaptic ends has shown to be associated with a decrease in miR-124 activity. Conversely, increase in miR-124 activity was able to restore the balance in homeostatic response by inducing more calcium permeable AMPA (CP-AMPA) (Hou et al. 2015). Other reports on miR-124 have shown the impact of serotonin (5HT) on moderating the expression level of this miRNA in a CREB-dependent manner (Rajasethupathy et al. 2009). Therefore, the result of this CREB-mediated miR-124 repression has shown to enhance 5HT-dependent long-term facilitation of sensory-motor neurons in sea slug, *Aplysia californica* (Rajasethupathy et al. 2009). Induced G protein α palmitoylation has been seen to cause dendritic shrinkage and reduced synaptic transmission through Rho-dependent signaling axis (Fukata and Fukata 2010). However, looking for a master regulator connected to this change in synaptic function pointed out the involvement of miR-138. miR-138 targets the whole regulatory circuits by sequestering the expression of acyl protein thioesterase1 (APT1) which is responsible for regulating the palmitoylation-mediated change in G protein α activity of hippocampal CA1 and DG neurons (Siegel et al. 2009). In addition to this, miR-138 was also found to regulate decapping mRNA 1B (DCP1B) which is a local protein in the synaptic compartment and know to regulate plasticity function in the neurons of the hippocampus and prefrontal cortex (Schroder et al. 2014). Interestingly, miR-138 was also found to build up a regulatory loop with Sirtuin1 expression, whose function directly contributes to the axonal regeneration of hippocampal DRG neurons. Induced expression of Sirtuin1 functionally affects miR-138 level by acting as an inhibitory factor for its transcriptional repression (Liu et al. 2013). Extending the search for other miRNAs potentially involved in regulating plasticity-related function of brain neurocognitive axis resulted in the identification of miR-9, miR-125a/b, and miR-188. Individually, three of these miRNAs demonstrated their epigenetic influences in regulating a battery of factors (REST, FXR1P, CAMKK2-AMPK, PSD-95, Bcl-W, Syn-2, Nrp-2, 2-Ag, and Bace1) directly or indirectly associated with synaptic plasticity function (Ye et al. 2016).

4.5 miRNA in Regulating Neuronal Stress Responses

Psychosocial stress has long been considered as a risk factor and found to be comorbid with several mental disabilities including major depression (Hammen 2005). Stress-induced pathophysiology of depressed brain is heavily influenced by adverse environmental cues and has been shown to have serious epigenetic intervention from various factors including miRNAs (Dwivedi 2014). In a recent study of corticosterone-induced rodent

model of depression, a transcriptome-wide change in miRNA expression was noticed in the prefrontal cortex (PFC) area of the brain critically involved in glucocorticoid feedback inhibition and maintenance of hypothalamic-pituitary-adrenal (HPA) axis equilibrium in response to stress (Dwivedi et al. 2015). Chronic corticosterone administration on rat was found to cause a significant change in 26 miRNAs from PFC. Of them, 20 miRNAs were upregulated (let-7i, miR-19b, miR-29c, miR-101a, miR-124, miR-137, miR-153, miR-181a, miR-181c, miR-203, miR-218, miR-324-5p, miR-365, miR-409-5p, miR-582-5p, miR-155, miR-29a, miR-30e, miR-721, and miR-699) and seven were downregulated (miR-146a, miR-200c, miR-351, miR-155, miR-678, miR-764-5p, and miR-135a*). The altered responsiveness to HPA axis could be related to this overall change in miRNA expression in the frontal cortex of depressed rats. However, a number of genes associated with inflammation, synaptic plasticity, cell differentiation, cell survival, cell adhesion, and epigenetic modifications were identified as targets of those significantly altered miRNAs. To name a few, CREB1, BDNF, CAMKIIa, AKT1, and NR3C1 were the potential targets which have shown significant downregulation in the frontal cortex of CORT-treated rat and established a strong negative correlation with miRNAs, miR-124, miR-101, miR-29a, miR-30e, miR-181c, miR-365, and miR-218. It will be worthwhile to mention a special note for miR-124 which was earlier shown to have significant role in regulating plasticity-related function of neurons. From this study, Nr3c1, the gene for coding glucocorticoid receptors and a bonafide target of miR-124, was found to be significantly repressed. This gives a clear indication of compromised glucocorticoid responsiveness toward impaired HPA axis functionality (Dwivedi et al. 2015). Earlier studies using learned helplessness model of depressed rats have shown a blunted response in PFC-based miRNA expression. A list of significantly altered miRNAs (miR-96, miR-141, miR-182, miR-183, miR-183*, miR-198, miR-200a, miR-200a*, miR-200b, miR-200b*, miR-200c, and miR-429) was found in depressed rats which were strikingly different than those in group of animals who had exhibited resilience to depression (Smalheiser et al. 2011). Moreover, in both the studies a coordinated pattern of miRNA expression was noticed which makes a more likely explanation for them to be cohesively regulated under a well-coordinated network. This type of coordinated network has shown a distinct pattern which is characteristic of depression phenotype (Smalheiser et al. 2011; Dwivedi et al. 2015). Chronic stress-induced change in miRNA expression was found to be brain region specific (Hollins and Cairns 2016). Study with chronic stress/recovery paradigm in rat brain has shown a significant decline in miR-709 expression in a cerebellum-specific manner which was not noticeable in either the hippocampus or frontal cortex and remains the same during recovery phase, whereas another candidate, miR-186, is found to be nonresponsive after 2 weeks of stress in the cerebellum. Differential responsiveness of miR-186 was further noted in the cerebellum of those rats during their recovery phase and has shown similarity in the hippocampus and prefrontal cortex (Babenko et al. 2012). In another study, the rat undergoing both chronic and acute immobilization stress has demonstrated changes in miRNA (miR-134, miR-17-5p, and miR-124) expression in CA1 region of the hippocampus and central nucleus of the amygdala in relation to altered dendritic spine morphology of neurons (Beveridge et al. 2009; Schratt et al. 2006; Yu et al. 2008). Both of these brain areas are known for their well-established role in stress responsiveness (McEwen and Gianaros 2010). Importantly, miR-134 and miR-183 shared a common predicted mRNA target, encoding the splicing factor SC35, a gene that promotes the alternative splicing of acetylcholinesterase (AChE) from the synapse-associated isoform AChE-S (Meerson et al. 2010). Animal model based on unpredictable chronic stress (UCS) has been shown to alter the expression landscape of 13 specific miRNAs (downregulated, miR-298, miR-130b, miR-135a, miR-323, miR-503, miR-15b, miR-532, and miR-125a; upregulated, miR7a, miR-212, miR-124, miR-139, and miR-182) in the hippocampus. From the list of 13 altered miRNAs, two (miR-125a and miR-182) of them were able to reinstate their expression status

when treated with an antidepressant (Cao et al. 2013). Involvement of miR-34c in central amygdala of stress-induced mice has shown a relationship with increased anxiety-like behavior (Haramati et al. 2011). Additionally, support from in vitro experiments has pointed out miR-34c-mediated repression of Crhr1gene which was earlier reported to modulate anxiety-like behavior (Heinrichs and Koob 2004). Reports on chronic unpredictable stress model suggest anhedonic behavior in rats with a concomitant change in let-7a expression possibly mediated through repression of Htr4 gene in the hippocampus (Bai et al. 2014). Study from the same group earlier reported a change in miR-16 expression which was closely associated with maternal deprivation rather than chronic unpredictable stress response. This change was more physiologically related to repress the BDNF expression in the hippocampus (Bai et al. 2012). Following the same line of evidences, studies have found that miR-124- and miR-18a-mediated downregulation of GR translation is important in susceptibility to stress (Vreugdenhil et al. 2009; Herman et al. 2012). Pathogenic modulation of neurotransmitter-related receptor function is one of the critical issues in the depressed brain. miRNA-mediated sequestration of those receptors participating in dopaminergic, serotonergic, and glutamatergic neural transmission has been well documented (Dwivedi 2014). In a recent study, effect of maternal deprivation and CUS was found to be repressive for miR-504 expression and shown to have a negative impact on D1 and D2 dopamine receptors in nucleus accumbens of rats (Zhang et al. 2013). This epigenetic interplay between dopamine transmission system with miR-504 was seen to have behavioral face value in those maternally deprived pups with increased vulnerability to stress during their adulthood (Zhang et al. 2013). Serotonin neurotransmitter dysfunction is well characterized in depression pathophysiology. Selective inhibition of 5HT receptor 1 and Slc6a4 transcripts from serotonergic system was shown to be mediated via miR-135 in a genetically engineered mouse model (Issler et al. 2014). Overexpression of miR-135 had antidepressant property with a detrimental effect on 5HT level. On the other hand, miR-135 knockdown mouse model showed inability to respond to antidepressant treatment as well as increased anxiety-like behavior (Issler et al. 2014). A recent interesting report on miR-124-3p-mediated epigenetic regulation on glutamatergic receptor system has added another layer to understand intricate molecular control of depression biology (Roy et al. 2017). The report focused in identifying the effect of miR-124-3p on Gria4 regulation in a stress-induced rat depression model where the frontal cortex was found to be affected. The report was considered important to show the methylation-mediated epigenetic alteration of miR-124-3p promoter in depressed frontal cortex and possibly responsible for induced expression of miR-124 (Roy et al. 2017).

Transgenerational epigenetic inheritance has been recently emerged as a potential mechanism to transfer epigenetic trait/s from one generation to next generation via miRNA (Smythies et al. 2014). In this context, a recent report by Rodgers et al. (2013) has demonstrated that paternal stress exposure can alter sperm miRNA content and pass on to the next generation to reprogram offspring HPA stress axis regulation (Rodgers et al. 2013). This could have a potential impact in the development of MDD and other stress-related disorders transmitted via epigenetic regulation of miRNAs. More recent follow-ups on the same study have interestingly identified an adult life-based defective corticosterone response upon injection of nine transgenerational miRNA (miR-29c, miR-30a, miR-30c, miR-32, miR-193-5p, miR-204, miR-375, miR-5323p, and miR-698) at single cell zygotic stage (Rodgers et al. 2015).

4.6 miRNA-Mediated Changes in Postmortem MDD Brain

Use of postmortem brain samples in understanding the histopathological changes associated with MDD is well appreciated. Unlike neuroimaging studies, analyzing postmortem brain tissue of subjects with this mental disorder helps to get deeper insights of associated neurochemical, cellular, and molecular changes (Stockmeier and

Rajkowska 2004). Though live brain neuroimaging studies are useful to show more likely changes associated with altered morphology of affected brain areas, but underlying biochemical changes have shown to be more critical to understand and effectively design therapeutic strategy against this disorder (Gold et al. 2015). In order to do so, past few years of postmortem studies have contributed immensely to classify the anomalies related to gene expression in the neurochemical circuits of MDD brain. With the increasing acceptance of miRNA as mega controller of gene regulatory event at the cellular level, over the past few years, emerging reports have started pouring in to define their discernible role as a critical molecular switch in postmortem brain of MDD subjects (Dwivedi 2016). With a pioneering study by Smalheiser et al. (2012), a dorsolateral prefrontal cortex (dlPFC)-specific global change in miRNA expression was found to be closely associated with depressive symptoms in suicide subjects (Smalheiser et al. 2012). An overall deficiency in miRNA expression was noticed in dlPFC and mapped to be linked with downstream regulation of genes known for their significant role in cellular growth, differentiation, and plasticity (UBE2D1 and UBE2W, CAMK2G, AKAP1, SMAD5, MITF, BACH2, MYCN, GABRA4, and CACNA1C). Due to close proximity of their chromosomal localization (miR-424 and 20b at Xq26.2-3, 377 kb apart; miR-142 and 301a at 17q22, 820kb apart; and miR-324-5p and 497 at 17p13.1, 205kb apart), and nature of being transcribed from same primary transcripts, half of the downregulated miRNAs from this study were shown to be a part of a miRNA co-expression network. Additional similarity was noted for those downregulated miRNAs, which have been shown to harbor identical seed sequence (miR-20a and 20b; miR301a and 130a; and miR-424 and 497) in order to achieve an overlapping pattern of target gene regulation (Smalheiser et al. 2012). Another interesting study following a candidate-specific approach was able to successfully link the aggravated expression of miR-185* with significant depletion of TrkB.T1 expression in the frontal cortex of suicide completers (Maussion et al. 2012). TrkB.T1 is the truncated isoform of Ntrk2 receptor gene and shown astrocyte restricted expression. Acknowledging the importance of astrocyte-related pathology in mood disorder progression, a marked decline in TrkB.T1 expression was able to provide an interesting clue about miRNA-mediated impaired neurotrophin signaling pathway in depressed suicide brain (Maussion et al. 2012). Metabotropic glutamate receptor GRM4, a participating receptor protein of glutamatergic, dopaminergic, GABAergic, and serotonergic neurotransmission was found to be affected by brain-enriched miR-1202 in depressed postmortem cortex (Lopez et al. 2014). A contrasting downregulation was noticed in GRM4 expression in the depressed brain with strong antidepressant history and negatively correlated with miR-1202 expression. Moreover, this study was able to indicate a strong negative relationship between miR-1202 expressions with MDD alone when compared with MDD subjects who committed suicide (Lopez et al. 2014). Dysregulated polyamine biosynthesis pathway is characteristics of MDD and suicide brain (Fiori and Turecki 2008; Gross and Turecki 2013). Earlier reports have shown aberrant changes in expression of SAT1 and SMOX genes from this pathway in suicide brain (Sequeira et al. 2006). Although the expression downregulation of SAT1 was partly explained by a promoter-specific polymorphism, other conventional gene regulatory mechanism was unable to correlate with the attenuated expression of SMOX gene (Sequeira et al. 2006; Fiori et al. 2009). However, identification of four miRNAs (miR-139-5p, miR-195, miR-320c, and miR-34c-5p) with significant expression upregulation in the prefrontal cortex of depressed suicide completers out of ten profiled miRNAs has shown to be promising (Lopez et al. 2014). Observation of a strong negative expression correlation between SAT1, SMOX genes, and three miRNAs (miR-139-5p, miR-320c, miR-34c-5p) was adequate to explain the possible epigenetic modulation in disrupting the polyamine biosynthesis function of the MDD suicide brain (Lopez et al. 2014). Further epigenetic modulation mediated by miR-511 was shown to compromise the GDNF-mediated signaling cascade in glial popu-

lation of depressed brain (Maheu et al. 2015). In basolateral amygdala (BLA) samples of depressed subjects, a marked increase was observed for miR-511 with a contrasting change in GDNF family receptor alpha 1 (GFRA1) mRNA expression. The inadequate expression of GFR1 gene in depressed BLA having an inversely correlated with miR-511 expression was further supported by in vitro neural progenitor cell line assay. Together the in vivo and vitro assays from this study jointly adjudicated the responsiveness of GFR1 to miR-511 mediate epigenetic repression in MDD brain, implicating a nonfunctional glial-specific GDNF signaling axis (Maheu et al. 2015).

In a recent study, expression variability of DCC (netrin-1 guidance cue receptor gene, deleted in colorectal cancer) gene known for their role in depression susceptibility was reported to be under influence of miR-218 in the prefrontal cortex of MDD suicide brain (Torres-Berrio et al. 2017). Reduced expression of DCC in PFC neurons is related to increased resiliency against stress-induced depression. Reversing this situation might have an opposite effect in behavioral manifestation. This was found to be true in postmortem cortex of MDD subjects where significant overexpression of DCC gene was admitted due to insufficient expression of miR-218 causing an overall reversal of silencing effect. As DCC receptors have the ability to control the axon arborization, dendritic growth, and synapse formation, the loss of antagonizing effect of miR-218 on DCC may possibly lead to the remarkable repatterning of synaptic connection in the pyramidal neuron of MDD brain (Torres-Berrio et al. 2017). Recent focus on anterior cingulate cortex of MDD brain demonstrated a distinct change in miR-184 and miR-34a expression with a functional influence on NCOAR1 and NCOR2 genes. Both of these genes have shown prior evidence to affect the glucocorticoid receptor gene-mediated transcriptional output of CRH gene in other neuropsychiatric disorders (Azevedo et al. 2016).

4.7 miRNA-Based Biomarker Analysis from Peripheral Tissues of MDD Patients

Over the past few years, peripheral biomarker analysis using noninvasive approach has been shown to be of primary interest in proper diagnosis of disease and its progression (Domenici and Muglia 2007). Understanding of noncoding RNA biology is rapidly increasing, and their predictive value in disease diagnosis has been critically assessed in recent past (Fernandez-Mercado et al. 2015). Emerging evidence has also shown that circulating form of miRNA from the noncoding RNA family has great potential to reflect the changes associated with CNS-related disorders (Sheinerman and Umansky 2013; Rao et al. 2013). The representative class of circulating miRNA could be easily found in various sources including body fluids such as plasma, serum, cerebrospinal fluid, and non-neuronal tissue or cells such as lymphocytes (Etheridge et al. 2011). More interestingly, disease-associated changes in miRNA profile of peripheral blood were found to be highly correlative with the changes in neuronal tissue of various CNS-related neurodevelopmental and degenerative disorders (Gaughwin et al. 2011; Liu et al. 2010). Furthermore, the changes elicited in miRNA expression profile of blood samples due to therapeutic administration of drugs could be carefully considered to predict the systemic response to a specific treatment regime (Murakami et al. 2010; Gamez-Pozo et al. 2012). In agreement with the above discussed points, Belzeaux and colleagues were the first group to show a transcriptome-wide change in miRNA expression of 16 patients assessed for their major depressive episode (Belzeaux et al. 2012). Individual analysis from this study identified changes in 14 miRNAs including mine upregulated and five downregulated miRNAs in blood samples of patients suffering from major depressive episode (MDE) when compared to base line (0 week) as well as after 8 weeks of

study inclusion. This study was also able to correlate changes in miRNA expression as observed by Smalheiser et al. (2012) in postmortem cortex of MDD brain (Smalheiser et al. 2012; Belzeaux et al. 2012). Later, a study in the serum of MDD patients showed changes in miR-132 and miR-182 expression. Both of these miRNAs were found to be significantly upregulated in patients; miR-132 had a positive correlation with depression. Moreover, the cell line-based study further concluded BDNF as direct target of these two miRNAs which was found to be in negative correlation with high depression score in MDD patients (Li et al. 2013).

Strength of miRNA-based biomarker prediction using peripheral blood mononuclear cells (PBMC) in extended set of 81 MDD patients was recently validated by identifying a marked change in 26 miRNAs as compared to control (Fan et al. 2014). Further validation confirmed the upregulation of five miRNAs (miRNA-26b, miRNA-1972, miRNA-4485, miRNA-4498, and miRNA-4743) with predicted downstream target genes known for their role in pathways related to CNS functions (Fan et al. 2014). In a recent study, an interesting observation was noticed in miRNA expression of MDD patients while analyzing their cerebrospinal fluid (CSF) samples as well as serum specimen (Wan et al. 2015). Notably, a change in four miRNAs was observed in both serum and CSF samples from same patients, of which three of the miRNAs were found to be upregulated (miR-221-3p, miR-34a-5p, and let-7d-3p) and one was downregulated (miR-451a). This study was able to establish a face value of representative miRNAs as biomarkers of MDD in the serum with similar casual changes in CSF samples (Wan et al. 2015). More recently a series of other studies have provided compelling evidences to further evaluate the association of a wide set of miRNAs (miR-144-5p, miR-320a, miR-451a, miR-17-5p, miR-223-3p, miR-335, let-7a-5p, let-7d-5p, let-7f-5p, miR-24-3p, miR-425-3p, miR-330-3p, miR-345-5p, let-7b, and let-7c) with the etiopathology of major depression and to screen for their differential signature in peripheral tissue for the disease prognosis as well as treatment response (Dwivedi 2016).

Our recent report on miR-124-3p in the serum sample of 18 antidepressant-free MDD patients also demonstrated close congruence with other studies as mentioned above (Roy et al. 2017). A significant 3.5-fold increase in miR-124-3p expression was documented after adjusting the result for age, gender, and race in MDD patient cohort which was similar to what we earlier found in postmortem MDD brain (Roy et al. 2017). Moreover, this was further supported by another study where a striking decline in miR-124 expression was monitored in 32 MDD patients after 8 weeks of antidepressant treatment (He et al. 2016). Taken together, all these remarkable studies have indicated a marked progress in utilizing extracellular small noncoding RNA like miRNA in predicting malignancies associated with major depression and acknowledging their competency to be used as peripheral biomarkers in disease prognosis.

4.8 miRNA as Therapeutic Targets

Critical involvement of miRNA in fine-tuning the flow of genetic information has been looked upon from all possible neurobiological aspects considering the MDD brain. However, amelioration-related issues associated with MDD pathology might need to be revisited for identification of possible scopes to develop better therapeutic approaches using miRNAs. Due to limitation of antidepressant treatment based on monoaminergic targets, an overarching need to design next-generation antidepressant drug has been long warranted. Not to every extent but from few recent reports, understanding miRNA and associated changes in gene expression in response to

antidepressant drugs has raised possibility to device effective therapeutic strategy against this disorder (Hansen and Obrietan 2013). Since selective 5HT reuptake inhibitors (SSRIs) reduce 5HT transporter (SERT) expression at translational but not at the transcriptional level, the role of miRNAs was examined in the regulation of SERT expression (Baudry et al. 2010). It was found that miR-16 has inverse correlation with SERT expression. Interestingly, treatment of mice with fluoxetine elevates the levels ofmiR-16 in serotonergic raphe nuclei and reduces SERT expression. Furthermore, the fluoxetine-mediated increase in miR-16 level in raphe is accompanied by a decrease in pre-/pri-miR-16 supporting the hypothesis that fluoxetine-induced upregulation of miR-16 in raphe nuclei involves enhanced maturation from pre-/pri-miR-16. Surprisingly, fluoxetine decreases the level of miR-16 in the noradrenergic locus coeruleus (Baudry et al. 2010). Enoxacin, an antibacterial fluoroquinolone compound, stabilizes TRBP–Dicer complex (Melo et al. 2011; Sousa et al. 2013). Treatment of rats with enoxacin for 1 week increased the expression of miRNAs in the frontal cortex and decreased the proportion of rats exhibiting learned helpless behavior following inescapable shock, suggesting that enoxacin may ameliorate depressive behavior, possibly due to upregulation of miRNAs (Smalheiser et al. 2014).

4.9 Conclusion and Future Directives

It is now established that miRNAs have direct roles in the etiopathogenesis of MDD. MDD is a complex disorder, and heterogeneity is inherently linked to this disease manifestation. Presence of miRNAs biogenesis machinery in the synapse may regulate gene expression locally. Since MDD is associated with altered synaptic plasticity, it will be interesting to examine whether miRNAs are synthesized at the synapse and whether these miRNAs regulate synaptic proteins involved in MDD pathogenesis. The presence of miRNAs in peripheral tissues, particularly, in blood cells provides a promising approach to use miRNAs as potential biomarkers for both diagnosis and treatment response. However, there are several issues that need consideration for the use of circulating miRNAs as biomarkers. For example, the source of miRNAs in blood cells is not clear at the present time. In this regard, profiling exosomal miRNAs derived from the brain may prove useful (Van Giau and An 2016; Banigan et al. 2013). The actively secreted miRNAs are enclosed in exosomes, which can cross blood–brain barrier and are well protected from degradation (Zhang et al. 2015; Cheng et al. 2014). Exosomal miRNAs are processed by the same machinery used in miRNA biogenesis and thus have widespread consequences within the cell by inhibiting the expression of target protein-coding genes (Cortez et al. 2011). Evidence showing that exosomal miRNAs are excreted physiologically in response to stress (Mendell and Olson 2012) and lend the credence that exosomal miRNAs can be ideally used as potential biomarker candidate.

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The Role of Early Life Stress in HPA Axis and Depression

5

Mario F. Juruena, Anthony J. Cleare, and Allan H. Young

5.1 Introduction

Current literature has demonstrated significant associations between traumatic events occurring in childhood and adolescence, called early life stress (ELS), with unfavorable outcomes for the individual's health. Moreover it is now widely accepted that ELS plays a key role in the development of psychiatric disorders. Recent studies have helped us to shed some light on the complex interaction, constant interplay, and possibly bidirectional modulatory effects that these systems have, even in embryo life. They also help us to understand how ELS modulates the capacity of adaptation and how it can produce "scars" that endure for a lifetime. Different areas of very specific subjects of research on different biological mechanisms are now beginning to be integrated, and that advance will hopefully improve our global understanding of mental disorders. It is imperative to find biological substrates and new therapeutic targets and diagnostic models in a psychiatric disease that play a pivotal role in this challenging and exciting task.

The effects of ELS negatively influence child development, affecting all spheres of an individual's life: behavioral, emotional, social, cognitive, and physical (Mclaughlin et al. 2010).

Over the past three decades, a consistent body of research has found childhood abuse to be an important psychosocial risk factor for the development of depression and has also been associated with a poorer clinical course of depression, including earlier illness onset (Gladstone et al. 2004), greater severity of symptoms (Wiersma et al. 2009), and comorbidity (Gladstone et al 2004; Wiersma et al. 2009).

5.2 Early Life Stress

The concept of early life stress is quite broad and includes the different traumatic experiences that occur during childhood and adolescence, which may have repercussions in adulthood. Among these are a parental loss, separation from parents, childhood illness, family violence, and deprivation of food, clothing, shelter, and love.

M.F. Juruena (✉)
Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience-King's College London, London, UK
PO72, London, UK
e-mail: mario.juruena@kcl.ac.uk

A.J. Cleare • A.H. Young
Centre for Affective Disorders, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience-King's College London, London, UK

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Childhood maltreatment is a major social problem. It is a complex global phenomenon that does not respect boundaries of class, race, religion, age, or educational level and can occur both publicly and privately, resulting in serious physical injury or even death. Moreover, its psychological consequences can acutely affect a child's mental health well into adulthood (Friedrich 1998).

Early life stress is associated with a diverse range of psychiatric consequences. In children and adolescents, it increases the risk of behavioral problems, including internalizing and externalizing behavior. Internalizing refers to behavioral symptoms reflected by anxiety, depression, somatic complaints, and inhibition. Externalizing refers to behavioral symptoms reflected by aggression, delinquency, and increased activity level. Sexual behavior problems most likely fall into this domain (Friedrich 1998).

Considerable evidence from various studies suggests a preeminent role for early adverse experiences in the development of mood and anxiety disorders. Child abuse and neglect can be perceived as agents for neurodevelopmental disruption and, depending on when it occurs, can cause serious neurological "scars" in some structures, which could make some individuals vulnerable to certain types of psychopathology, especially depression, post-traumatic stress disorder (PTSD), and substance abuse (Cohen et al. 2001; Heim et al. 2000).

Children and adolescents exposed to ELS experience serious consequences in their biopsychosocial constitution (Zavaschi et al. 2002). The literature shows that, during early childhood and adolescence, important brain structures are being formed, so the negative consequences of traumatic events are lasting and can remain during the life of the children (Teicher 2002). These children and adolescents may experience short- to long-term losses, including damage to health in general (fractures, lacerations, brain injuries) and mental health problems (anxiety, depression, social isolation, suicidal ideation and suicide attempts, substance abuse, conduct disorder, delinquency, and, more specifically, symptoms of post-traumatic stress disorder, such as numbness, chronic anxiety, helplessness, low self-esteem, and sleep and/or nutrition disturbances) at the entrance to adulthood (Koss et al. 2003). Other consequences of ELS are related to cognitive developmental delay, intellectual deficit, and school failure, as well as violence and crime in adolescence (Heim and Nemeroff 2001; Mclaughlin et al. 2010; Neigh et al. 2009; Vitolo et al. 2005).

Nanni et al. (2012) also found that exposure to ELS doubles the risk for depression recurrence. In this sense, researchers point out that approximately 60% of cases of depressive episodes are preceded by the occurrence of stressors, especially of psychosocial origin, so the influence of genetic factors in the development of depression could be due to an increased sensitivity to stressful events (Mello et al. 2009).

In the same direction, occurrence and severity of ELS increase three times the risk for developing depression in adulthood, according to a study presented by Wise et al. (2001). Similar data were found in a recent systematic review conducted by Martins et al. (2011), revealing that the severity of ELS is associated with the severity of depression and also that ELS subtypes are important risk factors for depression in adults. Gibb et al. (2007) have also shown an association between ELS subtypes, specifically emotional abuse, and increased depression symptoms in adulthood. Other studies suggest an increase in suicidal ideation in adulthood in depressed patients with ELS (Mullen et al. 1996; Tunnard et al. 2014).

5.3 Epigenetics and ELS

ELS is an important, although non-specific, risk factor for major psychiatric and medical disorders, and that includes intrauterine stress as well (Cowan et al. 2016; Lupien et al. 2009). Stress in pregnancy has been shown to have a programming effect on the offspring, and one of the most consistent findings is HPA axis alterations (Egliston et al. 2007). Although glucocorticoids (GC) play a vital role in the development of the embryo, prolonged exposures may have deleterious neural effects, especially in brain areas that are rich in cortisol receptors (Egliston et al. 2007).

Pivotal studies of the great Dutch famine of 1944–1945 showed that prenatal maternal

malnutrition was associated with a variety of physical conditions in offspring when adults (Painter et al. 2005), as well as an increased risk of schizophrenia spectrum disorder and depression (Hoek et al. 1998). The offspring of fathers that were intrauterine at that time (grandchildren of the malnourished) were found to have increased risk of obesity, suggesting a transgenerational effect (Veenendaal et al. 2013).

These studies are mentioned only to illustrate the magnitude and complexity of the effects of ELS, and when that can happen, being in childhood, intrauterine or, it seems, even before conception takes place. More studies are needed to elucidate the precise mechanisms of these effects and their relevance in human development and physical and mental health.

Studies of childhood maltreatment and their persistent effects throughout the life span have been more studied, and from now on, we will refer to ELS as stress that occurs in early childhood (Bernstein et al. 1994).

In agreement with Bernstein et al. (2003), childhood maltreatment may be subdivided into the following domains:

(a) Physical abuse: physical aggression by someone older, with the risk of or result of injury
(b) Emotional abuse: verbal aggression that affects the welfare or morals of the child or any conduct that humiliates, embarrasses, or threatens the child
(c) Sexual abuse: any sexual contact or conduct between a child and someone older
(d) Emotional neglect: failure of caretakers to provide for basic emotional and psychological needs such as love, motivation, and support
(e) Physical neglect: failure of caretakers to provide for basic physical needs such as feeding, a home, security, supervision, and health.

Childhood maltreatment significantly contributes to disease morbidity and mortality in adults (Grandjean and Heindel 2008), and it is essential to elucidate the mechanisms by which these early life events can elicit illnesses that become apparent decades after the presumed initial insult, and why some people can adapt yet others will present with an increased risk for psychiatric disorders, especially depression. It seems that complex interactions between genes and environment are responsible for these effects.

5.4 Stress Abnormalities in Depression

The most robust and consistent finding in major depression so far has been its link to the abnormalities of the stress response system. The stress response system is a complex, multilevel mechanism largely dependent on feedback regulation. The suppression of the subgenus prefrontal cortex and the activation of amygdala lead to the stimulation of the hypothalamic-sympathetic-adrenomedullary, or autonomic sympathetic axis, and the hypothalamic-pituitary-adrenal (HPA) axis (Diorio et al. 1993; Phelps and LeDoux 2005; Gold 2015). The autonomic sympathetic axis is responsible for the most rapid response and acts via the secretion of epinephrine by the adrenal glands; the HPA axis is activated minutes after the epinephrine surge and represents a cascade of events starting with the secretion of the corticotropin-releasing factor (CRF) from the paraventricular nucleus of the hypothalamus into the portal circulation, which stimulates the synthesis and release of adrenocorticotropic hormone (ACTH) by the pituitary. The ACTH further stimulates the synthesis and release of the glucocorticoid hormone cortisol by the adrenal cortex. Glucocorticoids are known to exert some functions, including gluconeogenesis, catabolic, antianabolic effects, mild inflammation, insulin resistance, and a prothrombotic state. The key role of glucocorticoids consists in maintaining homoeostasis in response to stress (Juruena 2014).

The basal secretion of cortisol follows a certain circadian pattern. In all species, peak levels are linked to the beginning of the activity period. In humans, cortisol levels increase rapidly within 30 min after awakening (a phenomenon is known as the cortisol awakening response). Further, cortisol levels steadily decrease until late afternoon

hours (4–6 pm) and then, following a short elevation, continue to decrease until they reach their nadir around midnight (Debono et al. 2009). Diurnal ACTH rhythms parallel those of cortisol, despite having a less pronounced amplitude (Carnes et al. 1988).

It is believed that GCs exert their function through two types of receptors: mineralocorticoid receptors (MR) are high-affinity, but low-specificity receptors, which means that they usually bind with basal cortisol which circulates in the blood at lower concentrations than in stress response situations, following a circadian pattern glucocorticoid receptors (GRs), on the other hand, exhibit lower affinity but higher specificity to GCs (De Kloet et al. 1998).

Abnormalities of the stress response system in affective disorders have been implied in several hundred studies (Stetler et al. 2013). In patients with major depression, multiple studies have indicated increases in basal plasma cortisol, urine, salivary, and cerebrospinal fluid (CSF) cortisol (Gibbons 1964; Vreeburg et al. 2009), as well as elevated levels CRF in the CSF compared to control subjects (Nemeroff et al. 1984). There have been contradictory results, Geracioti et al. (1992) for example reporting, a marked decrease in CSF CRH in depressed subjects, whilst other studies indicated significant confounding effects of factors such as disease course or early life stress on HPA axis measurements (Banki et al. 1992; Carpenter and Tyrka 2004). Alteration in diurnal activity patterns of cortisol secretion between depressed and healthy controls has also been demonstrated (Deuschle et al. 1997).

Along with basal measurements, much effort has been put into assessing the functional impairments of the HPA axis. For this aim, some challenge tests have been introduced. The first and most thoroughly investigated test that found application for depression studies is the dexamethasone suppression test (DST). Bernard Carroll et al. (1968) showed that depressed patients fail to suppress plasma cortisol to the same extent as non-depressed controls. The impaired feedback inhibition has been demonstrated in depressed patients by a variety of studies, many occurring in the 1970s and the 1980s, showing a lack of suppression of HPA axis activity by dexamethasone (Arana et al. 1985; Ribeiro et al. 1993). Despite the fact that high hopes were set on DST as a diagnostic test for melancholic depression in the 1980s (Hayes and Ettigi 1983), its sensitivity was quite low, and its specificity remained at 70–80%.

Gold et al. (1984) were the first to introduce a CRH test to assess cortisol and ACTH response in patients with depression, and they demonstrated that ACTH was significantly blunted in patients vs controls. Holsboer-Trachsler et al. (1991) introduced a combined DST/CRH test for depression, which demonstrated the failure of dexamethasone to prevent pituitary-adrenocortical activation by CRH (not attributable to decreases in dexamethasone levels) in depressed patients. They also demonstrated the normalization of plasma cortisol response to DST/CRH after treatment but not of ACTH response.

More recently, an alternative test to the DST was introduced—the prednisolone suppression test (Pariante et al. 2002). Prednisolone's affinity to GRs has been shown to be more comparable to that of cortisol compared to dexamethasone (Juruena et al. 2006). Besides, prednisolone also binds to MR, which, although not thoroughly evaluated to date, appears also to be dysfunctional in depression (Baes et al. 2014); therefore, the PST allows one to probe the function of both GR and MR receptors (Juruena et al. 2009, 2010).

In summary, the majority of the studies show that early life stress leads to permanent changes in the HPA axis and may lead to the development of depression in adults. The most consistent findings in the literature show increased activity of the HPA axis in depression associated with hypercortisolemia and reduced inhibitory feedback. These findings suggest that this dysregulation of the HPA axis is partially attributable to an imbalance between glucocorticoid (GR) and mineralocorticoid (MR) receptors. Evidence has consistently shown that GR function is impaired in major depression, but few studies have assessed the activity of MR in depression and early life stress (Baes et al. 2012).

5.5 ELS, HPA Axis, and Corticoid Receptors

Saridjan et al. (2010) found that infants experiencing social disadvantage and family adversity have higher cortisol response to awakening (CAR) than infants not exposed to social or familial adversity. Carpenter et al. (2007) established similar results that emotional neglect and sexual abuse strongly predicted maximal cortisol release. High levels of cortisol lead to hippocampal damage as seen in patients with major depressive disorder and a history of emotional neglect during childhood. These patients had reduced left hippocampal white matter compared to those without a history of emotional neglect (Frodl et al. 2010). This evidence indicates that childhood trauma changes hippocampal structures during brain development leading to a higher vulnerability for stress-related psychiatric disease later in life such as depression.

Childhood trauma is associated with decreased responsiveness to pharmacological treatment (Hayden and Klein 2001) and a higher likelihood of relapse (Lara et al. 2000). Among chronically depressed patients with no history of early trauma, combination of pharmacological (nefazodone) and psychotherapy treatment was most effective in attaining remission. In contrast, in chronically depressed patients with early life trauma, remission rates were significantly higher for psychotherapy alone versus nefazodone. For these patients with early life trauma, combination treatment did not have any further advantage over psychotherapy alone. This suggests that psychotherapy is an essential element of treatment for depressed patients with childhood trauma.

Dysregulation of the HPA axis is one of the most consistent findings in patients with depression and ELS (Heim et al. 2000; Juruena 2014). Patients with ELS are more likely to show hyperactivity of the HPA axis and present symptoms that are usually resistant to standard antidepressants but instead benefit from adjuvant treatment with psychotherapy (Nanni et al. 2012).

Evidence indicates that stress in the early phases of development can induce persistent changes in the ability of the HPA axis to respond to stress in adulthood and that this mechanism can lead to a raised susceptibility to depression. These abnormalities appear to be related to changes in the ability GCs to exert negative feedback on the secretion of HPA hormones through binding to GR and MR (Juruena 2014).

In humans, while MRs are thought to be involved in the tonic inhibitory activity within the HPA axis, GRs appear to "switch off" cortisol production at times of stress. It seems that MRs are necessary for GC regulation of HPA axis activity during mild stressors but not during stressors that result in a stronger corticosteroid response. It is proposed that the maintenance of corticosteroid homoeostasis and the balance in MR-/GR-mediated effects limit vulnerability to stress-related diseases in genetically predisposed individuals (Juruena 2014).

Three different mechanisms of GR resistance have been considered: (1) downregulation secondary to persistent hypercortisolism, (2) a primary alteration in the genetic structure, and (3) a decrease in GR function secondary to alterations in ligand-independent pathways. It has also been proposed that the balance between MR and GR is an important factor in resilience to stress, and studies suggest that there may be an imbalance in the MR/GR ratio in depression (Baes et al. 2014). Another possibility (that can happen concomitantly or independent) is the excessive production of corticotropin-releasing factor (CRF) from the hypothalamus.

This structure receives fibers from some brain areas, notably the brain stem (that receives input from all sensory systems), the prefrontal cortex, and the limbic system (i.e., amygdala) (Ulrich-Lai et al. 2009). The chronic overexpression of CRF in the amygdala is also associated with altered gene expression in the hippocampus and PVN, leading to increased hyperactivity (Flandreau et al. 2012). These afferents play an important role in HPA responses to behavioral and emotional stimuli. The elevated CRF secretion will persistently stimulate the HPA axis, leading ultimately to increase in GC levels and to possible mechanisms of dysfunction in GR and MR already described. The prolonged exposure to GC

has damaging effects on important brain structures, mainly the hippocampus, that are essential for HPA axis restraint, as well as memory consolidation. The role of GC and stress in memory was recently reviewed and linked with potential psychiatric disorders (de Quervain et al. 2017).

In clinical practice it is important to recognize that not everybody with childhood trauma develops depression and vice versa. Gaining a thorough background and history during the diagnostic interview and assessment becomes important to understand the role of trauma and/or neglect in our patients. Part of this process should also reflect the fact that our interpretation and understanding of trauma may differ greatly from our patients. Children often try to protect and defend their parents; they may minimize abuse or may not view certain actions as abuse. An adult that has experienced childhood trauma may not want to revisit these events.

It is clear from the above data that psychotherapy should be the core component of treatment for depressed patients with a history of early childhood stress. It is also important to consider the role of different types of traumas at different developmental stages to elucidate whether there are precise developmental time periods for prevention of the adverse outcomes of childhood trauma.

5.6 Depression and ELS

Major depression is undoubtedly one of the major healthcare issues in the twenty-first century. According to the latest WHO report on February 23, 2017, depression is now ranked as the single largest contributor of years lived with disability. From 2005 to 2015, there was an 18% increase in the prevalence of depression. This determines the growing economic burden and the pressing need for the determination of precise mechanisms leading to depression (WHO 2017).

Approximately eight out of ten people who experience a major depressive episode will have one or further episodes during their lifetime (i.e., a recurrent major depressive disorder); therefore, early diagnosis and effective treatment are vital for reducing the effect of depression on the life of the individual, family, and community (Fava et al. 2006). Studies estimate that the currently available antidepressant treatments are ineffective in 30–50% of depressed patients; treatment-resistant depression (TRD) is diagnosed in, those patients who do not respond to antidepressant treatment taken for a sufficient of time at an adequate dose.

Maltreated children have a moderately increased risk of depression in adolescence and adulthood, which will partially mirror the family context in which the maltreatment occurred. Depression is common. Approximately one-quarter to one-third of maltreated children will meet the criteria for major depression by their late 20s, thus representing a substantial public health burden. For many of the affected individuals, the onset of depression begins in childhood, underscoring the importance of focusing on early intervention before the symptoms of depression appear in the abused and neglected children (Mello et al. 2007).

In a meta-analysis Nanni et al. (2011) found that exposure to childhood maltreatment doubled the risk of both depressive episode recurrence and persistence. Both epidemiological (Asgeirsdottir et al. 2011) and clinical studies of patients with depression (Zisook et al. 2011) have reported associations between childhood abuse and suicidal behaviors. Childhood trauma in humans is associated with sensitization of the neuroendocrine stress response, glucocorticoid resistance, and increased HPA axis activity (Heim et al. 2008).

Hormones play a critical role in the development and expression of a wide range of behaviors. One aspect of the influence of hormones on behavior is their potential contribution to the pathophysiology of psychiatric disorders and the mechanism of action of psychotropic drugs, particularly in depression. Of the endocrine axes, the HPA axis has been the most widely studied. It plays a fundamental role in response to external and internal stimuli, including psychological stressors. Abnormalities in the function of the HPA axis have been described in people who experience psychiatric disorders (Nemeroff 1996).

Studies conducted in both animals and humans suggest that stress experienced during the early phases of development can induce persistent changes in the ability of the HPA axis to respond to stress in adulthood, increasing the susceptibility to depression (Glover and O'Connor 2002). Evidence suggests that neurochemical and molecular changes induced by stressful situations and depression trigger changes in the HPA axis. Findings derived from multiple lines of research have provided evidence that during the depression, dysfunction of limbic structures, including the hypothalamus and hippocampus, results in hypersecretion of corticotropin-releasing factor (CRF), dehydroepiandrosterone, and vasopressin, which in turn determines HPA activation. A flaw in this system caused by factors such as excessive stress, high glucocorticoid levels, social isolation, and depressive symptoms results in difficulty adapting to stress and can predispose the individual to depression by impairing hippocampal serotonergic neurotransmission that is related to depressive disorders.

According to Wiersma et al. (2009), ELS is associated with chronicity of depression, and multiple stresses early in life can be viewed as independent determinants of chronic depression. Still within the mood disorders, Leverich et al. (2002) believe that the presence of ELS leads to a more severe course of bipolar disorder.

Emotional neglect was associated with mood disorders in four studies (Wiersma et al. 2009). It was associated with both depressive episodes and depressive symptoms. It can be seen as an independent and significant determinant of chronicity of depression. It is associated with an earlier onset of the first depressive episode (Tofoli et al. 2011).

Recent studies have shown that depressed patients with a history of childhood trauma and chronic forms of major depression are more likely to show hyperactivity of the HPA axis and to present symptoms that are resistant to standard antidepressants but instead benefit from adjuvant treatment with psychotherapy (Nemeroff et al. 2003). It has been concluded from these studies that child maltreatment may lead to disruptions in HPA axis functioning and that factors such as the age of maltreatment, parental responsiveness, subsequent exposure to stressors, type of maltreatment, and type of psychopathology or behavioral disturbance displayed may influence the degree and pattern of HPA disturbance. However, results from studies examining the relationship between child maltreatment, psychopathology, and the HPA axis do vary. While most studies report HPA axis dysregulation, inconsistencies have been noted. Furthermore, results should be analyzed by gender and by type of stressor for maximum consistency, as the effects on the HPA axis may vary due to these factors.

5.7 Synthesis

Studies of the association between early life stress, circulating cortisol and psychiatric disorders should be evaluated carefully. No consensus has been reached in the literature regarding the concept of early life stress, and the respondents in these studies may have underestimated or overestimated the frequency/intensity of events. Much descriptive work has been published on the relationship between adult psychopathology and early adversities such as parental loss in childhood, inadequate parental care, divorce, "affectionless" or dysfunctional parenting, childhood physical and sexual abuse, and other childhood traumas. Importantly, mood disorders such as depression are most associated with the occurrence of early life stress subtypes. The results of existing studies suggest the importance of preventing early life stress and its consequences in both the short and long term. Intervention at an early stage can reduce the likelihood of developing health problems in the long term and re-victimization in adulthood. Furthermore, early interventions may reduce the burden of public spending on health care for abused individuals.

The more recent studies reviewed in the present chapter suggest that early life stressors are associated with an increased risk for mood disorders in adulthood. This review examined the emerging literature concerning the relationship between stress, HPA axis function, and depression and early life stress as an important risk

factor for HPA axis dysregulation. The most consistent findings in the literature show increased activity of the HPA axis in depression associated with hypercortisolemia and reduced inhibitory feedback. These findings suggest that this dysregulation of the HPA axis is partially attributable to an imbalance between GRs and MRs. Evidence has consistently demonstrated that GR function is impaired in major depression, resulting in reduced GR-mediated negative feedback on the HPA axis, but few studies have assessed the activity of MRs in depression. Thus, although a few studies suggested that MR activity remains intact or is possibly oversensitive to compensate for reduced GR function in depressed patients, more studies are needed to elucidate this issue (Young et al. 2003; Juruena et al. 2009).

Conclusion

Social and physical environments have an enormous impact on our physiology and behavior, and they influence the process of adaptation or allostasis. At the same time that our experiences change our brain and thoughts (i.e., changing our mind), we change our neurobiology. Although disturbances in the HPA axis are an important factor in the etiology of depression and severe treatment resistance, very little is known about the neurobiology of these disorders. Therefore, a psychometric assessment that quantifies the level of early life stress, recent stress, the evolution of affective symptoms and diagnosis, and neuroendocrine activity is essential. Childhood stressful events and HPA axis overactivity in adulthood are not specific to depressive states, but several studies have linked these conditions. As demonstrated in this review, early life stress can lead to permanent changes in the HPA axis and may lead to the development of depression in adulthood. Considering the importance of early detection of violence in childhood and adolescence, to prevent the development of severe and disabling psychiatric disorders in adulthood, further research is needed to elucidate the mechanisms involved in the association between early stress and the development of psychopathology in adulthood. Stressful life experiences also play a prominent role in the development of major depression; several lines of research suggest the possibility that personality or temperament may account for some of the association between stress, depression, and HPA axis hyperactivity.

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Part II

Molecular- and Cellular-Level Aspects of Depression

6 Complex Role of the Serotonin Receptors in Depression: Implications for Treatment

Meysam Amidfar, Lejla Colic, Martin Walter, and Yong-Ku Kim

6.1 Introduction

Monoamine serotonin or 5-hydroxytryptamine (5-HT) is a well-known neurotransmitter that has been implicated in the pathophysiology of major depressive disorder (MDD), as well as in the mechanisms of action of many antidepressants (Stockmeier 2003). In interaction with its receptors (5-HTRs) both in the brain and in peripheral tissues, 5-HT regulates various biological functions including mood, sleep, appetite, circadian rhythms, and energy balance (Baganz and Blakely 2012). Previous findings on reduced levels of serotonin metabolites in plasma and cerebrospinal fluid (CSF) of depressed patients, together with the effects of tryptophan depletion on mood, have pointed toward dysfunction of the serotonergic system in depression. The efficacy of selective serotonin reuptake inhibitors (SSRIs) in the treatment of MDD provides further evidence for the functioning of the serotonergic system as a susceptibility factor for developing MDD (Jans et al. 2007). Excitatory and inhibitory properties of different 5-HT receptor subtypes result in complex participation in the antidepressant-like effects of SSRIs (Stahl 1998). It is known that the expression of multiple 5-HTRs on individual neurons produces differential effects of 5-HT on neurons (Mengod et al. 2006). Therefore, individual 5-HT receptors—according to each discrete receptor profile—can be seen as candidates for creating a newer generation of antidepressants, which may be more beneficial and efficient than traditional ones such as SSRIs (Carr and Lucki 2011).

M. Amidfar
Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran

L. Colic
Clinical Affective Neuroimaging Laboratory, Department of Behavioural Neurology, Leibniz Institute for Neurobiology, Magdeburg, Germany

M. Walter
Clinical Affective Neuroimaging Laboratory, Department of Behavioural Neurology, Leibniz Institute for Neurobiology, Magdeburg, Germany
Center for Behavioral Brain Sciences, Magdeburg, Germany

Department of Psychiatry and Psychotherapy, University of Tübingen, Tübingen, Germany

Max Planck Institute for Biological Cybernetics, Tübingen, Germany

Y.-K. Kim (✉)
Department of Psychiatry, College of Medicine, Korea University, Seoul, South Korea

Department of Psychiatry, Korea University Ansan Hospital, College of Medicine, Ansan, South Korea
e-mail: yongku@korea.edu

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6.2 Physiological Function of Serotonin Receptors

At least 15 different 5-HTRs are divided into seven families (5-HTR1–7) in accordance with their signaling mechanisms, and 18 genes have been identified for mammalian 5-HT receptor subtypes (Barnes and Neumaier 2011). In the 5-HTR family, 5-HT3 receptors are the only ionotropic receptor type. They are Cys-loop, ligand-gated, nonselective, cation channels most permeable to Ca^{2+}, Na^{+}, and K^{+} (Bétry et al. 2011). All other 5-HTRs are members of the G-protein coupled receptor (GPCR) superfamily and are similar in their capacity to activate downstream intracellular second messenger cascades (Pauwels 2003). However, activation of these cascades originating from GPCR 5-HTRs activation is brought by varied mechanisms. Specifically, 5-HTR1 and 5-HTR5 decrease cyclic AMP (cAMP) in cells. In contrast, the stimulation of 5-HTRs 4, 6, and 7 is related to upregulated cAMP activity (Millan et al. 2008). Members of the 5-HTR2 family, on the other hand, are connected to the phospholipase C (PLC), inositol triphosphate (IP3), and diacylglycerol (DG) pathways, which lead to enhanced intracellular Ca^{2+} release, and, consequently, mediate excitatory neurotransmission (Barnes and Neumaier 2011). Table 6.1 and Fig. 6.1 summarize physiological and other properties of 5-HT receptors.

Table 6.1 Summary of structure, function, and localization of the 5-HT receptors

Receptor	Neuronal location	Structure	Mechanism of action	Type	Brain localization
5-HT1A	Somatic autoreceptor/ postsynaptic	Gi/G0-protein coupled	↓cAMP G-protein coupled K^{+} current	Inhibitory	Cerebral cortex, hippocampus, septum, amygdala, raphe nucleus
5-HT1B	Terminal autoreceptor/ postsynaptic	Gi/G0-protein coupled	↓cAMP	Inhibitory	Striatum, basal ganglia, frontal cortex
5-HT2A	Postsynaptic	Gq11-protein coupled	↑PLC	Excitatory	Prefrontal cortex
5-HT2C	Postsynaptic	Gq11-protein coupled	↑PLC	Excitatory	Prefrontal cortex, limbic system, basal ganglia, hypothalamus
5-HT3	Postsynaptic	Ligand-gated Na^{+}/ K^{+} channel	Ion conductance (K^{+}, Na^{+}, Ca^{2+})	Excitatory	Cortical areas, amygdala, brainstem, hippocampus
5-HT4	Postsynaptic	Gs-protein coupled	↑cAMP	Excitatory	Limbic system
5-HT6	Postsynaptic	Gs-protein coupled	↑cAMP	Excitatory	Cortical areas, limbic system
5-HT7	Postsynaptic	Gs-protein coupled	↑cAMP	Excitatory	Thalamus, hypothalamus, hippocampus, frontal cortex, amygdala

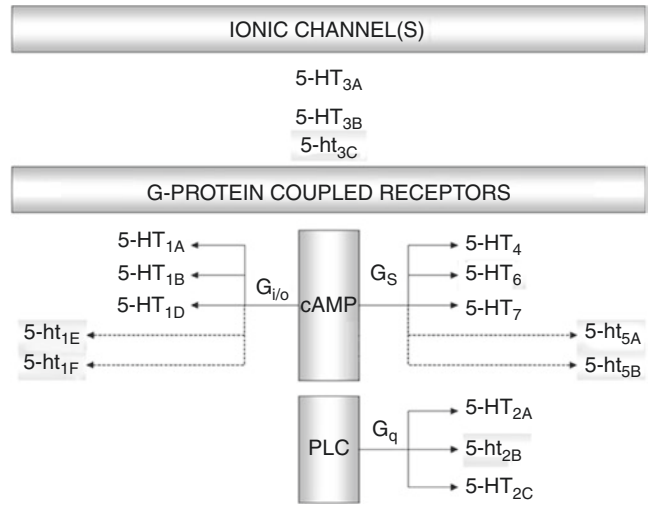

Fig. 6.1 Picture depicts division of the 5-HT receptors subtypes (Hoyer et al., 2002). The role of 5-HT receptor subtypes characterized by lower case label in antidepressant responses has not been elucidated. Abbreviations: cyclic adenosine monophosphate (cAMP); phospholipase C (PLC)

6.3 5-HT1A Receptors

Receptors identified as 5-HT1A receptors are distributed presynaptically as autoreceptors on the somatodendritic regions of serotonergic neurons and postsynaptically on the terminal fields of the serotonergic system. These receptors are located on both excitatory pyramidal cells and inhibitory interneurons of corticolimbic regions including the cerebral cortex, hippocampus, septum, amygdala, and raphe nucleus (Pytliak et al. 2011). Thus, inhibiting the 5-HT1A autoreceptor activation and stimulation of the 5-HT1A postsynaptic receptors could theoretically result in the enhancement of serotonin transmission (Mann 1999). Both the presynaptic and the postsynaptic neuronal 5-HT1A receptors inhibit cAMP formation, inactivate calcium channels, and activate potassium channels through Gi/Go-protein coupling (Barnes and Neumaier 2011). Numerous pharmacological, postmortem, positron-emission tomography (PET), and genetic studies have demonstrated the impact of the 5-HTR1A on the response to antidepressants. Several postmortem studies of suicide victims have revealed decreased somatodendritic and postsynaptic 5-HT1A receptor gene expression, binding, and/or quantity (Boldrini et al. 2008; Hirvonen et al. 2008). This is consistent with replicated PET analyses, which reported decreased 5-HT1A receptor binding potential in brain regions such as the dorsal raphe, medial prefrontal cortex (mPFC), amygdala, and hippocampus (Boldrini et al. 2008; Hirvonen et al. 2008). In humans, genetic studies have described the association between the G allele of a single-nucleotide promoter polymorphism (SNP) found within the promoter sequence of the 5-HT1A receptor gene (HTR1A:–1019C/G; rs6295) with an increase in the raphe 5-HT1A autoreceptor expression and, furthermore, with a decrease in the postsynaptic 5-HT1A receptor expression in patients with MDD (Lemonde et al. 2003; Parsey et al. 2008). Based on these findings, it is hypothesized that MDD patients carrying the G allele may experience upregulation of the auto-inhibitory somatodendritic 5-HT1A receptor expression and downregulation of the postsynaptic 5-HT1A receptor expression, which, as a consequence, results in decreased 5-HT release. Conversely,

depressed patients that are homozygous for the C allele have been reported to respond better to antidepressant (AD) drugs (Lemonde et al. 2004; Serretti et al. 2004). Upregulation of the postsynaptic 5-HT1A receptor signaling has been demonstrated through both direct and indirect effects of SSRIs, tricyclic antidepressants (TCAs), and electroconvulsive shock therapy (ECT) (Savitz et al. 2009). It has been hypothesized that ADs enhance serotonergic signaling either through desensitization of the somatodendritic autoreceptors in the raphe or by activating G-protein cascades via the postsynaptic 5-HTR1A (Savitz et al. 2009). The autoreceptor desensitization process which includes internalization and a reduction in numbers usually occurs after 2–3 weeks of medication with SSRIs, implying that the observed prolongation in therapeutic efficacy is due to the adaption of the serotonergic autoreceptors (Albert and Lemonde 2004; Blier et al. 1987). In accordance with the desensitization hypothesis (Blier et al. 1987), co-administration of a selective serotonin reuptake inhibitor and a 5-HT1A receptor antagonist causes an additional increase in extracellular serotonin levels, thereby accelerating a patient's response to antidepressant treatment (Cremers et al. 2000). Furthermore, numerous open-label and double-blind, placebo-controlled studies have demonstrated that addition of the 5-HTR1A antagonist pindolol to a treatment regimen led to a more rapid onset of AD activity, as well as an increase in the effectiveness of SSRI therapy (Martinez et al. 2000). Additionally, 5-HTR1A agonists such as buspirone, gepirone, and vilazodone, particularly when combined with pindolol or SSRIs, have shown positive results in placebo-controlled studies of depression (Blier et al., 1997; Blier and Ward 2003; Khan et al. 2014). This accelerated antidepressant response may be due to a bypassed 5-HT1A autoreceptor desensitization process by blocking this receptor (Blier and Ward 2003). Nevertheless, conflicting findings in pharmacological, postmortem, PET, and genetic studies are found within the existing literature, demonstrating the complexity of the 5-HT1A receptor function and its signaling system. This warrants further systematic studies of 5-HTR1A receptor modulators, with special regard to neuroanatomical location.

6.4 5-HT1B Receptors

Receptors known as 5-HTR1B are distributed through the CNS, with highest densities found in ventral striatum and globus pallidus surrounding the nucleus accumbens (NAc), regions that have shown an emerging role in the functional neuroanatomy of depression (Murrough et al. 2011). A large amount of evidence supports the role of 5-HT1B receptors in depression, including lower mRNA expression of the 5-HT1B receptor in the dorsal raphe nucleus of animal model, lower expression in the frontal cortex, and higher expression in the paraventricular nucleus of suicide subjects, as also lower 5-HT1B receptor binding potential in the ventral striatum of depressed subjects (reported by one PET study) (Murrough et al. 2011; Tiger et al. 2014). Moreover, a study found association between gene polymorphism of the 5-HT1B receptor and major depression (Yung-yu et al. 2003). Additionally, significant reduction of binding potential has been found after psychotherapy in dorsal brainstem (DBS), area that contains raphe nuclei (Tiger et al. 2014). These findings support therapeutic rationale for investigating 5-HT1B agonists as a new class of antidepressants (Murrough et al. 2011). In this regard, antidepressant effect of the 5-HT1B agonist anpirtoline in the forced swim test was found to be particularly dependent on the 5-HT1B heteroreceptors on dopaminergic neurons rather than on the autoreceptors on 5-HT neurons (Chenu et al. 2008). On the other hand, it has also been reported that combined administration of 5-HT1B receptor antagonists with paroxetine specifically facilitated antidepressant-like effects during forced swim tests in rats (Tatarczyñska et al. 2002). Additionally, it has been proposed that chronic treatment with ADs may induce downregulation of 5-HTR1B mRNA levels in the dorsal raphe. This may reduce the inhibitory efficacy of the

5-HT1B autoreceptors, thus leading to enhancement of 5-HT release (Anthony et al. 2000). Further, it has been reported that part of the therapeutic effects of citalopram and paroxetine are blocked by selective 5-HT1B receptor antagonists, showing that these particular drugs may exert their antidepressant effects through the 5-HT1B receptors (Chenu et al. 2008). In addition, infusion of a 5-HT1B agonist into a subject's caudate and putamen—but not into the hippocampus, substantia nigra, or frontal cortex—has indicated a location-specific antidepressant effect (Chenu et al. 2008). In sum, brain localization of the 5-HT1B receptors and their roles as heteroreceptors on non-serotoninergic neurons or as autoreceptors on serotoninergic neurons needs to be considered in order to accurately account for conflicting preclinical findings. This line of research will help determine the effects of this receptor subtype on depression and its antidepressant mechanisms.

6.5 5-HT2A Receptors

A high density of 5-HT2A receptors is found in prefrontal cortex (PFC), a brain structure involved with high-order cognitive and emotional processing (Pompeiano et al. 1994). Serotonergic neurotransmission and the resulting activation of the postsynaptic 5-HT2A receptors in the PFC have an important role in the control of neuronal activity in this area of the brain (Guiard and Di Giovanni 2015). Postmortem studies have revealed enhanced binding sites for the 5-HT2A receptors in the cortex of suicide depressive victims (Hrdina et al. 1993). Subsequent postmortem reports have shown an enhancement of the 5-HT2A receptor densities in the postmortem prefrontal cortex of patients with MDD and have suggested that it may be associated with decreased activity of protein kinase A (Shelton et al. 2009). This enhancement of binding sites was also demonstrated in vivo in medication-free patients with depression in a PET study (Bhagwagar et al. 2006). In parallel, chronic treatment with SSRIs and other ADs has been shown to cause decreased 5-HT2A receptor density in the frontal cortex of rodents (Peroutka and Snyder 1980). A PET study by Strome et al. (2005) showed that chronic electrocerebral silence (ECS) decreased 5-HTR2 binding in nonhuman primates, thus implicating the downregulation mechanisms of 5-HTR2Rs might be a compensatory response to increased 5-HT (Strome et al. 2005). Furthermore, variations in 5-HT2A receptor gene encoding have been associated with different outcomes of SSRI treatment in MDD patients (Lucae et al. 2010). Based on genetic association studies, the *C* allele and the rare *TT* variant of the *HTR2A* (rs6314, His452Tyr, *1354C/T*) single-nucleotide polymorphism were shown to be related to susceptibility and to severity of major depressive episodes in MDD patients (Petit et al. 2014). Drugs with prominent 5-HT2 receptor antagonist properties, together with SSRIs, effectively enhanced the therapeutic response in patients with major depression (Marek et al. 2003). Several open-label, double-blind, and placebo-controlled studies have reported that 5-HT2A receptor antagonists such as mianserin, olanzapine, and risperidone, in combination with SSRIs, rapidly induced antidepressant effects and further enhanced the efficacy of SSRIs, including patients with treatment-resistant depression (Marek et al. 2003).

6.6 5-HT2C Receptors

Regions including the prefrontal cortex, limbic system, basal ganglia, and hypothalamus appeared in the global distribution of 5-HT2C receptor mRNA expression (aan het Rot et al. 2009; Leysen 2004). The majority of the 5-HT2C receptors are postsynaptic, somatodendritic heteroreceptors, which exhibit modulatory action on GABAergic, on glutamatergic, and, in particular, on dopaminergic neurons in the mesolimbic and nigrostriatal pathways (Clemett et al. 2000; Jensen et al. 2010; Leysen 2004). Specific 5-HTR2C mRNA editing has been shown to produce functionally different isoforms with varying signaling cascades, desensitization rates, and

drug-induced functional activation (Jensen et al. 2010). Moreover, clinical research has demonstrated enhanced 5-HT2C receptor mRNA editing in the frontal cortex of depressed suicide victims (Martin et al. 2014). Several lines of evidence suggest that antagonists of the 5-HT2C receptors may be relevant for the treatment of major depression. For example, the improvement of symptoms with traditional antidepressants has been shown to co-occur with reduced 5-HTR2C function (Bristow et al. 2000). Common SSRIs such as sertraline, paroxetine, and citalopram (with the exception of fluoxetine) do not display affinity for the 5-HTR2C. On the other hand, other antidepressants including mianserin, mirtazapine, trazodone, and nefazodone show high affinity for this receptor (Sánchez and Hyttel 1999). Specific atypical antipsychotics, which are also 5-HTR2C antagonists, augment SSRI-induced increased extracellular 5-HT levels. Going forward, this pharmacological profile may suggest the efficacy of these drugs as agents to augment the therapeutic effects of SSRIs in treatment-resistant patients (Nelson and Papakostas 2009). Both 5-HTR2C agonists (Rosenzweig-Lipson et al. 2007) and antagonists—for example, mianserin and agomelatine (Cardinali et al. 2012)—are reported to have antidepressant effects in both animal models and clinical practice. Paradoxically, similar behavioral effects of the 5-HT2C receptor agonists and antagonists with opposite pharmacological profiles can be explained through diverse mechanisms (Carr and Lucki 2011). For example, global potentiation of postsynaptic receptors activates neurons and induces antidepressant effects. However, the 5-HT2C receptor antagonists may produce similar AD-like effects by facilitating the release of other neurotransmitters, such as norepinephrine and dopamine (Carr and Lucki 2011). Finally, genetic variation in the 5-HTR2C receptors (cys-23ser polymorphism) has been deemed as a vulnerability factor for affective disorders and suicide susceptibility (Martin et al. 2014).

6.7 5-HT3 Receptors

Receptors known as 5-HT3 receptors show global distribution in rodent corticolimbic structures, which are crucial for fear, memory, and emotion processing (Bétry et al. 2011). The specific location is however differential. In cortical areas, amygdala and brainstem receptors are located on axons and terminals, whereas in hippocampus, they are postsynaptic (Miquel et al. 2002). The 5-HT3 receptor has been recognized as a target for potential antidepressant drugs (Rajkumar and Mahesh 2010). Variable results have been reported for the antidepressant-like effects of 5-HT3 receptor agonists in rodent behavioral tests. Some studies have noted that 5-HT3 receptor agonists alone or in combination with other antidepressants are ineffective in forced swim tests in animal subjects, while other research even suggests that 5-HT3 receptor agonists decrease the effects of antidepressants in certain animal models (Nakagawa et al. 1998; Redrobe and Bourin 1997). On the other hand, 5-HTR3 antagonists including zacopride, ondansetron, and tropisetron have shown effects that are similar to the conventional antidepressants in a battery of behavioral animal models of depression (Bétry et al. 2011). Interestingly, the augmented efficacy of fluoxetine, venlafaxine, and citalopram combined with chronic ondansetron pretreatment has been reported in rodent forced swim tests. This result is likely due to the postsynaptic 5-HRT3 mediation (Ramamoorthy et al. 2008). It has been recently implied that due to a combination of SERT inhibition, paroxetine and 5-HT3 receptor blockage, ondansetron offers a synergistic 5-HT augmentation and antidepressant-like effect in forced swim, a measure of depression-like behavior in rodents (Bétry et al. 2015). Accordingly, it is worthwhile to test this combination strategy in depressed patients because both SSRIs and 5-HT3 receptor antagonists are already extensively used in clinical practice (Bétry et al. 2015). In addition, some antidepressants including imipramine, fluoxetine,

mirtazapine, and phenelzine show affinity for the 5-HT3 receptors (Rajkumar and Mahesh 2010). 5-HTR3 genetic polymorphisms also contribute to depressive phenotypes. The HTR3A "CC genotype" is related to changes in brain structures linked to emotion processing (Gatt et al. 2010). Furthermore, the HTR3A gene interacting with the BDNF gene may enhance the risk for depression via disturbance to emotion-processing networks (Gatt et al. 2010).

6.8 5-HT4 Receptors

A high density of serotonin 5-HTR4s can be found in limbic regions of the brain, including the nigrostriatal and mesolimbic systems, as well as the septum, hippocampus, and amygdala (Hannon and Hoyer 2008). Compared to traditional antidepressants, which show results only after 2–3 weeks of treatment, previous investigations have proposed that 5-HT4 receptor agonists are a putative class of antidepressants with a rapid onset of action (Lucas et al. 2007). Decreased 5-HTR4 density in rat brains has been found through chronic administration of fluoxetine or venlafaxine but not reboxetine (Samuels et al. 2016). Activation of the 5-HT4 receptors was suggested as one of the underlying mechanisms of the antidepressant-like effects of SSRIs (Samuels et al. 2016). The work of Lucas et al. (2007) demonstrated that partial agonists of the 5-HTR4—for example, prucalopride and RS 67333—produced behavioral and neurochemical antidepressant-like effects with a rapid onset of action. It was further elucidated that a 3-day regimen with the 5-HT4 agonist RS 67333 induced markers of antidepressant action, including desensitization of the 5-HT1A autoreceptors, increased tonus of the hippocampal postsynaptic 5-HT1A receptors, increased phosphorylation of the CREB protein, and neurogenesis in the hippocampus. These types of alterations are usually detected only after several weeks of treatment with traditional antidepressants (Lucas et al. 2007). In addition, the 5-HTR4 agonist RS 67333 displayed potential in several animal models of depression including forced swim test, olfactory bulbectomy, and chronic mild stress (Lucas et al. 2007). Interestingly, RS 67333 combined with fluvoxamine, citalopram, or fluoxetine displayed better behavioral effects in forced swim test than any of the agents given alone (Lucas et al. 2010). Additional action of the 5-HT4 receptor agonists on learning and memory, combined with their rapid antidepressant effects, has established them as unique antidepressive compounds (Carr and Lucki 2011; Meneses 2007). Furthermore, SL65.0155, a 5-HTR4 partial agonist, induced antidepressant-like properties in the forced swim test via changes in the expression of hippocampal transcription and the growth factors, including p-CREB, BDNF Bcl-2, and VEGF (Tamburella et al. 2009). Evidence from human studies indicated changes in both 5-HT4 receptor binding and cAMP concentration levels in a number of brain areas of depressed suicide victims (Rosel et al. 2004). Furthermore, it was reported that a polymorphism in gene encoding for the 5-HT4 receptor was related to unipolar depression (Ohtsuki et al. 2002).

6.9 5-HT6 Receptors

5-HT6 receptors have been found in corticolimbic areas of the brain (Wesołowska 2010). Pharmacologically, antipsychotic drugs such as clozapine, olanzapine, and quetiapine together with ADs such as clomipramine, amitriptyline, and doxepin have shown antagonistic properties without selectivity for the 5-HT6 receptor (Carr and Lucki 2011). Additionally, some tricyclic antidepressant drugs (such as amitriptyline) and some atypical antidepressants (such as mianserin) have also shown high-affinity and antagonistic activity at the 5-HTR6 (Wesołowska 2010). It has been further reported that both selective 5-HT6 receptor agonists and antagonists can augment cognitive behavioral outcomes in rodents,

suggesting an advantageous impact that may enhance the clinical effects of SSRIs (Carr and Lucki 2011). Antidepressant effects of 5-HT6 receptor agonists have been reported in depression tests in mice and rats. Reduced immobility time in the mouse tail suspension test was indicated after administration of the 5-HTR6 agonist EMDT. Correspondingly, the antidepressant effects of EMDT and fluoxetine were blocked by the 5-HT6 antagonist SB271046 (Svenningsson et al. 2007). On the other hand, augmented effects of antidepressant treatment with the 5-HT6 receptor antagonists have also been reported in animal models of depression (Wesołowska and Nikiforuk 2008). A possible explanation for these contradictory findings is that 5-HT6 receptor agonists and antagonists generate diverse downstream neurochemical effects in neurons that cause analogous behavioral results. With this in mind, reported behavioral effects of the 5-HT6 receptors are similar to the known SSRI mechanisms of action on the global stimulation of the postsynaptic 5-HT receptors and on the release of other neurotransmitters, namely, dopamine and norepinephrine (Carr and Lucki 2011). Data from two genetic association studies revealed both negative and positive associations between the 5-HTR6 (C267T) polymorphism and responses to antidepressants (Lee et al. 2005; Yu et al. 1999), indicating that more detailed research is needed. It was suggested that combined therapy with traditional antidepressants and 5-HT6 receptor antagonist might be very useful for patients to whom monotherapy provided insufficient efficacy. Furthermore, this antidepressant hybrid treatment might accelerate the onset of action and decrease side effects (Wesołowska 2010).

6.10 5-HT7 Receptors

The highest density of 5-HT7 receptors is found in the thalamus, hypothalamus, hippocampus, amygdala, and frontal cortex, revealing the role of this receptor not only in affective but also in sensory processing (Hannon and Hoyer 2008).

Previous findings have demonstrated that decreased 5-HT7 receptor function might generate AD-like behavioral effects. In this respect, genetic deletion of the 5-HTR7 or administration of 5-HTR7 antagonists showed AD-like effects in animal behavioral tests (Carr and Lucki 2011). Although a direct relationship of the 5-HT7 receptor blockade to SSRI effects is debatable, the potential of 5-HTR7 antagonists as adjunct antidepressants has been proposed in certain studies. For example, it was shown that a 5-HT7 receptor antagonist enhanced antidepressant-like behavior induced by citalopram in mice (Bonaventure et al. 2007). In preclinical studies, antidepressant-like effects of the antipsychotic amisulpride have been observed, likely due to a 5-HTR7 antagonist mechanism (Abbas et al. 2009). Early observations on the role of the 5-HTR7 in stress-related disorders (particularly stress-induced depression) showed that acute stress enhanced 5-HTR7 mRNA expression in hippocampus, while chronic antidepressant treatment decreased 5-HT7 receptor binding in hypothalamus (Mullins et al. 1999; Yau et al. 2001). It was found that application of SB 269970, a 5-HTR7 antagonist, resulted in antidepressant-like activity in both forced swim and tail suspension tests in rodents (Wesołowska et al. 2006). Further investigations have shown synergistic interactions between SB-269970 and other classes of antidepressants such as citalopram, imipramine, desipramine, and moclobemide on antidepressant-like behavior in rodents. The prefrontal cortex and the hippocampus were indicated as regions important in these interactions (Sarkisyan et al. 2010). Consistent with the pharmacological data, increased antidepressant-like activity in forced swim and tail suspension tests were reported for 5-HT7 knockout mice compared to wild-type controls (Hedlund et al. 2005). The mechanisms of antidepressant-like activity of the5-HTR7 blockade are unclear, and it was speculated that the observed behavioral effects result from downstream effects on the 5-HT (and possibly other neurotransmitter) systems (Wesołowska et al. 2006). Findings from preclinical and clinical trial for drug evaluation of a novel selective 5-HTR7 antagonist, JNJ-18038683, with suitable properties for human usage, showed that the antagonist was effective in mouse tail suspension tests. However, the conclusions of this

double-blind, placebo-controlled clinical trial do not indicate a definitive significant difference between JNJ-18038683 and a placebo in the treatment of MDD (Bonaventure et al. 2012). In addition, it has been reported that a 5-HT7 receptor antagonist, SB-269970, augmented the effects of citalopram on 5-HT transmission, for antidepressant-like behavior, and on rapid eye movement (REM) sleep suppression in rodents (Bonaventure et al. 2007). Taken together, these findings indicate that further studies are required to clarify the clinical efficacy of selective 5-HTR7 antagonists alone and in combination with SSRIs for the treatment of MDD (Table 6.2).

Table 6.2 Characteristics of the included clinical trial studies

Receptor	Name of ligand	Pharmacological properties	Design	Results	Reference
5-HT1A	Pindolol	Antagonist	Open-label studies with SSRIs + pindolol Double-blinded, placebo-controlled studies with SSRIs + pindolol	Augmentation strategy with decreased latency to improvement in symptoms	Martinez et al. (2000) (review)
	Buspirone	Agonist	Open-label study with buspirone + pindolol	Rapid and robust antidepressant response	
	Gepirone	Agonist	Double-blinded, placebo-controlled studies	Significant efficacy with high dose	Blier and Ward (2003) (review)
	Vilazodone	Agonist	Two multicenter, randomized, double-blinded, placebo-controlled studies	Significant improvement and greater rates of response and remission	Khan et al. (2014)
5-HT2A	Mianserin, olanzapine, risperidone	Antagonist	Open-label and double-blinded, placebo-controlled studies	In combination with SSRI-induced rapid therapeutic onset and greater efficacy	Marek et al. (2003) (review)
5-HT2C	Agomelatine	Antagonist	Open-label and double-blinded, placebo-controlled studies	Doses of 25–50 mg/day are effective in reducing the depressive symptoms	
5-HT3	Ondansetron	Antagonist	Randomized, double-blinded, placebo-controlled study	Decrease of depressive symptoms in patients with chronic hepatitis C, alcoholism, and bulimia nervosa	Bétry et al. (2011) (review)
5-HT7	JNJ-18038683	Antagonist	Multicenter, double-blinded, randomized, double-dummy, placebo- and active-controlled, parallel design study	No definitive conclusion regarding efficacy at doses of 20 mg/day for treatment of MDD	Bonaventure et al. (2012)

Conclusion

Major depressive disorder is a multi-etiological heterogeneous disease, with varied symptomatology and treatment efficacy. For long, depression was related to the malfunctioning of the serotonin system. Serotonin receptors are mainly distributed in emotional regulation and cognitive processing circuits, including brain areas such as the amygdala, hypothalamus, hippocampus, and prefrontal cortex, where each receptor subtype is specifically allocated. Dysregulation of these brain circuits is a hallmark of depression, thus connecting behaviors to an underlying biological substrate—the serotonergic system. This review examined how different 5-HT receptor subtypes participate in the pathogenesis and the treatment of major depression. Previous investigations have reported various—and often conflicting—pharmacological, postmortem, PET, and genetic findings, which illustrated the complexity of the different 5-HT receptor subtypes in signaling and downstream effects. In brief, 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, 5-HT3, 5-HT4, 5-HT6 and 5-HT7 agonists and antagonists, in combination with traditional SSRIs, reportedly led to a more rapid onset of the AD activity and increased the effectiveness of SSRI therapy. Antidepressant-like responses of both agonists and antagonists at some particular 5-HT receptors such as 5-HT6, may be connected with triggering various neurochemical effects that cause analogous behavioral results. It remains a challenge, however, for scientists investigating additional treatment options with respect to 5-HT receptors, to pinpoint most efficient ones, especially for treatment-resistant depression subtypes.

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7 Emerging Role of Glutamate Receptors in Pathophysiology of Depression

Kyoung-Sae Na and Yong-Ku Kim

7.1 Introduction

During decades, scientific researches have revealed major neuromolecular contributors for the pathophysiology of major depressive disorder (MDD). Neuroinflammation with pro-inflammatory cytokines (Kim and Na 2016), brain-derived neurotrophic factors (BDNF) (Na et al. 2016) with mammalian target of rapamycin (mTOR), and glucocorticoid receptor (Na et al. 2014) with hypothalamus-pituitary-adrenal gland (HPA) axis are the representative one.

Recently, glutamate and its receptors have been focused as a major pathophysiological factors and target of treatment in MDD. The enthusiasm for the glutamate in MDD substantially arose from the serendipitous discovery of rapid treatment effects of ketamine, an *N*-methyl-D-aspartate receptor (NMDAR) antagonist (Singh et al. 2017; Zarate et al. 2006). However, nowadays it has been known that the NMDAR is not the only one involving in the pathophysiology of depression. Rather, various glutamates and its related receptors play their own crucial role. In this chapter, we summarize the role of glutamate receptors on the pathophysiology of MDD in perspectives of preclinical and neuroimaging studies.

7.2 Glutamate

7.2.1 Distribution

Glutamate is one of the most abundant and pleiotropic molecules in the human brain (Schousboe 2017). The mean concentration is about 100 nmol/protein (Erecinska and Silver 1990). In other resources, glutamate was reported to have 1–15 mmol/kg (Schousboe 1981) or 1–15 mmol/kg in the brain (Danbolt 2001).

Contrary to the high proportion of glutamate in the CNS, only tiny fraction of glutamate is present in the extracellular space (ECS). Another majority of glutamate is in the intracellular space (ICS). Thus, the gradient of glutamate level between ECS and ICS is substantially large. Extracellular glutamate level is maintained to 100 nM or less, whereas intracellular glutamate is substantially larger (Herman and Jahr 2007). The level of glutamate in the ICS is roughly 1000-fold, maximum 1,000,000-fold than that in the ECS. In the ICS, most of glutamate is in the nerve terminal (Ottersen et al. 1996; Zerangue and Kavanaugh 1996).

K.-S. Na
Department of Psychiatry, Gachon University Gil Medical Center, Incheon, South Korea

Y.-K. Kim (✉)
Department of Psychiatry, College of Medicine, Korea University, Seoul, South Korea

Department of Psychiatry, College of Medicine, Korea University, Ansan Hospital, Ansan, Kyunggi Province, South Korea
e-mail: yongku@korea.edu

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7.2.2 Function

Along with the large amount and highly concentrated distribution, glutamate plays a pleiotropic role in the brain. Although there are a lot of interactions between glutamate and other key neuromolecular factors, the role of glutamate could be summarized as the following three. First, glutamate enhances neuroplasticity such as long-term potentiation (LTP) in an activity-dependent manner (Peng et al. 2011; Schmid et al. 2008). Second, glutamate is essentially involved in the energy metabolism (Hohnholt et al. 2017). The role of glutamate on the energy metabolism was suggested more than a half century ago (Krebs 1935). It has been estimated that excitatory neurotransmissions, mostly glutamatergic one, are responsible for up to 80% of the energy consumption in the gray matter (Sibson et al. 1998). Glutamate has an important role as the energy substrate in the astrocyte (McKenna 2013). Third, glutamate acts as both neurotransmitter and gliotransmitter in the tripartite synaptic space which consists of neurons and astrocyte (Schousboe 2017). In the tripartite synaptic space, glutamate interplays with a lot of neuromolecular factors which are all closely associated with regulation of cognition and mood.

7.2.3 Excitatory Amino Acid Transporters

To maintain the sharp gradient of the glutamate levels between ECS and ICS, several mechanisms, such as synthesis, release, degradation, and reuptake, could be considered. Glutamate is converted to glutamine in astrocytes. However, as numerous number of glutamate is oxidatively metabolized, the portion of conversion of glutamate to glutamine would be relatively few (Tzingounis and Wadiche 2007).

Hence, reuptake of glutamate from the extracellular or synaptic space is the most crucial stage in regulating intracellular bioavailability of glutamate. Excitatory amino acid transporters (EAAT) have the retrieving role for glutamate. EAAT are mostly expressed in the astrocytes, although also expressed in oligodendrocytes (Pitt et al. 2003; van Landeghem et al. 2007) and microglia (Beschorner et al. 2007; Chretien et al. 2004; Nakajima and Kohsaka 2001) in some extent. Thus, astrocyte primarily has the clearing role for the glutamate in the tripartite synapse (Verkhratsky et al. 2015).

There are five types of EAAT, EAAT1–EAAT5. EAAT2 plays the most important role in reuptaking glutamate into the glial cells (Petr et al. 2015).

EAAT2, the first EAAT which was immunocytochemically identified (Lehre et al. 1995), is responsible for the 95% of EAAT activity in the brain (Scofield and Kalivas 2014). Hence, the glutamate reuptake is often explained with the action of EAAT2. In the animal study, half of mice with nonfunctional EAAT2 died within the first month of birth (Matsugami et al. 2006). A recent study further elaborated the critical role of EAAT2 for the uptake of glutamate (Petr et al. 2015). In that study, effects of the EAAT2 knockout were separately investigated in glia and neuron. In the glial cells, the behavioral problems were severe as shown in the previous studies. However, in case of knockout of neuronal EAAT2, the degree of the behavioral problems was modest. The results suggested that astrocytic EAAT2 is predominantly involved in the clearance of tripartite glutamate, whereas the role of the EAAT2 on the presynaptic neurons was not critical.

In case of glutamatergic neurotransmission, timely clearance of glutamate from the synaptic space is as important as the release. The unnecessarily long release of glutamate without uptake results in the spillover and binding to the postsynaptic NMDAR (Thomas et al. 2011). As the extrasynaptic NMDAR has been considered major neuromolecular pathophysiology of MDD, the role of the astrocytic EAAT2 is particularly important (Barbour et al. 1994).

EAAT3 is mainly distributed in the hippocampus, although present throughout the whole brain region (Holmseth et al. 2012). One of distinguished features of EAAT3 from other EAAT is its expression in the γ-aminobutyric acid (GABA) ergic neuron (Kugler and Schmitt 1999). The

reuptake of glutamate to the GABAergic interneurons in the hippocampus enhances GABA synthesis (Stafford et al. 2010). The GABAergic neurotransmission inhibits their target postsynaptic neurons. EAAT3 is particularly expressed in the neuronal cell bodies and dendrites avoiding both axon terminals and astrocytes (Holmseth et al. 2012; Rothstein et al. 1994). Thus, the activity of EAAT3 is facilitated by the spilled glutamate. In the EAAT3 knockdown rat, GABA levels were decreased, and newly synthesis of GABA was impaired (Sepkuty et al. 2002). The impaired inhibitory GABAergic activity might contribute to the uncontrolled excitatory activity, such as spontaneous seizure (Sepkuty et al. 2002).

EAAT4 is a predominant residue in the dendrites of Purkinje cells in the cerebellum (Dehnes et al. 1998). EAAT3 and EAAT4 were reported to be associated with mood disorders such as MDD and BD. One study showed that EAAT3 and EAAT4, but not EAAT1 and EAAT2, were decreased in the striatum (McCullumsmith and Meador-Woodruff 2002).

EAAT5 is different to other EAAT in their class. The main distribution of EAAT5 is the retina but not brain (Lee et al. 2012). The main function of EAAT5 is to inhibit release of glutamate from the presynaptic neuron by hyperpolarizing, rather than reuptake of glutamate (Veruki et al. 2006). If the EAAT do not properly function, glutamate might not be taken back, and the spilled glutamates bind to the extrasynaptic NMDAR.

7.2.4 Vesicular Glutamate Transporters (VGLUT)

VGLUT is a glutamate transporter which takes glutamate up to the presynaptic vesicle. VGLUT is divided into the three classes, VGLUT1–VGLUT3. VGLUT1 is mainly expressed in the cortical regions and hippocampus. VGLUT2 is predominantly in the subcortical regions. VGLUT3 presents in the serotonergic neurons, cholinergic neurons, and GABAergic interneurons (Uezato et al. 2009).

A VGLUT is enhanced by lipopolysaccharide (LPS), a pro-inflammatory mediator (Mechawar and Savitz 2016). The increased activity of a VGLUT means that more glutamate could be put into the presynaptic vesicle (Daniels et al. 2006). Several studies have shown that VGLUT was increased in patients with MDD.

However, it is not certain whether the increase or decrease of VGLUT contributes to the pathophysiology of MDD. Studies reported that decreased expression of VGLUT is associated with depressive behaviors (Tordera et al. 2007; Uezato et al. 2009).

7.3 Glutamate Receptors

Although glutamate binds to the EAAT and VGLUT, the classifications of the glutamate receptors are generally ionotropic, metabotropic, and kainate receptors. Ionotropic glutamate receptors are classified to the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPAR), NMDAR, and kainite receptor. All the ionotropic receptors structurally consist of subunits that form tetramers. NMDAR consists of three subunits, GluN1–GluN3. Glutamate binds GluN2, whereas glycine binds GluN1 and GluN3.

7.3.1 Ionotropic Receptors

Ionotropic receptors commonly use ligand-gated ion channel for their fast-acting signal transduction. Metabotropic glutamate receptors use transmembrane G protein-coupled receptor, which in turn leads to the intracellular molecular second messenger cascade. Thus, the final effects of the metabotropic glutamate receptors develop slowly.

In the postsynaptic neuron, Ca^{2+} contribute to the gene expression and synaptogenesis by several pathways. Ca^{2+} bind calmodulin and form Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII). With the Ca^{2+}-induced Raf-MEK-ERK cascade and the activity of protein kinase A (PKA), those intracellular Ca^{2+}-dependent pathways induce trafficking of the AMPAR to the

receptor membrane (Herring and Nicoll 2016). Those processes of synaptogenesis and synaptic plasticity are essential for the long-term potentiation (LTP), which is closely associated with cognitive function. However, too much Ca^{2+} influx leads to excitotoxicity.

GABAergic neurotransmission inhibits calcium signals by K^+ channel. The consequent hyperpolarization decreases Ca^{2+} influx to the postsynaptic glutamate receptors, and then Mg^{2+} again block the core pore of the NMDAR (Deng et al. 2009). Quite a few GABAR activities are regulated by glutamatergic transmission. Glutamate directly acts on the surface GABAB of the GABAergic neuron. Sustained glutamatergic excitatory signals on the GABAergic neuron result in GABA endocytosis, which consequently reduce GABA receptors only in the cell body and dendrites (Vargas et al. 2008). The glutamate-induced endocytosis, which means removal of GABAB from the cell surface, consequently increases excitatory signal by reducing hyperpolarization by GABAB. Surface expression of the AMPAR was increased in the knockout mice in which GABAB phosphorylation does not occur (Terunuma et al. 2015). As the GABAB could not appropriately function in the absence of the GABA phosphorylation, that research demonstrates that loss of regulatory role of GABAB might enhance AMPAR expression.

Unlike AMPAR and kainite receptors, NMDAR has several distinguished properties. First, there are endogenous co-agonists (glycine and D-serine) and antagonists (Mg^{2+} and Zn^{2+}) for the NMDAR. Those presences of co-agonists and antagonists variably influence on the action and final effects of NMDAR. Second, when glutamate binds to the NMDAR, Ca^{2+} and Na^+ influx whereas K^+ efflux. It is different to that the AMPAR and kainite receptors only use Na^+. The chronic and excessive influx of Ca^{2+} has long been considered to contribute to the excitotoxicity and neurodegenerative diseases. However, recently, there has been reasonable controversy over the role of the NMDAR and Ca^{2+} influx for the excitotoxicity and its harmful effects (Lewerenz and Maher 2015). In that review, the authors persuasively argued there is no enough scientific evidence for arguing the detrimental role of increased glutamatergic transmission.

7.3.2 NMDAR Co-transporter

7.3.2.1 Magnesium

Magnesium (Mg^{2+}) blocks core pore of the NMDAR like an endogenous *N*-methyl-D-aspartate (NMDA) receptor antagonist (Mori et al. 1992). When Na^+ and Ca^{2+} influx, the ion channel is depolarized, and the Mg^{2+} is detached. Thus, altered level or intake of Mg^{2+} likely contributes to the neuropsychiatric conditions.

There have been several evidences suggesting that Mg^{2+} is associated with depression. First, Mg^{2+} deficiency or low intake induced depression-like behaviors and clinical depression in animals (Whittle et al. 2011) and humans (Aparicio et al. 2013). Second, Mg^{2+} administration ameliorated depressive-like behaviors and depression in animals and humans (Nechifor 2009). Third, patients with depression or at risk for depression had lower blood Mg^{2+} levels than controls (Kirov and Tsachev 1990). In some cases, rapid recovery from MDD by Mg^{2+} has also been reported (Eby and Eby 2006). Recent meta-analyses suggested that dietary supplement of Mg^{2+} is effective for the improvement of depression (Li et al. 2017).

7.3.2.2 D-Serine

NMDAR co-agonists have an important role in the opening of calcium channels, as both glutamate and co-agonists need to bind to NMDAR. D-serine is an endogenous ligand which binds to glycine sites of the NMDAR (Balu and Coyle 2015). Astrocyte-derived D-serine plays an important role in hippocampal synaptic plasticity (Schell et al. 1995; Yang et al. 2003), although recent studies have reported that neurons are also a major resource of D-serine (Balu et al. 2014).

Several properties of D-serine are important for the pathophysiology of MDD. First, D-serine has three times more potent binding affinity for the NR1/NR2 subunits of the NMDAR than that of glycine (Furukawa and Gouaux 2003). Second, D-serine primarily binds to the synaptic NMDAR (Papouin et al. 2012). Third, D-serine mainly

presents in the prefrontal cortex and hippocampus, which are important for cognition and emotion (Hashimoto et al. 1995). Insufficient D-serine led to hypofunction of NMDAR, which could be ameliorated after infusion of D-serine (Mothet et al. 2000). Recent studies have suggested that D-serine transport would be a useful therapeutic approach for MDD (Wang et al. 2017). However, as the optimal activation of the NMDAR is needed for healthy state, chronic elevation (Otte et al. 2013) and insufficiency of D-serine are both vulnerable factors for MDD.

7.3.3 Metabotropic Receptors

Metabotropic receptors are subdivided into three classes with group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4, mGluR6, mGluR7, and mGluR8).

One study reported that positive allosteric modulators for mGluR5 exerted neurotoxic effects, whereas negative allosteric modulators showed neuroprotective effects (Parmentier-Batteur et al. 2014).

mGluR5 has been widely studied in the field of neuropsychiatry. Several studies reported that abnormalities in the mGluR5 were associated with major psychiatric disorders such as MDD, bipolar disorder, and schizophrenia (Matosin et al. 2014). mGluR5 is mainly expressed in the prefrontal and limbic regions (Abe et al. 1992; Swanson et al. 2005). mGluR5 also regulates GABAergic neuronal activity, which in turn modulates excitatory signals (Hoffpauir and Gleason 2002).

Since the group I mGluR both act as an inhibitory presynaptic receptor and a facilitative postsynaptic receptor, the net results of the receptor action might not be easily predictive. Indeed, an animal study reported that group I mGluR exert contrasting effects on the striatal neurons (Partridge et al. 2014).

The group II metabotropic receptors mGluR2 and mGluR3 have approximately 70% of common amino acid sequence (Pin and Duvoisin 1995; Pin et al. 1995). mGluR2 is predominantly expressed in the perisynaptic space, although it is also found in the presynaptic and postsynaptic neuron. The major functional role of the mGluR2 is autoreceptor with negative feedback (Cartmell and Schoepp 2000). mGluR3 is frequently expressed in the glial cells and presynaptic neuron. Glial mGluR3 closely interacts with EAAT2 to appropriately regulate glutamate in the ECS (Aronica et al. 2003).

Several studies reported that negative allosteric modulators of the mGluR2 enhanced hippocampal LTP and cognitive function (Goeldner et al. 2013). However, increased expression of the mGluR2 was also beneficial for depression. For example, upregulation of the mGluR2 with acetyl-L-carnitine (ALC) in the prefrontal cortex and hippocampus resulted in antidepressive effects (Cuccurazzu et al. 2013). ALC has been also reported to be effective for ameliorating depressive symptoms in patients with fibromyalgia (Leombruni et al. 2015). mGluR2 has also anti-inflammatory effects (Yang and Gereau 2002). Since neuroinflammation accompanied by increased pro-inflammatory cytokines is closely associated with depression, the anti-inflammatory action of the mGluR2 is considered more favorable in regulating mood (Kim and Na 2016; Kim et al. 2016). Given the contrasting direction of the mGluR2 effects, Bruno et al. (2017) proposed to choose agents which differently act on the mGluR2. For depressed patients with cognitive dysfunction, negative allosteric modulators would be preferentially considered. On the other hand, for patients with low resilience for stress, positive allosteric modulators could be considered (Bruno et al. 2017).

Whereas group II mGluR is broadly distributed in the brain, mGluR2 and mGluR3 are particularly expressed in the prefrontal cortex, amygdala, hippocampus, thalamus, dorsal striatum, and ventral striatum (Gu et al. 2008; Petralia et al. 1996; Wright et al. 2001). As those regions are neuroanatomical core in MDD, the dysfunction of group II mGluR has been considered major pathophysiological factors for MDD.

Particularly, dysfunction of the mGluR2 is closely related to the vulnerability for stress. Animal studies found that mGluR2 knockout mice are vulnerable for chronic unpredictable

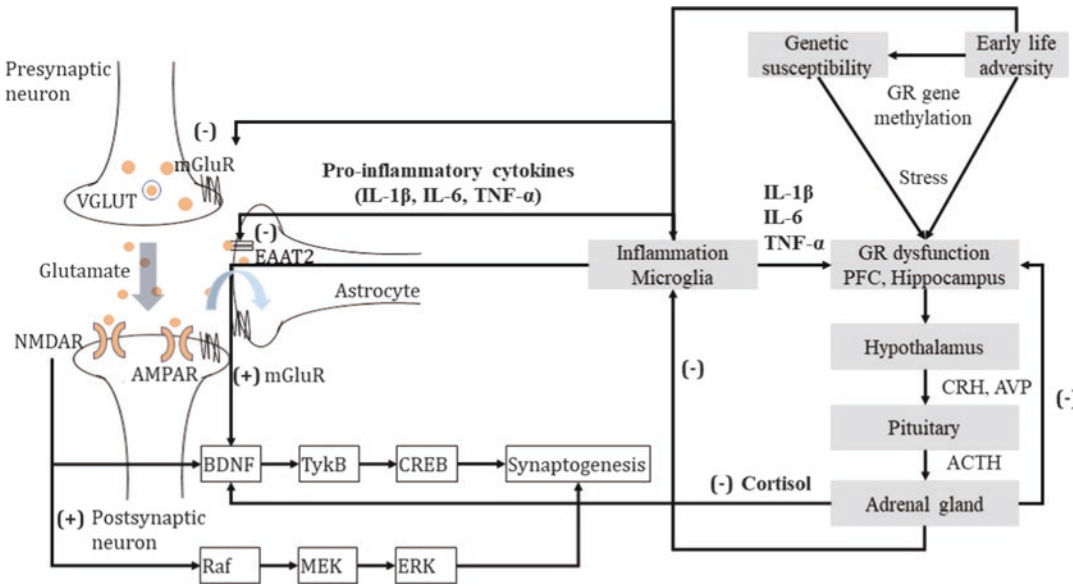

Fig. 7.1 Complex interaction of glutamatergic receptors and other systems

stress. Hippocampal mGluR2 expression was lower in mice vulnerable for stress than stress-resilient mice (Nasca et al. 2015).

Conclusion

The emerging role of glutamate receptors on the pathophysiology for the depression is not to be questioned. However, as summarized in Fig. 7.1, glutamate receptor function is modulated at various stages of glutamate cycles and other key factors such as pro-inflammatory mediators, BDNF, and HPA axis. Hence, no currently accepted hypothesis fully explains the exact role of glutamate and its receptors in the pathophysiology of depression. Some of seemingly contradictory findings regarding the mechanisms of glutamate receptors might arise from those complex interactions. Future studies should elucidate exact interactions of glutamate receptors and other systems.

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8 New Perspective on mTOR Pathways: A New Target of Depression

Gislaine Z. Réus, Zuleide M. Ignácio, Helena M. Abelaira, and João Quevedo

8.1 Introduction

Major depressive disorder (MDD) is a severe disorder that affects about 10% of the general population (Kessler 2012). In addition, according to the World Health Organization (WHO), MDD is a highly disabling disorder and in 2030 will rank first in the list of diseases with the highest overall disability burden (World Health Organization 2008). Although many studies with both MDD patients and animal models have allowed an advance in the understanding of many neuroanatomical and physiological aspects (Campbell and MacQueen 2006), the treatment of MDD is still not ideal. In fact, the mechanisms of action of many antidepressants are poorly understood. The therapeutic response to pharmacological treatments does not encompass all MDD patients, and in a large percentage of patients treated, remission is not complete (Schmidt et al. 2008; Krishnan and Nestler 2008; Chaves Filho et al. 2016). Thus, considering that acute availability of monoamines in the synapses does not provide an equally acute response, and a large number of patients do not respond satisfactorily, new research has emerged in the search for markers and biological mechanisms underlying MDD (Chaves Filho et al. 2016).

Evidence from clinical and experimental studies highlights the involvement of neurotrophic factors, cellular signaling pathways, and several intrinsic mechanisms involved with neuronal plasticity (Pittenger and Duman 2008; Réus et al. 2012) in the pathophysiology as well as treatment of MDD. Among the signaling pathways involved in protein translation, cell proliferation, and syn-

G.Z. Réus (✉) • H.M. Abelaira
Laboratório de Neurociências, Unidade Acadêmica em Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil
e-mail: gislainereus@unesc.net

Z.M. Ignácio
Laboratório de Neurociências, Unidade Acadêmica em Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil

Laboratório de Fisiologia, Farmacologia e Psicopatologia, Universidade Federal da Fronteira Sul, Chapecó, SC, Brazil

J. Quevedo
Laboratório de Neurociências, Unidade Acadêmica em Ciências da Saúde, Universidade do Extremo Sul Catarinense, Criciúma, SC, Brazil

Translational Psychiatry Program, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA

Center of Excellence on Mood Disorders, Department of Psychiatry and Behavioral Sciences, McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA

Neuroscience Graduate Program, The University of Texas MD Anderson UTHealth, Graduate School of Biomedical Sciences, Houston, TX, USA

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aptic plasticity, the mammalian target of rapamycin (mTOR) pathway has received prominence, based on the findings that glutamatergic antagonists targeting the *N*-methyl-D-aspartate (NMDA) receptor, such as ketamine, activate mTOR signaling and have a rapid antidepressant effect. Studies investigating the glutamatergic system and the mTOR pathway strongly suggest that these mechanisms are closely related and may play a pivotal role in MDD (Goswami et al. 2013).

The mTOR is a ubiquitous serine/threonine protein kinase, which is inserted into a complex signaling pathway that regulates transcription, protein synthesis, cell survival, growth, and proliferation (Hay and Sonenberg 2004). Importantly, synaptic plasticity in limbic and cognition-related regions seems to require, at least in part, the activation of mTOR signaling and translational effector mechanisms (Hoeffer and Klann 2010).

Among the trophic factors involved in neuronal plasticity, brain-derived neurotrophic factor (BDNF) has been growing exponentially in research. The observations that in both human (Dwivedi et al. 2003; Banerjee et al. 2013; Kavalidou and De Leo 2013) and animal models (Roceri et al. 2002; Duman and Monteggia 2006) the expression and functions of BDNF are impaired have prompted to search for the functional mechanisms of BDNF in MDD (Ignácio et al. 2014). BDNF is one of the important products resulting from the translational pathway of mTOR. Conversely, through tropomyosin-related kinase B (TrkB) receptor, BDNF activates the mTOR cascade and triggers protein synthesis, through initiation and elongation processes from downstream components in this pathway (Ignácio et al. 2016).

Considering that drugs, which exert an antidepressant effect in the clinic or antidepressant-like effect in animals, especially drugs that have a fast and more potent antidepressant effect, encompass the mTOR pathway, it becomes important to systematize and compile the research that addresses the involvement of mTOR signaling in depression and in the action of antidepressants. Therefore, in the sessions of this chapter, we will systematize the animal and human studies, which observed the involvement of the mTOR pathway in depression and antidepressant treatments.

8.1.1 mTOR Pathways in the Pathophysiology of Depression: Evidence from Experimental Studies

Chronic moderate stress (CMS) is widely used as a model of depression and is very useful for investigating the neurobiological mechanisms underlying MDD, being considered a model that covers all established criteria, exhibiting high construct, face, and predictive validities as an animal model (Willner 2005; Abelaira et al. 2013). Animal models that use chronic stress have been one of the motivations to uncover the components and mechanisms of the mTOR pathway that are supposed to underlie MDD-related phenomena, as well as mechanisms involved in the rapid antidepressant effects elicited by some compounds (Ignácio et al. 2016). In fact, the activation of the mTOR signaling cascade was reduced in the amygdala of rats exposed to the chronic unpredictable stress (CUS). The authors verified that phosphorylated mTOR levels and its upstream positive modulators, extracellular signal-regulated kinase (ERK1/2), protein kinase B/Akt (Akt1), and 70-kDa ribosomal protein S6 kinase (p70S6K) and phosphorylated ribosomal protein S6 (downstream signaling effectors) were reduced in the amygdala of animals subjected to 8 weeks of stress (Chandran et al. 2013). In addition, CMS induced a behavioral depressive-like effect, in parallel to a reduction of phosphorylated p70S6K and S6 levels in the medial prefrontal cortex (mPFC) (Zhu et al. 2013). Studies with mice also revealed that CUS induced depressive-like behavior and reduced the activity of hippocampal mTOR signaling (Zhong et al. 2014). In a series of earlier studies, some researchers observed that mice exposed to CUS had a significant reduction in hippocampal expression of phosphorylated ERK, in parallel to depressive-like behaviors. Interestingly, in the same series of studies, the authors found that deletion of mitogen-activated protein kinase (MAPK) phosphatase-1 (MKP-1) leads the animals to be more resilient to CUS, both in behavioral responses and in phospho-ERK expression. MKP-1 is a negative regulator, reducing phospho-

ERK expression and thus impairing synaptic plasticity and neuron survival (Duric et al. 2010). The expression of BDNF was also reduced in the hippocampus of immobilized stressed rats, in parallel to a reduction in the phosphorylated mTOR, Akt, GSK3β, and p70S6K (Fang et al. 2013).

8.1.2 mTOR Pathways in the Pathophysiology of Depression: Evidence from Human Studies

In addition to the evidence in animals, some studies have observed that mTOR pathway is altered in humans with MDD. Recent studies have suggested that mTOR signaling is compromised in pathophysiology of MDD (Jernigan et al. 2011; Ota et al. 2014). In fact, postmortem studies showed robust deficits in mTOR signaling in the prefrontal cortex (PFC) (Jernigan et al. 2011) and increased in peripheral blood (Denk et al. 2011) of subjects diagnosed with MDD. In fact, it was observed that MKP-1 mRNA levels were significantly increased in the postmortem hippocampus of MDD individuals (Duric et al. 2010). In addition, in individuals diagnosed with MDD, it was observed that both the mTOR protein and molecules of its positive downstream cascade for protein translation were reduced in the PFC (Jernigan et al. 2011). Other studies have shown that Akt activity, an upstream activator of mTOR signaling, was reduced, while activity of glycogen synthase kinase-3β (GSK-3β), an inhibitor of mTOR, was increased in the PFC of MDD subjects, who were victims of suicide (Karege et al. 2007). Furthermore, a decrease of the Akt activity in the hippocampus of suicide victims was also observed (Dwivedi et al. 2010). In two cohort studies of individuals with MDD, the expression of the RDD1 (regulated in development and DNA damage responses-1) protein was significantly increased in the postmortem dorsolateral PFC (Ota et al. 2014). RDD1 is a potent negative regulator of mTOR, possibly increasing the activity of the tuberous sclerosis complex gene products (TSC1/TSC2) (Corradetti et al. 2005). In order to find possible biomarker of in vivo research, in a study of MDD patients undergoing treatment, the researchers found a significant reduction in the proteinogenic branched-chain amino acid (BCAA) levels, namely, leucine, isoleucine, and valine in patients' blood (Baranyi et al. 2016). BCAAs, especially leucine, are potent activators of mTOR and its downstream translational effectors, namely, eukaryotic initiation factor 4E (eIF4E)-binding proteins (4E-BP) and p70S6K (Monirujjaman and Ferdouse 2014). Therefore, it has been suggested that a reduction in BCAA levels may be an important factor underlying the reduction of mTOR pathway activation and, thus, a biomarker of MDD (Baranyi et al. 2016). However, BCAAs compete with aromatic amino acids, such as tryptophan (Trp), tyrosine (Tyr), and phenylalanine (Phe), to enter the brain, and thus elevation of BCAAs may lead to a reduction in the synthesis of the monoamine neurotransmitters (Fernstrom 2005). By this reasoning it is important that BCAA levels are balanced with aromatic amino acid levels, and further studies should be designed to observe the behavioral effects and neurobiological mechanisms from an imbalance, in parallel to the effects of BCAAs on the mTOR pathway.

A wide range of research has been investigating the mechanisms underlying the mTOR pathway in depression. However, most research has focused on drugs that work as antidepressants in humans or antidepressant-like in animal models, whose mechanisms of action are, at least in part, underlaid by the mTOR pathway. Studies of the antidepressant function of these drugs, as well as their specific mechanisms of action on the mTOR pathway, will be addressed in the specific sessions below.

8.1.3 mTOR Pathways as Therapeutic Target for Depression: Evidence from Experimental Studies

Studies suggest that ketamine and other fast-acting antidepressants, mediated by glutamate and/or neurotrophic receptors, stimulate the mTOR path-

way in the PFC (Li et al. 2010; Pałucha-Poniewiera et al. 2014) leading to a transient activation of the downstream effectors, 4E-BP1 and p70S6K, which regulate gene expression and protein synthesis (Tang et al. 2015). Thus, these findings raise the possibility that mTOR signal pathways are potential therapeutic targets for antidepressant actions (Tang et al. 2015).

Stimulation of mTOR signaling is quickly followed by increased expression of synaptic proteins such as PSD-95 and synapsin-1 and increased spine synapse (Li et al. 2010). Inhibition of mTOR, or ERK and Akt activation, upstream of 4E-BP1 and p70S6K, blocks the synaptic protein synthesis and antidepressant-like effects of ketamine (Li et al. 2010). In fact, Holubova et al. (2016) showed that the pretreatment with the mTOR inhibitor, rapamycin, eliminated the ketamine effect in elevated plus maze test (a classical test to evaluate anxiety behavior) and led to cognitive impairment in bulbectomized rats. In addition, Abelaira et al. (2016) reported that the rapamycin, when administrated into the PFC, was able to block the antidepressant effects of ketamine in rats submitted to the forced swimming test and protect certain brain areas against oxidative stress. Also, previous study demonstrated that the infusion of rapamycin, in the rat PFC, also abolished the ketamine antidepressant effects on mTOR and reticulum stress parameters, suggesting that mTOR signaling inhibition by rapamycin could be involved, at least in part, with the mechanism of action of ketamine; and the ketamine antidepressant on reticulum stress pathway could be also mediated by mTOR signaling pathway in certain brain structures (Abelaira et al. 2016). Furthermore, chronic administration of combinations of alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and ketamine, at doses that were ineffective on their own, resulted in a significant antidepressant effect and were associated with an increase in hippocampal BDNF, synapsin, and mTOR (Akinfiresoye and Tizabi 2013). Moreover, ketamine at doses of 10 and 15 mg/kg showed a significant increase in the expression of hippocampal BDNF and levels of phospho-mTOR (Yang et al. 2013). Harraz et al. (2016) also showed that siahE3 ubiquitin protein ligase 1 (Siah1) degrades Ras homolog enriched in brain (Rheb) leading to a reduced mTOR signaling, while ketamine, conversely, stabilized Rheb that in turn enhanced mTOR signaling. Thus, these observations suggest that rapid changes in synaptic protein contents induced by mTOR activation may contribute to the fast-acting antidepressant effects of ketamine and similar drugs (Duman and Aghajanian 2012).

Few studies have examined whether antidepressant drugs (e.g., selective serotonin transporter inhibitors) stimulate the mTOR signaling pathway in animal models. Lin et al. (2010) reported that sertraline inhibits translation initiation by inhibiting mTOR signaling. In addition, Park et al. (2014) reported that escitalopram, paroxetine, and tranylcypromine (a monoamine oxidase inhibitor) significantly increased levels of phospho-mTOR and its downstream regulators (phospho-4E-BP-1 and phospho-p70S6K). More recently, it was reported that the NR2B antagonist Ro-35-6891 exerted antidepressant effects by elevating mTOR activity in mouse PFC (Workman et al. 2013). In addition, Moretti et al. (2014) demonstrated that antidepressant-like effect of ascorbic acid in the tail suspension test involves increased mTOR signaling and is associated with increased hippocampal phosphorylation of p70S6K and increased levels of PSD-95 in mice. Moreover, the antidepressant-like effect of guanosine, a purine-based nucleoside recognized as an extracellular signaling molecule, is also mediated by PI3K/mTOR pathway (Bettio et al. 2012).

Stress is known to be one of the causal factors for development of MDD. Based on this observation, the chronic unpredictable mild stress (CUMS) animal model has been developed to mimic the development and progress of clinical depression, such as reduced sucrose intake, altered weight gain, locomotor activity deficit, degradation of the physical state of the coat, and decrease in responsiveness to rewarding stimuli (Willner 1997). Recent animal studies indicate that CUMS exposure produces deficits in the mTOR signaling pathway components in the

amygdala of rats (Chandran et al. 2013) and in the hippocampus of mice (Lu et al. 2014). In fact, CUMS exposure significantly decreased sucrose preference, increased immobility time, decreased locomotor activity, and decreased the phosphorylation of Akt and mTOR in the hippocampus and PFC, while resveratrol treatment, a phenolic compound enriched in *Polygonum cuspidatum*, normalized these parameters (Liu et al. 2016). Chronic treatment with lurasidone, an atypical antipsychotic, was able to normalize CUMS-induced anhedonia and defects of PSD-95 and Gfap as well as changes in molecular regulators of protein translation at the synapse, including mTOR and eEF2 (Luoni et al. 2014). In addition, Zhuang et al. (2016) reported that alarin, a newly identified 25-amino-acid neuropeptide, produced antidepressant-like effects in CUMS-induced rodent depression models and restored CUMS-induced reductions of p70S6K and PSD-95 mRNA levels and of phospho-mTOR and phospho-4EBP1 in the brain structures related to the MDD. Furthermore, some drugs with antidepressant effects such as ketamine, monoacylglycerol lipase, and rapastinel (GLYX-13) were reported to reverse the stress-induced behavioral and synaptic deficits in an mTOR-dependent manner (Li et al. 2010; Akinfiresoye and Tizabi 2013; Lu et al. 2014; Zhong et al. 2014).

The findings in the literature cannot lead to firm conclusions regarding the relationship between mTOR-mediated changes induced by some antidepressant drugs and the clinical effects of these drugs. However, the results of these studies suggest that mTOR signaling may be a promising target for the development of new antidepressant drugs.

8.1.4 mTOR Pathways as Therapeutic Target for Depression: Evidence from Human Studies

Limited studies have investigated the role of mTOR and its pathways in MDD patients using antidepressant drugs. Boni et al. (2008) investigated if an intravenous injection of temsirolimus, an inhibitor of mTOR approved for treatment of renal cell carcinoma, could affect the pharmacokinetic disposition of the antidepressant desipramine. The results found no significant changes and low risk for drug interaction (Boni et al. 2008). Moreover, it was showed that patients with MDD with polymorphism in the promoter of the serotonin transporter (5-HTTLPR) and in a human promoter variant (rs334558*C) for GSK-3β (an inhibitor of mTOR) had a worse antidepressant response (Benedetti et al. 2012). On the other hand, in MDD patient's carriers of the rs334558*C variant, the 5-HTTLPR s/s was associated with better antidepressant response (Benedetti et al. 2012). In human U-87MG glioma cells, the treatment with imipramine (a tricyclic antidepressant) induced autophagic cell death by inhibition of PI3K/Akt/mTOR signaling (Jeon et al. 2011).

Many studies have been investigating the role of mTOR pathway in experimental studies. However, there are few studies reporting the classical antidepressant or fast-acting antidepressant effects on mTOR pathway in patients with MDD. Future clinical trials assessing peripheral markers and neuroimaging studies could be important to evaluate the role of mTOR in antidepressant responses.

Conclusion

Several experimental and clinical studies have been describing the involvement of the mTOR signaling pathway in the pathophysiology of stress and MDD. Changes in mTOR pathway linked to gene or total proteins were demonstrated both peripherally and at the central nervous system. The fact that ketamine fast antidepressant action is mediated by the mTOR pathway activation opens many expectative to the development of new antidepressant drugs to treat partially remissive and nonresponder MDD patients. Future studies, preclinical and clinical, are suggested to further explore the role of the mTOR pathway in both stress and MDD. Long-term effects of mTOR pathway alterations after antidepressant administration may be investigated since this pathway is also involved in the pathophysiology of cancer.

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Biological Markers to Differentiate the Subtypes of Depression

9

Je-Yeon Yun and Seung-Hwan Lee

9.1 Introduction

Major depressive disorder (MDD) is a prevalent health problem that affects more than 16% of the adult population in the Unites States during their lifetime (Berton and Nestler 2006; Kessler et al. 2003). The clinical symptom profile of MDD is heterogeneous, and the treatment response to the antidepressant varies. Moreover, even after the treatment with antidepressant at adequate dosage and duration, approximately two-thirds of patients with MDD do not experience sufficient symptom improvement (Fava 2003; Rush et al. 2006). Hence, finding pharmacological and/or neuromodulatory breakthroughs that enable therapeutic intervention of imbalanced brain network needs to be the primary goal of psychiatric research (Papakostas and Ionescu 2014). Furthermore, subtyping of MDD into homogeneous clusters based on the distinctive clinical presentation and pathophysiology would be an inevitable task prior to the development of personalized MDD treatment regimen.

Biological markers are objective measures of biological processes and can be found based on blood levels of single molecules, genetic variants, epigenetic changes, or neuroimaging findings (Boksa 2013; Kennedy et al. 2012). These biological markers can be utilized as a diagnostic tool or predictive indicators for treatment response (Biomarkers Definitions Working Group 2001). In this chapter, we searched previous studies about MDD subtyping and gathered evidence for the notion of subtyping of MDD. We believe that summarizing the biological correlates of MDD subtypes may help to understand the heterogeneity of MDD patients based on biological and psychological aspects.

9.2 Current Evidence of Subtypes of Depression

Patients diagnosed with MDD are heterogeneous for the clinical symptom profile (Wanders et al. 2016), course of illness, and degree of response to pharmacotherapy (Antonijevic 2006; Ghaemi and Vohringer 2011). For example, based on the differential clinical symptom profile, MDD has been typically classified into melancholic, nonmelancholic, and psychotic subtypes (Harald and Gordon 2012). First, the melancholic subtype of

J.-Y. Yun
Seoul National University Hospital, Seoul, South Korea

Yeongeon Student Support Center, Seoul National University College of Medicine, Seoul, South Korea

S.-H. Lee (✉)
Clinical Emotion and Cognition Research Laboratory, Inje University, Goyang, South Korea

Department of Psychiatry, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
e-mail: lshpss@paik.ac.kr; lshpss@hanmail.net

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MDD has been distinguished from the non-melancholic conditions by the presence of psychomotor disturbances and strong relationship with nuclear symptoms listed in the unidimensional melancholia subscale (HAM-D6; core items for depression selected from the Hamilton Depression Scale), including depressed mood, feelings of guilt, work and interests, psychic anxiety, and tiredness/pain. Second, the non-melancholic subtype of MDD shows more diverse clinical presentation and includes more specific subtypes of MDD such as atypical or anxious subtypes. Third, the psychotic subtype of MDD might be distinguished by the presence of psychotic features including delusions and/or hallucinations. In general, the severity of clinical symptoms in patients with MDD is typically distributed with a gradient from the mildest non-melancholic subtype to the most severe cluster of psychotic subtype (Bech et al. 1975; Caldieraro et al. 2015; Harald and Gordon 2012; Parker et al. 2010). This heterogeneity of MDD population has been attributed to the diversity of biological mechanisms related to MDD pathophysiology (Gillihan and Parens 2011). In other words, distinctive features of increased appetite, hypersomnia, proneness for metabolic syndrome, and elevated blood inflammatory markers characterize the atypical subtype of MDD. In comparison, the melancholic subtype MDD has been related to dysfunctional hypothalamic-pituitary-adrenal (HPA) axis (Baune et al. 2012; Harald and Gordon 2012; Kaestner et al. 2005).

Some studies reported relationship between the clinical symptom-based subtyping system and the diverse rate of symptom improvement after administration of antidepressants, elective convulsive therapy, psychotherapy, or cognitive behavioral therapy (Parker 2008). The presence of index depressive episode characterized by occurrence before 19 years of age showing severe dysphoria, anxiety, and suicidality predicts the persistence of mood symptoms and disease chronicity (van Loo et al. 2014). Moreover, brain-based biological markers of treatment response and/or long-term prognosis have also been raised in MDD; neuroimaging studies implied the presence of MDD subpopulation underpinned with characteristic patterns of neural networks. For instance, a graph theory approach [a mathematical decoding of brain structural or functional network to uncover the hierarchical relationship among segregated-integrated brain regions] for resting state functional connectivity network showed relationship between the altered nodal degree of the right dorsolateral superior frontal cortex versus the treatment resistance in patients with MDD (Hou et al. 2016). Furthermore, attenuated strength of resting state functional connectivity between the bilateral subgenual anterior cingulate cortices could distinguish a subpopulation of patients with MDD resistant to the recurrence of depressive episode (Workman et al. 2016b). Finally, data-driven clustering approach clarified the clinical implications for these MDD subgroups [or clusters]. For example, a canonical clustering approach for resting state functional connectivity network in patients with MDD revealed a total of four distinctive clusters of MDD subgroups, segregated based on symptom severity for two axes of anhedonia-psychomotor retardation [matched with the frontostriatal-orbitofrontal network] and anxiety-insomnia [the limbic network covering amygdala, ventral hippocampus, striatum, subgenual cingulate, and lateral prefrontal cortices] (Fig. 9.1); these brain functional network features could predict the degree of symptom improvement after transcranial magnetic stimulation targeting the dorsomedial prefrontal cortex (Drysdale et al. 2017).

9.3 Candidates for Biological Markers of Depression

9.3.1 Genetic Factors

The estimated heritability of MDD is 31–42% in general; however, this estimate differs according to the demographic and clinical characteristics such as sex [more heritable in women compared to men] and age of onset [those with a family history of MDD tend to experience the index mood episode at an early age with frequent recurrence]

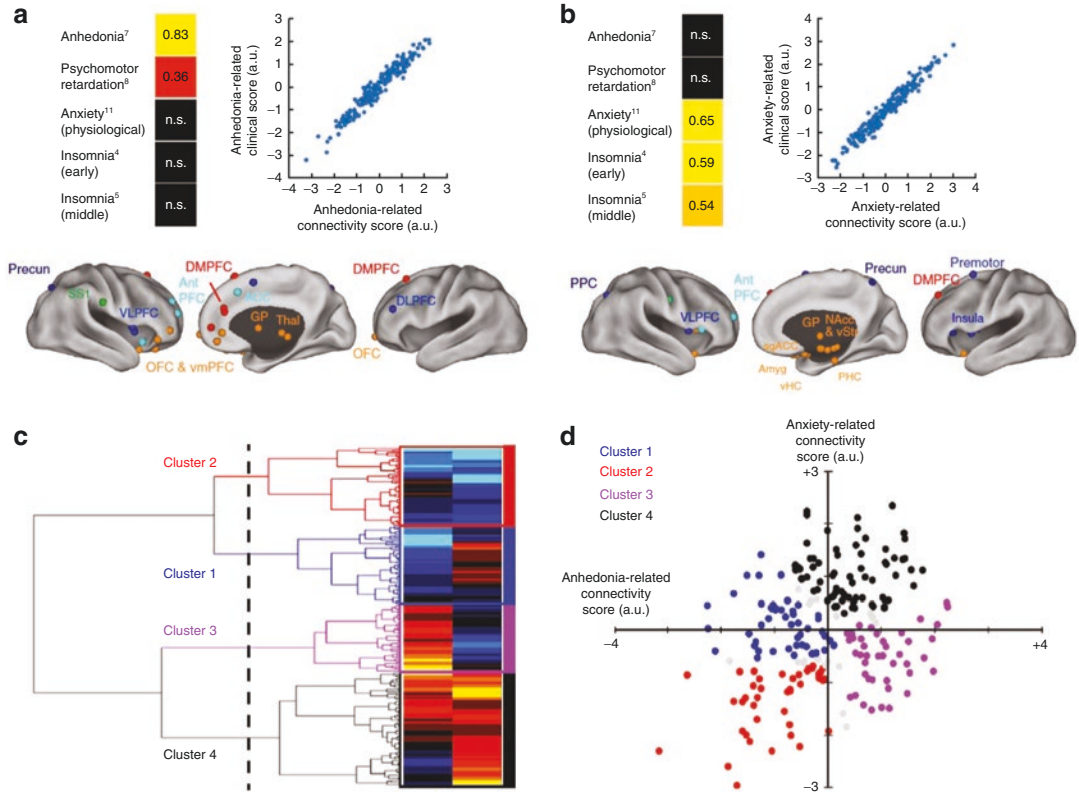

Fig. 9.1 Resting state functional connectivity-based biotypes of depression defined using canonical correlation analysis: (**a**) anhedonia-related and (**b**) anxiety-related biotypes of depression, (**c**) a total of four depression biotypes dissected using canonical correlation analysis, **(d)** displayed in the scatterplot along the two symptom-related dimensions of anhedonia (x axis) and anxiety (y axis) (Drysdale et al. 2017)

(Flint and Kendler 2014; Sullivan et al. 2000; Weissman et al. 2006). Moreover, typical environmental factors of childhood maltreatment and recent stressful life events interact with genetic factors by changing the transcription/translation patterns of MDD candidate genes such as *5-HTTLPR* (serotonin transporter-linked polymorphic region) (Bousman et al. 2017; Kinnally et al. 2010), among others.

Genome-wide association studies for MDD showed inconsistent findings and did not demonstrate meaningful signals reaching statistical significance (Flint and Kendler 2014; Ripke et al. 2013). On the contrary, other genetic studies for MDD using candidate gene approaches reported significant association from candidate genes such as *SLC6A4*, *APOE*, *DRD4*, *GNB3*, *HTR1A*, *MTHFR*, or *SLC6A3*. First, in relation to the HPA axis dysregulation of depression, a synonymous single nucleotide polymorphism (SNP) called *RS4309* within angiotensin converting enzyme (*ACE*) gene showed statistically significant association with depression (Buttenschon et al. 2017). Second, obesity-related gene *FTO* (fat mass- and obesity-associated) gene *rs9939609* A variant demonstrated inverse relationship with occurrence of depression (Samaan et al. 2013). Third, in accordance with the circadian dysregulation in patients with MDD, the transcription pattern of *CLOCK* gene was severely dysregulated in the anterior cingulate cortex tissue of patients with MDD (Bunney et al. 2015).

Based on the neurotrophin hypothesis of MDD [aberrant neurogenesis of the brain regions

that regulate emotion and memory in MDD], in addition to the classical MDD biological marker called brain-derived neurotrophic factor (BDNF), recent studies reported reduced mRNA expression and lower plasma levels of glial cell-derived neurotrophic factor (GDNF) [promotes neuronal survival] as well as increased plasma levels and mRNA expression of peripheral vascular endothelial growth factor (VEGF) [an angiogenic factor stimulating axonal outgrowth] in patients with MDD compared to healthy controls (Sharma et al. 2016). After incubation with antidepressant, the profile of cell proliferation and gene expression in lymphoblastoid cell lines (LCLs), derived from patients with depression, revealed a correlation between the basal gene expression of *SULT4A1* [related to metabolism of dopamine and norepinephrine] and clinical treatment response, as well as between fold changes in WNT2B [plays a supportive role in gastrulation and organogenesis including olfactory bulb] gene expression and clinical symptom remission (Breitfeld et al. 2016; Meltzer et al. 2008; Tsukiyama and Yamaguchi 2012). Moreover, efforts to understand the pathophysiology of MDD using the neuro-inflammatory hypothesis found higher level of *IL-6* [one of the key pro-inflammatory cytokines] mRNA expression compared to healthy controls in a group of drug-naïve patients with MDD (Han Chinese); furthermore, significant association between single nucleotide polymorphism *rs1800797* [located in the promoter region of *IL-6* gene] with MDD diagnosis in addition to the degree of *IL-6* expression in the frontal cortex was also revealed (Zhang et al. 2016a). However, most of those MDD candidate genes lost their explanatory power after meta-analytic integration across studies (Flint and Kendler 2014).

Therefore, future genetic studies for MDD might require both targeting of more homogeneous subpopulations of MDD [regarding the inconsistent previous findings] and utilization of sensitive/statistically powerful methods of testing the genetic association. For example, a recent study using a large family- and population-based Scottish cohort (N = 19,896) that employed haplotype-block-based regional heritability mapping [HRHM; which estimates the localized genetic variance explained by common variants within haplotype blocks to integrate the effects of multiple variants] successfully detected a haplotype block across a 24-kb region within the *TOX2* gene reaching genome-wide significance with MDD. The expression of TOX2 and a brain-specific long noncoding RNA RP1-269M15.3 in the frontal cortex and nucleus accumbens basal ganglia, respectively, were significantly regulated by MDD-associated SNPs within this region (Zeng et al. 2016). More research is required in this field.

9.3.2 Blood and Cerebrospinal Fluid

Exposure to traumatic events or repeated experience of psychosocial/environmental stressors could affect the vulnerability of developing MDD, partly mediated by synaptic plasticity deficit, dysregulated neurotransmitter system, and epigenetic changes (Christoffel et al. 2011; McLaughlin et al. 2010). In relation to the characterizing symptoms of depression such as anhedonia and amotivation, dysfunction of the dopamine system has also been linked to the pathophysiology of depression (Eshel et al. 2016). Specifically, low level of homovanillic acid (HVA) in the cerebrospinal fluid (CSF) of patients with MDD implies the importance of dopamine-related pathway in the pathophysiology of MDD and also suggests the possible role of reduced HVA level in the CSF as a biological marker for MDD subgroup showing better treatment response to dopamine agonist (Kunugi et al. 2015; Reddy et al. 1992).

Patients with MDD are prone to the presence of thyroid peroxidase antibodies (TPOAb) (van de Ven et al. 2012), obesity (Luppino et al. 2010), hypertension (Scott and Happell 2011), diabetes (Mezuk et al. 2008), and elevated serum leptin level (Milaneschi et al. 2015) compared to healthy controls. Specifically, patients with MDD with "atypical subtype" revealed significantly higher level of body mass index, waist circumference, serum triglyceride, and decreased serum level of high-density lipid cholesterol compared

to the healthy controls or patients with MDD with melancholic subtype, respectively (Capuron et al. 2008; Lamers et al. 2016). Moreover, the association between atypical MDD and dysregulated immune system, such as increased plasma levels of immune markers, tumor necrosis factor (TNF), and IL-6, has been reported (Dowlati et al. 2010; Howren et al. 2009). All of the aforementioned findings could be biological manifestation of the potential influence of psychological stress on the increased vulnerability to depression mediated by the elevation of circulating pro-inflammatory cytokines (Steptoe et al. 2007; Wohleb et al. 2016). The relationship between the increased level of peripheral inflammatory markers, such as cytokines or C-reactive protein (CRP), with attenuated strength of the functional connectivity between the ventromedial prefrontal cortex and ventral striatum [which in turn revealed correlation with severity of anhedonia] also implies the role of inflammatory dysregulation in the pathophysiological mechanism of atypical depression (Felger et al. 2016; Lamers et al. 2016).

In addition to the neuroimmune interaction, another facet of dysregulated stress-responsive system is the neuroendocrine HPA axis that regulates glucocorticoid production (Keller et al. 2016). Chronic neuro-inflammation results in the inhibition of glucocorticoid receptor functioning and escalates the activity of pro-inflammatory cytokines (Kim et al. 2016b). In 40–60% of patients with MDD, signs of HPA axis dysregulation such as hypercortisolemia and flattened circadian rhythm in addition to the increased level of other HPA axis hormones including the corticotropin-releasing hormone (CRH), vasopressin (arginine vasopressin; AVP), and adrenocorticotropic hormone (ACTH) were reported (Belvederi Murri et al. 2014; Herbert 2013; Keller et al. 2016; Moylan et al. 2013). Postmortem studies also revealed the increased expression of glucocorticoid receptors in the amygdala of patients with MDD (Wang et al. 2014).

In relation to the treatment response, blunted suppression in the dexamethasone/CRH test showed association with poor treatment response to antidepressants in MDD (Ising et al. 2007). Likewise, the patterns of cortisol-related stress response showed differential patterns between women [blunted cortisol response to psychosocial stress] and men [increased cortisol response], implying one of the underlying mechanisms for sex-related differences in treatment response rate after the administration of antidepressants (Sramek et al. 2016; Zorn et al. 2016).

9.3.3 Neuroimaging

As the selected features extracted from neuroimaging data could efficiently differentiate patients with MDD from healthy controls or from other psychiatric patients at the individual level, these neural underpinnings might be potentially useful as MDD biological markers. For instance, multivariate statistical methods using selected structural brain imaging markers classified patients with MDD from healthy controls with 70–88% sensitivity and 71–92% specificity (Kambeitz et al. 2016) even from a multiethnic community sample (Sankar et al. 2016). In particular, decreased gray matter volume of the insula and hippocampus could explain the effect of MDD diagnosis compared to healthy controls (Lefebvre et al. 2017; Matsubara et al. 2016). Furthermore, in a recent meta-analytic integration of a total of 73 studies using whole brain voxel-based morphometry, compared to bipolar disorder (BPD), patients with MDD demonstrated smaller gray matter volume of the dorsolateral prefrontal cortex, hippocampus, parahippocampal gyrus, inferior parietal lobule, and cerebellar vermis. However, the degree of gray matter volume reduction in the insula, superior temporal gyrus, anterior cingulate, and superior medial frontal cortices was comparable between patients with BPD and MDD (Wise et al. 2016). In addition, treatment-naive patients in their first major depressive episode exhibited decreased global efficiency [impaired network integration] and exaggerated modularity [increased segregation] as a whole; specifically, patients with MDD revealed decreased local efficiency in the default mode network [the hippocampus, parahippocampal gyrus,

precuneus, and superior parietal lobule] and increased local efficiency across the insula and posterior cingulate cortex (Chen et al. 2017).

In addition to the classical MDD symptoms such as depressive mood, patients diagnosed with MDD typically reveal proneness to negative effect in terms of attention to and memory of cognitive stimuli as well as negatively biased decoding of facial emotion (Gotlib et al. 2004; Leppanen 2006; Yoon et al. 2016). Specifically, studies using functional magnetic resonance imaging acquired during emotional processing tasks demonstrated abnormal patterns of blood oxygenation level dependent (BOLD) signal changes in the brain regions including the amygdala, nucleus accumbens, insula, anterior cingulate/medial prefrontal cortices, and orbitofrontal cortex. Moreover, patients with depression also revealed reduced capacity of executive control and working memory that engages the dorsolateral prefrontal cortex (Ma 2015). In addition, during semantic verbal fluency tasks, significant brain hypoactivation at the insula and angular gyrus was demonstrated in patients with MDD compared to healthy controls (Takamura et al. 2017). On the other hand, during an experience of monetary loss, patients with MDD displayed increased functional connectivity among the ventral striatum and midline cortical structures related to cognitive control (Quevedo et al. 2016).

Likewise, in the resting state functional connectivity network, patients with MDD revealed increased functional connectivity of the limbic regions including the amygdala and hippocampus as well as the subcortical thalamic nuclei, not only among these regions but also with other brain regions. In contrast, the nodal efficiency of cognitive control regions such as the dorsolateral prefrontal and anterior cingulate cortices was decreased in patients with MDD compared to healthy controls (Hou et al. 2016; Ye et al. 2016). In addition, the temporal homogeneity of the regional functional brain activity during resting state calculated using regional homogeneity (ReHo) demonstrated altered balance of ReHo in patients with MDD in the middle-inferior frontal and middle cingulate cortices, precuneus, superior temporal and parahippocampal gyri, and insula, compared to healthy controls (Yang et al. 2016a). Another measure of regional functional brain activity reflecting the low-frequency oscillations, namely, amplitude of low-frequency fluctuations (ALFF), revealed imbalance in the limbic network comprising attenuated orbitofrontal ALFF and increased insular ALFF in the first-episode patients with MDD (Zhang et al. 2016c).

Collectively, altered profile of the brain structure and/or function in patients with MDD could be possibly attributed to either current severity of clinical symptoms [=state marker] or biological vulnerability to certain psychopathology (or psychiatric disorder) [=trait marker], the delineation of which might not be simple in a patient population with active mood episode. From this viewpoint, shallow depth of the olfactory sulcus, which itself reflects the extent of neurodevelopment of the olfactory system, in both current and remitted patients with MDD compared to healthy controls was suggested as a trait marker of vulnerability to MDD (Takahashi et al. 2016). Moreover, studies in the familial members of patients with MDD, who share a part of genetic vulnerability for MDD and currently do not experience clinically meaningful psychiatric symptoms, could be more informative. For example, decreased fractional anisotropy [a measure of water diffusion directionality] of the brain white matter fiber tract in the anterior part of the corpus callosum of healthy co-twins of patients diagnosed with mood disorder [whether bipolar disorder or MDD] could be regarded as a possible trait marker for vulnerability of affective disorders (Macoveanu et al. 2016).

Altered profile of the brain neurochemical composition measured using proton magnetic resonance spectroscopy (^{1}H-MRS) revealed low N-acetyl-aspartate and elevated glutamine/glutamate (Glx) in the hippocampus and reduced Glx in the subgenual anterior cingulate cortex (Matsubara et al. 2016; Njau et al. 2016). In addition, increased choline [an index of membrane phospholipid integrity] concentration at the dorsolateral prefrontal cortex compared to healthy controls was reported in treatment-resistant adolescent patients with MDD (Yang et al. 2016b).

9.3.4 Electroencephalogram (EEG)

The EEG oscillatory activities, rhythmic electrical events reflecting communications among the large populations of neurons, are related to the regulation of information processing in the brain; these might provide reliable biological markers of altered brain function in psychiatric disorders including MDD (Basar et al. 2000; Klimesch et al. 2003; Leuchter et al. 2012; Mendez et al. 2012). The frequency distribution of EEG oscillations in MDD demonstrated increased percent power ratio of the frontal theta, global alpha, and beta oscillations, in addition to the decreased occipital-parietal theta and global delta oscillations. Assuming EEG as a medium of functional communication among different brain regions, the patterns of disturbed synchrony, such as decreased complexity of EEG oscillatory patterns (Nandrino et al. 1994), interhemispheric imbalance of strong alpha oscillations in the left frontal and right parietotemporal regions (Bruder et al. 2005; Coan and Allen 2003), might reflect altered patterns of interregional functional communication underlying MDD pathophysiology. Specifically, symptom severity of MDD patients was correlated with the strength of coherence [quantified degree of spectral synchrony of brain oscillations among separated regions] among short-distanced brain regions for alpha and theta oscillations (Fingelkurts et al. 2007).

The event-related potential (ERP) is a waveform of averaged EEG activity, time-locked to a stimulus in a cognitive task (Hegerl and Hensch 2014). The amplitude component of ERP demonstrates the degree of brain activation that reflects the recruitment of attentional resources during cognitive task performance. In addition, the latency of an ERP component represents the processing time required to perceive or to recognize the target stimuli (Olofsson et al. 2008). Reflecting the inhibitory deficit for negative emotional stimuli in MDD across the early stage of attentional allocation [reducing the interference from the emotional distractors] as well as the late evaluative stage [shifting attention away from the emotional stimuli already processed], patients with MDD showed priority for negative face expression by increased amplitude of occipital P1, occipitotemporal N170, and parietal P3 component in response to the subliminal exposure to or salience detection task (=visual oddball paradigm) with face stimuli (Chen et al. 2014; Wu et al. 2016; Zhang et al. 2016b). Moreover, attenuated response inhibition for sad faces accompanying decreased central no-go P3 amplitude was uncovered in MDD during implicit emotional go/no-go tasks (Monnart et al. 2016; Yu et al. 2017).

Of note, the loudness dependence of auditory evoked potentials (LDAEP) was introduced as a possible marker of brain sensitivity in terms of mood lability, anxiety, and depression (Kim et al. 2016a). Several studies were conducted to explore the relationship among LDAEP and clinical variables such as depression severity, suicidality, and genetic underpinning (Jang et al. 2015; Lee et al. 2014, 2015; Park et al. 2014). While there are some promising findings, more research is required to reach a conclusive result in this ERP component.

9.4 Biological Marker of Melancholic Depression

Patients with MDD with melancholic subtype show pronounced neuropsychological impairment for verbal/visual memory, executive functioning, sustained attention, and psychomotor speed in proportion to the increased cognitive load (Bosaipo et al. 2017). Reflecting the impaired cognitive performance of patients with melancholic MDD, decreased strength of the resting state functional connectivity of the subgenual cingulate cortex (SCC) with the right parahippocampal gyrus and left amygdala distinguished patients with melancholic MDD from those with non-melancholic MDD and healthy control groups, respectively, even in the symptomatically remitted status (Workman et al. 2016a). Moreover, during the flanker task, patients with melancholic MDD in remission revealed decreased difference in the peak amplitude between correct response negativity (CRN) and error-related negativity (ERN) compared to those with non-melancholic MDD in remission

or healthy controls, respectively (Weinberg et al. 2016). The ERN, a negative-going deflection in the ERP waveform at the fronto-central sites after 0–100 ms following the commission of an error, reflects an alarm signal to increase cognitive control and adjust behavior; on the other hand, the CRN measured in the same time window and sites for the correct trials reflects generic response monitoring.

Among these widespread cognitive impairments, "motivational anhedonia" [a loss of motivated behavior or a lack of effort-based decision-making under time demands or cognitive load demands] is a prominent behavioral feature of melancholic depression (Bracht et al. 2014; Treadway et al. 2012; Treadway and Zald 2011; Wacker et al. 2009; Withall et al. 2010). Likewise, patients with MDD with melancholic features also demonstrated reduced reward sensitivity, revealed as the reduced ability to reward-related behavior modulation and reduced response bias during probabilistic reward task. Furthermore, MDD patients with melancholic subtype also showed slow explicit identification of and low implicit priming effect of happy faces (Day et al. 2015; Fletcher et al. 2015). In other words, the source-localized middle cingulate cortex activity of feedback-related negativity (FRN; reflects affective response to negative feedback) demonstrated an inverse relationship with severity of anhedonia in patients with MDD (Mueller et al. 2015).

Several studies reported a few possible biological markers related to the molecular mechanism of neural dysfunction in melancholic depression. For instance, the S100 calcium binding protein B (S100B) is expressed in astrocytes and in oligodendrocytes (Gos et al. 2013). The S100B stimulates neurite outgrowth, enhances neuronal survival, and supports the development of serotonergic neurons (Eriksen and Druse 2001). Among patients with MDD with melancholic features, low serum levels of S100B at baseline predicted treatment non-responsivity to venlafaxine and imipramine after 7 weeks and 6 months, respectively, suggesting that elevated S100B levels might contribute to successful MDD treatment (Ambree et al. 2015). Moreover, in patients with melancholic MDD, plasma levels of an excitatory neurotransmitter called aspartic acid, and inhibitory neurotransmitters such as glycine and gamma-aminobutyric acid are decreased. In addition, a gaseous neurotransmitter named nitric oxide demonstrated elevated plasma concentration in patients with melancholic MDD compared to healthy controls. These alterations in the plasma concentration of neurotransmitters named did not change after 2 months of treatment with selective serotonin reuptake inhibitors (SSRIs). Hence, these results indicate the possibility of altered plasma concentrations of some neurotransmitters serving as trait marker for melancholic MDD (Lu et al. 2014).

9.5 Biological Markers of Atypical Depression

MDD with atypical features (atypical depression) is characterized by mood reactivity in addition to two or more of the following symptoms: increased appetite or weight gain, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity (Harald and Gordon 2012). The lifetime prevalence of atypical depression has been reported as 10.23–24.7% (Blanco et al. 2012; Gili et al. 2012) and appears to be more common in women than men (Halbreich and Kahn 2007). Related clinical pictures of atypical depression are earlier age of onset for initial depressive episode, long duration of mood episode, presence of comorbid axis I and II disorders, high suicidal risk, and increased functional impairment (Agosti and Stewart 2001; Blanco et al. 2012; Matza et al. 2003; Posternak 2003; Posternak and Zimmerman 2002). Furthermore, patients with bipolar I disorder show atypical features of depression more frequently than those with MDD (Blanco et al. 2012).

Patients with MDD with atypical features have a tendency of increased appetite, weight gain, show high incidence of metabolic syndrome, and a steep increase in waist circumference and fasting glucose level (Lasserre et al. 2016). For instance, a recent prospective cohort study including 35-to-66-year-old randomly selected urban residents demonstrated an association among the atypical MDD subtype and a

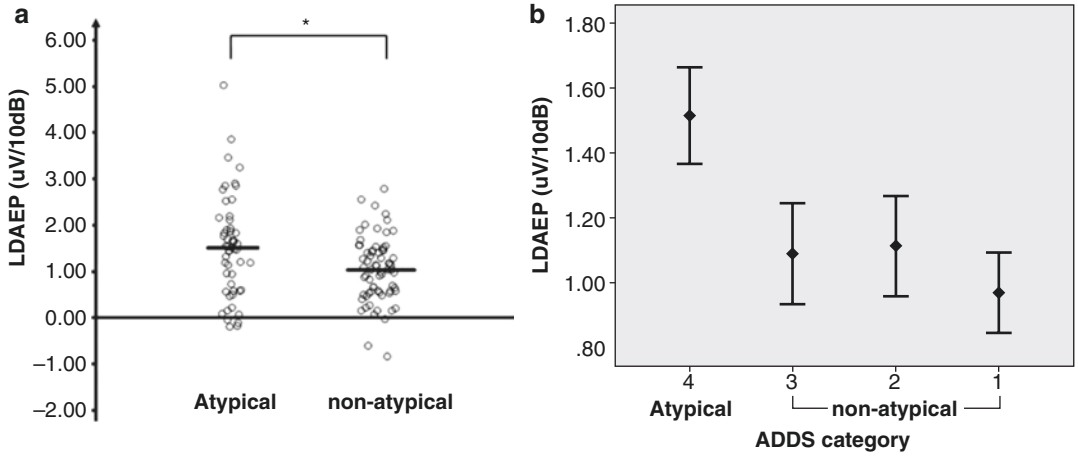

Fig. 9.2 (**a**) The strength of loudness dependence of auditory evoked potential (LDAEP) was decreased in patients with major depressive disorder (MDD) with non-atypical subtype compared patients with atypical MDD. (**b**) Patients with non-atypical MDD were divided into the three subgroups, namely, "probably atypical depression" [categorized as "3" according to the Atypical Depression Disorder Scale (ADDS)], "simply mood reactivity depression" [categorized as "2" for ADDS], and "non-mood reactivity depression" [categorized as "1" for ADDS]. Means and standard error bars are presented. *Asterisk* indicates a significant difference of $P < 0.05$ (Lee et al. 2014)

2.49 times higher incidence of the metabolic syndrome, a steep increase in waist circumference, and a marked elevation of the fasting glucose level during follow-up periods of 5.5 years on average (Lasserre et al. 2016).

LDAEP has been proposed as a biological marker of central serotonergic activity in MDD with relevance to the clinical response to serotonergic antidepressants (Gallinat et al. 2000; Linka et al. 2004). Lee et al. (2014) reported that patients with atypical depression had stronger LDAEP values than those with non-atypical depression. The value of LDAEP showed a pattern of gradual decrease according to Atypical Depression Diagnostic Scale (ADDS) score hierarchy in patients with MDD (Fig. 9.2). The results suggest a relatively deficient serotonergic activity in patients with atypical depression. In addition, LDAEP was demonstrated to be a useful biological marker in individuals who attempted suicide and to be a reliable biological marker of treatment response to SSRIs in MDD (Kim and Park 2013; Lee et al. 2015; Uhl et al. 2012). Kim and Park (2013) reported that LDAEP values differed significantly between suicide attempters and non-suicide attempters. Suicide attempters were characterized by a strong LDAEP value, indicating low serotonergic activity. Uhl et al. (2012) also reported increased LDAEP values about one week after suicide attempt. Recently, it has been shown that serotonin plays an important role in behavioral inhibition of human, possibly through prefrontal-subcortical circuitry (Drueke et al. 2013). Evidence from animal studies suggests the involvement of 5-HT (serotonin) depletion in the failure of response inhibition (Eagle et al. 2008; Yamada et al. 2013).

Bruder et al. (1991) reported that patients with atypical depression show preserved latency and hemispheric asymmetry of P3 component, while patients with melancholic depression show long P3 latency and abnormal lateral asymmetry. Fitzgerald et al. (2009) reported that patients with MDD with melancholic features had a significantly weaker LDAEP slope than patients with non-melancholic MDD, independent of depression severity or age.

9.6 Future Research Suggestions

Thorough consideration for epigenetic mechanism of gene-environment [childhood adversity, traumatic events, as well as chronic stress]

interaction would broaden our understanding of MDD pathophysiology (Smart et al. 2015). Moreover, future studies are required to elucidate the robustness of candidate biological markers for the differential diagnosis of depression subtypes and/or prediction of interindividual variations in treatment response for the introduction of personalized medicine in the psychiatric field (Kambeitz et al. 2016; Olbrich et al. 2015).

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Part III

Neural Circuit-Level Aspect of Depression

10 Structural, Functional, and Molecular Neuroimaging in Depression

Kai Zhang, Jing Huang, Jin Feng, Hong Zhang, and Mei Tian

10.1 Introduction

Depression is a globally prevalent psychiatric disorder, which is associated with genetic, environmental, and psychological factors. It is ranked as the second medical condition with the greatest disease burden worldwide (Global Burden of Disease Study 2015) and is projected to be the leading by the year 2030 (Lepine and Briley 2011). Despite considerable effort to date, much remains to be learned about the biomedical and neurobiological changes in depression. In vivo neuroimaging modalities have been used for in-depth understanding of depression, particularly magnetic resonance imaging (MRI) and radionuclide imaging approaches including positron emission tomography (PET) and single-photon emission tomography (SPECT).

Characteristics of these imaging modalities are summarized in Table 10.1. Structural, functional, and molecular abnormalities in depression have been observed in widespread brain regions with different imaging modalities. In this chapter, we will give a brief introduction of each neuroimaging approach first before going to summarize and discuss the findings of recent neuroimaging studies in depression.

10.2 Magnetic Resonance Imaging (MRI)

MRI is capable of in vivo visualizing both the morphology and function of tissue via the use of magnetic field and radiofrequency (Blamire 2008). The predominant superiority of MRI as a primary neuroimaging modality is its sophisticated spatial resolution accurate to micrometers. Thus, morphological alteration of the brain in depression is keen interest in the field of MRI studies. Imaging techniques for structural MRI include not only conventional voxel-based morphometry (VBM) technique for evaluating regional gray matter (GM) volume but also the relatively novel diffusion tensor imaging (DTI) method that captures microstructural changes within white matter (WM). Apart from the structural study, exploring cerebral functional changes in depression is another focus. Functional MRI (fMRI) acts as a noninvasive approach to identify neural activity changes by measuring hemodynamic response (blood flow) of neural activation (Logothetis 2002). It has been conceived as

K. Zhang • J. Huang • J. Feng • H. Zhang • M. Tian (✉)
Department of Nuclear Medicine, The Second Hospital School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

Zhejiang University Medical PET Center, Hangzhou, China

Institute of Nuclear Medicine and Molecular Imaging, Zhejiang University, Hangzhou, China

Key Laboratory of Medical Molecular Imaging of Zhejiang Province, Hangzhou, China
e-mail: meitian@zju.edu.cn

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Table 10.1 Characteristics of imaging modalities

	MRI	PET	SPECT
Spatial resolution	25–100 μm	1–2 mm	0.5–5 mm
Temporal resolution	Min-hours	Sec-min	Min-hours
Acquisition time (s) (per frame)	60–3000	1–300	60–2000
Anatomical information	High	Low	Low
Functional and molecular information	Moderate	Very high	High
Probe concentration	mM-μM	pM	nM-pM
Radiation	No	Yes	Yes
Signal quantification	Moderate	High	Moderate
Advantages	Sophisticated spatial resolution; morphological and functional imaging; relatively low cost of examination	Ultrahigh sensitivity; directly reflects metabolic and molecular changes	Directly reflects molecular changes; high sensitivity; relatively longer half-life time of radionuclides
Limitations	Low sensitivity; contraindicated in patients suffering from claustrophobia or in patients equipped with cardiac pacemakers or metal implants	Lack of precise anatomical information; radiation to subjects; short half-life time of radionuclides; ultrahigh cost of examination	Lack of precise anatomical information; radiation to subjects; high cost of examination

Adapted from Jiang et al. (2011) with modifications

a powerful technology to reveal functional connectivity among brain regions involved in emotional processing, cognitive control, self-representation, and external stimulus (stress, distress) interactions.

10.2.1 Voxel-Based Morphometry of Gray Matter

VBM is an even-handed MRI approach, allowing a far more comprehensive whole-brain assessment of anatomical abnormalities without the a priori selection of regions of interest, thus making it less time-consuming and more objective (Ashburner and Friston 2000). Besides, it enables to detect and quantify abnormalities in GM volume that is invisible with the naked eyes (Zoons et al. 2011). With the use of VBM, mounting evidence has implicated the crucial role of prefrontal-subcortical regions associated with GM deficits in the neurobiology of depression.

Reduced GM volume in the prefrontal-subcortical regions may be related to affective and cognitive dysfunctions in depression. A VBM study demonstrated that depressed adults had reduced GM volume in the anterior cingulate cortex (ACC), dorsolateral and dorsomedial prefrontal cortex (PFC), lateral and medial orbitofrontal cortex, and posterior temporal and parieto-occipital cortex compared with healthy controls (Grieve et al. 2013). Similarly, GM volume deficits were also observed in the ACC, superior frontal cortex in adults with treatment-resistant depression versus healthy controls (Machino et al. 2014). Another VBM research revealed a significant GM volume reduction of the ACC in depressed females compared to healthy female controls (Depping et al. 2015). The brain areas related to GM alterations are not completely consistent, probably attributable to the heterogeneity of demographics data and data processing. However, in accordance with those results, it is likely that the GM volume reduction in ACC plays a crucial role in depression (Bora et al. 2012; Lai 2013; Du et al. 2012). The ACC is involved in a range of functions, such as decision-making, empathy, conflict monitoring, working memory, attention, and information processing

(Zhang et al. 2016). Its atrophy may account for the brain functions compromised in depression and clinical symptoms in depressed patients.

Besides the prefrontal cortices, the subcortical regions or limbic system including hippocampus, insula, thalamus, and amygdala has been reported to show GM deficits in depression as detected by VBM (Yang et al. 2017; Liu et al. 2014; Zou et al. 2010; Malykhin and Coupland 2015). A previous VBM study performed in first-episode, drug-naive, non-late-life adult depression patients demonstrated that depressed patients showed significant GM volume deficits in the bilateral limbic system, particularly in hippocampus (Zou et al. 2010). Hippocampus is involved in memory (Turner et al. 2012; Kaymak et al. 2010) and develops nerve fiber connectivity with emotion-related brain regions like the PFC and amygdala (Liu et al. 2017). Therefore, hippocampal atrophy may be involved in the pathophysiology of depression. Insula is a critical brain region that connects to the middle and inferior frontal cortex, and to the ACC (Cauda et al. 2011), and is believed to be implicated in social-emotional regulation, cognitive control, affective processing, and general bodily awareness (Stephani et al. 2011; Critchley et al. 2001; Uddin 2015). Thus, reduced GM in this region is suggested to be associated with emotional, affective, and cognitive impairments in depression. Similarly, given that the thalamus is connected to the negative emotion-generating limbic structures particularly amygdala and to the cortex (Price and Drevets 2010), reduced thalamic and amygdala GM volume may account for deficits in top-down regulation of negative affect and be associated with emotional abnormalities among depressed individuals.

Prefrontal-subcortical GM deficits in the depression are perceived to be attributed to stress-related and/or repeated neurotoxic processes associated with cumulative exposure to stress and depressive symptomatology (MacQueen et al. 2003; Warner-Schmidt and Duman 2006; Stratmann et al. 2014). However, whether these alterations are part of the pathogenesis of depression or consequences of depression is still not conclusive and needs further exploration. Notably, a recent meta-analysis study did not observe any effect of illness duration on the GM volume (Wise et al. 2016), providing some evidence against the latter hypothesis. Likewise, a VBM study on the high-risk familiar depression daughters revealed that familiar depression group showed GM volume reduction in the right temporoparietal region and the dorsomedial PFC compared with matched control group (Ozalay et al. 2016), suggesting that GM volume alterations might present before the onset of illness.

10.2.2 Diffusion Tensor Imaging of White Matter and Structural Connectivity

DTI is a powerful MRI approach that allows to noninvasively assess the orientation and integrity of WM tracts in vivo by evaluating the diffusion of water in neural tissue (Sexton et al. 2009). It is an available technique mainly to detect abnormalities in WM, as well as to assess structural connectivity among brain regions (Mori and Zhang 2006).

With the use of DTI, emerging evidence has revealed aberrant structural circuits connecting the frontal regions with limbic regions in depression (Korgaonkar et al. 2014; Price and Drevets 2010; Korgaonkar et al. 2011), thereby resulting in a "disconnection syndrome" due to WM deficits (Liao et al. 2013). Frontal-limbic circuits are considered to be central to the regulation of motor, motivational, and cognitive processes which are compromised in depression (Sexton et al. 2009). Thus, it is suggested disruption or disorganization in these circuits contributes to the pathogenesis of depression. Besides, measured by DTI-derived fractional anisotropy (FA) which is expressed as an indication of the location and strength of WM fibers, lower FA values have been observed in other white tracts involved in the communication of somatosensory information, including the inferior and superior longitudinal fasciculus, internal and external capsule, in depression (Bessette et al. 2014; Jiang et al. 2016). Meanwhile, significantly lower FA values in the corpus callosum were detected in depression patients (Won et al. 2016; Choi et al. 2015;

Korgaonkar et al. 2011; Ota et al. 2015), as well as in depression rodent models (Zalsman et al. 2016). Corpus callosum is the biggest white matter structural architecture mediating interhemispheric communication (van der Knaap and van der Ham 2011), with crucial function like emotional processing (Bae et al. 2006). It interconnects the regions of the primary motor network, visual network, and two singular networks overlapping bilateral prefrontal and posterior precuneus regions (van den Heuvel et al. 2009). Thus, impairment in this region may result in dysfunctional information transduction and be implicated in the asymmetrical brain morphology and activity of depression subjects.

10.2.3 Resting-State Functional Magnetic Resonance Imaging of Neural Networks

fMRI provides a dynamic image of the brain and aids in elucidating the neural activity based on detecting the blood-oxygen-level-dependent signal in living subjects (Logothetis 2002). In most previous investigations, fMRI was carried out on subjects who were required to perform given tasks (task-state fMRI). In recent decades, however, studies have focused on imaging brain functional changes at rest state with fMRI (resting-state fMRI), since resting-state fMRI enables to monitor fluctuations in the spontaneous activities of thousands of brain regions simultaneously and provide deeper insight into functional changes without the interference of cognitive ability to perform a given task (Zuo and Xing 2014). It serves as a predominant tool for identifying functional connectivity in macroscale brain regions, given that functionally connected regions have related spontaneous time series (Smith et al. 2013).

Estimated from resting-state fMRI data, functional networks including default mode network (DMN), cognitive control network (CCN, also referred to as the "central executive network" or the "cognitive-executive network"), affective network (AN), and salience network (SN) have been identified compromised in depression (Mulders et al. 2015). Among these networks, the DMN has drawn most attention in resting-state fMRI investigations of depression. The DMN, a collection of brain regions including the posterior cingulate cortex, medial PFC, precuneus, and temporoparietal cortex, has been considered involved in self-referential/internally oriented processes (Posner et al. 2013; Andrews-Hanna et al. 2010). It is deactivated during goal-directed behaviors while activated during resting condition. Emerging evidence has revealed that DMN is hyperactive in depression subjects relative to healthy controls, and the aberrant DMN might account for the rumination state of depression (Broyd et al. 2009). The CCN comprising the dorsolateral PFC, pregenual ACC, and the posterior parietal cortex (Rogers et al. 2004; MacDonald et al. 2000) has been deemed to participate in the regulation of attention-dependent executive ability, task switching, decision-making, and emotional processing, particularly via the dorsolateral PFC (Corbetta and Shulman 2002; Phillips et al. 2003). Dysfunction of this network may explain aberrant cognitive regulation of emotional processing in subjects with depression. The AN, a set of interconnected neural structures consisting of the amygdale, subgenual ACC, hypothalamus, hippocampus, orbitofrontal cortex, and nucleus accumbens, has been identified to be implicated in emotion, appetite, libido, and sleep; thus, abnormalities of this network may underlie affective and vegetative disturbances in depression (Sheline et al. 2010). The SN, predominantly consisting of anterior insular cortex and dorsal ACC, serves to evaluate the correlation of internal and external salient stimuli to direct and orient appropriate responses and behaviors (Seeley et al. 2007). Hyperactivation in response to negative stimuli has been reported in SN, probably indicating heightened SN response selectivity to negative stimuli (Manoliu et al. 2013). Therefore, the aberrant SN might explain the negative interpretation bias in depression (Hamilton et al. 2012). In brief, the abnormal functional networks may be an extremely crucial neurobiological mechanism of depression (Leistedt and Linkowski 2013).

Taken together, depression is associated with both structural and functional abnormalities as

uncovered by MRI studies. Decreased GM in prefrontal-subcortical brain regions involved in the cognitive, affective, and emotional regulation, altered WM connecting those brain regions, and, more importantly, impaired functional networks exerting characteristic functions has been demonstrated in depression with the use of diverse MRI techniques. All of these abnormalities may account for the neurobiology of depression, as well as provide potential imaging biomarkers in identifying depression.

10.3 Radionuclide Techniques

Radionuclide imaging approaches, especially PET and SPECT, are representative molecular imaging modalities that utilize radiolabeled molecules to detect molecular interactions in biological processes in vivo (Phelps 2000). They possess the advantages of great intrinsic sensitivity and unlimited depth penetration, as well as specificity to molecular targets (Jones et al. 2012), and thus are capable of in vivo visualizing molecular events such as energy metabolism and neurotransmitter distribution (Zhang et al. 2016).

10.3.1 Positron Emission Tomography (PET)

PET enables to noninvasively visualize the biological processes at the cellular and molecular level in vivo, based on detecting pairs of gamma rays (in an opposite direction of each other) emitted indirectly via annihilation radiation (Politis and Piccini 2012). Compared with SPECT, PET has a rather higher sensitivity, higher spatial resolution, and relatively faster acquisition of dynamic data. Using PET with specific radiotracers, serotonergic system dysfunctions and abnormal brain metabolism have been detected in depression.

10.3.1.1 PET Imaging of Serotonergic System

The serotonin (5-HT) as a monoamine neurotransmitter is identified to mediate diverse physiological functions such as cognitive control and emotion regulation (e.g., affective and personality behaviors, mood, sleep, pain, anxiety, impulsivity, and aggression) (Lee and Kim 2016). It is released from serotonergic neurons mainly located in raphe nucleus and ascendingly projects to the cerebral cortex, hippocampus, amygdala, basal ganglia, thalamus, and hypothalamus that contain 5-HT receptors (Lesch et al. 2012). Among the various 5-HT receptor subtypes, the 5-HT1A receptor is the most abundant in the brain. They are divided into presynaptic inhibitory autoreceptors in the raphe nuclei and postsynaptic hetero-receptors in cortico-subcortical 5-HT terminal fields in the brain. Somatodendritic 5-HT1A autoreceptors suppress raphe serotonergic neuron firing, thereby reducing the frequency of 5-HT release from terminals (Sullivan et al. 2015). By using PET with selective 5-HT1A receptor radioligands such as ^{11}C-WAY 100635, ^{18}F-MeFWAY, ^{11}F-MPPF, and ^{11}C-MPT (Kumar and Mann 2014), numerous studies have been committed to quantify the distribution and exploring pharmacological role of 5-HT1A receptor in depression (Parsey et al. 2006; Miller et al. 2013; Lothe et al. 2012).

With the use of ^{11}C-WAY 100635 PET, converging evidence has demonstrated a higher 5-HT1A receptor binding as quantified with binding potential (BP_F) in the raphe nuclei of depression subjects (Miller et al. 2013). It is suggested that higher raphe nuclei 5-HT1A receptor binding in depressed subjects may lead to lower neuronal firing and less serotonin release at terminal projection regions in the forebrain (Jacobsen et al. 2012), in line with the 5-HT deficiency hypothesis in depression. In addition, by using ^{11}C-WAY 10065 PET, a study discovered that the severity of suicidal ideation in depression is positively associated with brainstem raphe and PFC 5-HT1A receptor BP_F (Sullivan et al. 2015). This suggests a role for 5-HT1A signaling in both regions in determining suicidal ideation, and 5-HT1A receptor BP_F of these two regions may predict suicide risk in depression patients (Sullivan et al. 2015). Moreover, lower levels of serotonin release at key brain projection sites, particularly the PFC, may favor more severe

suicidal ideation and higher-lethality suicide attempts (Sullivan et al. 2015).

Additionally, 5-HT1A receptor binding is expected as a potential predictor of treatment effect in depression. As investigated in a ^{11}C-WAY 100635 PET study which included 24 current depression patients in a current depressive episode, higher baseline 5-HT1A receptor binding (BP_F) in raphe nuclei predicted remission following standardized chronic treatment with the selective 5-HT reuptake inhibitors (SSRIs) escitalopram (Miller et al. 2013). It is hypothesized that SSRI activates autoreceptors in raphe nuclei, further lowering the firing rate of serotonergic neurons and the release of 5-HT with acute SSRI treatment (Miller et al. 2013). Nevertheless, chronic administration of SSRIs induces 5-HT1A autoreceptor desensitization in the raphe nuclei, and, subsequently, the desensitization of autoreceptor combined with reduced reuptake of 5-HT to presynaptic neurons contributes to the progressively elevated serotonergic transmission (Miller et al. 2013). 5-HT then binds post-synaptically to 5-HT1A hetero-receptors and, hence, triggers the antidepressant effects of SSRIs. Another ^{11}C-WAY 100635 PET study demonstrated that 5-HT1A receptor BP_F in the raphe was reduced in depressed patients following chronic SSRI treatment (Gray et al. 2013), suggesting that SSRI may cause down-regulation of 5-HT1A receptor, not only desensitization. However, since the ^{11}C-WAY 100635 binds to both low- and high-affinity states of 5-HT1A receptors, future investigation is essential to use PET radioligands that selectively bind to the high-affinity 5-HT1A receptors, therefore capable of identifying desensitization and determining whether it may be related to clinical response.

Meanwhile, the 5-HT transporter (SERT or 5-HTT), located in the cell bodies and terminals of serotonergic neurons, is deemed as a specific marker for the number and integrity of presynaptic terminals of serotonin-producing neurons. The SERT is known to modulate the release of 5-HT via reuptaking 5-HT from the synaptic cleft into presynaptic neurons. Utilizing PET with specific radiotracers, the distribution of the SERT in the brain is likely to be visualized. Moreover, PET with these radiotracers has been applied to assess the association between differential SERT binding and variables, particularly suicide attempt and depression severity in depression patients. In a recent investigation using quantitative in vivo 4-[^{18}F]-ADAM PET in 17 depression patients, it was shown that depression patients had a relatively lower level of SERT binding in the midbrain, thalamus, and striatum relative to the healthy controls (Yeh et al. 2015), indicating the mesencephalic-thalamic-striatal circuits may play a critical role in depression. Additionally, lower SERT binding in midbrain was apt to be observed in more serious depression patients (Yeh et al. 2015). Furthermore, depressed suicide attempters presented notably higher PFC/midbrain SERT binding ratio compared with the depressed non-suicide attempter, supporting a role for both PFC and midbrain in suicidal actions (Yeh et al. 2015).

10.3.1.2 PET Imaging of Cerebral Metabolism

Cerebral glucose metabolism could serve as an index of neuronal integrity and functional state of the synapse (Sokoloff 1981, 1999). Alterations of regional cerebral metabolic rates of glucose (rCMRglu) in depression patients have been detected via PET with [^{18}F]-fluoro-2-deoxyglucose (^{18}F-FDG), a glucose analogue.

Regional brain glucose uptake measured by ^{18}F-FDG PET has been proposed as a potential neurobiological biomarker for diagnosing depression, predicting treatment response, and evaluating suicide risk. A recent voxel-based meta-analysis of ^{18}F-FDG PET studies demonstrated that brain metabolism was remarkably decreased in widespread brain regions including cingulate cortex, insula, basal ganglia, thalamus, and cerebellum (Su et al. 2014). It was hypothesized that these regions might play a pivotal role in the pathophysiology of depression, and,

moreover, proposed ^{18}F-FDG PET might be of great value in diagnosing depression (Su et al. 2014). In addition, another ^{18}F-FDG PET study observed that relatively lower regional brain activity estimated by rCMRglu prior to antidepressant medication treatment in the midbrain in depression might predict treatment remission (Milak et al. 2009). Serotonergic nuclei are known to be mostly converged in the midbrain; therefore, altered cerebral metabolic activity in the midbrain has been considered to be probably reconciled with serotonergic system dysfunctions such as aberrant 5-HT1A autoreceptor and 5-HTT (Milak et al. 2009). Besides antidepressant medications, pretreatment rCMRglu in the insula and precuneus has been reported as a potential biomarker to evaluate effects of psychodynamic psychotherapy (Roffman et al. 2014) and repetitive transcranial magnetic stimulation therapy (Baeken et al. 2015). Furthermore, as described in a ^{18}F-FDG PET study, lower rCMRglu in right dorsolateral PFC was likely to distinguish suicide attempters from non-attempters in depression patients (Sublette et al. 2013).

Taken together, a series of PET studies on depression with specific 5-HT1A receptor and SERT radiotracers indicated elevated activity of 5-HT1A autoreceptor and decreased availability of SERT in the midbrain raphe nuclei, along with altered activity in projecting terminal brain regions particularly in PFC, amygdala, and hippocampus through a complex neuronal circuit or negative feedback. Coincidently, by using ^{18}F-FDG PET, these brain regions have been reported to manifest altered cerebral glucose metabolism, indicating altered cerebral energy metabolism involved in these areas might in part derive from the dysfunction of serotonergic system. Thus, altered serotonergic transmission and glucose metabolism in these brain regions are hypothesized to be involved in the neurobiology of depression. In addition, the binding level of 5-HT1A receptor or SERT radiotracers in raphe nuclei, as well as the level of cerebral glucose metabolic in specific brain areas, may be potential predictors of biomarkers for depression severity or treatment response. Moreover, with the employment of PET and 5-HT1A receptor radiotracers, SERT radioligands or ^{18}F-FDG, it becomes possible to discriminate suicide attempters from non-attempters in depression. Besides, as highlighted in PET studies, serotonergic system dysfunction in both the midbrain raphe and PFC is suggested to be of great significance in the ideation and action of suicide, the utmost devastating consequence of depression.

10.3.2 Single-Photon Emission Computed Tomography (SPECT)

SPECT detects a single gamma radiation directly emitted by the tracer, thereby leading to a relatively lower spatial resolution than PET. The SPECT scan, however, is less expensive than the PET scan owing to its employment of longer-lived and more easily obtained radioisotopes, making it become another valuable imaging modality for exploring the neurobiology underlying depression.

Most studies utilize SPECT with specific radiotracers to image the serotonergic system particularly the SERT in depression. Using SPECT with ^{123}I-ADAM, a highly selective SERT radioligand, various investigations have revealed diminished SERT binding in several brain regions such as midbrain, thalamus, medical temporal lobe, and basal ganglia in depression patients versus healthy controls (Newberg et al. 2005; Newberg et al. 2012; Ho et al. 2013), in line with the findings of PET studies (Yeh et al. 2015; Reimold et al. 2008; Selvaraj et al. 2011).

Apart from the serotonergic system, brain dopaminergic system is another focus of SPECT studies on depression. Dopamine (DA) as a neurotransmitter is conceived to be involved in mood regulation (Camardese et al. 2014). Emerging evidence has supported the hypothesis of DA deficiency in the neurobiology of depression

(Lattanzi et al. 2002; Meyer et al. 2001; Lambert et al. 2000; Nutt 2006). Diminished DA signaling may derive from either reduced DA release from synaptic neurons or from impaired signal transduction and result in alterations in receptor number or function and/or altered intracellular signal process (Dunlop and Nemeroff 2007). Of the SPECT studies exploring the role of the dopaminergic system in depression, presynaptic DA transporter (DAT) is a principal concern. Nevertheless, controversies have been demonstrated, which may be attributable to the heterogeneity of the variables including the employment of diverse rating scales, the diversity of sample size, and clinical variables. However, judging from the results of the two studies (Hsieh et al. 2010; Amsterdam et al. 2012) which have clearly clarified a greater striatal DAT availability only in patients examined a depressive episode other than in a euthymic state, it is postulated that a great DAT availability measured by the specific radioligand ^{99}Tc-TRODAT-1 SPECT might be a potential state marker of a depressive episode.

In addition, the dysfunction of cholinergic system is suggested to play a role in the pathophysiology of depression. Nicotinic acetylcholine receptors (nAChRs) have an ubiquitous role in the modulation of multiple neurotransmitter systems considered crucial in the pathophysiology of depression, such as 5-HT, DA, and glutamate (Sher et al. 2004). As presented in a recent ^{123}I-5-I-A-8530 (a β_2-subunit-containing (β_2*) nAChRs radioligand) SPECT study (Saricicek et al. 2012), β_2*-nAChR availability was significantly lower in cortico-subcortical regions in depressed subjects than in the matched comparison subjects. Further postmortem results showed no difference in β_2*-nAChRs number between groups, implying the lower β_2*-nAChR availability in vivo may be attributable to the greater endogenous ACh in depression rather than a downregulation of receptors (Saricicek et al. 2012). Moreover, the persistent enduring low β_2*-nAChR availability in completely recovered, euthymic medication-free depression subjects was detected, suggesting that the β_2*-nAChR availability alterations in depression may be associated with trait vulnerability to depression rather than serving as an epiphenomenon of treatment or illness (Saricicek et al. 2012). Whether the cholinergic system dysfunction may also reflect a cause or effect of dysfunction in other neurotransmitter systems needs to be further clarified.

In brief, SPECT studies in depression reveal the potential role of the striatal dopaminergic system and cortico-subcortical cholinergic system in the neurobiology of depression, as well as further support the crucial role of serotonergic system in the pathogenesis of depression.

10.4 Conclusion and Prospective

Depression is a debilitating mental disorder, associated with widespread structural, functional, and molecular abnormalities as detected by neuroimaging modalities. Emerging neuroimaging studies have observed brain structure and activity altered in depression, particularly in prefrontal-subcortical regions involved in cognitive and affective control, such as the dorsolateral and dorsomedial PFC, ACC, precuneus, amygdala, thalamus, and hippocampus. Dysfunctional functional networks and monoamine deficiency, particularly 5-HT and DA deficiency, have been identified with the applications of radionuclide imaging and MRI techniques. Furthermore, potential imaging biomarkers may to be associated with depression severity, characteristic symptoms, and even therapeutic effects. Findings from the diverse neuroimaging studies seem to be related, and each imaging modality contributes supplementary information. How the monoamine deficiency is related to the abnormal functional networks or to the alterations of the brain structure and activity, however, needs to be further clarified. Exploring the implications of these molecular, structural, functional changes for the behavior and cognitive of depression is warranted, as well.

Since each imaging modality possesses its own advantages and limitations (Table 10.1), multimodal imaging combining two or more modalities together enables to provide complementary information and accomplishes synergistic advantages over any single modality alone. Thus, for in-depth exploration of the potential relationship among the findings of the neuroimaging modalities and richer understanding of the neurobiology of depression, multimodal neuroimaging of depression carried out in multiple sites with standardized quality control methods are essential in the future.

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11 Why Do We Need Psychopathology? From the Brain's Resting State to "Spatiotemporal Psychopathology" of Depression

Georg Northoff

Neither the "brainless" psychiatry of the middle of the 20th century, nor the "mindless" variety of the past 30 years should be taken to represent the most we can achieve. The future should yield a synthesis. (Panksepp 2004, p 17)

11.1 Introduction

Neuroscience has made enormous progress in the last 20–30 years on all levels ranging from the genetic over the molecular to the regional and network level of neural activity. This has also affected psychiatry as in Biological Psychiatry. Various psychiatric disorders including schizophrenia, major depressive disorder (MDD), and bipolar disorder (BP), as well as others like addiction, personality disorders, etc. show molecular, genetic, regional, and network abnormalities in the brain. However, despite all progress in Biological Psychiatry, we still fall short in explaining the exact neuronal mechanisms of the various psychopathological symptoms. Specifically, Biological Psychiatry cannot yet explain how the brain's neuronal changes transform into the mind's alterations, the psychopathological symptoms.

Traditionally, the explanation and understanding of psychopathological symptoms have been the focus of psychopathology. Put in a nutshell, psychopathology concerns the empirical and theoretical framework in which symptoms, behavior, and experiences in psychiatric patients can be described, categorized, and classified (Parnas et al. 2008, 2013; Stanghellini 2009a, b; Stanghellini and Broome 2014). Different empirical and theoretical frameworks have been suggested in past and present approaches to psychopathology. However, how the different approaches to psychopathology (see below for details) are linked to the brain and its various neuronal mechanisms remains unclear.

Taken all together, we are facing a divide between Biological Psychiatry and Psychopathology. The advocates of Biological Psychiatry tend to claim that all we need is the brain: the more we understand the brain and its abnormal changes in psychiatric disorders, the better we will understand and explain the psychopathological symptoms. This makes psychopathology as separate scientific discipline (Stanghellini and Broome 2014) meaning- and senseless and thus superfluous. Conversely advocates of psychopathology resist such interpretation. There is "more" to psychopathological symptoms than just the brain, and this "more"

G. Northoff
Mind, Brain Imaging and Neuroethics Research Unit, Institute of Mental Health Research, University of Ottawa, Ottawa, Canada

Royal Ottawa Mental Health Centre, Ottawa, Canada
e-mail: Georg.Northoff@theroyal.ca

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consists in the central role of experience or consciousness, i.e., the mind (Parnas et al. 2008, 2013; Stanghellini 2009a, b; Stanghellini and Broome 2014). Taken in this view, Biological Psychiatry remains as "mindless" as Psychopathology is "brainless," to pick up our initial quote.

How can we resolve the divide between brain and mind/symptoms and thus Biological Psychiatry and Psychopathology? The aim in this paper is to show that a novel approach, "Spatiotemporal Psychopathology," can bridge this divide by providing a "common currency" between brain and symptoms—that "common currency" is supposed to consist in spatiotemporal features that transform abnormal neuronal activity in psychopathological symptoms.

11.2 Spatiotemporal Psychopathology: Determination and Distinction

11.2.1 Psychological Approaches to Psychopathology

Roughly, one may want to divide between psychological and experiential approaches to psychopathology. Psychological approaches focus on specific psychological features like cognitive functions (as Cognitive Psychopathology) or affective functions (as in Affective Psychopathology) (David and Halligan 2000; Halligan and David 2001) and affective psychopathology (Panksepp 2004). With the development of neuroimaging, these approaches are now able to link the objectified changes in cognitive and affective functions onto the brain. However, such "mapping" of cognitive into neural functions leaves open how and why abnormal changes in the brain's neural activity are transformed into psychopathological symptoms.

How can more strongly link cognitive and affective and cognitive functions to the brain and its neuronal mechanisms? We would need to unravel a yet unclear "common currency" that allows to transform neuronal into psychological activity. To be clear, I am not raising the question which regions or networks in the brain are related to cognitive functions. Such "cognitive-neural mapping" has been well established in cognitive neuroscience that showed how cognitive functions like executive functions, attention, memory, etc. are related to specific regions or networks in the brain (Gazzaniga 2010). This and the respective changes in those regions and networks have been well researched intensely over the last 10–20 years. Instead, I am raising the question why and how the brain's neuronal activity in those regions and networks transforms into cognitive (and affective functions) rather than remaining merely neuronal (and non-cognitive).

What is needed is a "common currency" between neural and cognitive functions—due to such yet unclear "common currency" neural activity translates into cognitive function basically by default. And it is this transformation or translation that seems to be altered in psychiatric disorders that can indeed be characterized by numerous cognitive deficits (see, for instance, Sheffield et al. 2016 in schizophrenia). I postulate that the spatial and temporal features of the brain's spontaneous activity provide such "common currency"—cognitive symptoms are spatiotemporal symptoms for which reason I speak of "Spatiotemporal Psychopathology."

11.2.2 "Common Currency" Between Brain and Cognition

We are confronted with a divide between the brain on the one hand and cognition on the other. Biological Psychiatry focuses on the brain while leaving out the mind and its experience. While psychological approaches to psychopathology focus on cognitive functions and the relation of their contents to the brain. Neither has yet provided a full-fledged explanation and understanding of psychopathological symptoms though. We are thus confronted with a divide between brain and cognition.

Psychological approaches to psychopathology focus on contents, i.e., cognitive, affective, sensorimotor, and social contents and their related functions. The cognitive, affective, sensorimotor,

and social contents are then "mapped" upon the brain and its various regions and networks—this is where psychological approaches to psychopathology converge with Biological Psychiatry. This neglects one central dimension of the contents though. The contents are organized and structured in a particular way, and this organization is mainly spatial and temporal. Spatiotemporal Psychopathology as suggested here focuses on the temporal and spatial organization of the contents rather than the nature of the contents themselves, i.e., cognitive, affective, sensorimotor, or social.

Spatiotemporal Psychopathology aims to unravel the spatiotemporal organization and structure within which the various kinds of contents are embedded hence the name "Spatiotemporal Psychopathology." Alterations in cognition in psychiatric disorders are consequently not related to specific contents, i.e., cognitive, affective, etc. Instead, abnormal cognition is related and traced to abnormal spatial and temporal organization within which the contents are embedded.

Let us give an empirical example. Duncan et al. (2015) recently demonstrated that early childhood traumatic experience is manifest in adulthood in the spatiotemporal patterns of the brain's spontaneous activity (as indexed by entropy) which, in turn, impacts subsequent stimulus-induced activity in relation to aversive stimuli. The early childhood traumata were thus encoded in terms of spatiotemporal features, i.e., entropy, rather than in terms of specific contents and cognitions. Sure, the very same spatiotemporal pattern impacts the contents and their subsequent cognition—however, it is clear that the latter has a spatiotemporal basis in the spatiotemporal features of the brain's spontaneous activity. Hence early childhood trauma is primarily a matter of spatiotemporal organization of the contents, i.e., life events, rather than being directly related one to one to the life event and its content itself.

Taken together, the spatiotemporal organization of the brain's spontaneous activity may provide the "currency" that translates directly into the cognitive level with the cognition of contents. Spatial and temporal features as manifest in both the brain's spontaneous activity and our cognition of contents may consequently provide the "common currency" between brain and cognition. Changes in cognition as in psychiatric disorders may then be traced to alterations in the resting state's spatial and temporal features. This would link the psychological approaches to psychopathology even more tightly to the brain while, at the same time, providing a new view on the brain and especially its resting state, a spatiotemporal rather than cognitive view (Northoff 2014a).

11.2.3 Experiential Approaches to Psychopathology

In contrast to psychological approaches to psychopathology, experiential approaches focus on the subject's experience, i.e., subjective experience, of self, world, and body rather than on objectified cognitive and affective functions. The hallmark experiential approach is Phenomenological Psychopathology which takes the subject's experience of self, body, and world and thus the structure of its consciousness as explanatory framework for psychopathological symptoms (Jaspers 1963; Fuchs 2007, 2013; Parnas et al. 2008, 2013; Stanghellini 2009a, b; Stanghellini and Broome 2014).

Siblings of Phenomenological Psychopathology include existential psychopathological that focuses on the existence as the deeper layer underlying experience and the hermeneutical psychopathology that emphasizes the meaning of symptoms in a wider biographical and environmental context (Stanghellini 2009a, b). Despite the difference in focus or emphasis, the overall explanatory framework in all three approaches consists in experience or consciousness for which I reason I subsume under the "experiential approaches" to psychopathology.

Phenomenological Psychiatry takes experience or consciousness itself as starting point and focuses on exploring first-person experiences in detail (Parnas et al. 2008, 2012; Stanghellini 2009a, b). Specifically, the focus is on the first-person experience of time and space as well as body, self, and world. The brain, in contrast,

nowhere surfaces in experience in particular, and phenomenology in general, since it cannot be accessed in experience in first-person perspective but only in observation as in third-person perspective. The brain is thus excluded in experience of the own self, body, and world including time and space in particular and phenomenology in general. Such exclusion of the brain in experience or consciousness occurs by default, e.g., on methodological grounds, since the brain cannot be accessed in experience in first-person perspective. Importantly, this leaves the link to the brain open and renders the experiential approaches to psychopathology ultimately as "brainless" (as picking up our initial quote).

11.2.4 "Common Currency" Between Brain and Experience

How can we close the gap between experience and the brain? Closing this gap is central for psychiatry since we need to understand the processes that transform abnormal neuronal into phenomenal states which psychiatric patients experience in first-person perspective. How can we apprehend these transformative processes, e.g., neuronal-phenomenal transformation? For that we may want to search for a shared overlap or "common currency" between neuronal and phenomenal states that drives the transformation of the former into the latter.

The shared overlap or common currency between neuronal and phenomenal states, e.g., brain and experience, may consist in spatiotemporal features. On the side of the brain, it is the spontaneous activity (rather than its stimulus-induced or task-evoked activity) that may be central in providing or constituting such spatiotemporal structure (see below for details). The brain's spontaneous activity shows certain spatiotemporal features, a particular spatial and temporal structure in its neural activity that surfaces in and is transformed into phenomenal state, e.g., experience (see Northoff 2014a for many examples). One would consequently expect a common, similar, or analogous spatiotemporal structure between the brain's spontaneous activity and the phenomenal features of experience.

Such common, similar, or analogous spatiotemporal structure between brain and experience amounts to what I describe as "spatiotemporal correspondence." The concept of spatiotemporal correspondence means that the brain's spontaneous activity and the phenomenal features of experience show corresponding or analogous spatial and temporal features: the spatial and temporal configuration or structure of the neural activity in the brain's spontaneous activity surface in the spatial and temporal features within which the contents of experience (like specific objects or events including body, self, and world) are integrated and thus structured and organized.

For instance, a recent study of ours demonstrated that private self-consciousness is directly related to the temporal patterns of spontaneous or resting state activity across different frequency ranges (as indexed by what is described as "power law") (Huang et al. 2016). This suggests that mental features like self may be rooted in spatiotemporal features of the brain's spontaneous activity. The self as mental feature may then be characterized in spatiotemporal terms, that is, by specific spatiotemporal schemata or structure

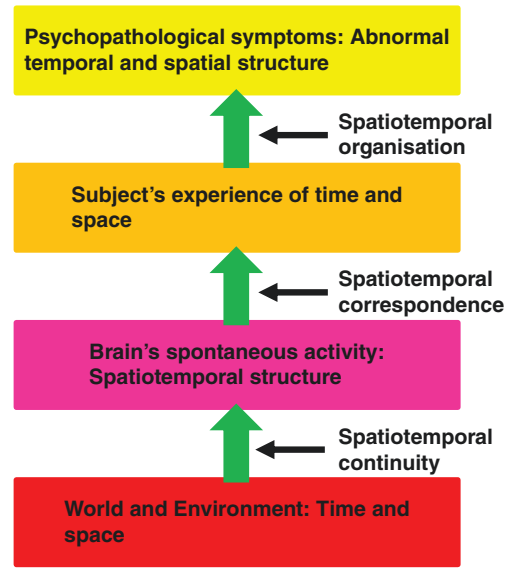

Fig. 11.1 Different levels in Spatiotemporal Psychopathology

rather than by cognition of particular contents (see Fig. 11.1).

Unlike Biological Psychiatry that focuses on the brain itself independent of its respective ecological context, Phenomenological Psychiatry emphasizes the integration of experience including the subject of experience within the ecological context of the world. There is continuity between experience and world with such continuity often assumed to be mediated by the body, e.g., experience of the body as lived body (see, for instance, Northoff and Stanghellini 2016). Such continuity between subject and world is deemed central for making experience including the first-person perspective itself first and foremost possible.

11.3 Spatiotemporal Psychopathology: Depression and Bipolar Disorder

11.3.1 Spatiotemporal Psychopathology: Bipolar Disorder and Neuronal Variability

How about spatiotemporal changes in the resting state in bipolar disorder (BP)? Several resting state investigations observed changes in functional connectivity in the default mode network in bipolar disorder though the phases, i.e., depressed, euthymic, and manic, are rarely specified (see Martino et al. 2016a). Going beyond functional connectivity, we investigated neuronal variability in different resting state network in manic, euthymic, and depressed phases of BP as well as healthy subjects. Neuronal variability is measured by the root means square of the amplitude; in that it reflects the change in the amplitude over time and the degree to which these changes vary over time. Taken in this sense, neuronal variability can be considered a measure of the temporal structure and, more specifically, the temporal dynamics of the ongoing spontaneous activity.

We focused on neuronal variability (SD) in the main neural networks, default mode network (DMN), central executive network (CEN), salience network (SN), and sensorimotor network (SMN) (Martino et al. 2016b). Depressed BP patients showed significantly decreased SD in the sensorimotor network, while their SD was significantly increased in the DMN. The other neural networks like SN and CEN did not show any SD changes. We then calculated the ratio or balance between DMN SD and SMN SD; this was tilted significantly toward the DMN SD at the expense of the SMN SD.

What does this mean? Neuronal variability may be linked to the initiation of internally directed cognition in DMN and movements/actions in SMN. The more often the neuronal variability change surpasses a certain threshold, the more often the respective regions internally, i.e., by itself independent of external stimuli, initiate either cognition or action. Let us be more specifically regionally. The DMN has been associated with internally directed cognition as in spontaneous cognition and mind wandering (Christoff et al. 2016; Smallwood and Schooler 2015). If now neuronal variability is abnormally high in the DMN, there is a higher likelihood that spontaneous thoughts will be initiated. This is exactly what one can observe in depressed BP where the patients suffer from increased spontaneous thought which are described as rumination.

How about the SMN? In that case, neuronal variability may be related to the spontaneous or internal initiation of movements and actions. If now neuronal variability in SMN is decreased, one would expect decreased internal initiation of movements and actions. This, again, is exactly what can be observed in depressed BP where patients often suffer from psychomotor retardation. Most interestingly, it seems that the balance between DMN SD and SMN SD is central since the balance correlated significantly positively with depressive symptoms (as measured with Hamilton depression scale): the more the SD balance was shifted toward the DMN at the expense of the SMN, the more and stronger depressive symptoms.

The reverse could be observed in the manic phase. Here SD was significantly lower in the DMN and abnormally high in the SMN; the

balance between DMN SD and SMN SD is consequently tilted toward the SMN at the expense of the DMN. This is symptomatically manifest in increased internal initiation of movement/action as it is reflected in the well-known psychomotor agitation in mania. In contrast, internally directed cognition like spontaneous thought are no longer initiated internally as much—this is reflected in the fact that many manic patients say "that they do not think much or not at all" in the manic episode.

11.3.2 Spatiotemporal Psychopathology: From Neuronal Variability to Cognition and Experience

What do these findings tell us about the nature of psychopathological symptoms? There is still internal initiation of movements as related to SMN and internally directed cognition, i.e., spontaneous thought as based on DMN. However, the neuronal mechanism potentially underlying such internal initiation, i.e., neuronal variability, is expressed to an abnormal degree. It is either too high or too low which leads to either increased or decreased internal initiation of the respective function. That very same neuronal mechanism is temporal, i.e., SD, and spatial, i.e., in different networks like DMN and SMN, and can therefore be considered "spatiotemporal mechanism" as I say (see Fig. 11.2).

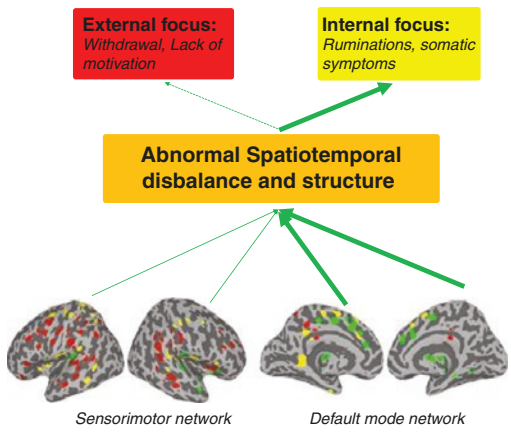

Fig. 11.2 Network disbalance and abnormal spatiotemporal structure in depression

Let me be more precise. The function, i.e., internal initiation of movements/action and internally directed cognition, is still intact by itself—the bipolar patients are still able to internally initiate them. This distinguishes psychiatric patients from neurological patients. In the latter, the region itself is lesioned which makes impossible the internal initiation of, for instance, movement and action as in Parkinson's disease. However, the function of internal initiation of movement/action and internally directed cognition is expressed in an abnormally high or low way due to some spatial and temporal abnormalities in the brain's spontaneous activity, i.e., SD in SMN and DMN. The resulting abnormalities in movement/action and internally directed cognition, i.e., the psychopathological symptoms, are thus based on and can be traced to spatiotemporal changes in the brain's spontaneous activity. Rather than being primarily motor, as in Parkinson's disease, the psychomotor changes in mania and depression are thus spatiotemporal at their very basis.

The same holds analogously for internally guided cognition. Unlike in neurological lesion patients, the bipolar patients can still initiate internally directed cognition like spontaneous thought. However, that very same internal initiation is temporally disorganized by the abnormal high neuronal variability in DMN in depression and the low SD in DMN in mania. The cognitive symptoms like rumination (or decreased thought) are consequently not primarily cognitive but rather spatiotemporal as they are related to spatiotemporal changes in the brain's spontaneous activity.

Taken together, the example of BP nicely demonstrates that cognitive and motor symptoms in both depression and mania are not related to primary dysfunction in either cognitive or motor functions. Instead, the basic function, i.e., cognitive or motor, is preserved by itself but abnormally organized in spatial and temporal terms. Therefore, the symptoms are spatiotemporal rather than cognitive and motor. What is described as cognitive in Cognitive Psychopathology is based on and can be traced spatiotemporal abnor-

malities in the brain's spontaneous activity and thus Spatiotemporal Psychopathology.

The same holds for experience and Phenomenological Psychopathology. Depressed patients often experience their "inner time," i.e., the time of their own self, as extremely slow which, when taken as reference, lets them perceive the "outer time," i.e., the time in the environment, as extremely fast (Fuchs 2015; Northoff et al. 2017). We measured neuronal variability in the neural network underlying "inner time," i.e., the somatosensory network (SS), and the one related to "outer time," i.e., primary sensory regions like visual cortex (VS). This yielded decreased SD in the SS and increased SD.

How are these findings related to the experience or perception of time? Neuronal variability indicates change in neural activity, and the more change there is, the faster the time. Decreased SD in SS thus indicates slower "inner time," while increased SD in VC reflects faster "outer time"—this corresponds exactly to the experience of time depressed patients report (Northoff et al. 2017 for details). The opposite SD pattern with increased SD in SS and decreased SD in VC was observed in manic patients—this corresponds well to their experience of faster "inner time" and slower "outer time."

Taken together, these findings indicate how a temporal measure like neuronal variability is translated into experience or perception, i.e., the experience of the speed of time. Hence, experience of the speed of time may be traced to and be based on a corresponding neuronal measure that indicates the speed of the brain's time, i.e., neuronal variability. Hence, the change in the brain's time speed, i.e., its neuronal time as indexed by neuronal variability, is transformed into corresponding experience or perception, i.e., the experience of the speed of time. Experience of time and experience in general is thus spatiotemporal by itself and thereby based on the spatiotemporal features of the brain's spontaneous activity. Experiential approaches like Phenomenological Psychopathology are thus ultimately based on and can be traced to spatiotemporal features and hence Spatiotemporal Psychopathology.

Conclusion

How can we bridge the divide between brain and cognition and hence between Biological Psychiatry and Cognitive Psychopathology? I demonstrated how cognitive changes like rumination in depression and decreased cognition in mania are related to abnormal expression of spatial and temporal mechanisms of the brain's spontaneous activity. Hence, I postulate that what is described as abnormal cognition in Cognitive Psychopathology is based on and can be traced to abnormal spatial and temporal organization of cognitive functions—this entails what I describe as "Spatiotemporal Psychopathology." Accordingly, I postulate that the spontaneous activity's spatial and temporal features provide the bridge between brain and cognition. Therefore, Spatiotemporal Psychopathology provides the bridge between Biological Psychiatry on the one hand and Cognitive Psychopathology on the other.

How about the divide between brain and experience and hence between Biological Psychiatry and Phenomenological Psychopat hology? I showed how the abnormal experience of time in depression and mania may be based on abnormal temporal features like neuronal variability in the brain's spontaneous activity. Experience is thus based on spatiotemporal features—the spatiotemporal features of the brain's spontaneous activity transform into experience which thereby can be characterized as spatiotemporal. Hence, the spontaneous activity's spatiotemporal structure allows linking brain and experience and can therefore bridge the divide between Biological Psychiatry and Phenomenological Psychopathology.

The initial question and title in this paper is: Why do we need psychopathology? We need psychopathology to bridge the gap between brain and cognition as well as the one between brain and experience. This does not only provide common link between biological, cognitive, and experiential forms of psychopathology but also a novel, i.e., spatiotemporal, understanding of both brain and symptoms. I postulate that Spatiotemporal

Psychopathology as sketched here provides exactly that form of psychopathology that allows us to understand the brain and how its neural activity transforms into cognition and experience and subsequently the kind of symptoms we observe in our patients.

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Neuroimaging in Depression: A Tool Toward Individualized Prediction of Treatment Outcome

12

Boudewijn J.H.B. de Pont, Jeroen A. Van Waarde, and Guido A. van Wingen

12.1 Introduction

Major depressive disorder (MDD) affects one in five people over the course of their life; however, only 50% of these patients reach symptomatic remission after initial treatment (Kessler et al. 2005). The diagnosis of MDD is based on clinical observations often combined with questionnaires. A summation of symptoms provides a syndromal diagnosis that can be classified as MDD. Patients suffering from this syndrome have phenotypical similarities, but there are no known common genotypical or pathophysiological pathways that cause the disease. After a patient is diagnosed with MDD, a treatment plan is chosen based on several characteristics, such as age, course of the illness, presence of suicidality, and psychotic features. Based on this treatment plan, the clinician provides either psychotherapy, pharmacotherapy, brain stimulation, or a combination of these therapies. Until now, the prediction of outcome of treatments has been based on patient characteristics that are only predictive on a group level.

To arrive at a diagnosis and treatment in medicine, one tends to look for deviation of shape or structures to understand the disease. Additionally, in biological psychiatry, there has been a longstanding desire to localize psychiatric diseases in the brain to better understand the disease and develop cures. The first brain imaging studies in MDD research focused on structural or volumetric differences between patients and controls, which sought to localize psychiatric diseases; later studies aimed to detect local differences in brain activity between patients and controls. The modern neuroimaging studies of today focus on networks abnormalities rather than isolated local changes or differences, which perhaps does more justice to the complex pathophysiology of MDD than previous methods.

Recent studies show that it is possible to distinguish MDD patients from controls on an individual level using multivariate analysis of neuroimaging data. Kambeitz et al. have analyzed 33 such studies with a total of 912 patients diagnosed with MDD and 894 controls. They subsequently found that neuroimaging-based diagnostic models could differentiate between patients and controls with a 77% sensitivity and 78% specificity. Resting-state fMRI and DTI were more sensitive and specific than anatomical MRI and task-based fMRI studies (Kambeitz et al. 2016). These studies have led to an improved understanding of the diagnosis and concept of

B.J.H.B. de Pont (✉) • J.A. Van Waarde
Department of Psychiatry, Rijnstate Hospital, Arnhem, The Netherlands
e-mail: bdepont@rijnstate.nl

G.A. van Wingen
Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

Amsterdam Neuroscience, Amsterdam, The Netherlands

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MDD but do not contribute to more specific treatment options for an individual patient. Nevertheless, there seems to be certain brain characteristics that are predictive of treatment outcome on the group level. Fu et al. (2013) performed a meta-analysis of studies that aimed to predict treatment outcome and found that higher activity in the medial prefrontal cortex, lower activity in the basal ganglia and insula, and larger hippocampal volume were associated with better treatment response.

From a clinical perspective, an accurate tool that helps to predict treatment outcome in MDD with greater precision—also on an individual level—would be highly desirable. It is important therefore to know what specific treatment may cure a certain patient with his or her specific personal characteristics and set of symptoms. Predicting which treatment is optimal for an individual in terms of positive outcome and side effects would consequently save patient burden, time, and money (Murray et al. 2013). Such individualized medicine is considered state of the art in the field of oncology, where the individual properties of the patient and cancer characteristics make treatment more effective and reduce side effects.

A personalized approach to find cures is especially important in diseases that are defined by heterogeneous syndromes without a specific underlying pathophysiology. MDD is, despite all efforts to find a common pathophysiological pathway, a heterogeneous disease. Most studies have focused on understanding the pathophysiological origin of MDD to enable improved and personalized treatment. An alternative approach, instead of focusing on the pathophysiology, could be to work backward from treatment outcome to patient characteristics. This "top-down" approach may or may not reveal a causal pathophysiological relationship but could be very helpful in choosing an optimal treatment modality for individual patients. Neuroimaging is consequently a fascinating and promising tool for this approach. To analyze neuroimaging patterns, machine learning techniques (such as the support vector machine (SVM)) are excellent but rather complex statistical methods.

Machine learning is a multivariate technique that is optimally suited to detect different patterns of brain structure or function. The algorithm is trained to distinguish different treatment outcome groups of individuals maximally, and its accuracy is tested on independent data. Thus, it divides individuals into groups based on their brain patterns by using multivariate input, which can also be enriched with clinical and demographic data. After training, data from a new subject can be analyzed, and the algorithm can assign this subject with a certain probability to either group. Studies that have used this approach to distinguish individual depressed patients from controls have been comprehensively reviewed elsewhere (Wolfers et al. 2015; Patel et al. 2016; Arbabshirani et al. 2017). Here, we shall focus on using such an approach for individual prediction of treatment outcome.

This chapter gives an overview of the most commonly used neuroimaging modalities and recent literature regarding the prediction of outcome of MDD treatment on an individual basis. A discussion of some of the limitations that were identified follows this overview. The literature overview is based on a PubMed search for articles published between 2009 and February 2017 with a combination the following search terms: "Depression" [Mesh], "Depressive Disorder" [Mesh], "Magnetic Resonance Imaging" [Mesh], "Functional Neuroimaging" [Mesh], "Neuroimaging" [Mesh], "Biomarkers" (All Fields), "Outcome" (All Fields), "Response" (All Fields), "Prediction" (All Fields), "Remission" (All Fields), and "Treatment Prediction" (All Fields). In total, 465 articles were found; however, 455 were excluded because the articles were irrelevant, did not focus on individual pretreatment outcome prediction, or had biases because their original study design had no primary focus on pretreatment imaging to predict treatment outcome. Ultimately, ten articles were included for this chapter. The characteristics of these studies are described in Table 12.1, and the results are discussed below (Costafreda et al. 2009a, b; Crane et al. 2017; Dunlop et al. 2015; Korgaonkar et al. 2014, 2015; Patel et al. 2015; Redlich et al. 2016; Ribeiz et al. 2013; Tenke et al. 2011; van Waarde et al. 2015).

Table 12.1 Studies that have used different neuroimaging modalities for individualized treatment outcome prediction in major depressive disorder (MDD)

Reference	N	Imaging modality	Treatment modality	Outcome parameter	Statistical analysis used	Sensitivity/specificity in predicting outcome
Costafreda et al. (2009b)	37	sMRI	CBT or medication	Response HDRS <7	SVM	89%/89%
Ribeiz et al. (2013)	30	sMRI	Medication	Remission MADRS ≤10	Logistic regression	77% accuracy
Patel et al. (2015)	33	sMRI	Medication	Response HDRS <10	SVM	89%/90%
Korgaonkar et al. (2015)	83	sMRI	Medication	Non-remission HDRS <7	ROC	85% accuracy
Redlich et al. (2016)	23	sMRI	ECT	Response HDRS 50% reduction	SVM	100%/78%
Korgaonkar et al. (2014)	34	DWI	Medication	Remission HDRS <7	Logistic regression	82%/58%
Costafreda et al. (2009b)	16	fMRI	CBT	Remission HDRS <7	SVM	71%/86%
Van Waarde et al. (2015)	45	fMRI	ECT	Remission MADRS ≤10	SVM	84%/85%
						80%/75%
Crane et al. (2017)	36	fMRI	Medication	Remission HDRS <8	Leave-one-out cross validation	84%/80%
Tenke et al. (2011)	41	EEG	Medication	Response CGI-I	Logistic regression	93%/50%

sMRI structural magnetic resonance imaging, *fMRI* functional magnetic resonance imaging, *SVM* support vector machine, *ROC* receiver operator characteristics, *CBT* cognitive behavioral therapy, *ECT* electroconvulsive therapy, *EEG* electroencephalogram, *HDRS* Hamilton depression rating scale; *MADRS* Montgomery-Åsberg depression rating scale; *CGI-I* clinical global impression-improvement scale

12.2 Different Neuroimaging Modalities for Treatment Prediction

Five studies used structural magnetic resonance imaging (sMRI) to predict treatment outcome on an individual level (Korgaonkar et al. 2015; Redlich et al. 2016; Patel et al. 2015; Ribeiz et al. 2013; Costafreda et al. 2009b). MRI uses magnetic radiofrequency fields to manipulate the magnetic direction of hydrogen atomic nuclei in the brain, which results in very short change of the magnetic field that differs between distinctive brain tissues. The scanner measures this change in a magnetic field, and a software-enhanced three-dimensional image is calculated. Measures that can be obtained with structural MRI include volumetry and morphometry.

Only one study was found that used diffusion-weighted imaging (DWI) to predict treatment outcome on an individual level (Korgaonkar et al. 2014). DWI focuses on white matter organization. DWI data are used to calculate the extent of inequality of water diffusion in all directions, which is related to the amount of alignment of white matter bundles. One of the resulting measures is fractional anisotropy (FA), which is the degree of anisotropy of diffusion of water molecules and which serves as the basis for tractography.

Three studies were identified that investigated individual prediction of outcome and used functional magnetic resonance imaging MRI (fMRI) as a neuroimaging modality (Costafreda et al. 2009b; Crane et al. 2017; van Waarde et al. 2015). This imaging technique uses the blood oxygenation

level dependent (BOLD) signal: the assumption is that the increase of neural activity results in a local change of oxygen-rich versus oxygen-low blood flow. This subsequently changes the magnetic properties of the blood, which can be detected by the MRI scanner (Weingarten and Strauman 2015). Functional MRI can be used to measure the responses of specific brain regions to emotional and cognitive challenges or to measure functional connectivity between distinct brain regions either during a challenge or while at rest.

Although positron emission tomography (PET) is an interesting imaging modality, no studies investigated PET brain analyses to predict treatment outcome on an individual level. PET focuses on metabolic activity, blood flow, or receptor binding. Through intravenous injection, radioactively labeled compounds are administered to patients and/or controls. This radioactive compound is absorbed by the brain, and concentrations of the compound in specific brain regions can then be quantified by PET scanners. Brain metabolism is dependent on glucose, and therefore quantified concentrations of radioactively labeled glucose are correlated to brain activity (Weingarten and Strauman 2015).

One study used electroencephalography (EEG) alpha band prominence to predict treatment outcome on an individual level (Tenke et al. 2011). EEG is considered to be the oldest neuroimaging modality. Its use is widely spread in epilepsy diagnosis but has perhaps received only limited focus in psychiatric research—at least in the last decades. EEG measures electrical activity of the brain with many electrodes placed on the scalp. An EEG can measure spontaneous electrical activity of the brain cortex or its response to stimuli. Indeed, many aspects of EEG measurements can be investigated. Differences in alpha, beta, delta, and theta waves between patients and controls are possible biomarkers as well as epileptic or paroxysmal patterns. Connectivity between brain areas can also be investigated as well as event-related potentials (Olbrich et al. 2015).

To conclude, in our literature search for biomarkers to predict MDD treatment outcome, structural and functional MRI, DWI, PET, and EEG modalities were found. Availability, cost-effectivity, and clinical implementability may determine the choice for a specific neuroimaging modality to predict treatment outcome on an individual level: possibly more so than theoretical etiological constructs. In the next section, a summation of the retrieved neuroimaging prediction studies is presented and, for the sake of readability, ordered by neuroimaging modality (structural MRI (sMRI), DWI, fMRI, and EEG, respectively).

12.3 Studies

In 2009, Costafreda investigated 37 MDD patients and 37 healthy controls. Prior to treatment with fluoxetine or CBT for a period of 8 weeks, all were scanned in a 1.5-T MRI scanner. Remission was defined when the HDRS score was less than 7. Voxel-based morphometry was applied to the structural MRI images. SVM was used to predict treatment outcome in the medication group. Whole brain anatomy could predict remission with 88.9% sensitivity and specificity (Costafreda et al. 2009b).

Ribeitz et al. investigated 30 patients older than 60 years who met the criteria for MDD. They were treated for 24 weeks with medication. Before treatment, patients and controls underwent structural MRI scanning using a 1.5-T MRI scanner, and voxel-based morphometry was used to analyze the data. Remission was defined as ≤ 8 on the Montgomery-Åsberg Depression Rating Scale (MADRS). Logistic regression could classify remitters and non-remitters with 76.7% accuracy when combining significant volumetric gray matter reduction in the left orbitofrontal cortex and baseline cognitive impairment (Ribeiz et al. 2013).

Patel et al. published a paper in 2015 where 33 elderly non-psychotic MDD patients and 35 non-depressed elderly people were examined. The MDD patients were treated with either duloxetine, venlafaxine, nimodipine, or escitalopram for a period of 12 weeks. A posttreatment HDRS score lower than 10 was defined as response. Before treatment, patients and controls were scanned with 3-T MRI and fMRI. A machine learning model, trained with demographics, cognitive abilities,

MRI-derived brain characteristics (atrophy and global white matter burden), and functional connectivity prior to treatment, could predict the diagnosis with an accuracy of 87.3% and treatment response with an accuracy of 89.5% (Patel et al. 2015).

In the international Study to Predict Optimized Treatment in Depression (iSPOT-D), 83 MDD patients were scanned using 3-T MRI with voxel-based morphometry analysis prior to an 8-week treatment with either escitalopram, sertraline, or venlafaxine. A HDRS score of less than 7 defined remission. A receiver operator characteristics (ROC) analysis was used to create a decision model with the first 50% of the treated patients. This decision tree was tested for replication in the remaining participants. Pretreatment MRI measurements showed that left middle frontal and right angular gyrus volumes could identify the 55% of patients who did not response to treatment with 85% accuracy (Korgaonkar et al. 2015).

In 2016, Redlich et al. published a non-randomized prospective study with 67 patients and controls. In this study, 23 MDD patients received ECT in addition to antidepressant treatment, 23 MDD patients were treated with antidepressants alone, and 21 healthy controls were investigated. Gray matter structure was measured twice at 6-week intervals using a 3-T MRI and voxel-based morphometry. Machine learning was used to predict ECT response by structural MRI, which was performed before treatment. Response was defined as having at least 50% relief on patients' individual Hamilton Depression Rating Scale (HDRS) scores. SVM could differentiate ECT responders and nonresponders with a sensitivity of 100% and a specificity of 78.3%. Regression analyses showed that the subgenual cingulate gyrus was the area that contributed most to the classification of response (Redlich et al. 2016).

Korgaonkar et al. investigated 74 MDD patients who were treated with either sertraline, escitalopram, or venlafaxine for 8 weeks. Before treatment, they underwent a DWI scan using a 3-T MRI scanner. Logistic regression statistics were used to test the prognostic value of DWI fractional anisotropy for antidepressant treatment outcome. Remission was defined as an HDRS of less than 7. Altered structural connectivity of the cingulum, part of the cingulate cortex, and the stria terminalis white matter tracts, combined with age, predicted remission in MDD patients treated with antidepressant medication with 74% accuracy (Korgaonkar et al. 2014).

Costafreda et al. (2009b) investigated whether the pattern of brain activity in reaction to sad faces could predict response to treatment with CBT in 16 MDD patients. Remission was defined as an HDRS of less than 7. Before treatment, all patients were scanned in a 1.5-T scanner during an event-related fMRI task (standardized facial expression of sadness). Machine learning analyses could identify who would fully respond to CBT with 71% sensitivity and 86% specificity. Regions with the largest contribution to this prediction were the anterior cingulate cortex, superior and middle frontal cortices, paracentral cortex, superior parietal cortex, precuneus, and cerebellum (Costafreda et al. 2009a).

Van Waarde et al. investigated 45 MDD patients before treatment with ECT. Prior to ECT, all patients underwent fMRI using a 1.5-T MRI scanner. A MADRS score $\leq$10 after ECT was considered as remission. Multivariate pattern analyses of resting-state fMRI scans before ECT revealed two networks in the dorsomedial prefrontal cortex and in the anterior cingulate cortex, which could predict treatment outcome with a sensitivity of, respectively, 84 and 80% and a specificity of 85 and 75% (van Waarde et al. 2015).

In 2017, Crane et al. published a paper in which 49 MMD patients were investigated; 36 patients completed a 10-week treatment period with either escitalopram or duloxetine. Functional MRI obtained during the performance of a parametric go/no-go test using a 3-T MRI scanner was used to predict treatment outcome. Remission was reached when the score on the HDRS was less than 8. Leave-one-out cross validation demonstrated a prediction model that could predict remission with a sensitivity of 84.2% and a specificity of 80% (Crane et al. 2017).

In 2011, Tenke et al. published a paper in which EEG was recorded from 41 MDD patients

prior to treatment with either escitalopram, fluoxetine, sertraline, escitalopram in combination with bupropion, duloxetine, or venlafaxine. Response was evaluated using the Clinical Global Impression-Improvement scale (CGI-I). Patients who did not respond to treatment had significantly less alpha current source density on the EEG compared to responders or controls using logistic regression. Those who responded could be predicted with a sensitivity of 93.3% and a specificity of 50% (Tenke et al. 2011).

In summary, several interesting studies provide initial evidence for the usefulness of neuroimaging in predicting MDD treatment outcome. The sensitivity and specificity to predict outcome for depression treatment ranged between 71 and 100% and 50 and 90%, respectively, and thus indicated a range from good to poor predictive power.

12.4 Limitations

Several limitations should be mentioned before general conclusions can be drawn from the studies described above on individualized medicine regarding treatment outcome of MDD. Firstly, MDD is a heterogeneous syndrome with various phenotypic appearances and genotypic origins; its symptoms have a great deal of overlap with other psychiatric syndromes such as anxiety disorders, post-traumatic stress disorder (PTSD), personality disorders, psychotic disorder, and substance abuse disorders. Additionally, several somatic disorders can mimic depressive syndromes, such as thyroid disorders and malignancies. Therefore, this heterogeneous aspect of the MDD syndrome could lead to problems with generalizability to regular clinical samples. It is also unlikely that the entire spectrum of MDD patients has been investigated in all the studies, which may lead to lower accuracy when such biomarkers are implemented in clinical practice.

Secondly, the different statistical analyses of the data are a point for consideration. All the included studies used some form of statistical validation, and, although all studies used cross validation, a complete independent dataset to verify the machine learning algorithm would be preferable. Another problem was the relative small sample size of all the presented studies, while the amount of data in one single scan is enormous. This may lead to overfitting; the algorithm model describes noise rather than the patterns of interest, which can lead to good performance on the original dataset and poor replication on independent datasets (Arbabshirani et al. 2017). In addition, the small samples presumably also reflected a specific subsample of the entire population of MDD patients. The relative homogeneity of the samples may have led to higher accuracy than can be obtained with larger heterogeneous samples (Schnack and Kahn 2016).

Thirdly, some specific neuroimaging limitations must be outlined concerning the different modalities. The neuroimaging modalities differed in terms of what was actually measured; electrical currents form the surface of the cortex (EEG), direct magnetic response of tissue (sMRI, DWI), or indirect measurements of brain activity (fMRI, PET). In MRI and PET, assumptions are made that the BOLD signal or glucose metabolism are, respectively, directly or indirectly related to brain activity, but this may not be the case. EEG, on the other hand, is a direct method to measure brain electricity differences; however, it only measures electrical activity at the surface of the brain. Moreover, all neuroimaging modalities generate statistical images, which are an indirect reflection of reality. Even regarding research sites (laboratories), the used neuroimaging devices all have considerable differences when compared to each other. For example, there are different MRI vendors with different head coils and different MR sequences. Additionally, the specific environment in which the MRI device is used influences the magnetic fields and therefore differs from site to site. Thus, caution must be used when extrapolating results from different research sites, even within a neuroimaging subgroup.

Despite all these limitations, there is a growing international interest and a clinical need for genuine individualized treatment prediction of optimal treatment for MDD. The presented

studies are very promising and should be replicated with advanced pretreatment diagnostic assessment, standardized imaging settings, and larger, independent datasets. There is a general consensus that clinical application can only be achieved when there are large open data sharing practices (Walter and Lord 2015). Furthermore, the integration of several biomarkers together may prove to have greater power than any moderator alone (Dunlop 2015).

Conclusion

MDD affects one in five people in their lifetime, and only half of the patients reach remission after treatment. Because MDD is a heterogeneous syndrome without a clear pathophysiology, it is difficult to distinguish from other psychiatric diseases. Nowadays, the treatment plan for MDD is chosen based on several clinical markers that may or may not be predictive on the group level, such as age, comorbidity, presence of psychotic features, and suicidality. In the mission to understand the concept of MDD—its etiology, its origin, the biological and psychological background, and its treatment options—neuroimaging seems indispensable. Nonetheless, despite the effort that has been made in this area, not one single brain structure or network deficit has been causally related to a specific psychiatric disease or treatment.

Regarding treatment, medicine and psychiatry has seen a gradual paradigm shift from one-size-fits-all treatment to personalized medicine. In these individualized treatment modalities, several patient characteristics should be considered. Neuroimaging seems to be one of the key ingredients in this state-of-the-art treatment paradigm. To predict what specific treatment could be effective for an individual would significantly help patients, their caregivers, and clinicians all over the world. In this chapter, different neuroimaging modalities have been presented; these initial studies have produced promising results and show fascinating pretreatment neuroimaging characteristics that may predict treatment outcome on an individual level. All these studies need replication with independent and larger datasets to verify the results.

To achieve a specific treatment regimen for individual patients, studies must be designed with integrated neuroimaging methods (e.g., EEG and fMRI), which would confirm clinical diagnoses and examine pretreatment imaging features that may predict outcome. These studies must be confirmed with independent datasets to be clinically useful. Even more promising would be a more integrated view that combines genetic, demographic, epigenetic, and neuroimaging information; this may be the key to personalized medicine.

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13 Cortical–Subcortical Interactions in the Pathophysiology of Depression

Kang Soo Lee and Sang Hyuk Lee

13.1 Introduction

Past pathophysiological theories of depression highlighted the involvement of specific neurotransmitters (Fava and Kendler 2000). However, recently depression has been recognized not as the result of a single brain region or specific neurotransmitter system dysfunction but as a multidimensional disorder affecting functionally integrated cortical–subcortical pathways to regulate emotion. Depression has been proposed as the result of dysfunctional coordination of cortical–subcortical pathways (Mayberg 1997). In this model, a dorsal part is proposed to regulate cognitive symptoms of depression such as apathy, psychomotor retardation, inattention, and executive dysfunction. A ventral part is thought to mediate the somatic symptoms of depression, including sleep disturbance and appetite changes. Dysfunction of the cingulate, which has a regulatory role for the interactions between the dorsal and ventral regions, may result in depressed mood, as well as cognitive and somatic symptoms of depression (Tekin and Cummings 2002). While the pathophysiology of depression is not yet characterized, multiple factors including genetic vulnerability and environmental stressors might contribute to disease progression (Kendler et al. 2001). Depression with acquired brain lesions commonly involves the frontal cortex and striatum (Starkstein and Robinson 1993). Similarly, though less consistently, neuroimaging studies in patients with primary depression report focal volume loss in frontal cortices and hippocampus (Rajkowska 2000).

13.2 Frontal–Subcortical Circuits

There are five frontal–subcortical circuits: motor, oculomotor, dorsolateral–prefrontal, orbital frontal, and anterior cingulate circuits. They originate in the prefrontal cortex, project to the striatum, and interact with the globus pallidus, substantia nigra, and thalamus (Alexander et al. 1986). Each circuit forms a closed loop linked back to the frontal cortex, as well open loop connections projected to and from other cortical and subcortical structures related to each circuit (Alexander et al. 1990). The motor circuit and the oculomotor circuit are dedicated to motor functions, and the dorsolateral–prefrontal, orbital frontal, and

K.S. Lee
Department of Psychiatry, School of Medicine, CHA University, CHA Bundang Medical Center, Seongnam, South Korea

S.H. Lee (✉)
Department of Psychiatry, School of Medicine, CHA University, CHA Bundang Medical Center, Seongnam, South Korea
e-mail: drshlee27@gmail.com

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anterior cingulate circuits are involved in emotional processing and executive function (Mayberg 1997).

13.3 Neurotransmitter Interactions

In the frontal–subcortical circuits, information processing is modulated by dopamine (DA), acetylcholine, serotonin, glutamate, and gamma-aminobutyric acid (GABA) neurotransmitter systems (Bronstein and Cummings 2001). Dopamine D1 receptors mediate the inhibitory connections between substantia nigra and the indirect pathways of the frontal–subcortical circuits. Dopamine D2 receptors mediate the excitatory connections between substantia nigra and the direct pathways of the frontal–subcortical circuits. Dopamine D2 receptors inhibit acetylcholine release, whereas dopamine D1 receptors enhance acetylcholine release. Dopamine D3 and D4 receptors connect the substantia nigra with the limbic circuits (Mega and Cummings 1994). The nucleus basalis of Meynert send cholinergic input to the cortex, and the striatal cholinergic interneurons modulate the thalamic activation of the cortex (Mesulam 2000; Parent et al. 1988). Acetylcholine enhances striatal DA release via nicotinic and muscarinic receptors located on the presynaptic dopamine terminals (McGeer and McGeer 1993). The 5-HT1 receptors in the basal ganglia and 5-HT3 receptors in the ventral striatum, hippocampus, and amygdala modulate mesocortical and mesolimbic dopaminergic pathways. Glutamate acts primarily on corticostriatal and thalamocortical circuits via NMDA receptors. Glutamate stimulates striatal DA release, and NMDA receptor blockade decreases cholinergic release. Inhibitory GABA is the predominant neurotransmitter in the basal ganglia and striatal fibers, extending to the globus pallidus and substantia nigra.

13.4 Neuroimaging

MRI studies have revealed structural brain abnormalities associated with MDD in limbic and prefrontal regions, which are key areas involved in emotional processing and regulation. The most robust finding from volumetric MRI studies assessing patients with MDD in comparison with healthy controls is that patients with MDD have significant gray matter volume reduction within the prefrontal cortex (PFC) and limbic areas (Atkinson et al. 2014; Bora et al. 2012a; Cole et al. 2012; Du et al. 2012; Kempton et al. 2011; Lorenzetti et al. 2009; Sacher et al. 2012). The PFC is particularly important in top-down emotional control over limbic regions. The medial part of the PFC includes the orbitofrontal cortex (OFC), dorsomedial prefrontal cortex, and the anterior cingulate cortex (ACC), which are essential in regulating emotional behaviors (Ongür and Price 2000; Phillips et al. 2008). The lateral part of the PFC includes the dorsolateral–prefrontal cortex (DLPFC), which is involved in top-down modulation of emotions (Beauregard et al. 2001; Lévesque et al. 2003; Phillips et al. 2008). In MDD, volume reductions in PFC have been demonstrated consistently across studies, including meta-analyses (Bora et al. 2012b; Delvecchio et al. 2012). These results indicate that emotion processing dysfunctions when there is dysregulation of limbic subcortical activity due to PFC dysfunction. The DLPFC has consistently been reported to have a reduced volume in patients with MDD (Kong et al. 2014; Lai and Wu 2014; Salvadore et al. 2011). In a study of medication-naïve subjects, abnormalities in white matter fibers were found to compromise the connectivity within dorsolateral–prefrontal circuits (Leung et al. 2009). Decreased gray matter concentration in the DLPFC is correlated with increased depression severity and worsened executive function, as well as attentional bias toward negative cues (Leung et al. 2009; Vasic et al. 2008). As the

DLPFC plays an important role in working memory and executive function, disruptions of the DLPFC contribute to diminished cognitive function and disturbances in emotional regulation (Phillips et al. 2003). Abnormalities in depression may also involve the thalamus and ventral striatum, which are implicated in the processing of emotional information. Interactions between the prefrontal cortex and ventral striatum (VS), amygdala, and dorsal raphe nucleus (DRN) have been implicated in the pathophysiology of MDD. The medial PFC (mPFC) can exert a regulatory effect on the VS through dense glutamatergic projections (Admon and Pizzagalli 2015; Haber and Knutson 2010; Heshmati and Russo 2015). Animal studies have shown that the basal and lateral amygdala have reciprocal connections to the mPFC (Price 2003). The amygdala has glutamatergic outputs involved in motivation to the ventromedial striatum, hypothalamic, and brainstem areas. In MDD, it has been suggested that there is an amygdala-mPFC hypoconnectivity in response to emotional stimuli and that this normalizes with treatment (Phillips et al. 2015). The dorsal raphe nucleus, the site of serotonin synthesis, receives direct glutamatergic inputs from the ventromedial PFC (vmPFC) (Challis and Berton 2015). A potential role for the DRN in MDD is evidenced by the fact that SSRIs are one of the primary current treatments for MDD. One of the most replicated findings of structural neuroimaging studies of MDD is hippocampal volume reduction (Kempton et al. 2011), which is evident in the first episode of depression (Cole et al. 2011). Recurrent episodes can lead to further volume reductions in the hippocampus, which may also explain cognitive dysfunction in MDD (aan het Rot et al. 2009). Interactions between the hippocampus and PFC appear to be dysfunctional in MDD, with decreased connectivity between the hippocampus, mPFC, and other default mode network structures in patients with depression compared with healthy controls (Kaiser et al. 2015). A central role for the hippocampus and prefrontal–hippocampal interaction in the pathophysiology of MDD is associated with the regulation of the hypothalamic–pituitary–adrenal (HPA) axis as well as neurogenesis in the human brain (McEwen 2001; McEwen 2012; Sahay and Hen 2007). The hippocampus appears to have an important role in the formation of emotional memories through glutamatergic projections to the nucleus accumbens and the amygdala (Krishnan and Nestler 2010). Decreased hippocampal size and gray matter density are consistently reported in patients with depression; moreover, the number of depressive episodes is negatively correlated with hippocampal size (Singh and Gotlib 2014).

It has been suggested that resting-state connectivity abnormalities may reflect dysregulated self-representation in MDD (Marchetti et al. 2012; Northoff et al. 2011; Sheline et al. 2010). A recent meta-analysis found overall frontoparietal hypoconnectivity and overall increase in default mode network connectivity in MDD (Dichter et al. 2015; Dutta et al. 2014; Kaiser et al. 2015). While the majority of resting-state studies examining abnormalities in MDD have focused on the default mode network, a growing body of literature has specifically examined cortical–subcortical interactions. Resting-state functional connectivity studies have found decreased vmPFC-VS connectivity to be associated with the number of depressive episodes and MDD severity (Furman et al. 2011). These findings suggest that the striatum's connectivity is associated with the course of episodes in MDD.

Furthermore, recent meta-analyses have generally found hypoconnectivity between the mPFC and amygdala (Dutta et al. 2014; Kaiser et al. 2015; Northoff 2016). A recent meta-analysis of studies using DTI in MDD reported no specific abnormalities in the major white matter pathways connecting the PFC and VS. However, it has been reported that melancholic MDD may be associ-

ated with specific abnormalities in these white matter pathways, whereas non-melancholic depression appears to not be associated with these abnormalities (Bracht et al. 2014, 2015a, 2015b). A meta-analysis of whole brain voxel-based DTI studies in patients with MDD identified decreased fractional anisotropy in the uncinate fasciculus, the primary white matter bundle connecting the PFC and amygdala (Liao et al. 2013).

Conclusion

In conclusion, depression is a debilitating disorder that is characterized by dysfunction in specific neural circuits including cortical–subcortical interactions (Heller 2016). Integrating functional and structural neuroimaging with animal models has facilitated better understanding of the characteristics of MDD. The dysfunction in prefrontal–subcortical circuits including the amygdala, ventral striatum, hippocampus, and dorsal raphe nucleus is associated with MDD severity and comprises an integrative framework for understanding motor, cognitive, and emotional functions in a major depressive disorder.

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14 Pathophysiology and Treatment Strategies for Different Types of Depression

Hwa-Young Lee and Yong-Ku Kim

14.1 Introduction

Major depressive disorder (MDD) is a clinically heterogeneous disorder, and diagnosis is based on a patient's symptoms, as opposed to on any laboratory tests. As such, the pathophysiology of MDD is not clear. MDD results from multiple genetic factors interacting with many various environmental factors, such as childhood adversity and the occurrence of many stressful life events (Caspi et al. 2003).

Although work in this area has been inconclusive, many animal, postmortem, clinical, and genetic studies have produced results implicating at least three neurobiological systems in the pathogenesis of MDD: the monoamine system, the hypothalamic-pituitary-adrenal axis (HPA axis), and neuroplasticity. Additionally, other biological factors, including inflammatory markers, neurophysiologic markers, and neuroimaging markers, might be associated with MDD.

An increasing amount of data shows that depressive disorders are heterogeneous and therefore can vary with regard to HPA axis activity, immune function, and treatment response. Considering the biological mechanisms of depressive subtypes, it is helpful to understand the pathogenesis of each depressive disorder in order to more accurately predict an individual's response to a specific treatment for depression.

In the DSM-5, different specifiers are given to diagnose the specific subcategories of major depression, including depression "with melancholic features," "with atypical features," "with anxious distress," "with mixed features," "with mood-congruent psychotic features," "with mood-incongruent psychotic features," "with catatonia," "with peripartum onset," and "with seasonal pattern" (American Psychiatric Association 2013).

In major depression with melancholic features, the patient either has anhedonia or a lack of mood reactivity, together with at least three of six other symptoms (depression that is subjectively different from grief, severe weight loss or loss of appetite, psychomotor agitation or retardation, early morning awakening, excessive guilt, and worse mood in the morning) (American Psychiatric Association 2013).

Atypical depression is a subtype of depression that the DSM-5 defines as featuring reactive moods (including the tendency to respond emotionally to environmental cues), increased appetite, hypersomnia, leaden paralysis, and interpersonal rejection sensitivity (American Psychiatric Association 2013). Patients with atypical depressive episodes generally have a

H.-Y. Lee
Department of Psychiatry, College of Medicine, Soonchunhyang University, Asan-si, South Korea

Y.-K. Kim (✉)
Department of Psychiatry, College of Medicine, Korea University Ansan Hospital, Ansan, South Korea
e-mail: yongku@korea.edu

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younger mean age of onset than those with typical depression [3–7]. Individuals with atypical depression are two to three times more likely to be women and often have a more chronic, unrelenting course of depression than individuals with typical depression. In a sample of 8116 individuals aged 15–64 years, 17.1% of the patients with a diagnosis of MDD had a history of atypical depression [13]. Of 1500 outpatients studied in the Sequenced Treatment Alternatives to Relieve Depression (STARD) trial, 18.1% of trial patients had depression with atypical features, and women were found to be 70% more likely to have atypical depression [5]. Studies of clinical populations have shown that 18–36% of patients with MDD present with atypical depression (Thase 2007).

In this chapter, we discuss the pathophysiology and treatment strategies for different types of depression (melancholic and atypical subtypes in particular).

14.2 Different Mechanisms Between Melancholic and Atypical Depression

14.2.1 Hormonal Axis

Major depressive disorder (MDD) generally features hyperactivity of the hypothalamic-pituitary-adrenal (HPA), a neuroendocrine abnormality (Holsboer 1999). To explain the pathophysiology of MDD, the corticosteroid receptor hypothesis has been proposed. The corticosteroid receptor hypothesis focuses on corticosteroid receptor resistance, which results in reduction of the negative feedback of cortisol, increased production of corticotropin-releasing hormone (CRH), and, ultimately, hypercortisolism (Holsboer 2000).

Studies regarding the causes of a dysregulated HPA axis in depression have focused mainly on two elements: (1) glucocorticoid receptor (GR) feedback mechanisms and (2) the CRH signaling system.

Reduced sensitivity to cortisol, leading to an impaired negative feedback mechanism, has been attributed to resistant GR function (Pariante and Miller 2001). In contrast, the CRH peptide mediates the regulation of the HPA axis as well as autonomic and behavioral responses during stress (Arborelius et al. 1999). Furthermore, the functional action of antidepressants has been linked to the HPA axis (Holsboer 2000; Nemeroff and Owens 2002). Consequently, a proper clinical response to antidepressant treatment involves normalization of the dysregulated HPA axis (Holsboer and Barden 1996; Nemeroff 1988).

Most studies in melancholic depression have found that, relative to non-depressed states, HPA axis hyperactivity occurs and that this hyperactivity is more likely to occur in more severe forms of depression (Lightman 2008). In addition to increased production of corticotropin-releasing hormone (CRH), the HPA axis overdrive in depression has been attributed to both insensitivity to glucocorticoid feedback and to the overproduction of other corticotrophin secretagogues, which are insensitive to glucocorticoid feedback, such as arginine vasopressin (Dinan et al. 2004; Dinan and Scott 2005). Corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) are the main secretagogues of the HPA/stress system. Produced in the parvicellular division of the hypothalamic paraventricular nucleus, the release of these peptides is influenced by input from monoaminergic neurons. In depression, anterior pituitary CRH1 receptors are downregulated, and the resultant response to CRH infusion is blunted. In contrast, vasopressin V3 receptors on the anterior pituitary show an enhanced response to AVP stimulation, and this enhancement plays a key role in maintaining HPA hyperactivity in depression (Dinan and Scott 2005).

Contrary to melancholic depression, atypical depression has reversed vegetative symptoms (i.e., hypersomnia and hyperphagia). Patients with melancholic depression show hypercortisolism and more disturbed sleep, as is strongly associated with high nocturnal adrenocorticotropic hormone (ACTH) and cortisol secretion (Antonijevic et al. 2000). Weight loss is correlated with hypercortisolism and dexamethasone non-suppression (Casper et al. 1987; Miller and Nelson 1987). Moreover, depressed patients without hypersomnia or increased appetite have

been shown to have elevated urinary cortisol concentrations in comparison to normal morning plasma cortisol levels, as well as a higher incidence of cortisol non-suppression after dexamethasone in comparison to normal subjects (Casper et al. 1988). In contrast to typically depressed patients, depressed patients with hypersomnia and hyperphagia showed no changes in morning plasma cortisol level or dexamethasone suppression tests (DSTs) (Casper et al. 1988; Thase et al. 1989).

Research has reported that a relatively hyperactive HPA axis leads to symptoms of melancholic depression, while a relatively hypoactive stress response leads to symptoms of atypical depression (Gold and Chrousos 2002). That is, CRH hypersecretion and hyposecretion correlate with the symptomatic patterns of melancholic and atypical depression, respectively. A recent meta-analysis of 40 years of conducted HPA axis research has identified a pattern of relative hypocortisolemia in atypical depression in comparison to melancholic depression (Stetler and Miller 2011).

14.2.2 Neurotransmitter Systems

It has been hypothesized that a deficiency in serotonin is an essential determinant in the pathogenesis of MDD. Consequently, the serotonin system has been thoroughly investigated in a variety of MDD studies. The serotonin system projects from the dorsal raphe nucleus to all regions of the brain, including the cerebral cortex and hippocampus. In depressed patients, diminished function and activity of the serotonin system have been confirmed in postmortem serotonin transporter and serotonin receptor studies.

Imipramine binding might be a putative biological marker of depressive disorder. Imipramine binds to the serotonin transporter 5-HTT on platelets, and decreased imipramine binding might indicate depressive disorder. A meta-analysis showed a highly significant decrease in maximal binding values in depressed subject groups. This decrease was further shown to be even greater among depressed subjects who had been free of medication for 4 weeks at the time of investigation (Ellis and Salmond 1994).

The norepinephrine (NE) system has been studied in depression, particularly in terms of the action of NE reuptake inhibitors. Monoaminergic neurobiology, including norepinephrine, has been associated with the mechanisms of action of serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), and tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants. Furthermore, the antidepressant effects of mirtazapine seem to be due to the dual enhancement of central noradrenergic and serotonergic neurotransmission stemming from a blockade of adrenergic α2 receptors (Herman 1999; Kasper 1997; Preskorn 1997).

The dopamine (DA) system has been reported to be highly associated with the symptomatology of depression, as the proposed pathogenesis of melancholic depression involves decreased DA transmission (Geracitano et al. 2006).

In addition to HPA axis activity, distinct alterations of the serotonergic system might also play critical roles in melancholic and atypical forms of depression—namely, a reduced restraint of serotonin synthesis via 5-HT (1A) autoreceptors in the former and reduced serotonin synthesis in the latter. Thus, the melancholic subtype of depression, with noradrenergic and HPA axis overdrive, seems to be associated with reduced 5-HT1A autoreceptor function, leading to enhanced serotonergic activation of the HPA axis, as well as an acute-phase immune reaction. The latter contributes to HPA axis stimulation and reduces negative feedback inhibition from corticosteroid receptors. The resulting hypercortisolism can further impair the functioning of 5-HT1A receptors, creating a vicious circle that might not be effectively resolved by most selective serotonin reuptake inhibitors (SSRIs) (Gold and Chrousos 2002; Tsigos and Chrousos 2002). On the other hand, patients with features of atypical depression and low HPA activity seem to have reduced noradrenergic and serotonergic afferent stimulation, possibly due to reduced serotonin (5-HT) synthesis. Furthermore, unlike patients with melancholic depression, patients with

atypical depression demonstrate unimpaired functioning of 5-HT1A autoreceptors (Gold and Chrousos 2002; Owens and Nemeroff 1994).

Moreover, for the treatment of atypical depression, MAOIs have been repeatedly found to be more effective than tricyclic antidepressants (TCAs), which have potent noradrenergic properties. This distinction between MAOIs and TCAs might indicate different biological mechanisms at work in patients with atypical or melancholic depression [18, 19].

14.2.3 Neuroinflammatory Systems

It has been suggested that dysregulation of the immune system, including the cytokine network, is associated with the etiology and pathophysiology of depression (Kim et al. 2007; Miller et al. 2009). Peripheral cytokines can communicate with brain cells by various mechanisms. Many studies have suggested that imbalances in the cytokine network are associated with the pathophysiology of depression (Kronfol 2002; Schiepers et al. 2005).

Many studies have suggested that pro-inflammatory cytokines, which initiate inflammatory immune responses, are associated with depression. First, patients and animals administered IL-2 and IFN-α have been shown to experience "sickness behaviors" resembling depression, including insomnia, decreased appetite, loss of interest in aspects of their environment, and fatigue. These "sickness behaviors" improved when subjects were treated with antidepressants or when the cytokines were withdrawn (Bonaccorso et al. 2002; Capuron et al. 2000). Second, patients with depression (who are otherwise healthy) appear to have activated inflammatory pathways, with increased pro-inflammatory cytokines, acute-phase proteins, and increased expression of chemokines and adhesion molecules. Third, chronic inflammatory diseases such as multiple sclerosis and rheumatoid arthritis are frequently accompanied by depression.

Pro-inflammatory cytokines have been found to have profound effects on the metabolism of brain serotonin, dopamine, and noradrenaline in mice and rats (Dunn et al. 1999). Indeed, the activation of inflammatory pathways within the brain is believed to contribute to a confluence of decreased neurotrophic support and altered glutamate release/reuptake, as well as oxidative stress, leading to excitotoxicity and loss of glial elements consistent with neuropathologic findings that characterize depressive disorders (Miller et al. 2009). A recent meta-analysis convincingly suggested that IL-6 and TNF-alpha levels are elevated in depressive patients (Dowlati et al. 2010).

Adipocytes, the source of leptin, also produce cytokines such as TNF-α and IL-6. Indeed, in obese subjects, it has been estimated that about 30% of circulating IL-6 is derived from adipose tissue (Yudkin et al. 2000). However, the effects of leptin are generally opposite to the effects of pro-inflammatory cytokines and include the induction of anorexia, anhedonia, and increased sympathetic nervous system activity (Haynes et al. 1997).

The immune system plays an important role in the regulation of leptin production [79]. This communication between the immune and adipose systems is bidirectional, because leptin is involved in the regulation of immune responses. Indeed, leptin regulates pro-inflammatory immune responses by upregulating both phagocytosis and the production of pro-inflammatory cytokines. Moreover, leptin deficiency is accompanied by an increased susceptibility to endotoxin-induced lethality and a decreased induction of anti-inflammatory cytokines in rodents (Faggioni et al. 1999), further suggesting close connections between leptin and the immune system.

Hypersomnia is one of the main symptoms of atypical depression. Among many factors involved in sleep regulation, cytokines are important sleep regulatory substances. Among cytokines, interleukin IL-1 and TNF-α have been determined to be important sleep-promoting substances. Early studies in humans have shown that sleep onset is associated with the increased activity of IL-1, followed by elevations of IL-2, which appeared to be related to a decline in plasma cortisol level and the appearance of slow wave sleep

(Moldofsky et al. 1986). One antisomnogenic cytokine, IL-4, inhibits the production or release of other substances implicated in sleep regulation, including nuclear factor kappa B.

One study linked atypical depression to decreased level of IL-4 and increased level of IL-2 relative to individuals without features of atypical depression (Yoon et al. 2012), while another study reported decreased IL-2 in atypical depression in comparison to healthy controls (Anisman et al. 1999). Individuals with atypical depression had significantly higher levels of inflammatory markers than persons with melancholic depression and control subjects (Lamers et al. 2013). Overall, findings on inflammatory markers among patients with melancholic versus atypical depression have been contradictory. Based on a meta-analysis finding that body mass index might interact with C-reactive protein and IL-6 to yield a potential tri-directional relationship between adiposity, inflammation, and depression (Howren et al. 2009), it was further postulated that high BMI level in subjects with atypical depression might indicate a differential association between atypical depression and inflammation in comparison to melancholic depression (Gold and Chrousos 2002).

14.2.4 Neuroplasticity

A time lag in clinical responses following the administration of an antidepressant drug suggests that alterations in monoamine metabolism alone cannot explain antidepressant effects. In this respect, it was suggested that the mechanisms of action of antidepressant drugs might be associated with intracellular signal transduction pathways, which are linked to the expression of specific genes (Duman et al. 2000).

The neuroplasticity hypothesis proposes that depression results from an inability to produce the appropriate neuronal proliferation in response to stress (Popoli et al. 2002). Brain-derived neurotrophic factor (BDNF), an important member of the neurotrophin family, is a key component of the neuroplasticity hypothesis. The molecule acts on neurons at both presynaptic and postsynaptic sites by binding to its tyrosine kinase receptor (TrkB), resulting in the internalization of the BDNF TrkB complex-signaling endosome (Lu 2003).

Low serum BDNF level has been found in depressed patients. No single study, however, has systematically investigated whether depression subtypes contribute differentially to the low BDNF level found in depressed subjects. One study including 1070 patients with a diagnosis of major depressive disorder within a 6-month timeframe from the Netherlands Study of Depression and Anxiety (NESDA) was reported. Items from the Composite International Diagnostic Interview (CIDI) and the Inventory of Depressive Symptoms (IDS) were tested individually in separate multiple regression analyses, using serum BDNF level as the dependent variable and CIDI or IDS items as independent variables. Subsequently, BDNF levels were compared between patients with seasonal affective disorder (based on the Seasonal Pattern Assessment Questionnaire) and melancholic depression, atypical depression, and moderate depression (based on a latent class analysis). Serum BDNF level did not significantly differ between patients with melancholic depression, atypical depression, and moderate depression (Bus et al. 2014).

Another study with the same sample subjects (NESDA) examined the association between serum level of BDNF and plasma levels of IL-6 and tumor necrosis factor-alpha (TNF-α) in patients with MDD ($n = 1070$) and non-depressed controls ($n = 379$). Multiple regression analyses were conducted with serum BDNF level as the dependent variable, and the presence of BDNF-cytokine associations in DSM-IV-assigned melancholic MDD patients was tested. Stratified analyses showed that BDNF level was positively associated with IL-6 levels in MDD patients but not in non-depressed controls. When further stratified for melancholic and non-melancholic MDD, IL-6 emerged as a robust positive predictor of BDNF only in the melancholic sample, wherein serum BDNF level was accordingly enhanced. Post hoc exploratory analyses verified an accentuated positive association of BDNF level with leucocyte count in melancholia. No

significant associations emerged between BDNF and TNF-α (Patas et al. 2014). Another study found that IL-6 and TNF-α specifically enhanced BDNF secretion in monocytes, whereas typical Th1- and Th2-cytokines did not show any effects on monocytes. Otherwise, only IL-6 and TNF-α were found to have the ability to enhance extracellular BDNF level in human monocytes. Intriguingly, levels of BDNF in antidepressant-free melancholics—the group presenting with the most clear-cut BDNF-IL-6 association—were not significantly different from non-melancholics or controls, suggesting that low serum BDNF might not be a hallmark of melancholia (Schulte-Herbruggen et al. 2005). This finding is concordant with a recent study showing that serum BDNF levels of antidepressant-free melancholic patients were not different from healthy controls (Kotan et al. 2012).

Although BDNF is believed to be transported across the blood-brain barrier (Karege et al. 2002) and significant correlations have been found between peripheral BDNF and measures of central neuroplasticity (Lang et al. 2007), we cannot be sure that measuring serum BDNF adequately reflects the brain expression of BDNF. Currently, however, measuring BDNF in the peripheral blood of subjects is the only feasible method, as other methods would be far more invasive.

Conclusively, these few studies suggest that there is not a significant possibility of different neuroplastic mechanisms between atypical and melancholic depression.

14.2.5 Neuroimaging Factors

Recent neuroimaging studies have focused on the neurobiological differences between healthy controls and abnormalities associated with MDD, such as dysfunctional or structural differences in cerebral regions, including the prefrontal cortex, amygdala, anterior cingulate cortex (ACC), and hippocampus (Canli et al. 2004; Frodl et al. 2004; Henriques and Davidson 2000; MacQueen et al. 2003).

Because depression is heterogeneous, subtyping the disease will be helpful for understanding imaging results. However, few imaging studies have been conducted according to depression subtype. There is no voxel-based morphometry (VBM) study.

One chimeric faces study measured perceptual asymmetry, demonstrating that subjects with atypical depression differed from subjects with typical depression and control subjects in showing an abnormally large right hemisphere bias. A chimeric face fuses a neutral right half face with a smiling left half face. Its mirror image (creating a neutral left half face fused with a smiling right half face) is randomly placed above or below the original chimeric face. The task is for a subject to quickly determine which of the two faces is happier. A subject's preference for choosing one side as happier relative to the other has been interpreted as reflecting increased activation of the contralateral parietal lobe (Heller 1993), although inhibitory mechanisms could also be hypothesized. This right hemisphere bias was present in patients having either MDD or dysthymia and was not related to anxiety, physical anhedonia, or vegetative symptoms. In contrast, patients with melancholic depression showed essentially no right hemisphere bias. The authors suggest that this is further evidence that atypical depression is a biologically distinct subtype, thereby underscoring the importance of this diagnostic distinction for neurophysiologic studies (Bruder et al. 2002).

Single-photon emission computerized tomography (SPECT) in 50 depressed patients with MDD, including subtype assessment, indicated differential brain activity in patients with atypical depression in comparison to the brain activity of patients with typical depression (Fountoulakis et al. 2004). Patients with melancholic depression ($N = 16$) and patients with undifferentiated depression ($N = 20$) each differed from controls ($N = 20$) in 10 brain regions but did not differ from each other in any of 17 regions. In contrast, patients with atypical depression ($N = 14$) differed from patients with melancholic depression in nine regions and from patients with undifferentiated depression in ten regions. Patients with atypical depression showed differences from controls in five brain regions. In two brain

regions, patients with atypical depression differed from both control subjects and from at least one of the other depressed groups. Conclusively, patients with atypical depression had increased frontal, temporal, and parietal perfusion coupled with decreased occipital perfusion relative to the other two groups of depressed patients. Patients with atypical depression also had increased right frontal perfusion, whereas those with melancholia and undifferentiated depression had decreased perfusion relative to controls in the majority of non-occipital regions. Thus, all three groups of patients with depression showed abnormal perfusion, but the patterns differed. Melancholia and undifferentiated depression had similar patterns of abnormal perfusion, which differed from the patterns in subjects with atypical depression. The findings of these imaging studies are consistent, suggesting that atypical depression does not share the biological features of melancholia.

14.3 Treatment Strategies for Different Types of Depression

While the idea that diagnostic subtypes such as melancholic and atypical depressive subtypes moderate or predict treatment outcomes is a popular hypothesis, few existing studies have tested it.

An important reason for this gap is that most trials focus on patients with major depression in general and aim only to determine whether treatment is effective in the overall patient group. Few studies have been designed to examine whether a clinical characteristic, such as a diagnosis of melancholic or atypical depressive subtype, moderates outcome (Cuijpers et al. 2012; Uher et al. 2011).

Melancholic depression is associated with hyperactivity of the HPA axis. The glucocorticoid receptors are downregulated and lead to feedback resistance. Consequently, hypersecretion of glucocorticoids further increases, potentially decreasing neuroplasticity in the frontal cortex, PFC, and hippocampus, causing, for example, neurogenesis in the dentate gyrus or dendritic remodeling in the CA3 region of the hippocampus (McEwen 2001; Sapolsky 2000).

It has been shown that various types of stress or corticosteroid administration induce a rapid and transient increase in extracellular glutamate in the PFC and hippocampus (Moghaddam et al. 1994; Venero and Borrell 1999). Moreover, it has been shown that acute stress can rapidly increase the levels of circulating corticosteroids, which, via mineralocorticoid receptors and rapid non-transcriptional action, induces the release of glutamate in the hippocampus (Olijslagers et al. 2008). Via glucocorticoid receptors, this in turn induces the release of glutamate in the PFC and frontal cortex (Musazzi et al. 2010). Inversely, it has been shown that a MAO-A inhibitor produces an increase in brain corticosteroid receptors, suggesting reduced neuroendocrine responsiveness to stress by antidepressants (Reul et al. 1994).

If new antidepressants can dampen states of hyperglutamatergic activity and the subsequent excitotoxicity, chronic use of these drugs could have considerable neuroprotective potential in major depression, especially melancholic depression (Michael-Titus et al. 2000). Thus, NMDA receptor antagonists such as ketamine seem to address the limitations of currently available SSRIs or SNRIs, including limitations of slow-onset efficacy and the relative likelihood of treatment resistance with existing SSRIs or SNRIs.

In atypical depression, symptoms such as fatigue, psychomotor retardation, and decreased sympathetic activity can be mainly attributed to disturbances in dopaminergic and noradrenergic systems. Drugs that increase all monoamines are more successful in treating these symptoms (Trivedi et al. 2006). Furthermore, it is expected that TRIs and MAOIs are particularly effective for atypical depression because they increase all three monoamine concentrations (Thase et al. 1995). The superiority of monoamine oxidase inhibitors (MAOIs) in comparison to other antidepressants in the treatment of major depression with atypical features has been frequently reported. One meta-analysis reported that MAOIs might be more effective for atypical major depressive disorder than tricyclic antidepressants (Henkel et al. 2006). The available data are insufficient for a direct comparison between MAOIs and selective serotonin reuptake inhibitors.

Conclusion

Major depressive disorder is considered a clinically heterogeneous disorder. Diagnosis is based on a patient's symptoms, as opposed to on any laboratory tests. Consequently, the pathophysiology of MDD is uncertain. Current consensus among researchers has determined that MDD results from the interaction of multiple genetic factors and various environmental factors, such as childhood adversity and many stressful life events. Although the development of antidepressant drugs has skyrocketed in recent decades, the neurobiological effects underlying the therapeutic actions of these agents remain poorly understood. Considering the biological mechanisms of depressive subtypes, it is helpful to understand the pathogenesis of each depressive disorder in order to predict an individual's response to treatment for MDD. For example, melancholic depression is associated with hyperactivity of the HPA axis, while atypical depression is associated with hypoactivity of the HPA axis. Researchers have searched for biological mechanisms according to depression subtype in an effort to understand their pathogenesis for the sake of bettering treatment.

If new antidepressants can dampen states of hyperglutamatergic activity and the resulting excitotoxicity, chronic use could have considerable neuroprotective potential in major depression, particularly melancholic depression.

With regard to pharmacological treatment, it has been reported that a group of patients with atypical depression showed a significantly higher cortisol response to desipramine (a relatively selective noradrenaline reuptake inhibitor) than a group of patients with no atypical symptoms and a group with mood reactivity as the only atypical depressive symptom. That finding indicated that atypical depression might be associated with lesser impairment of the noradrenaline neurotransmitter system. Similarly, hypersecretion of corticotropin-releasing hormone (CRH) and the resulting hypercortisolism were not found in patients with atypical depression.

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The Effect of Neurostimulation in Depression

15

Rafael C.R. Freire and Antonio E. Nardi

15.1 Historical Overview

There have been reports of the medical use of electricity since the classical antiquity (Fig. 15.1), but only in the second half of the eighteenth century the effects of electricity in animals and humans were systematically studied, establishing the foundations for the electroconvulsive therapy (ECT), magnetic seizure therapy (MST), transcranial direct-current stimulation (tDCS), vagus nerve stimulation (VNS), deep brain stimulation (DBS), and repetitive transcranial magnetic stimulation (TMS) (Priori 2003). Luigi Galvani and Giovanni Aldini found that electrical currents, applied through electrodes, could stimulate nerves and produce muscle contractions in frogs and other animals. With the newly developed electric pile, Aldini applied electrical currents through the motor cortex of deceased people and obtained massive facial muscle contractions. In some of the experiments, transcranial electrical stimulation was performed in patients with mental disorders, and this technique was demonstrated effective in the treatment of *melancholy madness* (major depressive disorder—MDD). In this form of stimulation, the intensity of the electrical current was low, the patients remained seated during the procedure, and there were no seizures (Fig. 15.2) (Aldini 1804; Parent 2004). In the following years, there were few studies regarding the treatment with mental disorders with electricity. After more than 100 years of those studies, intensive research on electrical stimulation of the human brain resumed (Priori 2003).

Fig. 15.1 Marbled electric ray—*Torpedo marmorata*. In 43–40 AC, Scribonius Largus used torpedo fish like this to treat headaches. He placed the live ray on the patient's head and it delivered a strong direct electrical current, eliciting a sudden transient stupor and pain relief. Source: By Philippe Guillaume (originally posted to Flickr as fear me) (CC BY 2.0 (http://creativecommons.org/licenses/by/2.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3ATorpedo_marmorata2.jpg

In the first half of the twentieth century, based on observations of patients with epilepsy and psychosis who improved after spontaneous

R.C.R. Freire (✉) • A.E. Nardi
Laboratory of Panic and Respiration, Institute of Psychiatry, Federal University of Rio de Janeiro, Rio de Janeiro, RJ, Brazil
e-mail: rafaelcrfreire@gmail.com

Y.-K. Kim (ed.), *Understanding Depression*, https://doi.org/10.1007/978-981-10-6580-4_15

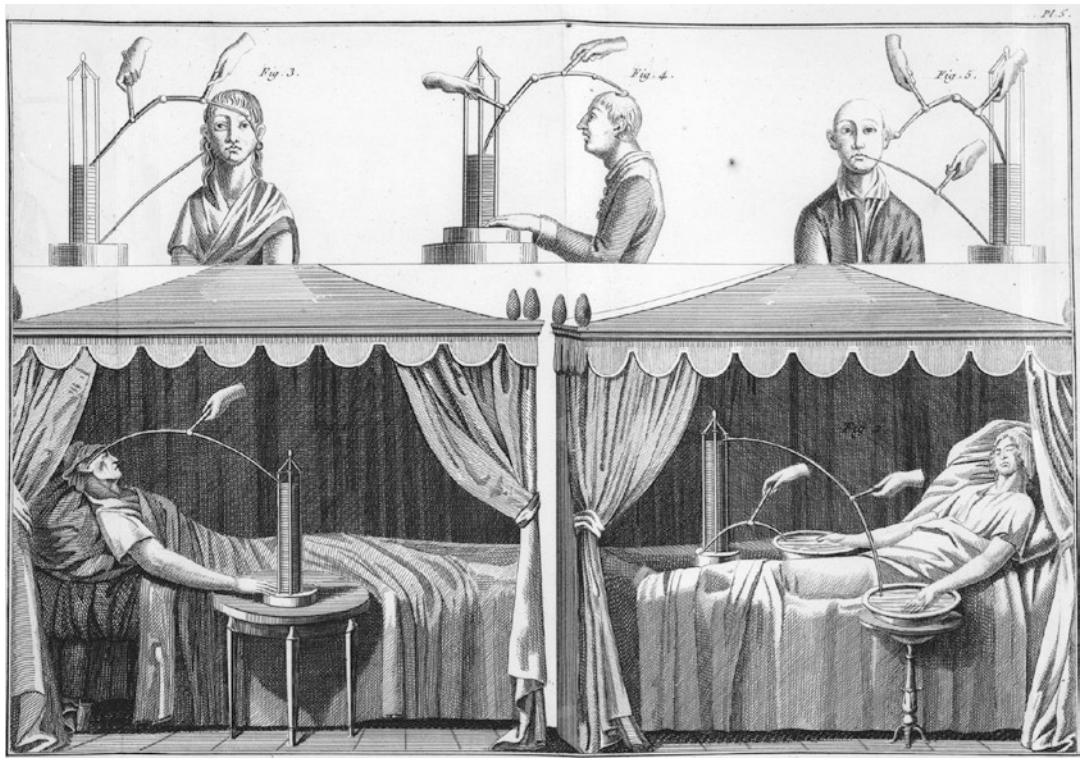

Fig. 15.2 Experimental treatment of melancholia with electrical currents. Source: Gionanni Aldini (1804). See page for author (CC BY 4.0 (http://creativecommons.org/licenses/by/4.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3AGiovanni_Aldini%2C_Essai…sur_le_galvanisme…_Wellcome_L0023896.jpg

seizures, Ladislaus von Meduna studied methods to produce seizures in schizophrenic patients. In 1934, this researcher found that camphor injections induced seizures and significant improvements of psychotic symptoms. von Meduna also demonstrated that pentylenetetrazol, a gamma-aminobutyric acid (GABA) receptor inhibitor, also produced seizures and clinical improvements. In 1938, the Italian researchers Luigi Bini and Ugo Cerletti documented the therapeutic effects of electrically induced seizures in humans (Isenberg and Zorumski 2000).

Bini and Cerletti studied the effects of electrical currents in animals and found that a direct-current flow through the heart kills them, but if the current is applied across the head, there are no significant cardiac risks. After several experiments with animals, they began the experiments with humans and demonstrated the efficacy of electrically induced seizures in treating psychotic patients (Fig. 15.3). The induction of seizures with electricity was safer and more reliable than the one produced by drugs. In a few years, ECT was disseminated through the globe. In the 1950s, when few pharmacological treatments for mental disorders were available, ECT was studied in the treatment of many of them and became the most important treatment for MDD. The development of antidepressants and the increased prejudice against ECT led to a decline in its use, although ECT is still considered one of the safest and most effective treatments for mood disorders (Isenberg and Zorumski 2000).

In the last 80 years, ECT techniques were improved, and there was a significant reduction of risks and side effects. The intense muscle contractions induced by the electrical currents provoked bone dislocation and fractures of spine and long bones. However, the use of muscle relaxants resolved these problems. The routine use of

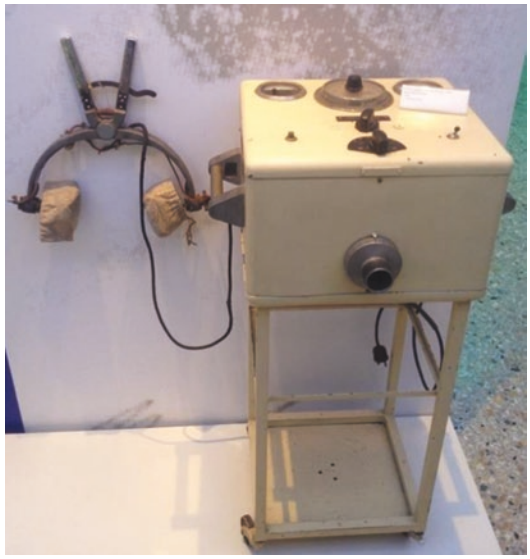

Fig. 15.3 Electroconvulsive machine designed by Bini and Cerletti to treat mental disorders. Source: By Francesca.pallone (Own work) (CC BY-SA 3.0 (http://creativecommons.org/licenses/by-sa/3.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3AMacchina_elettroshock_Ugo_Cerletti.jpg

Fig. 15.4 Repetitive Transcranial Magnetic Stimulation application. Source: By Baburov (Own work) (CC BY-SA 4.0 (http://creativecommons.org/licenses/by-sa/4.0)), via Wikimedia Commons. https://commons.wikimedia.org/wiki/File%3ANeuro-ms.png

general anesthesia, vigorous oxygenation throughout the procedure, and cardiac and respiratory monitoring resulted in a decreased risk of hypoxia and cardiopulmonary complications. Other techniques such as brief-pulse electrical stimulation and unilateral ECT were developed to reduce the side effects of this treatment even more. For a long time, it was believed that electrical currents could produce therapeutic effects only if they resulted in seizures (Isenberg and Zorumski 2000).

Research with low-current stimulation of the cortex was resumed in the 1980s. Merton et al. (1982) found that short electrical pulses applied to the motor cortex produced a synchronous muscle action potential and a twitch in the adductor of the thumb and other muscles. At the same time, experiments with magnetic stimulation carried out by Barker et al. (1985) indicated that rapid time-varying magnetic fields could produce electrical currents in the cerebral cortex. They also found that each magnetic pulse on the motor cortex produced a muscle action potential and a twitch in the muscle. The major advantage of the magnetic stimulation over the electrical stimulation is that the first is pain-free, while the last may produce pain in the scalp. Both methods were effective to stimulate superficial cortex but did not reach deep brain regions. In the last 30 years, several techniques and protocols were developed to increase the efficacy of the transcranial magnetic stimulation, including the use of repetitive pulses, neuronavigation systems, and several models of magnetic stimulators and coils. TMS has been studied in many different medical conditions, and it demonstrated efficacy in the treatment of mood disorders, schizophrenia, chronic pain, stroke rehabilitation, and others (Fig. 15.4) (Ziemann 2017). Since 1995, TMS has been studied as a treatment for MDD, including the treatment-resistant clinical presentation (Anderson et al. 2016).

There is a risk of seizure in TMS applications, especially if a larger dose of magnetic stimulation is administered. This evidence made researchers question if seizures induced by magnetic stimulation would produce the same therapeutical effects as ECT, without the side effects of this technique (Engel and Kayser 2016). In 1998, Lisanby et al. (2001a, 2001b) started experiments with magnetically induced seizures in nonhuman primates and later in humans. New devices were available in the 2000s, and they were capable of stimulating continuously for up to 10 s at a 100 Hz frequency, inducing seizures reliably. As in ECT, general anesthetics and

muscle relaxants are administered before MST sessions to prevent muscle contractions (Engel and Kayser 2016).

The belief that electrical currents had to induce seizures to produce therapeutic effects led to a loss of interest in nonconvulsive electrical stimulation methods in the first half of the twentieth century. However, recently there has been a resurgence of interest in tDCS. Since the 1960s, systematic studies on tDCS and depression have been made, and most of them indicate that this form of neurostimulation is effective. It was found that direct currents induce polarization, modulating spontaneous neuronal firing, unlike ECT that excites neurons, inducing convulsive activity. tDCS does not produce seizures, loss of consciousness, and memory deficits as ECT does. In addition, the use of sedatives and muscle relaxants are not needed for tDCS (Priori 2003).

The cortical effects of the vagus nerve electrical stimulation have been a subject of interest to scientists since the late 1930s. Studies with cats, dogs, and monkeys indicated that VNS could produce neuronal activity in the orbital gyrus, lateral frontal cortex, anterior rhinal sulcus, and amygdala. Studies with experimental epilepsy in dogs indicated that VNS has anticonvulsant properties; subsequent studies demonstrated the efficacy of this technique in humans too. In 1997, the American FDA approved VNS for the treatment of epilepsy. Currently, the stimulation of the left cervical vagus nerve is made with implantable, bipolar pulse generators. The efficacy of VNS in the treatment of epilepsy and depressive disorders was demonstrated in recent studies (Chae et al. 2001).

The electrical stimulation of deep brain regions with implanted electrodes has been studied in the last 30 years. It is well established that the stimulation at different targets within the basal ganglia is effective in the treatment of Parkinson's disease (Chae et al. 2001). Recent studies also indicate that DBS may be effective in the treatment of treatment-resistant depression (Morishita et al. 2014). Both VNS and DBS are neurostimulation methods that require surgery, an obvious disadvantage compared to ECT, tDCS, and TMS, which are not invasive (Akhtar et al. 2016).

All forms of neurostimulation have acute effects, which occur during the stimulation, and aftereffects, which occur in a period of time from a few minutes to several months. In treatments administered in sessions, such as ECT, MST, TMS, and tDCS, the acute effects and the aftereffects are unambiguous. In methods with continuous stimulation, such as DBS and VNS, it is hard to distinguish between acute effects and aftereffects. Evidence indicates that the therapeutic benefits of neurostimulation are due to these lasting effects, which include changes in neuronal excitability, neurogenesis, changes in glial function, gene activation/regulation, de novo protein synthesis, morphological changes, homeostatic processes, neuroendocrine changes, and changes in neurotransmitters (Bolwig 2011; Cirillo et al. 2017; Isenberg and Zorumski 2000; Martinotti et al. 2011; Nordanskog et al. 2010; Walker et al. 1999).

15.2 Electroconvulsive Therapy

The goal of an ECT session is to induce a generalized seizure of adequate duration in the central nervous system. Electrical stimuli that do not induce seizures, or produce only partial seizures, or produce seizures with short duration are not considered effective (Isenberg and Zorumski 2000). A significant difference between ECT and the other neurostimulation methods is that, in the former, the electrical current affects the whole brain; it is not targeted to a specific area or brain structure.

There are two types of ECT devices, the constant-current stimulators and the constant-voltage stimulators. It is easier to calculate the charge administered (charge = current × time) in the constant-current stimulators, compared to constant-voltage stimulators, in which information about impedance is needed to calculate the administered charge. Older ECT devices are alternating current sine-wave generators. These waves have a frequency of 60 cycles per second, and each half sine wave has an 8.3 ms duration. Neuronal cells fire after a few milliseconds, but they remain refractory for several milliseconds

(ms) after that. As a result, much of the current flow occurs during inexcitable periods in the sine-wave stimulus. Modern ECT devices administer repeated brief square-wave pulses with a duration from 0.5 to 2.0 ms, which are much more effective than old devices to produce generalized seizures. In current devices, there may be only positive pulses or alternating positive and negative pulses, and the usual frequency is between 30 and 100 Hz. The total charge of an ECT session can be calculated by multiplying the duration of each pulse by the number of pulses by the total train duration (Isenberg and Zorumski 2000).

If ECT electrodes are placed bitemporally and a minimally suprathreshold electrical dose is administered, the treatment produces significant clinical benefits. When the electrodes are placed unilaterally in the non-dominant hemisphere, a charge as high as 2.5 times the seizure threshold is needed to produce clinical improvement. An adequate seizure should last for about 25 s. Many patient characteristics influence the seizure threshold, including age, gender, and medications in use. Compared to brief-pulse stimulus, sine-wave stimulus is ineffective and yields higher seizure thresholds. Electrical dosing schedules begin with a low electrical charge, which is increased until a generalized seizure is obtained (Isenberg and Zorumski 2000).

The efficacy of ECT in the treatment of mood disorders is unquestionable. However, it is still not entirely clear how it works. There are three main theories to explain how ECT works: (1) the generalized seizure theory, (2) the normalization of neuroendocrine dysfunctions theory, and (3) the hippocampal neurogenesis and synaptogenesis theory (Bolwig 2011).

The first hypothesis is based on the effect of generalized seizures produced by the ECT. Evidence indicates that actual ECT is more effective than nonconvulsive electrical stimulation methods such as tDCS and TMS in patients with severe mental disorders (Ren et al. 2014). In addition, unilateral ECT induces seizures, which are not as generalized as the seizures induced by bilateral ECT. Consequently, unilateral ECT is not as effective as bilateral ECT. The seizure is important for ECT to take effect, and the greater the generalization, the stronger the brainstem is activated. However, the presence of generalized seizures does not guarantee the efficacy of ECT because in some cases, even when generalized seizures are produced, this technique is ineffective (Bolwig 2011). Over the course of treatment, there is a decrease in the seizure threshold and duration, producing an anticonvulsive effect. Studies indicate that the GABA, endogenous opioids, adenosine, and glutamate may play a role in both clinical and anticonvulsive effects of ECT. This therapy also seems to have important actions on the transmission of monoamines, such as serotonin, dopamine, and noradrenaline, contributing to the antidepressant effect of ECT (Isenberg and Zorumski 2000).

The neuroendocrine theory explains only the effect of ECT in MDD. This theory states that ECT works to restore neuroendocrine dysfunction associated with this condition. Several studies indicate that severe depression of the melancholic subtype is associated with extensive neuroendocrine dysfunction, including abnormalities in the hypothalamic-pituitary-adrenal axis, increased corticotrophin-releasing hormone (CRH), cortisol hypersecretion, and blunted response to the dexamethasone test. Supporting this theory, there is abundant evidence demonstrating that ECT corrects these dysfunctions in humans by stimulating the diencephalon and inducing extensive release of several hormones and neuropeptides, such as adrenocorticotrophin (ACTH), prolactin, vasopressin, and neuropeptide Y (Bolwig 2011).

Finally, the neurogenesis theory states that ictal activity induces neurotrophic effects in the limbic system, which would be crucial for the therapeutic efficacy of ECT. On the one hand, recent evidences indicate that untreated depression is correlated to impaired hippocampal neurogenesis and hippocampus volume decrease in humans. On the other hand, animal studies demonstrated increased hippocampal volume and increased levels of BDNF and synaptogenesis in this region after serial electroconvulsive stimulation. Neuronal activation is correlated to increased endothelial cell proliferation in the hippocampus

too (Bolwig 2011). In humans, ECT series also induce significant increases in hippocampal volume and in brain-derived neurotrophic factor (BDNF) (Martinotti et al. 2011; Nordanskog et al. 2010). Both in humans and animals, there seems to be a correlation between the number of sessions and the neurotrophic effect of ECT (Bolwig 2011). Electroconvulsive stimulation induces a rapid increase of tissue plasminogen activator (tPA) in the plasma and in the central nervous system, which activates matrix metalloproteinases. These endopeptidases are essential in central nervous system regeneration and repair processes, such as neurogenesis, angiogenesis, and vascular remodeling. According to this hypothesis, tPA also participates in additional mechanisms implicated in neurogenesis that include activation of BDNF, activation of vascular endothelial growth factor, and increased bioavailability of zinc, indicating that tPA may play a crucial role in ECT-induced neurogenesis (Hoirisch-Clapauch et al. 2014).

15.3 Repetitive Transcranial Magnetic Stimulation

TMS devices produce magnetic fields and deliver magnetic pulses to the cortex. These pulses induce electrical currents in the brain tissue, depolarizing target neurons. High-frequency TMS, with more than one pulse per second, activates the stimulated regions, while low-frequency TMS, with one or less pulse per second, inhibits the target cortical areas. The position of the stimulator is critical for an effective TMS treatment. The motor cortex is the target area for motor localization and motor thresholding, while the prefrontal cortex is the main target in the treatment of MDD. Excitatory TMS over the left prefrontal cortex has been well studied and demonstrated to have an antidepressant effect. On the other hand, inhibitory rTMS is still under investigation, and a functional correlation has been found for inhibition of the right prefrontal cortex with depression. Both excitation and inhibition of cortical areas by TMS seem to be effective for the treatment of MDD (Akhtar et al. 2016).

In addition to acute changes in neural excitability, recent evidence indicate that several other mechanisms may contribute to the lasting effects of TMS. These effects are probably explained by changes in cortical synaptic transmission, resembling the long-term potentiation/long-term depression (LTP/LTD) process, and additional regulatory mechanisms from cellular to brain networks level. However, the cellular processes directly influenced by TMS are not entirely clarified (Cirillo et al. 2017).

In standard TMS protocols, the frequency ranges from 5 to 20 Hz; the stimulation is delivered in trains from 2 to 10 s, with intervals from 10 to 60 s; and the sessions last from 15 to 45 min. In theta-burst stimulation (TBS) protocols, bursts of three pulses at 50 Hz repeated at 200 ms intervals are delivered in a 1–6 min session. Despite the short session duration, TBS induces aftereffects with the same or longer duration than conventional TMS. In continuous TBS, a single train of burst lasting 20–40 s is delivered, and it has inhibitory effect in the cortex. Intermittent TBS, which consists of the same burst train split into twenty 2 s sequences, repeated every 10 s, has an excitatory effect. Two pulses delivered at 1.5 or 2 ms interstimulus intervals, repeated every 5 s, (I-wave TMS) produces bidirectional changes in excitability with high temporal fidelity. Studies also indicate that the delivery of four subthreshold pulses (quadripulse stimulation) at 1.5 ms or longer intervals could induce bidirectional plastic changes on a broader temporal scale (Cirillo et al. 2017; Milev et al. 2016).

Therapeutic neurostimulation application requires the induction of long-lasting changes. In humans, modifications dependent to N-methyl-D-aspartate receptor (NMDAR) and Ca^{2+} channels induced by TMS protocols point to long-term synaptic changes similar to the synaptic plasticity demonstrated in cellular and animal studies. Nevertheless, early modifications of synaptic function are needed, and they are produced by: (1) changes in Ca^{2+} dynamics and activation of Ca^{2+}-dependent enzymes, modulation of the glutamate alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)/NMDAR expression, and induction of immediate-early genes; (2) modulation of neu-

rotransmitters release; (3) effects on neurotrophic factors; (4) effects on neuroendocrine systems; and (5) effects on the glial network, inflammation, oxidative stress, and prevention of neuronal cell death (Cirillo et al. 2017).

15.3.1 Intracellular

Changes in the level of neural excitability and initiation of action potential are produced by TMS. It also alters channel/receptor properties and membrane resting potentials and thresholds, consequently changing spontaneous activity, synaptic connectivity, and/or timing dynamics of cellular gating components (Cirillo et al. 2017).

Animal studies also demonstrated morphologic changes with magnetic stimulation. On the one hand, 1 T low-frequency stimulation produced extensive dendritic/axonal arborization, increased synapses density, and other modifications in hippocampal neurons. On the other hand, the same kind of stimulation, but with a stronger magnetic field (1.55 T), reduced the axonal and dendritic arborization, consequently decreasing the number of synapses (Ma et al. 2013). In vitro studies demonstrated that high-frequency magnetic stimulation could produce changes in dendritic spines morphology (Cirillo et al. 2017).

Magnetic stimulation produces increases in glutamatergic transmission, MNDAR activation and sensitization, changes in the AMPAR, and increased conductance of Ca^{2+} channels. There is an activation of immediate-early genes, which, in turn, activate other genes. The downstream genes modulate the expression of several proteins, producing functional and structural modifications in the neurons. These changes include the expression of second messengers and membrane receptors. Immediate effects of neurostimulation become long-lasting effects through the activation of immediate-early genes. It was also demonstrated that TMS may modulate histone H3 and H4 acetylation, changing the expression of genes associated with neuronal function and structure (Cirillo et al. 2017).

15.3.2 Neurotransmission

Studies demonstrated that TMS can interfere with 5-hydroxytryptamine (5-HT) receptors, including 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A}. Changes in these receptors could produce increased serotonergic transmission, explaining the antidepressant effect of TMS. Magnetic stimulation also alters dopaminergic neurotransmission. Acute stimulation increases dopamine in several brain areas, while repeated stimulation modulates the expression and activity of monoamine transporters. GABA modulates cortical excitability, which is also influenced by TMS. Depending on the stimulation protocol, the cortical excitability could be increased or decreased, probably producing opposite effects in GABAergic neurotransmission. Currently, it is not entirely clear how magnetic stimulation affects the (inhibitory) GABA system, but it has been established that this kind of stimulation increases the (excitatory) glutamate neurotransmission. Acetylcholine has an important role in the central nervous system neuroplasticity and seems to mediate the long-term effects of neurostimulation (Cirillo et al. 2017).

15.3.3 Neurotrophins

Neurotrophins play a major role in synaptic plasticity and neuronal survival and differentiation. In vivo animal studies demonstrated that TMS may increase brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and other neurotrophins (Cirillo et al. 2017).

15.3.4 Neuroendocrine

The activation of the hypothalamo-pituitary-adrenal (HPA) and the sympathoadrenal systems is an important element of the physiological response to stress. The glucocorticoids, which are the end-products of the HPA axis activation, are also involved in synaptic plasticity. Studies with TMS indicate that this neurostimulation method probably modulates the HPA axis,

decreasing the cortisol levels in resting state and in response to stress as well (Cirillo et al. 2017).

15.3.5 Neuroinflammation and Glial Network

Neuroinflammation is a response to external stressors, and it is characterized by the activation of astrocytes and microglia. Consequently, pro-inflammatory mediators are released, and free radicals are produced, including reactive oxygen species, which lengthen the inflammatory state. This state induces maladaptive synaptic plasticity and imbalanced neurotransmitter homeostasis. Magnetic stimulation leads to the release of pro-inflammatory mediators and produces a pro-oxidative state, which, in turn, activates the anti-inflammatory/antioxidant systems. The activation of these systems restores the balance of anti-/pro-inflammatory mediators and protects the central nervous system. TMS modulates the activation of astrocytes and microglial cells (Cirillo et al. 2017).

15.4 Other Neurostimulation Methods

The short-term and long-term changes produced by ECT and TMS have been extensively studied, although studies on modifications induced by newer neurostimulation techniques such as MST, tDCS, DBS, and VNS are still scarce. One may hypothesize that many of these effects obtained with ECT and TMS could also be achieved with MST, tDCS, DBS, and VNS.

15.4.1 Magnetic Seizure Therapy

One of the main technical problems with ECT is that high-skull impedance shunts most of the electrical stimulus through the scalp and cerebrospinal fluid, and away from the brain, reducing the control over the spatial distribution and magnitude of intracerebral current density. This limitation precludes refining convulsive therapy and reducing its side effects, especially cognitive deficits. In ECT, there is a widespread stimulation of cortical and subcortical regions. Bitemporal ECT, which is associated with higher shunting and deeper brain stimulation, is also associated with more severe cognitive side effects (Cretaz et al. 2015).

Noninvasive stimulation of specific areas in the cerebral cortex through nonconvulsive magnetic stimulation has some advantages and disadvantages over ECT. TMS is more focal than electrical stimulation because it avoids the impedance of the scalp and skull and results in an induced electric field confined to superficial cortex. Therefore, the current path and density are more controlled. The high safety and few side effects of TMS may be explained by the high control over electrical currents. Despite the demonstrated antidepressant effect, TMS is not as effective as ECT in the treatment of treatment-resistant depression and suicidality (Cretaz et al. 2015).

In TMS, seizures are considered side effects and are avoided by decreasing the intensity of the stimulation. In MST, an intense magnetic stimulation is administered to produce seizures, aiming at the same antidepressant effect produced by ECT. Although, more accurate and focal seizures triggered by magnetic stimulation could lead to fewer adverse effects than seizures induced by ECT. Commercially available coils permit targeting specific brain areas, and the magnetic pulses penetrate only a few centimeters deep. These pulses induce seizures, which are originated in superficial cortex, and there is no direct electrical stimulation of temporal lobe structures, such as the hippocampus, which are implicated in ECT-related memory impairment. Actually, clinical studies demonstrated the superiority of MST over ECT regarding cognitive side effects, but the former was not as effective as the later in the treatment of treatment-resistant depression (Cretaz et al. 2015). The long-term effects of MST were not adequately studied yet, but one could infer that it could produce the same neurobiological changes produced by ECT, including neurogenesis/synaptogenesis, neuroendocrine modifications, and changes in GABA, endogenous opioids, adenosine, glutamate, and monoamines.

15.4.2 Transcranial Direct-Current Stimulation

In tDCS, a weak constant current (1–2 mA) is applied to the brain for 5–20 min using a pair of saline-sponged electrodes, inducing changes in cortical excitability. One of the electrodes is placed on the scalp, above the cortical area to be modulated, while the other electrode is placed distantly. Changing the polarity of the current produces opposite effects on cortical excitability. Depolarization of neuronal compartments closer to the electrode and consequent increased cortical excitability can be achieved by anodal tDCS. Neuronal hyperpolarization and decreased cortical excitability may be produced by cathodal tDCS. The polarity, duration, and intensity of tDCS vary according to the protocol in use. This neurostimulation technique produces polarity-dependent changes of cortical excitability, but the membrane depolarization is not sufficient to elicit action potentials (Cirillo et al. 2017).

It was demonstrated that tDCS may induce long-term potentiation in mouse motor cortex and rat hippocampus. The long-term potentiation may produce several changes in the central nervous system, including promoting synaptic plasticity and activating immediate-early genes. Unlike TMS, tDCS does not increase the levels of BDNF, NGF, and other neurotrophins. However, it was demonstrated that tDCS decreases the activation of HPA and sympathoadrenal systems, leading to a cortisol reduction and a heart rate variability increase. Like TMS, tDCS also modulates glial cell functions (Cirillo et al. 2017).

15.4.3 Deep Brain Stimulation

The most invasive and precise neurostimulation method is the DBS. The neurostimulator is implanted under the skin, and a thin electrode is inserted directly into a specific brain structure. Then, different currents are applied at varying intensities until the desired effect is produced. On the one hand, high-frequency (>50 Hz) stimulation creates a transient functional lesion and inhibits a brain region from normal participation in brain activity. On the other hand, low-frequency stimulation may intermittently activate a region. DBS in subthalamic nucleus has been reported to produce acute depression, laughter, imaginative associations, and feelings of well-being. However, the neuronal network associated with affective symptoms has not yet been identified, and it remains to be determined if stimulation of this network has therapeutic potential in treating mood disorders (Chae et al. 2001).

15.4.4 Vagal Nerve Stimulation

An implantable, multiprogrammable, bipolar pulse generator is implanted in the left chest wall to deliver electrical signals to the left vagus nerve through a bipolar lead. This bipolar lead is wrapped around the left vagus nerve near the carotid artery through a separate incision at surgery and is connected to the generator. There is an external programming system, which includes a programming wand, a software, and a computer. The clinician can identify, read, and change device settings through this system (Chae et al. 2001).

The vagus nerve is composed of about 20% efferent fibers and about 80% afferent sensory fibers, carrying information to the brain from the head, neck, thorax, and abdomen. These fibers relay information to the nucleus tractus solitarius and then to many areas of the brain. This brain structure passes along incoming sensory information to higher brain regions such as the reticular formation in the medulla and ascending projections to the forebrain. These projections include connections with the parabrachial nucleus, hypothalamus, locus coeruleus, thalamus, amygdala, insula, bed nucleus of stria terminalis, and prefrontal cortex. Positron emission tomography studies indicate that VNS acutely increases synaptic activity in structures directly innervated by central vagus structures and areas that process left-sided somatosensory information. In addition, VNS acutely alters synaptic activity in multiple limbic system structures bilaterally, such as amygdala, hippocampus, and cingulate gyrus. It

seems that the brain undergoes substantial changes over the course of treatment with VNS. Functional magnetic resonance imaging studies in depressed patients implanted with VNS generators show that VNS activates many anterior paralimbic regions. Animal and clinical studies demonstrated that treatment with VNS also produces changes in serotonin, noradrenaline, GABA, and glutamate, which are neurotransmitters associated with the pathophysiology of depressive disorders. Mood improvements were observed in patients with epilepsy treated with VNS, indicating that the indirect stimulation of limbic structures could improve mood regulation (George et al. 2000; Walker et al. 1999).

Conclusions

The neurostimulation methods are diverse. The most important difference between these methods is that ECT and MST induce seizures, while the other methods produce more subtle acute effects. Magnetic stimulation methods seem to produce an effect that is similar to the one induced by direct electrical stimulation. Nevertheless, all techniques induce electrical currents in the brain, producing functional and structural modifications. Clearly, the immediate target of these neurostimulation methods is the polarity of the neuron. Calcium channels, NMDAR, AMPAR, and other receptors/channels in the cellular membrane are affected by neurostimulation by means of neuronal depolarization and increase or decrease of neuron excitability. These immediate effects are followed by a cascade of changes within the neuron, including changes in gene expression and second messengers. Neurostimulation modulates glutamatergic, serotonergic, dopaminergic, GABAergic, and cholinergic neurotransmission. The HPA and sympathoadrenal systems are also modulated by neurostimulation, which reduces the release of corticotrophins and cortisol. These techniques also play a significant role in the regulation of glial cell activity, neuroinflammation, and oxidative stress.

Recent studies demonstrated that neurostimulation produces several neurobiological changes in the brain, but it is still not entirely clear which of these mechanisms produce the improvement of depressive symptoms. Both antidepressants and neurostimulation techniques, which are effective in the treatment of MDD, play a major role in the modulation of several neurotransmitter systems. This is probably the most promising mechanism to explain the antidepressant effect of neurostimulation.

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Part IV

Multicellular System-Level Aspect of Depression

Chronic Inflammation and Resulting Neuroprogression in Major Depression

16

Brian E. Leonard

16.1 Introduction

The concept that the immune system plays a role in mental ill health goes back to antiquity. Hippocrates, in the fourth century BC, suggested that melancholia was caused by black bile thereby suggesting that some endogenous factor(s) were responsible for the mood state. By the nineteenth century, it was widely recognised that bacterial and parasitic infections could contribute to altered mental states and, in the case of syphilis infection, to dementia. However, it is only relatively recently that clinicians have observed that chronic neuroinflammation plays an important role in the pathophysiology of affective disorders and other major psychiatric illnesses.

The purpose of this review is to summarise the evidence that chronic neuroinflammation has a major impact on brain structure and function. Of the various components of the immune system involved, the cytokines appear to play a prominent part and will therefore receive major attention in describing how the proinflammatory cytokines may trigger irreversible neuronal damage and thereby precipitate neurodegenerative changes.

Neuroinflammation is a key factor in the genesis of neurodegenerative, developmental and stress-related brain disorders. Such changes are an expression of inflammation-induced dysfunction of neuroplasticity which is expressed in deficits in learning, memory and cognition. Major neurological disorders, such as Alzheimer's and Parkinson's disease, and psychiatric disorders, as illustrated by major depression, schizophrenia and bipolar disorder, are important examples of the chronic impact of neuroinflammation (Altamura et al. 2013; Schwarz and Schechter 2010). However, besides the pathological consequences of neuroinflammation which arises when the immune system is activated by stress, infection, trauma, etc., neuroinflammation also plays an important physiological role in brain homeostasis involving such inflammatory mediators as the proinflammatory cytokines, prostaglandins and various neurotrophic factors which promote synaptogenesis. Hippocampal long-term potentiation is an expression of such a role. The neurotoxic effects of these mediators arise when they are over-produced in pathological situations (Yirmiya and Goshen 2011; Xanthos and Sandkuehler 2014).

In recent years, depression research has extended from the consideration of the consequences of neurotransmitter dysfunction to the role that the endocrine and immune systems may contribute to the pathophysiology of the disorder. There are a number of reasons for these changes. Thus, the occurrence of low-grade inflammation

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B.E. Leonard (✉)
National University of Ireland, Galway, Ireland
e-mail: psycholeonard@gmail.com

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has been shown to impact on neurotransmitter function and shown to be associated with many of the metabolic changes associated with depression (Leonard 2010; Maes 1995; Smith 1991). These observations have led to the identification of a link between the consequences of chronic inflammation and an increase in the frequency of type 2 diabetes and heart disease in chronically depressed patients and also with the increased possibility of dementia in the elderly patient (McIntyre et al. 2012; Leonard 2013).

The question therefore arises whether such disparate changes are epiphenomena of a chronic psychiatric condition reflecting lifestyle changes involving nutrition and poor diet, lack of self-care associated with exposure to pathogens, etc. or more fundamentally that the metabolic changes are initiated by cytokines and other inflammatory mediators that are ultimately responsible for the psychopathological and chronic physical ill health which characterise many chronic psychiatric disorders.

Of the many processes that may be involved in linking inflammation with neurodegenerative changes in the brain, the role of the tryptophan-kynurenine pathway has recently received much attention. Overactivity of the glutamatergic system results in damage to neuronal networks. The link between the activation of the microglia by stress and major psychiatric and neurological disorders results in an increase in the release of proinflammatory cytokines. While proinflammatory cytokines activate many different neurodegenerative processes, the activation of indoleamine dioxygenase (IDO) activates the catabolism of tryptophan to kynurenine in many areas of the brain. The proinflammatory cytokines also activate the enzymes in the neurodegenerative arm of the tryptophan-kynurenine pathway which results in the synthesis of quinolinic acid. Quinolinic acid is an agonist for the *N*-methyl-D-aspartate (NMDA)-glutamate receptor and acts as a neurotoxin when present above physiological concentrations thereby affecting the functional integrity of the neuronal circuits (see Fig. 16.1).

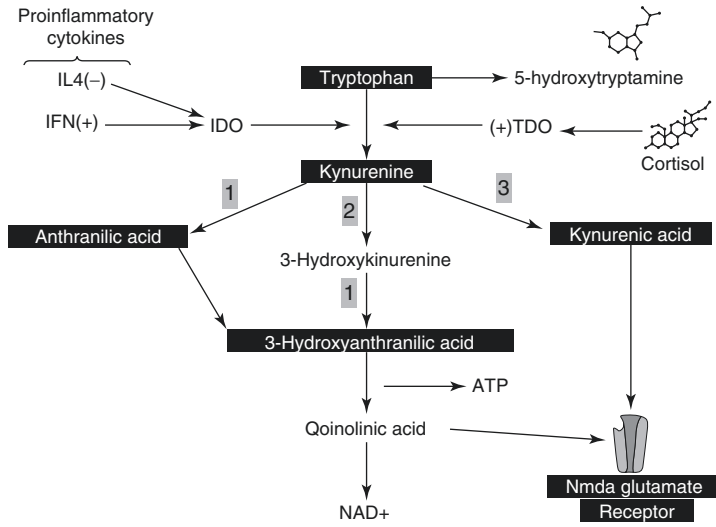

Fig. 16.1 The tryptophan-kynurenine pathway links neuroinflammation to chronic depression (adapted from Leonard 2017). *IDO* indoleamine dioxygenase, *TDO* tryptophan dioxygenase, *IFN* interferon gamma and other proinflammatory cytokines, *IL 4* interleukin 4 and other anti-inflammatory cytokines, *NAD+* nicotineamide adenine dinucleotide, *NMDA N*-methyl-D-aspartate, activated by quinolinic acid and blocked by kynurenic acid. 1 = kynureninase; 2 = kynurenine oxygenase; 3 = kynurenine aminotransferase

16.2 Epidemiological Factors Implicating Chronic Depression with Brain Neurodegenerative Processes

Epidemiological studies have reported that the frequency of Alzheimer's disease and other neurodegenerative disorders increases in those who have chronic depression in comparison to an age- and gender-matched control population (Geerlings et al. 2000; Green et al. 2003). These observations are supported by the finding that a history of depression is an important risk factor for dementia in later life (Jorm 2001).

Pathological findings have also shown that the frequency of amyloid plaques and neurofibrillary tangles is also greater in patients with Alzheimer's disease who have been diagnosed with major depression (Rapp et al. 2006; Sun et al. 2008). Furthermore neurodegenerative changes in the hippocampus and prefrontal cortex occur in patients with major depression (Seline 2002). Thus, there is substantial evidence to indicate that neurodegenerative changes, and severe cognitive deficits, are a frequent outcome of depression. Such changes become more prevalent in middle-aged and elderly depressed patients. Further support for this hypothesis has been reviewed by Leonard (2001) and by Leonard (2006).

16.3 The Link Between Brain Neurodegenerative Changes and Neurotoxic Changes

From a historical perspective, the potential importance of the components of the tryptophan-kynurenine pathway was recognised following the behavioural changes induced in rodents by some of the main components of neurodegenerative arm of the pathway. Thus, 40 years ago, Lapin and colleagues, from the Bekhterev Psychoneurological Research Institute in Leningrad, published a series of experimental studies demonstrating the importance of the tryptophan-kynurenine pathway in the action of imipramine and suggested that depression resulted as a consequence of the adverse effects of the metabolic products of this pathway (Lapin and Oxenkrug 1969; Lapin 1973). As such metabolic products included quinolinic acid and 3-hydroxykynurenine that were shown experimentally to cause anxiety and stress-like changes in rodents, Lapin further characterised the 'neurokynurenines' as the neurochemical link between depression and anxiety states (Lapin 2003).

Since that time, there have been a plethora of experimental and clinical studies that demonstrate changes in the tryptophan-kynurenine pathway (Stone 1993; Myint and Kim 2003, 2014; Oxenkrug 2011) and which implicate quinolinic acid and 3-hydroxykynurenine as important neurotoxins which compromise neuronal function by enhancing oxidative stress (3-hydroxyanthranilic acid and 3-hydroxykynurenine) and by activating the *N*-methyl-D-aspartate glutamate receptor thereby causing neuronal apoptosis (Guillemin and Brew 2002).

16.4 The Tryptophan-Kynurenine Pathway and Deficits in Intermediary Metabolism of Glucose

In recent years, attention has centred on the neurotoxic consequences of the increase in quinolinic acid and the intermediates formed from kynurenine in the tryptophan-kynurenine pathway. While such neurotoxins undoubtedly play a critical role in the neurodegenerative changes associated with chronic psychiatric disorders such as depression and schizophrenia, it is often overlooked that quinolinic acid is also an important substrate for the formation of nicotinamide adenine dinucleotide (NAD+). As NAD+ is a key component of the respiratory chain, chronic pathological changes that reduce its formation are liable to have adverse consequences for intermediary metabolism particularly in neurons that are critically dependent on high-energy sources. It is estimated that approximately 99% of tryptophan that is not used for protein and serotonin synthesis

is metabolised to NAD+ via the tryptophan-kynurenine pathway, and therefore this pathway is important for the synthesis of this vital cofactor (Gal and Sherman 1980; Han et al. 2010).

16.5 The Link Between Brain Energy Metabolism, Inflammation and Neurodegeneration

Although there are numerous experimental studies to illustrate how low-grade inflammation produces changes in brain structure and function, it is only relatively recent that changes in the human brain have been evaluated. Thus, Harrison et al. (2014) demonstrated that peripheral inflammation impairs spatial memory by reducing glucose metabolism in the medial temporal lobe. This provides evidence for a link between inflammation, dysfunctional brain energy metabolism and neurodegenerative changes and will be considered further in this review.

At the cellular level, dysfunctional brain energy metabolism which occurs in major depression and schizophrenia is linked to a decreased expression of insulin receptors in the dorsolateral prefrontal cortex (Bernstein et al. 2009; Zhao 2006).

This situation would be compounded by a reduction in the availability of insulin, a key factor in the transport of glucose into neurons (Oxenkrug 2013). As there is evidence that insulin receptor resistance is a frequent feature of depression, and other major psychiatric disorders and with age-related pathology associated with the dementias (Lee et al. 2013), it seems reasonable to conclude that a chronic decrease in high-energy substrates resulting from a deficit in glucose and essential cofactors may be of crucial importance in understanding the causes of increased neuronal apoptosis (Lee et al. 2013). This situation is further complicated by mitochondrial dysfunction in depression which results in a decrease in the synthesis of adenosine triphosphate (ATP) and related high-energy molecules, combined with an increase in oxidative damage, while the synthesis of superoxide radicals resulting from a decrease in the respiratory chain increases the damage to the mitochondrial membranes by opening the permeability transition pores (Sas et al. 2009). In addition, oxygen-free radical synthesis is enhanced by xanthine, uric acid and 3-hydroxykynurenine which are formed in the brain as a result of the inflammation-enhanced tryptophan-kynurenine pathway. However, it still remains to be unequivocally established that the changes in brain glucose are a reflection of defective cellular mechanisms rather than a reflection of reduced neuronal activity which is a characteristic feature of major affective disorders and schizophrenia.

Peters et al. (2004) proposed the selfish brain hypothesis to explain the changes in brain glucose that has been observed in major psychiatric disorders.

This hypothesis postulates that the brain regulates glucose flux preferentially at the expense of other tissues. Thus, even though the brain occupies only about 2% of the body mass, it consumes at least 20% of the available glucose. The selfish brain hypothesis also accounts for the dietary changes which occur in some patients with depression or schizophrenia who prefer a carbohydrate-rich diet rather than a balanced, healthy diet. This might be a mechanism for increasing brain glucose availability.

An essential cofactor in the control of many of the intermediates in the tryptophan-kynurenine pathway is pyridoxal-5-phosphate (P5P), the active form of vitamin B6. It is well established that vitamin B6, together with vitamin B12 and folate, is involved in the methylation reactions that contribute to the synthesis of the monoamine neurotransmitters, phospholipids and nucleotides, all of which are functionally compromised in depression. Thus, a deficiency of dietary vitamin B6 could have an impact on depression, and recent studies have demonstrated that low plasma P5P levels are inversely correlated with the severity of depressive symptoms particularly in the elderly (Merete et al. 2008). Other investigators have reported that the B vitamins reduced the symptoms of major depression in post stroke patients (Almeida et al. 2010), while, in a Japanese study, a higher vitamin B6 status was associated with a decreased risk of depression

(Nanri et al. 2013). It should be noted however that not all epidemiological studies on the vitamin status have reported the beneficial effects of vitamin B6 (Sanchez-Villegas et al. 2009).

Conclusion

The hypothesis which links the activation of the tryptophan-kynurenine pathway by proinflammatory cytokines to dysfunctional brain energy metabolism may help to explain how chronic neuroinflammation contributes to the neurodegenerative processes which characterise some major psychiatric and neurological disorders.

However, there are many aspects of this hypothesis which must be addressed.

For example, why do a substantial number of elderly patients with chronic affective disorders not develop dementia even though there are many well-designed clinical studies to indicate that neuroinflammation commonly occurs? What determines the differences in the behavioural and neurochemical changes in patients with affective and psychiatric disorders, and to what extent are the changes induced by genetic and environmental factors? Furthermore, if the common pathway leading to neurodegeneration involves dysfunctional brain glucose metabolism, to what extent is it possible to limit or, even reverse, the neurodegenerative changes by normalising brain glucose metabolism? Perhaps the selfish brain hypothesis has opened up a new chapter in our understanding of the relationship between neuroinflammation and neuroprogression!

Conflict of Interest None.

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Gut-Microbiota-Brain Axis and Depression

17

Alper Evrensel and Mehmet Emin Ceylan

17.1 Introduction

The effects of gut microbiota on the brain and behavior are a new area of interest for the scientific world (Hsiao et al. 2013). More than 90% of the thousands of articles regarding gut-brain axis were published in recent years (Evrensel and Ceylan 2017). Microorganisms colonized in guts and their metabolites (endotoxins in the form of lipopolysaccharide) are in communication with intestinal epithelium cells (enterocytes) and the immune system (Evrensel and Ceylan 2015a). This communication plays role in the formation of autoimmune diseases such as asthma; metabolical diseases such as obesity, insulin resistance and diabetes mellitus; and neuropsychiatric disorders such as depression and autism (Evrensel and Ceylan 2015a). There is a vast amount of evidence regarding the existence of a bidirectional and strong relationship between the brain and the gut. This relationship starts with the intrauterine period and continues through life (Sharon et al. 2016).

While microbiome refers to the genetic material of all microorganisms (bacteria, viruses, archaea, fungi), microbiota refers to the microorganisms living in different floras of the body (e.g., oral microbiota, skin microbiota, gut microbiota, vagina microbiota) (Khanna and Tosh 2014). The Human Microbiome Project (HMP) is run with the purpose of understanding microbiome diversity and determines the role of microorganisms in health and illness (NIH HMP Working Group et al. 2009). HMP is supported by National Institutes of Health (NIH).

17.2 Gut Microbiota

There are 3.8×10^{13} (380 trillion) microorganisms in the human gastrointestinal system. The number of microorganisms is tenfolds more than the total number of cells in an adult human (Sender et al. 2016). There are 3.3 million nonhuman genes belonging to microorganisms in the human guts (Zhu et al. 2010). On the other hand, 23,285 genes employed in protein production in humans were defined in the ENSEMBL databases (Stilling et al. 2014). Thus, these microorganisms have about 140–150 times more genes than those in the human genome (Lozupone et al. 2012). It appears that commensal microorganisms have taken the upper hand both in their number and genetically.

17.2.1 Historical Background of Microbiota

The brain-viscera interaction was defined in 1880 by William James and Carl Lange (James 1884). However, the importance of microbiome for

A. Evrensel (✉) • M.E. Ceylan
Department of Psychiatry, Uskudar University, Istanbul, Turkey
e-mail: alperevrensel@gmail.com

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human health was firstly revealed in the studies of the Russian scientist Elie Metchnikoff. According to Metchnikoff's hypothesis, it is possible to lead a long and healthy life with the help of regulating gut microbiota using friendly microorganisms found in yogurt. Metchnikoff received a Nobel prize in physiology or medicine in 1908 due to his contributions on understanding the cellular and humoral immune system (Mackowiak 2013). Two years later, there was a groundbreaking article published. In this article, with an intuitive forward thinking, it was suggested that probiotic bacteria may be used in depression treatment (Phillips 1910). However, the interest on this issue did not continue, maybe because this article was not very influential at the time. The relationship between gut microbiota and the brain was not investigated in the following years. Thus, unfortunately, Phillips' article was not cited for longer than 100 years.

17.2.2 Old Friends and Coevolution

Phillips' idea was based on the consideration that microorganisms might not be only harmful. Seventy-nine years later than Phillips' article, this idea was considered again. Strachan found a relationship between allergic disease incidence and reduced contact with microorganisms due to hygienic lifestyle associated with disinfectants and urbanization (Strachan 1989). Rook looked at the host-microbe relationship from a broader angle. According to Rook's hypothesis, Homo sapiens and "old friend" microorganisms evolved through millions of years in interaction and by gene exchange (Rook 2010; Rook et al. 2015). While the microbe-host coevolution has been going on for 500 million years, the details of the interaction and epigenetic mechanisms are still not completely clear (Stilling et al. 2014).

17.2.3 Gut Microbiota Composition

Human gut composition is a complex ecosystem (Macedo et al. 2017). Bacteria, viruses, fungi, and archaea live in this microflora. While they are ten times more than the cells in an adult human body in terms of number, their total weight is about the same as the brain, approximately 1.5 kg on average (Stilling et al. 2014).

Human gut microbiota contains 1800 genera and more than 40,000 bacterial strains (Forsythe and Kunze 2013). Firmicutes, bacteroidetes, actinobacteria, and proteobacteria are bacteria families mostly living in the guts (Khanna and Tosh 2014). About 70–75% of the microbiota are firmicutes and bacteroidetes; the firmicutes/bacteroidetes ratio in an adult person is 10.9 (Mariat et al. 2009). Moreover, the microbiota composition in each person is different and unique. This is because microbiota is a dynamic form affected by diet, genetics, age, geography, stress, and drugs intensively (David et al. 2014; Dash et al. 2015; Macedo et al. 2017). Disruption of the microbiota composition is called dysbiosis. Stool bacteria composition may be determined by 16S ribosomal RNA (16S rRNA) gene sequencing (Woese and Fox 1977).

The effects of the environment on microbiota were presented by several studies. In rodents, following a 21-day olanzapine administration, the levels of firmicutes increased, while the levels of proteobacteria and actinobacteria decreased (Davey et al. 2013). In rhesus monkey newborns, the stress induced by separation from the mother led to a decrease in bifidobacterial and lactobacillus levels (Bailey and Coe 1999). The situation is similar for rat newborns. A decrease in fecal lactobacillus levels was observed starting with the third day in rat pups separated from their mothers (O'Mahony et al. 2009).

Gut bacteria are active in the human metabolism. Lactobacillus and bifidobacteria produce gamma-amino butyric acid (GABA) (Barrett et al. 2012). *Escherichia*, *Bacillus*, and *Saccharomyces* synthesize norepinephrine; *Candida*, *Streptococcus*, *Escherichia*, and *Enterococcus* synthesize serotonin; *Bacillus* and *Serratia* synthesize dopamine (Lyte 2011). Microorganisms in the guts produce neuroactive substances such as brain-derived neurotrophic factor (BDNF), postsynaptic density (PSD)-95, and synaptophysin. The substances affect the development of the brain by playing roles on neuroplasticity

(Diaz Heijtz et al. 2011; Douglas-Escobar et al. 2013).

17.2.4 Gut Microbiota and Immunity

Microorganisms living in the guts play a critical and determinant role on innate and acquired immunity (Round et al. 2010). The effects of microbiota on natural killer T lymphocytes start in the perinatal period and continue along the life time (Olszak et al. 2012). The interaction between microbiota and gut mucosa affects the production of various cytokines and chemokines (interleukin-8, interleukin-1, interleukin-10, and transforming growth factor B) (Neish 2009).

Gut microorganisms are in interaction with enterocytes (Dinan and Quigley 2011). This interaction takes place with the help of toll-like receptors (TLRs) which are from the pattern recognition receptor (PRR) family (Carvalho et al. 2012; Lucas and Maes 2013). In the immune system, there are ten types of TLRs (Takeuchi and Akira 2010). TLRs are the first step in cytokine production, and they are found in abundance in the neural cell membrane (McKernan et al. 2011; McCusker and Kelley 2013).

Pro-inflammatory cytokines may be playing a role in the etiopathogenesis of depression (Jeon and Kim 2016). There is a bidirectional causal relationship between depression and neuroinflammation (Kim et al. 2016). Inflammatory cytokines (such as interferon alpha) may lead to depression, and this depression may be prevented by antidepressant drugs (McNutt et al. 2012; Udina et al. 2012). Antidepressants, in addition to their effect on monoamine levels in synapses, also show anti-inflammatory effects by increasing IL-10 (strong immunoregulatory cytokine) (Maes et al. 2005). Probiotics, like antidepressants, also increase the levels of IL-10 (Levkovich et al. 2013). When experimental animals were given Lactobacillus GG, which is probiotic, it was observed that their IL-10 levels increased. This was also found in their pups (Kopp et al. 2008). The changes in the microbiota composition taking place in the development of a newborn may lead to life-long results (Costello et al. 2012).

Another way of interaction between the immune system and microorganisms is dendritic cells. Subepithelial dendritic cells are some of the fundamental cells of the immune system in the guts. These cells extend their dendrites into the gut lumen through enterocytes and contact the bacteria in the lumen and their metabolites. These metabolites are taken into dendritic cells in form of lipoprotein vesicles (exosomes). Inside the exosomes, there are nutrients, endotoxins, and bacterial genomes. Dendritic cells transfer their exosomes to T cells in lymph nodes. This way, bacterial metabolites and nucleic acids are able to reach neurons by joining the systemic circulation. This may lead to conditions that allow neuropsychiatric disorders, especially depression (Smythies and Smythies 2014).

17.2.5 Leaky Gut

The gut epithelium is the widest mucosa in the body. This surface area growing due to the ciliary outgrowths of enterocytes has an approximate size of 260–300 m^2 (about as large as a tennis court) (Helander and Fändriks 2014). In healthy intestinal epithelium, tight junction proteins (occludin, adhesion molecule, and zonula occludens) and the mucus layer provide a physical barrier between the bacteria and foreign antigens and the host (Borre et al. 2014). As a result of the change in microbiota composition and increase in endotoxins, micro-damages take place in the intestinal epithelium wall, and intestinal epithelium permeability increases. Therefore, microorganism-derived endotoxins join the systemic circulation (Hornig 2013). This is called "leaky gut" syndrome (Maes et al. 2012). As are result of antigens from pathogen microorganisms joining the systemic circulation, immune response may take place (Fetissov and Déchelotte 2011). In experimental animal, as a result of disruption in intestinal permeability, bacteria-led lipopolysaccharides (LPS, endotoxins) may enter blood circulation. As a result of this, the production of inflammatory cytokines increases by the stimulation of TLRs (especially TLR4) (Ait-Belgnaoui et al. 2012).

17.2.6 Germ-Free (GF) Animals

GF animal experiments are in the center of understanding the effects of gut microbiota on the immune system and brain functions. Experimental animals grown in strict sterile conditions and do not contain microbiota are called GF (Stilling et al. 2014). In these experiments, GF animals are exposed to certain bacteria, and the resulting behavioral changes are interpreted. This way, it is aimed to understand the effects of gut bacteria composition on immune, hormonal, and brain functions.

To obtain a GF animal, the pup must be taken out by Caesarean section, and it must be fed by hand with sterile milk in a sterile and isolated area. GF experimental animals are obtained by natural birth after mating of several animals grown in this way in sterile conditions (Stilling et al. 2014).

GF and other gnotobiotic experimental animals were developed for the first time in the early 1900s (Stilling et al. 2014). Behavioral changes were shown for the first time in gnotobiotic piglets (Bähr 1970). The first study showing the brain function changes in GF mice was published 34 years later. In this study, decreases of levels of BDNF and NMDA (N-methyl D-aspartate) 2a were seen in the hippocampus of GF mice (Sudo et al. 2004). A normal gut microbiota is needed for healthy development of brain plasticity. Plasma serotonin levels are high in GF mice (Collins and Bercik 2009). In experimental mice made genetically prone, experimental autoimmune encephalomyelitis does not develop. However, this protection is gone after these mice become adults and normal intestinal colonization develops (Berer et al. 2011). GF animal experiments become more important every day in explaining the gut-brain relationship in detail.

17.3 Microbiota-Depression Relationship

17.3.1 Infantile Microbiota and Its Effects on Brain Development

In an infant born vaginally, its mother's vaginal microbiota (*Lactobacillus* and *Prevotella* types) is colonized (Dominguez-Bello et al. 2016). When the infant is born with Caesarean section, the mother's skin microbiota containing intensive amounts of *Staphylococcus* and *Corynebacterium* types takes place in the infant (Bäckhed et al. 2015). This exposure in the beginning of life has a very long-lasting effect on the health and development of the infant (Sharon et al. 2016). Another significant external effect impacting the microbiota composition is antibiotic drugs. Usage of antibiotics under the age of 1 year is correlated with depression development in further parts of life (Slykerman et al. 2017). When experimental animals are given a nonabsorbable antibiotic (e.g., vancomycin) for 7 days, decreases are observed in anxiety-like behavior. However, this effect lasts shortly and disappears in 2 weeks, probably because the intestinal bacteria colonization goes back to its previous state (Bercik et al. 2011). Long-term usage of wide-spectrum antibiotics leads to permanent composition changes in the gut microbiota, and this change is influential on brain chemistry and behavior (Desbonnet et al. 2015).

17.3.2 Neurobehavioral Effects of Gut Microbiota Change

How does lack of microbiota affect the host's behavior? In GF mice, the anxiety-like responses to anxiety tests such as elevated plus-maze test, open-space test, and light-dark box tests are lower than those in conventional mice (Neufeld et al. 2011). GF mice also show changes seen in depression patients such as decrease in BDNF levels and 5-hydroxytryptamine (serotonin) receptor 1A ($5HT_{1A}$) expression. These changes are independent from inflammatory processes (Bercik et al. 2011). In the light of these preclinical studies, the existence/nonexistence and composition of gut bacteria are highly important for brain and behavior development (Macedo et al. 2017).

17.3.3 The Effects of Stress on Gut Microbiota

The fecal microbiota 16S rRNA gene profile changes in experimental animal pups on which a depression model was formed by maternal sepa-

ration (O'Mahony et al. 2009). In the stool of mice exposed to chronic stress, *Bacteroides* spp. species decreased, and *Clostridium* spp. species increased (Bailey et al. 2011). In the depression model led by exposure to chronic mild stress by mice, plasma LPS and LPS-binding protein levels increased, and levels of LPS receptors and TLR4 increased in their brain. Additionally, the pro-inflammatory cytokine levels increased in the brain tissue of these mice, and anti-inflammatory cytokine levels decreased. In administration of streptomycin sulfate and penicillin G, these changes were reversed. In the light of this, the authors of the article recommended that antibiotics effective on gram-negative bacteria may be added to antidepressants in depression treatment (Gárate et al. 2011).

It is considered that the effect of stress on gut microbiota is related to sympathetic stimulation and cortisol. Cortisol makes it easier for bacteria-derived endotoxins to enter systemic circulation by changing intestinal permeability. Moreover, it also changes the gut bacteria composition and leads to increases in the numbers of more enterotoxigenic bacteria such as *Coprococcus*, *Pseudobutyrivibrio*, and *Dorea* (Bailey et al. 2011; Cryan and Dinan 2012).

17.3.4 Dysbiosis and Depression

A recent cohort study with a wide sample found a positive relationship between depression and enterovirus infection (Liao et al. 2017). There is a chronic and mild inflammation in depression patients. The source of this inflammation may be dysbiosis and leaky gut (Berk et al. 2013).

Gut microbiota and depression relationship has been investigated in numerous studies. *Bifidobacterium infantis* was given to rats for 14 days, and antidepressant-like changes were seen in immune, neuroendocrine, and monoaminergic activities (Desbonnet et al. 2008). In another experiment, rat pups depressed by separation from the mother were taken into two groups. One group was given *Bifidobacterium infantis*, while the other was given citalopram. No difference was found between the antidepressant effects of *Bifidobacterium infantis* and citalopram (Desbonnet et al. 2010). *Bifidobacterium infantis* is a commensal bacterium living in newborn gut microflora, and it is named as "psychobiotic" due to its antidepressant effect (Dinan et al. 2013). In mice given *Lactobacillus rhamnosus* for 28 days, reduction was observed in the scores of both anxiety and depression (Bravo et al. 2011). Among animal experiments, maybe the most interesting study was conducted by Kelly et al. In their study, among depression-diagnosed individuals, rats whose gut microbiota was cleaned using antibiotics (ampicillin, metronidazole, vancomycin, ciprofloxacin, and imipenem) were subjected to fecal microbiota transplantation. As a result of the implementation, depression and anxiety-like behaviors and physiological changes were seen in the experimental animals (Kelly et al. 2016).

In a study where 112 depression patients and 28 healthy controls were compared, levels of lipopolysaccharide which is a commensal bacteria metabolite, serum antibodies (IgM and IgA) were measured. An increase was observed in the IgM and IgA levels of depression patients. This was interpreted as evidence of immune system activation and intestinal permeability disorder in depression (Maes et al. 2012). In another study, fecal bacteria gene analysis was conducted on 37 depression patients and 18 healthy controls. In depression patients, *Bacteroides* levels were high, and *Lachnospiraceae* levels were low (Naseribafrouei et al. 2014).

Another study compared 46 depression patients and 30 healthy controls. In depression patients, fecal *Bacteroides*, proteobacteria, and actinobacteria levels increased, while firmicutes decreased. Again, in depression patients, *Alistipes* and *Enterobacteriaceae* levels increased, and *Faecalibacterium* levels decreased (Jiang et al. 2015). Alistipes species metabolize tryptophan (Song et al. 2006). As serotonin is synthesized from tryptophane, increase in *Alistipes* species may be disrupting the balance of the serotonergic system. *Lactobacillus plantarum*, *Morganella morganii*, *Klebsiella pneumoniae,* and *Hafnia alvei* also synthesize serotonin (O'Mahony et al. 2015).

In the light of these findings, it may be stated that local and systemic immune response is triggered in depression patients due to dysbiosis, leaky gut, and bacterial translocation.

17.3.5 The Effects of Antidepressants on Gut Microbiota

The first drug whose antidepressant effects were noticed was an anti-tuberculosis agent, iproniazid (Chessin et al. 1957). It started to be used in treatment of depression in 1950s due to its euphorian effects on tuberculosis patients (López-Muñoz and Alamo 2009). This is because as much as iproniazid is a bacterium cell wall synthesis inhibitor, it is also a monoamine-oxidase (MAO) inhibitor (Johnston 1968). In the following years, it was shown that other antidepressants also have antibacterial effects via various mechanisms. Tricyclic antidepressants have antiplasmid effects and are effective on *Escherichia coli*, *Yersinia enterocolitica* (Csiszar and Molnar 1992), *Plasmodium falciparum* (Bitonti et al. 1988), *Leishmania* spp. (Zilberstein and Dwyer 1984), and *Giardia lamblia* (Weinbach et al. 1992). SSRIs are efflux inhibitors in bacteria cell walls (Bohnert et al. 2011) and are antibiotically effective on gram-positive bacteria such as *Enterococcus* and *Staphylococcus* (Munoz-Bellido et al. 2000; Coban et al. 2009). Ketamine, which is NMDA antagonist drug, also has antimicrobial effects (Gocmen et al. 2008) and is effective against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa*, as well as *Candida albicans* (Begec et al. 2013; Gocmen et al. 2008). Antidepressant effect might be achieved not only via the monoamine system, but it may also be that changes in microbiota composition are also effective via the immune system (Evrensel and Ceylan 2015a, 2017).

17.4 Restoration of Gut Dysbiosis

Gut microbiota dysbiosis may be repaired in a few different ways. These are prebiotics, probiotics, activated charcoal, and fecal microbiota transplantation (Evrensel and Ceylan 2015b, 2016a). Microbiota transfer therapy (MTT) is a method that is similar to FMT (Kang et al. 2017).

17.4.1 Prebiotics-Probiotics

Like other living things, bacteria also need food. Nutrients and substances which lead to heightened increase of reproduction in certain gut bacteria over others are called prebiotics (Evrensel and Ceylan 2016a). For example, *Bacteroides fragilis* and *Faecalibacterium prausnitzii* synthesize fatty acid metabolites (acetate, butyrate, and propionate) from fibers. Fatty acid molecules lead to anti-inflammatory effects (Macfarlane and Macfarlane 2003; Bollrath and Powrie 2013). Therefore, fiber is a prebiotic food. In order to manipulate the microbiota, a special microorganism may be taken orally or rectally into the body. The bacteria taken to the gut this way are called probiotics (Khanna and Tosh 2014).

There are lots of studies reporting the benefits of probiotics in depression treatment (Messaoudi et al. 2011; Messaoudi et al. 2011). In a study reviewing ten randomized controlled trials (RCT) published in the period of 1990–2016, it was found that probiotics have positive effects on depression and anxiety symptoms (Pirbaglou et al. 2016). Moreover, in a study conducted between 2005 and 2012 on 18,019 people, no relationship was found between probiotics and low depression rates (Cepeda et al. 2017). In another recent RCT, an 8-week long *Lactobacillus helveticus* and *Bifidobacterium longum* application was not found to be effective on depressive symptoms (Romijn et al. 2017). While more than 100 years has passed after the first usage of probiotic bacteria (lactic acid bacillus) in depression treatment (Phillips 1910), the effects of probiotics and prebiotics have not yet been cleared with all their details today.

17.4.2 Activated Charcoal

Activated charcoal is used in treatment of drug poisoning. It forms chelate by binding toxins and provides absorption from the gut. Similarly, it also binds toxins secreted by the microbiota and helps reduce GIS complaints (Fond et al. 2014).

While there is literature on its benefits in manic episode treatment (Hamdani et al. 2015), there is no literature on its usage in depression treatment.

17.4.3 Fecal Microbiota Transplantation

Fecal microbiota transplantation is transferring the stool of a healthy donor to the gut of the patients in order to repair the disrupted gut flora (Xu et al. 2015). The first known implementation was made in China in the fourth century (Zhang et al. 2012). The feces suspension call "yellow soup" was given to diarrhea patients orally. FMT did not appear in medicine in the following centuries. In modern medicine, it was first applied in a case of pseudomembranous enterocolitis in 1958 (Eiseman et al. 1958). Interestingly, it was 20 years later that Clostridium difficile caused this pseudomembranous enterocolitis case and others treated successfully via FMT (Bowden et al. 1981). Studies regarding the issue have grown like an avalanche in the last 35 years. Today, a large part of studies on FMT is related to treatment of *Clostridium* difficile infection (CDI). However, there is also a potential for usage in neuropsychiatric disorders (Evrensel and Ceylan 2016b).

There is no clinical study where FMT was used for depression treatment. Depression could be transferred via FMT in mice (Kelly et al. 2016). Similarly, depressive patients may be given microbiota with antidepressant properties via FMT. Healthy gut microbiota may be added onto unhealthy microbiota via FMT. This way, it may be expected that there will be benefits in neuropsychiatric disorders' treatment via immunological settings (Evrensel and Ceylan 2016a). Despite this expectation, much more evidence is needed to use FMT in depression.

17.4.4 Microbiota Transfer Therapy

MTT is a form of FMT with some changes (Hamilton et al. 2012; Kang et al. 2017). In this method, for 14 days, oral vancomycin (a nonabsorbable wide-spectrum antibiotic) is given to the patient. This way, the bacterial microbiota in the gut is eliminated to a large extent. After 12–24 h of starvation, the gut is cleaned via enema. Then recolonization is achieved via capsules containing standardized human gut microbiota (SHGM) (Kang et al. 2017). SHGM preparation is partially similar to FMT. Feces taken from healthy donors subjected to various immunologic, serologic, and metabolic tests are put into special capsule and frozen in minus 80° (Youngster et al. 2014). Before usage, it is left in minus 20° for 1–2 h and finally taken orally or rectally (Evrensel and Ceylan 2016a).

Conclusion

The microbiota-body relationship plays an important role in maintaining health and occurrence of diseases. The guest microorganisms in the human body are usually not pathogen but helpful. Symbiotic relationship with microorganisms starts in the intrauterine period. Microorganisms are most prevalently colonized in guts. Our food is also their food. The medication we take (especially antibiotics and antidepressants) also affects them. Unhealthy nutrition, alcohol, and drugs disrupt the gut microbiota composition and lead to dysbiosis. Intestinal epithelial permeability increases, and this causes leaky gut. Bacterial metabolites lead to immune and metabolic changes by entering the systemic circulation. Gut microbiota-led immune disorders play an important role in depression etiopathogenesis. Antidepressants affect not only neurons but also gut bacteria and change the microbiota composition by creating an antibiotic effect. Dysbiosis may be restored by probiotics, prebiotics, and FMT. "Psychobiotic antidepressant bacteria" could be defined in the future.

There are still several mysteries concerning the microbiota-brain axis despite all these striking discoveries.

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18 Modulating Microglial Activation As a Possible Therapeutic Target for Depression

Mina Sato-Kasai, Takahiro A. Kato, Masahiro Ohgidani, Hideki Horikawa, Yoshito Mizoguchi, Akira Monji, and Shigenobu Kanba

18.1 Introduction

Major depressive disorder (MDD) is a common psychiatric disorder of unknown etiology that will affect up to 20% of the population at some point in the individual's lifetime (Kessler et al. 2005). The monoamine hypothesis of depression has long been proposed due to some historical research that tricyclic antidepressants inhibit the reuptake of monoamine transmitters, thereby, presumably, increasing the concentration of monoamines available to interact with synaptic receptors (Coppen 1967). Recently, inflammation in the central nervous system (CNS) has been indicated to have a close relationship not only to neurodegenerative disorders but also to psychiatric disorders (Dowlati et al. 2010). Microglia play a major immunological/inflammatory role as a brain macrophage in the CNS (Kettenmann et al. 2011), and microglia are known to communicate with neurons and other glial cells such as astrocytes and oligodendrocytes (Kettenmann et al. 2011), and over-activation of microglia is suggested to induce brain damages via microglia-neuron interactions, which may be a key pathological mechanism of psychiatric disorders including depression (Kato et al. 2013b).

Postmortem studies have revealed microglial over-activation in the brain of patients with depression and schizophrenia, especially suicide patients (Steiner et al. 2013). A recent human positron emission tomography (PET) imaging study has revealed microglial over-activation in the brain of patients with depression (Setiawan et al. 2015). We have recently shown that reduction of plasma metabolites, linking to the kynurenine pathway such as kynurenine, kynurenate, and 3-hydroxykynurenine, is involved in severity of some depressive symptoms, especially suicidal ideation (Setoyama et al. 2016). The kynurenine pathway is strongly associated with the modulation of microglia and astrocytes in the brain, and abnormalities of the kynurenine pathway and glial maladaptive activation have recently been highlighted to understand the underlying pathophysiology of various psychiatric and/or stress-related conditions including depression (Muller 2014; Myint et al. 2013). Recent rodent studies have shown that both acute and chronic stress activate microglia (Hinwood et al. 2012; Hinwood et al. 2013; Tynan et al. 2010; Walker et al. 2013). We have reported that hippocampal tumor necrosis factor (TNF)-α level is significantly elevated after acute stress using the model of water-immersion resistant stress

M. Sato-Kasai • T.A. Kato (✉) • M. Ohgidani
H. Horikawa • S. Kanba
Department of Neuropsychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
e-mail: takahiro@npsych.med.kyushu-u.ac.jp

Y. Mizoguchi • A. Monji
Department of Psychiatry, Graduate School of Medical Sciences, Saga University, Saga, Japan

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(WIRS) in mice, suggesting that acute stress activates hippocampal microglia (Ohgidani et al. 2016). Chronic stress in rat model has also been reported to induce microglial activation in the prefrontal cortex (Hinwood et al. 2012), which is inhibited by minocycline, an antibiotic drug with microglial inhibitory effects (Hinwood et al. 2013).

We have long been proposing the possibility that microglial modulation may be a key target in the treatment of various psychiatric disorders especially depression and schizophrenia based on our findings from a series of in vitro studies regarding the effect of psychotropic drugs including antidepressants and antipsychotics on microglial activation (Bian et al. 2008; Horikawa et al. 2010; Kato et al. 2008, 2007, 2011b; Monji et al. 2009; Sato-Kasai et al. 2016; Seki et al. 2013). Herein, we briefly introduce up-to-date knowledge of these effects on microglia and discuss the relevant mechanisms.

18.2 Antidepressants

Recent blood biomarker studies have shown that C-reactive protein and/or pro-inflammatory cytokines are associated with severity of depressive symptoms and that these blood levels are normalized after symptomatic improvement (Anisman 2009; Dowlati et al. 2010; Kohler-Forsberg et al. 2017), suggesting that the altered immune function in the CNS is related to the pathophysiology of depression. Microglia play an important role in neuroinflammation (Kettenmann et al. 2011). A postmortem study revealed increased microglial densities in patients with depression who had committed suicide (Steiner et al. 2008, 2006). In addition, we have recently shown that some kynurenine pathway metabolites, which are associated with microglial modulation, are liked to depressive symptoms, especially suicidal ideation (Setoyama et al. 2016). These human data have suggested an association between microglial maladaptive activation and depressive symptoms especially suicide-related behaviors/thoughts.

On the other hand, in vitro studies using rodent microglial cells have shown that microglia are activated by lipopolysaccharide and/or interferon (IFN)-γ and produce pro-inflammatory cytokines and/or free radicals (Kato et al. 2011a, 2013c). IFN-γ is a typical Th1 cytokine, and some studies have indicated a link between depression and IFN-γ as shown in the finding that serotonin deficiency, which results from IFN-γ-induced indoleamine 2,3-dioxygenase activation, is related to suicide in patients with depression (Hurlock 2001; Schwarz et al. 2001). We have reported that selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and sertraline inhibit the production of nitric oxide (NO) and/or TNF-α from IFN-γ-activated microglial cells (Hashioka et al. 2007; Horikawa et al. 2010). Other researchers have revealed that various antidepressants, regardless of their classification (such as tricyclic antidepressants (TCAs) or SSRIs), inhibit the production of pro-inflammatory cytokines and/or free radicals from LPS/IFN-γ-activated microglial cells (Hwang et al. 2008; Lee et al. 2011; Liu et al. 2011).

The inhibitory effects of antidepressants on microglial activation have also been confirmed by rodent in vivo experiments. For example, imipramine has been reported to inhibit the expression of IL-6, IL-1β, and TNF-α in microglia from social defeat stress model mice and to inhibit the expression of CD11b in hippocampal microglia from rat chronic stress model (Ramirez and Sheridan 2016; Rossetti et al. 2016).

18.3 Minocycline

Minocycline is a second-generation semisynthetic tetracycline and a broad-spectrum tetracycline antibiotic drug, commonly used to treat infections of the respiratory tract, acne, and mild rheumatoid arthritis. Minocycline inhibits bacterial proliferation through the inhibition of protein synthesis. Minocycline easily crosses the blood-brain barrier and attenuates inflammation related to microglial activation (Henry et al. 2008; Yrjanheikki et al. 1998).

Minocycline has been suggested to inhibit the production of pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and INF-γ via the suppression of microglial proliferation/activation (Dean et al. 2012; Kim and Suh 2009) and inhibit the calcium reaction through ATP receptors in microglia, consequently leading to anti-inflammatory effects (Gilbert et al. 2016). It has also been reported that minocycline has antioxidant effects (Baptiste and Fehlings 2006; Morimoto et al. 2005). Animal models of psychiatric disorders including depression and schizophrenia have revealed that minocycline ameliorates behavioral abnormalities associated with each disorder through inhibiting microglial activation (Kim and Suh 2009; Zheng et al. 2015). Human studies have reported that minocycline improves depressive symptoms (Soczynska et al. 2012), and minocycline add-on therapy significantly improved both depressive and psychotic symptoms in psychotic depression (Miyaoka et al. 2012). Moreover, minocycline is also known to have therapeutic effects in schizophrenia (Chaudhry et al. 2012; Xiang et al. 2017). Interestingly, we have reported that minocycline may modulate human trusting behaviors and risk-taking behaviors in the trust game experiment for healthy male volunteers (Kato et al. 2013b, 2012; Watabe et al. 2012, 2013). However, the primary target of minocycline has yet to be fully elucidated, and further investigations should be conducted.

18.4 COX-2 Inhibitor

It is well known that prostaglandins are related to inflammation (Vane et al. 1998). Cyclooxygenase (COX) is a rate-controlling enzyme that catalyzes the synthesis of prostaglandins from arachidonic acid (Vane et al. 1998). There are two known COX isoforms, COX-1 which is constantly expressed in various tissues and COX-2 which is induced in inflammation. COX-2 is induced by various inflammatory mediators such as pro-inflammatory cytokines and growth factor, and the suppression of COX-2 has anti-inflammatory effects (Bartels and Leenders 2010; Minghetti 2004). COX-2 has been hypothesized to be involved in a variety of neurodegenerative diseases, such as multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease (Minghetti 2004). Interaction of microglial cells with apoptotic neurons has been reported to selectively promote COX-2 expression, and COX-2 may mediate microglial activation and may play a key role in amplifying the inflammatory response with toxic effects (Bartels and Leenders 2010; De Simone et al. 2004).

Rodent in vivo studies have shown that celecoxib, a selective COX-2 inhibitor, has anti-inflammatory effects, as evidenced by the attenuation of LPS-induced increases in the number of activated microglia and in the concentration of IL-1β in neonatal rat brains. In addition, the application of celecoxib has been reported to be involved in reducing systemic LPS exposure-induced dopaminergic neuronal dysfunction and in protection against LPS-induced sensorimotor behavioral abnormalities (Kaizaki et al. 2013).

COX-2 inhibitors have been suggested to have protective effects on neural cells via microglial suppression (Acarin et al. 2002; Choi et al. 2003), thus the regulation of COX-2 has been recognized as a candidate therapeutic target in psychiatric disorders. Interestingly, a meta-analysis study has revealed that celecoxib reduces depressive symptoms compared with placebo (Kohler et al. 2014). Further clinical trials are needed to judge the effectiveness of the COX-2 inhibitors in depression (Eyre et al. 2015). With regard to schizophrenia, meta-analysis studies have shown that the use of COX-2 inhibitors has beneficial effects, especially in early stages of the disease or in its initial manifestations (Muller 2013; Nitta et al. 2013; Sommer et al. 2012).

18.5 Serotonin

Serotonin has long been suggested to have links to various psychiatric disorders especially depression (Meltzer and Massey 2011). Serotonin has received growing attention in light of the effects

on neurons and synapses as neurotransmitters, while recent studies have suggested the direct effects on microglia. Serotonin receptors in microglia have been shown to regulate microglial activities (Kettenmann et al. 2011). The expressions of serotonin receptors, such as 5-HT1 (1a and 1f), 5-HT2 (2a, 2b and 2c), 5-HT5a, and 5-HT7 receptors, have been identified in murine microglial cells (Krabbe et al. 2012). A rodent study has reported that 5-HT increases microglia motility toward a laser injury and decreases phagocytic capacities of amoeboid microglia (Krabbe et al. 2012). Another in vitro study has suggested that serotonin does not inhibit the production of TNF-α from LPS-stimulated microglial cells and did not show anti-inflammatory effects (Tynan et al. 2012). On the other hand, Glebov et al. have reported that 5-HT2a, 2b, and 5-HT4 receptors are expressed in mouse primary microglia and BV2 microglial cells, and their functions have been implicated in exosome secretion, which is considered to be involved in secretion of certain cytokines, by microglia (Glebov et al. 2015). A recent study has shown that microglial 5-HT2b receptors could be involved in various functions such as modulation of microglia extensions, chemoattraction, and phagocytic capacities during brain development (Kolodziejczak et al. 2015). Further studies are required to investigate interactions between serotonin and microglia.

18.6 Noradrenaline

Noradrenaline has been reported to have suppressive effects on microglial cells (Ishii et al. 2015). Microglial cells are known to express adrenergic receptors (Mori et al. 2002), and especially β2 receptors are regarded to play a critical role in microglial activation (Farmer and Pugin 2000; Markus et al. 2010; McNamee et al. 2010; Qian et al. 2009). An in vitro study has shown that noradrenaline inhibits LPS-induced NO production, via activation of β2 receptors with elevation of intracellular cAMP (Dello Russo et al. 2004). Noradrenaline has been shown to have neuroprotective effects in LPS-treated neuron-microglia cocultures by suppressing iNOS expression, NF-κB nuclear translocation in microglial cells, and the subsequent phosphorylation of signal transducer and activator of transcription 1 (Ishii et al. 2015). An in vivo study has revealed that microglia respond to cell death by extending their processes toward ATP released at the site of damage and that noradrenaline induces process retraction in resting and activated microglia through β2 and α2A receptors, respectively (Gyoneva and Traynelis 2013). In addition, cortical microglial inflammatory responses are reported to be increased when noradrenaline levels are depleted, suggesting that noradrenaline can reduce microglial activation (Madrigal et al. 2005). A recent study has demonstrated that noradrenaline depletion enhances LPS-induced dopaminergic neuron loss in the substantia nigra and that noradrenaline inhibits NADPH oxidase 2 (NOX2)-generated superoxide, which contributes to the anti-inflammatory, anti-oxidative, and neuroprotective effects of noradrenaline (Jiang et al. 2015).

18.7 Aripiprazole and Fingolimod

Based on a series of rodent in vitro experiments, we have demonstrated that various psychotropic drugs, including antipsychotics and antidepressants, generally have suppressive effects on microglial activation (Bian et al. 2008; Hashioka et al. 2007; Horikawa et al. 2010; Kato et al. 2008, 2007, 2011b; Seki et al. 2013). However, the intracellular mechanisms of effects of such psychotropic drugs have not been well elucidated. Just recently, we have reported one possible inhibitory mechanism of aripiprazole, a unique antipsychotic drug (Sato-Kasai et al. 2016). Aripiprazole is mainly used as an atypical antipsychotic drug and also has therapeutic effects on mood disorders including both depression and bipolar disorders (Kamijima et al. 2013; Weber et al. 2008). Furthermore, our previous rodent in vitro studies have suggested that aripiprazole is the most effective antipsychotic, which directly and significantly inhibits microglial activation (Kato et al. 2011b; Seki et al. 2013). In

addition, our coculture experiments have shown that microglial over-activation induces cellular damages of neurons and/or oligodendrocytes, and aripiprazole can mimic these damages in the process of neuron-glia communication (Kato et al. 2011b; Seki et al. 2013).

We have recently hypothesized a possible mechanism responsible for inhibitory actions of aripiprazole on microglia using a typical activator of microglial cells, polyinosinic-polycytidylic acid (polyI:C or Toll-like receptor 3 ligand) (Sato-Kasai et al. 2016). PolyI:C has recently been used as an appropriate animal model of psychiatric disorders to generate psychosis-related behavioral abnormalities and depressive-like behaviors (Chijiwa et al. 2015; Piontkewitz et al. 2009). Using the polyI:C-induced rodent microglial cells, we conducted in vitro experiments focusing on intracellular Ca^{2+} signaling which is important for the regulation of microglial activation (Sato-Kasai et al. 2016). We have revealed that polyI:C consistently increased intracellular Ca^{2+} concentration ($[Ca^{2+}]i$) in murine microglial cells by influx of extracellular Ca^{2+}, and polyI:C activates microglia via transient receptor potential melastatin 7 (TRPM7) channels, using the specific TRPM7 inhibitor, FTY720 (fingolimod). Aripiprazole and fingolimod significantly suppressed the polyI:C-induced microglial activation. In addition, aripiprazole attenuated polyI:C-induced sustained $[Ca^{2+}]i$ elevation and the mRNA expression of TRPM7 channels in murine microglia, suggesting that the inhibitory effects of aripiprazole on polyI:C-induced microglial activation may be partially mediated by its effect on TRPM7 channels (Sato-Kasai et al. 2016). The TRPM7 inhibitor, FTY720 (fingolimod), is now clinically applied as a novel drug for the treatment of multiple sclerosis (Brinkmann et al. 2010; Cohen et al. 2010). Interestingly, depression is frequent in people with multiple sclerosis (Marrie et al. 2015), and a study in mice has suggested that fingolimod may have an antidepressant effect, reducing the immobility time in the forced swim test (di Nuzzo et al. 2015). Now, we are proposing that TRPM7 may be a novel therapeutic target for psychiatric disorders especially depression and schizophrenia. Figure 18.1 shows the possible intracellular mechanisms of aripiprazole, fingolimod, and other psychotropic drugs that may act on microglia. Further studies to examine molecular mechanisms and translational studies to confirm the effects in human are needed.

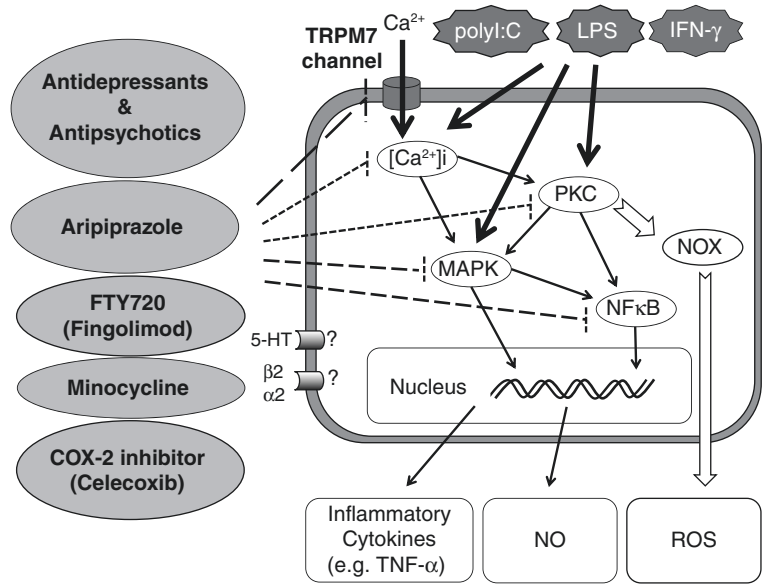

Fig. 18.1 Possible intracellular mechanisms of microglia-targeting drugs. (Modified from Kato et al. Curr Med Chem 2013)

18.8 Microglia Hypothesis of Psychiatric Disorders Including Depression

Therapeutic targets of psychiatric disorders have long been regarded to be within neuronal networks including synapses and neurotransmitters, thus psychotropic drugs have dominantly been understood only to affect neurons or neural networks (Kato et al. 2013b, 2013c). Recently, as shown above, microglia have received increased attention, and a series of rodent studies have suggested that psychotropic drugs including antidepressants and antipsychotics act on microglia, leading to anti-inflammatory effects via the suppression of microglial activation. Interestingly, a recent randomized controlled trial has shown that infliximab, a TNF-α antagonist, ameliorates depressive symptoms in patients with high levels of inflammatory biomarkers, high-sensitivity C-reactive protein (hs-CRP) (Raison et al. 2013), suggesting that immunosuppressive drugs may be therapeutic targets for depression. Based on such evidence, we have been proposing the microglia hypothesis of psychiatric disorders that modulating microglia may be a key target in the treatment of various psychiatric disorders including depression (Fig. 18.2) (Kato et al. 2013a, 2011a, 2013c; Monji et al. 2009, 2013).

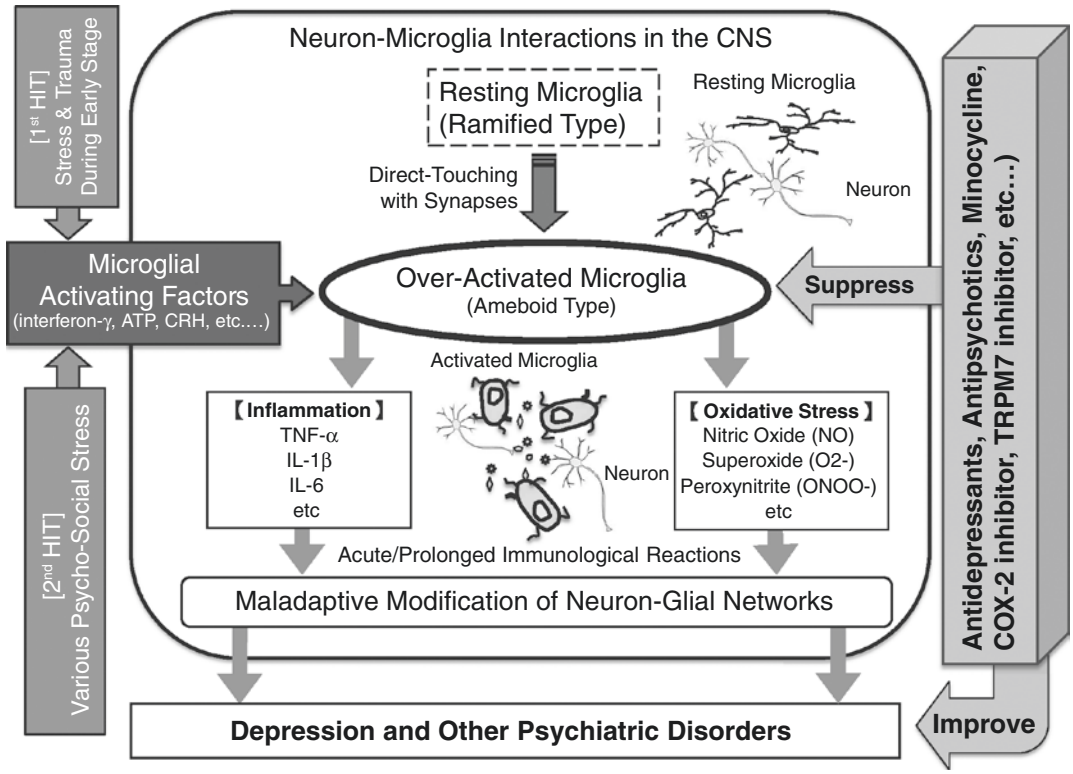

Fig. 18.2 Microglia hypothesis of depression and other psychiatric disorders. (Modified from Kato et al. Curr Med Chem 2013)

18.9 Future Perspective-A Novel Translational Approach Using iMG Cells

To verify this hypothesis, translational research using both animal models and clinical trials for patients with psychiatric disorders should be conducted. In our lab, we have recently developed a unique technique to create directly induced microglial-like (iMG) cells from human peripheral blood (monocytes) within 2 weeks with two cytokines (GM-CSF and IL-34) and have started to employ this tool as the center of a novel translational research technique (Ohgidani et al. 2014). We suppose that iMG cells may express different activated patterns based on diagnosis, pathophysiology, and symptom severity in each patient and may show different responses to psychotropic drugs including antidepressants. Our preliminary study has revealed that iMG cells show different responses to aripiprazole between healthy volunteers (Sato-Kasai et al. 2016). We generated iMG cells from three healthy volunteers (Ms. A, B, and C) and examined whether or not the cells could be activated by polyI:C and how aripiprazole and FTY720 affected this activation. Aripiprazole inhibited this increase in iMG cells from two of the three individuals but not from one individual (Sato-Kasai et al. 2016). Thus, iMG cells may be useful as a tool for predicting drug responsiveness before actual treatments and, in diagnosis, consequently leading to tailored therapies in the future (Ohgidani et al. 2015). On the other hand, as another pilot study, we have recently analyzed gene profiling patterns of iMG cells from three patients with rapid cycling bipolar disorder during both manic and depressive states, respectively (Ohgidani et al. 2017). We revealed that the gene profiling patterns are different between manic and depressive states. The profiling pattern of one case showed that M1 microglia is dominant in the manic state compared to the depressive state. CD206, a mannose receptor known as a typical M2 marker, was significantly downregulated in the manic state among all three patients. This pilot study indicates the importance of shifting microglial M1/M2 characteristics, especially the CD206 gene expression pattern between depressive and manic states (Ohgidani et al. 2017). We believe that such novel translational research using iMG technique will be helpful for exploring the operation of human microglia that are considered to play an important role in psychiatric disorders (Ohgidani et al. 2015).

Conclusion

In this brief review article, we have shown up-to-date knowledge about the effects of psychotropic drugs, especially aripiprazole, on microglial modulation and the relationship between microglia and neurotransmitters such as serotonin and noradrenaline. Finally, we have introduced a novel translational research tool, iMG cells, from human peripheral blood. Further translational studies combining human clinical studies and animal experiences are needed to dig up the microglial roles in the underlying biological mechanisms of depression and other psychiatric disorders.

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19 Experimental Animal Models for Depressive Disorders: Relevance to Drug Discovery

Boldizsár Czéh, Ove Wiborg, and Eberhard Fuchs

19.1 Introduction

Depressive disorders are characterized by a substantial disturbance in persistent emotional state or mood. In the category of depressive disorders, the following illnesses are included: disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance-/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder (for details see the DSM-5 diagnostic manual). Because most of the currently available animal models aim to mimic major depressive disorder, thus, in this chapter we will focus only on these.

Major depressive disorder (MDD) is a severe mental disorder affecting millions of people worldwide (Kessler and Bromet 2013). According to a recent WHO analysis, depression will be the leading cause of disease burden globally by 2030 (WHO report EB130/9 2011). Effective therapeutic interventions are available, but the currently existing antidepressant treatments are far from being optimal, and there is an urgent need for new, faster-acting, more effective drugs and also for preventive treatment strategies.

Despite extensive research efforts, the pathophysiology of mood disorders remains unresolved. The first effective antidepressant drugs were discovered only by serendipity. Hydrazine derivatives (e.g., isoniazid, iproniazid) were originally developed for the treatment of tuberculosis and only by coincidence were found to have euphoric effects (Ramachandraih et al. 2011). These compounds were the first nonselective, irreversible monoamine oxidase inhibitors (MAOIs). The first tricyclic antidepressants, most prominently imipramine, were derived from antihistaminic compounds. At the beginning, the mood-elevating characteristics of these drugs were viewed with great skepticism among doctors, but then, in the 1950s, together with the discovery of chlorpromazine, they revolutionized the treatment possibilities of mental disorders (Healy 1999). The tricyclic antidepressants, which are believed to act by inhibiting the plasma membrane transporters of serotonin and/or norepinephrine, provided a template for the development of the modern-day classes of antidepressants, such as the selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (NRIs), and dual serotonin/noradrenaline reuptake inhibitors (SNRIs).

B. Czéh (✉)
MTA – PTE, Neurobiology of Stress Research Group, Szentágothai Research Center, Pécs, Hungary

Institute of Laboratory Medicine, University of Pécs, Medical School, Pécs, Hungary
e-mail: czeh.boldizsar@pte.hu

O. Wiborg
Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

E. Fuchs
German Primate Center, Leibniz Institute for Primate Research, Göttingen, Germany

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These discoveries led to the development of the monoamine theory which was formulated in the 1960s as an explanation for the pathophysiology of depressive disorders. Since then, numerous limitations of the monoamine theory have been revealed, and the more recent concepts emphasize the involvement of various other neurotransmitter systems, as well as changes of neuroplasticity in limbic brain areas, epigenetic mechanisms, dysregulation of the hypothalamic-pituitary-adrenal axis, potential inflammatory mechanisms, or even the disturbances of gut microbiota.

According to our present comprehension, MDD develops as a result of interactions between a genetic predisposition and environmental factors. The depressive episodes are typically triggered by psychosocial stressors (Klengel and Binder 2013; Mandelli and Serretti 2013). Having this in mind, most of the currently available experimental models either apply some kind of genetic manipulation or use an environmental stressor to generate animals with a behavioral phenotype that resemble to the symptoms of MDD. But there are other models as well, such as the olfactory bulbectomy model, the learned helplessness model, the selective breeding models, or the drug-withdrawal-induced anhedonia model (for more details see, e.g., Czéh et al. 2016).

Typically animal models for depressive disorders are used for the following two purposes: (1) to understand the pathophysiology of the illness and (2) to develop new treatment strategies (Willner 1997, 1984; Cryan et al. 2002; Willner and Mitchell 2002; Cryan and Holmes 2005; Cryan et al. 2005a, b; Berton and Nestler 2006; Nestler and Hyman 2010; Berton et al. 2012; Bouwknecht 2015; Willner and Belzung 2015; Czéh et al. 2016). Academic scientists usually aim to provide insight into the underlying neurobiology of the disorder, and therefore they tend to apply more complex and time-consuming models, e.g., they generate a new transgenic animal or use a chronic stress model to mimic some aspects of the etiological factors (Willner 1997, 1984, 2005, 2016a, b; Cryan and Mombereau 2004; Anisman and Matheson 2005; Pryce and Fuchs 2016). Drug companies are interested in developing new drugs; therefore, on one hand they are always open to new and expensive technologies; on the other hand, they need simple, high-throughput, and reliable behavioral models for compound screening (Berton and Nestler 2006; Cryan and Slattery 2007). Notably, the pharmaceutical industry has become severely disappointed during the recent years because of their lack of success in the development of new drugs for the treatment of mental disorders. They have condemned mental disorders as a challenge that is "too difficult" to attract major investment (Hyman 2014). We have to face the fact that the traditional expectation on antidepressant development has collapsed. In other words, it is now believed that it is unlikely that we can find new "druggable" targets in the brain (e.g., receptors or transporters), and then, based on that finding, we can develop new pharmaceutical agents to rectify the neuronal (or glial) dysfunctions. Although exceptions do exist, see, for example, the recent discovery of agomelatine, the first melatonergic antidepressant (de Bodinat et al. 2010). In sum, experts suggest that a radical paradigm switch is needed in the field of antidepressant drug research, if we really want to step forward (Insel et al. 2013).

19.2 Criteria for Valid Animal Models of Depression

Numerous attempts have been made to create animal models of depression and several criteria for their evaluation have been established. The most widely cited criteria were developed by McKinney and Bunney nearly 50 years ago (McKinney and Bunney 1969). The authors proposed the following minimum requirements for an animal model of depression: (1) it is "reasonably analogous" to the human disorder in its manifestations or symptomatology; (2) there is a behavioral change that can be monitored objectively; (3) the behavioral changes observed should be reversed by the same treatment modalities that are effective in humans; and (4) it should

be reproducible between investigators. Later Willner (1984) formulated that a valid animal model for depression should have three major criteria: face validity, predictive validity, and construct validity. *Face validity* describes the similarity between the behavioral phenotype and the clinical symptom profile. For *predictive validity* the amelioration or attenuation of the symptoms by clinical effective antidepressant treatments and, conversely, absence of changes by clinically ineffective treatment of the human disorder is required. For the criterion *construct validity*, similar neurobiological underpinnings are required. The fourth criterion, *etiological validity*, was originally introduced by Abramson and Seligman (1977) and states the triggering events that are known to be important for eliciting the human disorder should be the same used in animals. Unfortunately, none of the currently available animal models fulfills these four criteria completely. There are complex models that replicate some symptoms of MDD and a few simple behavioral "screens" (such as the forced swimming test) that have been useful for testing the efficacy of a specific group of antidepressant compounds (viz., the SSRIs).

19.3 Animal Models for Understanding the Pathophysiology of Major Depressive Disorder

Numerous different models are used in preclinical research (for details, see e.g., Willner 1997, 1984; Cryan et al. 2002; Willner and Mitchell 2002; Cryan and Holmes 2005; Cryan et al. 2005a,b; Berton and Nestler 2006; Nestler and Hyman 2010; Berton et al. 2012; Bouwknecht 2015; Willner and Belzung 2015; Czéh et al. 2016). Due to the space limitations, we can only briefly summarize here the most commonly used models and the most interesting recent developments. We recommend that the reader should look up the cited excellent reviews for more detailed descriptions on these models.

19.3.1 Genetic and Optogenetic Models

The production of genetically engineered mouse lines gives us the possibility to investigate the consequences of silencing or overexpressing specific genes that are thought to contribute to the pathophysiology of the disease. There are two possibilities: forward or reverse genetics. Forward genetics is an unbiased approach in which a large number of random mutations are generated in an organism (e.g., mice) using simple mutagenic techniques, followed by breeding and screening for individuals with the desired depressive-like behavioral phenotype. Afterward the responsible gene can be identified. Typically, the reverse genetic approach is used which means targeted genetic manipulations that result in either loss- or gain-of-function mutants. "Knockout mice" are the most well-known examples, in which a specific target gene is disrupted, resulting in a loss-of-function mutant. Conversely, gain-of-function mutant mice carry additional copies of a specific gene in their genome or have been generated by knock-in techniques. There is a continuous and rapid development of technologies in this field, for example, the discovery of conditional strategies (Branda and Dymecki 2004) or the development of new genome editing tools, for example, ones that are based on CRISPR-Cas systems (Heidenreich and Zhang 2016).

In the beginning, most genetic models focused on the key players of the monoaminergic neurotransmission and generated, for example, the 5-HT1A receptor knockout mouse model (Heisler et al. 1998; Parks et al. 1998; Ramboz et al. 1998) or the noradrenaline transporter knockout mouse model (Xu et al. 2000). Later models targeted the regulators of the HPA-axis and produced corticotropin-releasing hormone receptor-1 (CRH-R1) knockout mice (Timpl et al. 1998; Müller et al. 2003; Refojo et al. 2011) or the type II glucocorticoid receptor knockout mouse model (Pepin et al. 1992; Montkowski et al. 1995). More recently, the epigenetic events have been in the focus of investigations on the genetic back-

ground of depressive disorders. Numerous data imply that transcriptional dysregulations may contribute to the behavioral manifestations of many psychiatric disorders, including major depression (Tsankova et al. 2007; Sun et al. 2013; Nestler 2014), and the very recent knockout mouse models were generated to prove that. For example, the demonstration that mutation in the gene of a chromatin modifier (Kdm5c gene) results in impaired social behavior, memory deficits, and aggression and that Kdm5c-knockout mouse brains exhibit abnormal dendritic arborization and spine anomalies (Iwase et al. 2016). Others emphasize the role of environmental stressors in epigenetic plasticity (Nasca et al. 2015).

Technical progress in molecular biology has led to the development of a wide array of methods that enable the blockade or stimulation of neuronal activity with high anatomical, genetic, and temporal precision. For a brief overview of these techniques, see, e.g., www.openoptogenetics.org or recent reviews (e.g., Kim et al. 2017; Jazayeri and Afraz 2017). Optogenetic tools have been applied to investigate the neurobiology of various mental disorders (for review, see, e.g., Steinberg et al. 2015; Marton and Sohal 2016) including depressive disorders (Chaudhury et al. 2013; Tye et al. 2013; Proulx et al. 2014). There are high expectations in the optogenetic toolkit since this approach may—in the long term—lead to the development of truly novel treatment strategies for depressive disorders (Covington et al. 2010; Friedman et al. 2014).

19.3.2 Animal Models Based on Stress

Stress—the physiological response to an environmental challenge—is a fundamental scientific, clinical, and societal concept, which was initially described by Hans Selye some 80 years ago (Selye 1936; Fink 2016). Today we know that repeated, or chronic stress, is an important risk factor for numerous affective and somatic disorders. The substantial evidence showing that chronic stress can increase the likelihood of major depressive disorder and anxiety disorders served as building block for the stress hypothesis of mood and anxiety disorders (e.g., Gold 2015). In consequence, this hypothesis has stimulated the development of a number of experimental manipulations of the environment in animals, with the aim of causing changes in behavior and brain that have relevance to stress-related psychopathologies in humans (for recent reviews, see, e.g., Nestler and Hyman 2010; Slattery and Cryan 2014). Consequently, we will focus here on the stressors rather than the stress response.

It is believed that psychosocial stress paradigms are more relevant to the human situation than nonsocial stress paradigms, because the vast majority of stressors reported by patients suffering from psychiatric disorders are social in nature (Keller et al. 2007). Therefore, there is a growing consensus that social stress paradigms are better placed to reveal the behavioral, neuroendocrine, or immunological mechanisms underlying chronic stress-induced pathology. However, in order to maximize our understanding of the mechanisms underlying stress-related disorders, various different models are necessary, including models employing neurogenic pain (e.g., painful stimuli such as foot shock) or pharmacological (e.g., corticosterone) stressors (Reber and Slattery 2016). These stressors are not in the focus of this chapter; instead this chapter comprises contributions that focus on psychogenic stressors.

19.3.2.1 Models Based on Social Stress

The social environment is a considerable source of stressors, and the two processes of fighting for control and losing control are of central importance to the psychosocial situation of individuals (Barnett 1958, 1964). Loss of rank, social status, and/or control are examples of the more general class of loss events, which are increasingly recognized as a characteristic of risk factors for major depressive disorder (Brown 1993; Keller et al. 2007). Based on these ideas, new animal models were established using social perturba-

tions as stressors and have been validated. These models have heuristic value because they investigate the environmental challenges that an animal may meet in its everyday life. In social settings, this might mean loss of control by social defeat.

The resident-intruder paradigm, which is specific to rodents, is the most popular model of social defeat/stress and uses social conflict between members of the same species to generate emotional psychological stress. Classically, in this experimental setting, a male, the intruder, is transferred into the home cage of another male, the resident. If the animals are allowed to fight on a single occasion, it is regarded as an acute stress exposure; if the intruder is exposed to the resident at several occasions, ranging from days to even weeks, it is regarded as a model of chronic stress. In some models, the intruder is transferred to the cage of a singly housed resident, whereas in other cases, the intruder replaces a cohabitating female in the resident's cage. In all settings, the intruder is quickly attacked and subjugated. After the physical exposure, the intruder is often placed in a small protective cage before being returned to its home cage. In the protective cage, the animal is exposed to stressful psychogenic signals that are emitted by the resident, without experiencing physical harm. For a more comprehensive review of the different social defeat protocols in mice and rats, we refer the reader to the recent review by Hollis and Kabbaj (2014).

In various laboratory settings, this approach works well when male individuals are being investigated. Until recently, it was thought that this approach does not work in female rodents because they do not fight with each other in a resident-intruder paradigm (Palanza 2001). However, recent studies have demonstrated social defeat in female rats when using older, lactating individuals as residents (Holly et al. 2012). An interesting finding was reported by Jacobson-Pick et al. (2013), who showed that in female mice, the stress-induced behavioral effects were more pronounced 2 weeks after exposure to the stress than they were 2 h afterward.

As pointed out by Koolhaas et al. (1997), social defeat is a special kind of stressor and distinguishes itself from other stress paradigms with respect to the magnitude and the quality of the stress response. Moreover, it should be emphasized that social defeat induces changes in a variety of physiological and biochemical parameters, each of which may have different temporal dynamics (Koolhaas et al. 2016). In this context, it should be mentioned that the diurnal time point of exposure to a stressor is also critical. Mice subjected to chronic social defeat stress during the active phase developed more pathophysiological signs compared with those subjected to stress during the inactive phase (Bartlang et al. 2012).

19.3.2.2 The Chronic Mild Stress Model

The chronic mild stress (CMS) model is recognized as an extensively validated depression model with high translational potential (Willner 1997, 2005, 2016a). There are several different names (mild, unpredictable, variable stress) for the model, but they refer essentially to similar protocols. Typically, rats or mice are exposed to a number of mild stressors in an unpredictable order for several weeks, and over time they reduce voluntary intake of rewards (Wiborg 2013). This is interpreted as a decreased motivation, or reduced sensitivity, for rewards and believed to be the biological underpinning for anhedonia, the cardinal depression symptom in humans. In addition to realistic inducing conditions, important disease characteristics of MDD, like the chronic and episodic nature of the disease, make the CMS model one of the most realistic animal models of depression; once stressors are discontinued, animals recover spontaneously.

Sucrose intake is mainly applied as a readout on anhedonic-like behavior, and when using an outbred rat strain, animals show an individual and graduated stress response, some become anhedonic-like, while others cope with the applied stressors in order to maintain homeostasis (Bergström et al. 2008). This is an additional advantageous feature of the model allowing for studies on stress-resilience mechanisms. If stress exposure is combined with chronic antidepres-

sant administration, a subgroup of the anhedonic-like rats recovers over time; however, a substantial fraction of the rats do not respond to treatment, corresponding to clinical treatment refraction (Christensen et al. 2012). The treatment responses represent additional interesting features of the model allowing for addressing antidepressant drug efficacy as well as time point for onset of action, which are both key issues in the development of novel antidepressant medication. In addition to anhedonic-like behavior, the chronic stress paradigm also induces long-lasting changes in behavioral, neurochemical, neuroimmune, and neuroendocrinological parameters resembling dysfunctions observed in depressed patients (Willner 1997, 2005; Wiborg 2013).

19.3.2.3 Models Based on Early-Life Stress

Early-life stress models are based on the observation that unfavorable events and experiences that occur during this critical developmental period of early life may cause a vulnerability for developing various types of diseases in later life. The models are based on initial studies performed in rodents (Weininger 1953; Levine 1957, 1967) and in nonhuman primates (Harlow and Zimmermann 1959).

Over recent decades, evidence from epidemiological studies has indicated that prenatal (fetal) and/or postnatal (infant/child) environmental factors are associated substantially with the etiology of neuropsychiatric disorders. Negative experiences in early life, such as parental loss, abuse, and emotional and physical neglect, significantly increase the risk of developing an affective disorder later in life (for review, see, e.g., Heim and Nemeroff 1999; Heim et al. 2010; Lanius et al. 2010; Heim and Binder 2012; Mandelli et al. 2015).

To date, many experimental approaches aimed at inducing early-life stress in rodents and nonhuman primates at critical developmental periods have been described. Many of these manipulations produce physiological and behavioral changes that persist well into adulthood and represent a risk factor for psychopathology (see, e.g., Newport et al. 2002; Pryce et al. 2005).

Maternal separation is an experimental procedure that is used widely in this context. Many studies performed in rats have shown that a single or repeated separation of the pups from the mother leads to acute or long-term effects on physiology and behavior. Although maternal separation is the most common model of disruption of the mother-offspring relationship, the reports of its effects show contradictory findings for almost all parameters investigated (for review, see, e.g., Daly 1973; Lehmann and Feldon 2000). A possible explanation for this inconsistency may be that maternal separation has become a collective term for a variety of extremely different experimental manipulations (Lehmann and Feldon 2000). For example, the maternal deprivation stress, as a model for parental neglect, induces long-lasting structural and functional consequences (e.g., Oomen et al. 2010, 2011). In contrast the repeated maternal separation model promotes and increases the extent of maternal care. Obviously it is less stressful for the pups (Enthoven et al. 2008; Schmidt et al. 2011) and thus often results in opposite effects compared to the deprivation models. Interestingly, in a recent comprehensive review of this issue, Schmidt and colleagues question the validity of early-life stress paradigms such as maternal separation—at least in rodents—as robust models of depression (Schmidt et al. 2011). Based on the literature available, those authors conclude that future studies should investigate the extent to which the interplay between genetic predisposition and aversive or nonaversive stimuli in adulthood determines the outcome of early-stress experiences in later life challenges.

Recently, a chronic early-life stress model has been also developed which has both acute and long-lasting effects on the HPA system as well as on cognitive functions in adulthood. In this model the dam-pup interaction is disrupted by limiting the nesting and bedding material of the cages which results in abnormal, fragmented dam-pup interactions. Rearing pups in this stress-provoking environment has long-lasting effects, e.g., impaired hippocampus-dependent learning and

memory functions as well as reduced survival of adult-born neurons (Rice et al. 2008; Naninck et al. 2015).

19.3.2.4 Simple Screening Tests or "Acute Behavioral Despair Models"

The development of animal models for depression has been strongly influenced by the needs and goals of the pharmaceutical industry. Their principal objective is the discovery of drugs that are faster acting or more effective and/or safer than the already existing ones. These aims impose pragmatic constraints on the experimental designs. Drug development requires simple and reliable behavioral tests that can screen for the activity of a large number of compounds rapidly. Exactly for this purpose, tests have been developed, which are typically called "behavioral despair models." These are actually simple models in which animals are subjected to an acute stressful situation, for example, they are immersed into water (forced swim test) or suspended by their tails (tail suspension test) (Porsolt et al. 1977a,b, Lucki 1997; Cryan et al. 2005a,b). In these tests, the animals either struggle or they become immobile, and then these behaviors are interpreted as "active coping" or "behavioral despair." These tests have been repeatedly criticized that immobility simply demonstrates a positive behavioral adaption in order to save energy and swimming is a reflex when animals are immersed in water. These tests proved to be valuable tools when researchers developed the selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitors (SNRIs) (Lucki 1997; Cryan et al. 2005a,b). The problem is that these tests are increasingly used to demonstrate a "depressive-like" behavior of animals that has been exposed to stress and/or genetic modifications (Barkus 2013). This is an erroneous practice because experts of this field repeatedly point out that the behavioral response to a forced swim stressor does not reflect depressive behavior (e.g., de Kloet and Molendijk 2016).

19.4 Animal Models in Drug Discovery: Needs and Pitfalls

During the recent decades, we experienced a severe disappointment in the usefulness of animal models for the development of novel antidepressant drugs. On several occasions, pharmacological targets which were strongly supported by data from rodent models failed to show convincing results when tested in clinical trials. A careful analysis of the literature revealed that in some cases, clinical efficacy has been predicted on the basis of inappropriate animal models, or some clinical trials have not targeted the appropriate dose or clinical population (Belzung 2014). To avoid such disappointments, experts of this field repeatedly point out that we should preferably use more complex animal models (Peters et al. 2015) that involve species that have better homological validity and we should try to model subtypes of depression. Compounds under development should be tested in various models, and not only their behavioral effects should be investigated, but one should measure other biomarkers as well, for example, neuroendocrine changes or functional and morphological changes in relevant brain areas (Rupniak 2003). Another problem that should be solved in the future is that many research groups make modifications on the original protocol of the complex models which then leads to a confusing variability in the experimental outcomes between research groups using the same models (Yin et al. 2016).

In summary, we should emphasize the following points: (1) in vivo models will keep their important role in drug discovery, simply because these models are still more realistic than the in silico and in vitro models; (2) the studies should be properly designed with sufficient sample sizes, analyzed by appropriate statistical tests, and the conclusions should be data-driven; and (3) there is no perfect model and specific needs require specific models (see, e.g., Willner and Belzung 2015).

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20 The Use of Animal Models in Defining Antidepressant Response: A Translational Approach

Michel Bourin

20.1 Introduction

Animal models are an important topic of preclinical research on neurobiology of psychiatric disorders and help in screening putative drugs for treating the disorder and permit a better comprehension of mechanisms implicated. The choice of the most appropriate animal model according to the condition to be studied is delicate and fundamental in order to be able to validate the extrapolation that will be made to the man afterwards. The ideal animal model would not only replicate the essential features of depression but also reliably predict antidepressant activity in a novel compound. However, an animal model in psychopharmacology must be able to predict the validity of the action of the substance studied in the pathology considered. Moreover, what is considered by the face validity must show similarities or other behaviours between the animal model and the disease that it wants to represent. Finally, construct validity must demonstrate the theoretical rationality of the model (Willner 1984). Animal models cannot take into account all aspects of a mental illness, depression any more than another one. Animal models of depression can take into account one or more symptoms of the disease, such as anhedonia, the retardation or certain biochemical deficiencies caused by the illness.

Observation of symptoms presented in patients presenting with depression has led to various hypotheses concerning the aetiology of depression. Among these hypotheses researchers have built animal models given corresponding more or less to the core symptoms of depression. The existing antidepressants, mainly the tricyclic drugs at that time, were used to define the models. Thus, some models of depression have been constructed according to the mechanism of action of tricyclic antidepressants which are supposed to increase noradrenaline (NA), serotonin (5-HT) or dopamine (DA) in the synaptic cleft. This theory has been modified to take into account the adaptation of receptors which appear to correlate with the onset of the antidepressant response and the action of antidepressants in blocking the inhibitory feedback, their action at the second messenger level as well as a postsynaptic action (Bourin and Baker 1996).

In the absence of spontaneously depressed animals, psychopharmacologists have used pharmacological interactions, stress models or brain damage models to predict such an activity. Historically, pharmacological interactions were used to predict antidepressant activity (Bourin 1990). The antagonism of the effects of reserpine was one of the first depression models used (Costa et al. 1960). Reserpine depletes central stores of 5-HT, NA and DA via blockade of

M. Bourin
Neurobiology of Anxiety and Mood Disorders, University of Nantes, Nantes, France
e-mail: michel.bourin@univ-nantes.fr

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uptake into vesicles, and drugs are assumed to reverse reserpine-induced symptoms by elevating the intersynaptic concentrations of these amines. Different parameters were measured (Bourin et al. 1983), e.g. antagonism of hypothermia, ptosis and antagonism of reduced motor activity. This pharmacological interaction model was abandoned due to its lack of specificity for an antidepressant effect and its sensitivity to non-antidepressant drugs (Willner 1984). Other pharmacological models were used: the antagonism of oxotremorine-induced effects, the antagonism of high-dose apomorphine (Puech et al. 1981) and the yohimbine test (Quinton 1963). But in the mid-1970s, the behavioural animal models of depression replaced the pharmacological interaction methods. Among the animal models used in screening antidepressant activity, we have chosen to discuss the following rodent behavioural models, the forced swimming test (FST) (Porsolt et al. 1977), the tail suspension test (TST) (Steru et al. 1985), the chronic mild stress model (CMS) (Willner et al. 1992), the learned helplessness (LH) model (Seligman et al. 1975) and one paradigm based on neuronal deficits, the olfactory bulbectomy (OB) (Cairncross et al. 1977), as they are the most commonly utilised models.

20.2 Description of the More Frequently Used Models in Depression

20.2.1 Stress Models

The hypothesis that chronic stress can induce depression is questionable. It seems that vulnerability to depression in humans could be compared to behavioural conditions induced by stress in animals. It has been shown that chronic stress causes an increase in stress hormone cortisol and that in parallel it decreases 5-HT and DA and probably other important neurotransmitters in the depressive symptom. In fact clinical symptoms of depression in human are more complex than those induced by stress which is more in the field of anxiety. The rodent models of anxiety are more built on fear. Animal models based on the hypothesis that depression is induced by stress include the mouse/rat FST, the TST, the CMS and the LH. In these models, animals are exposed to uncontrollable stress resulting in maladaptive behaviours. The shocks necessary to induce a depressive symptomatology like in animals must be uncontrollable by the latter and especially unpredictable.

20.2.1.1 The Mouse Forced Swimming Test (FST)

The mouse FST is a model that was built to predict the antidepressive action of new molecules now for years, using tricyclic antidepressants as reference (Porsolt et al. 1977). Mice are individually placed into glass cylinders (height, 25 cm; diameter, 10 cm) containing 10 cm of water maintained at 23–25 °C and leaving them there for 6 min. After vigorous activity, swimming attempts cease and the animal adopts a characteristic immobile posture. The animal is judged to be immobile when it floats in an upright position and makes only minimal movements to keep its head above water. This state of immobility has been named "behavioural despair", because probably of an anthropomorphic idea based on the assumption that the animals have the feeling they cannot escape from the cylinder (Petit-Demouliere et al. 2005). The decrease of the duration of immobility, which is recorded during the last 4 min of the 6-min test period, leads to think that the drug assessed is potentially an antidepressant. FST is very useful to study neurobiological mechanisms to better understand through the drug responses what is depression in humans (Porsolt 2000; Lucki et al. 2001). This behavioural test, far of the reality of depression clinical features, is a good translational approach (Bourin 2010).

The researches in discovering new drugs for treating depression are performed with FST as a core behavioural model. As we know neurotrophic factor could be a potential antidepressant agent. So an infusion of brain-derived neurotrophic factor (BDNF) was injected in the ventral tegmental area in mice. As a result, it induced a shorter latency to immobility relative to control animals, in the FST in rats (Eisch et al. 2003).

Other researchers pointed out when using FST, a significant decrease in the immobility time compared to vehicle-infused controls after BDNF infusion (Siuciak et al. 1997). On the other hand, other potential mechanisms of antidepressants using FST K^+ as channel openers and K^+ channel blockers were studied (Guo et al. 1995, 1996; Redrobe et al. 1996; Slattery et al. 2004). The FST is not only for screening antidepressant-like effects, but as well to better understand neurobiology of depression, mainly to study the role of monoamines. Nevertheless, this model of depression is not only linked to monoamines. A classic treatment of depression, the electroconvulsive seizures, was performed on animals in FST (Nestler et al. 2002) and was effective in increasing the swimming time.

The FST showed this ability to use genetically modified animals, which are useful to understand the mechanisms of action of antidepressants (Gardier et al. 2001; Holmes et al. 2002; Cryan et al. 2001). These studies are the following of those using specific ligands (Redrobe and Bourin 1998a)

20.2.1.2 The Rat Forced Swimming Test

The rat FST was performed before the one in mouse. The main problem with the rat is the fact that the animal dives to the bottom of the tank. The typical procedure involves placing a rat in a cylinder for 15 min on day 1 of the test. As a result of this exposure, escape attempts eventually cease and the animal is immobile by the end of the session. The following day, the animal is returned to the cylinder for a period of 5 min, at which point immobility time is recorded. Drug treatment (single or repeated) is performed between the first and the second exposure to the cylinders. Effective antidepressant treatments reduce immobility time in the second exposure. More recently, an improvement to the rat FST was proposed: with swimming time, two other parameters are scored, immobility and climbing behaviour. Lucki (1997) suggested that climbing behaviour is involved in initial response to the test situation, whereas swimming may be secondary exploratory behaviour associated with escape. SSRIs reduce immobility and increase swimming, whereas the selective noradrenaline reuptake inhibitors reduce immobility and decrease climbing without affecting swimming.

20.2.1.3 The Tail Suspension Test (TST)

The TST is based on the observation that a mouse suspended by the tail shows alternate periods of agitation and immobility, similar but not identical to that observed in the mouse FST (Steru et al. 1985). So it is almost the same paradigm to the FST. In the TST immobility is induced in mice simply by suspending them, using adhesive Scotch tape, to a hook connected to a strain gauge that picks up all movements of the mouse and transmits them to a central unit, which calculates the total duration of immobility during a 6-min test. This test has been automated (ITEMATIC-TST) and measures duration of immobility and the energy expended by each animal, the power of the movements (Steru et al. 1987) which can distinguish different classes of psychotropic activity. The TST procedure bypasses several problems of the swimming model: the immobility is objectively measured and no hypothermia is induced by immersion in cold water. The mouse TST can predict antidepressant activity of numerous components. It will be shown later on in this chapter that the combination of both tests (TST and FST) can help in discrimination of mechanisms of action of antidepressants when used in a purpose of screening.

20.2.1.4 Chronic Mild Stress (CMS)

Chronic sequential exposure to a variety of mild stressors (chronic mild stress) has been found to decrease the consumption of and/or preference for a palatable weak sucrose solution in rats or mice (Willner et al. 1992). Animals are exposed to various types of stressors which change over a period of weeks or months, e.g. overnight illumination, cage tilt and change of cage mate, resulting in a decrease in sucrose preference for several weeks, which reflects a generalised decrease in the sensitivity to rewards or anhedonia. Along with a state of anhedonia, various other behavioural changes due to depression are shown, per-

sisting weeks after stimuli cessation (Gorka et al. 1996). The model has predictive validity since the reversal of pathologic behaviour requires 3–4 weeks of treatment, as in human depression. In fact, this model has the ability to demonstrate a potential early onset of action of antidepressant treatment. This test presents with the advantage of the chronicity, it looks more of the treatment of depression which takes several weeks to be active. The problem is that time for rats is difficult to compare with humans.

20.2.1.5 Learned Helplessness Model

The LH model is the most familiar simulation of depression and also the most controversial. The model mimics some of the main features of depression, particularly of the kind that are precipitated by unfavourable environmental stress. The model, described by Seligman et al. (1975), consists of exposing animals to unavoidable and uncontrollable stressors such as electric foot shock, after which learning deficits on subsequent tests are observed where animals are found to be unable to learn to avoid an aversive stimulus and remain motionless and helpless in such a situation. This state has been named "learned helplessness" and is not found in animals exposed to identical but controllable stress. It has been shown that the persistent immobility of the animal to respond is confined to the learned immobility that has been required during the unavoidable shock situation. Thus the learned helplessness behaviour does not generalise to other types of behaviour that has been learned in the absence of the shock. Seligman and coauthors have suggested that animals learn that responding to uncontrollable shock is futile and that the cognitive and motivational deficits produced in this paradigm are parallel to human clinical depression. The helpless animal enters a learning situation with a generalised associative set that its actions are without consequence. It therefore responds less or not at all. In addition to an acquisition deficit, other features of the helpless animal parallel clinical dimensions of depression, deficits in motivation and emotion . Changes in activity, food intake and weight have also been reported.

20.2.2 Neuronal Deficit Models

20.2.2.1 Olfactory Bulbectomy Model (OB)

Apart from models based on stress, there are animal models of depression that are based on the hypothesis that depression is caused by neuronal regulatory deficit. One example in the OB proposes that depression is a biological disorder that develops in individuals who are predisposed due to neural regulatory deficits in the brain (Cairncross et al. 1977). The major brain damage model involves bilateral lesions of the olfactory bulbs, which form part of the limbic system in the rodents. Rats subjected to this operation display a variety of behavioural changes, including irritability, hyperactivity and an elevation of circulating levels of plasma steroids. A disconnection of the olfactory bulbs has shown to produce abnormalities in emotional behaviour, termed "bulbectomy syndrome" due to a disruption in the homeostatic regulation of impulse traffic in the limbic system (Jesberger and Richardson 1985). The hyperactivity exhibited by bulbectomised rats when they are subjected to a stressful novel environment such as the open field, as well as deficits in passive avoidance tasks, is reversed by the chronic administration of antidepressants.

20.3 The Use of Animal Models to Define Antidepressant Response

Animal models of depression are increasingly being used to better understand the mechanisms of action of antidepressants but as well for screening potential new antidepressants (Darcet et al. 2016). The basic requirement for an animal model of depression is its sensitivity and/or responsiveness to an antidepressant drug and lack of false positives (e.g. neuroleptics, stimulants and/or anxiolytics). All models presented above are called animal models of depression due to their responsiveness to antidepressant drugs. However, it is not possible to choose among these models the one which would be the most specific of the characterisation of one antidepressant

rather than another. However, we will see later that the combination of several models associated with different strains of animals can contribute to the discrimination of antidepressants. False positives must not be readily rejected as many non-antidepressant drugs have not been adequately tested for their possible antidepressant activity in controlled clinical trials. Also the co-administration of certain drugs can increase the efficacy of antidepressant drugs and reduce the time of onset of action (e.g. pindolol, buspirone) (Pérez et al. 1997). It is clear that not all symptoms of human depression can be modelled in animals and no universal model representing all these symptoms as yet exists. The model must however be robust and reproducible.

The OB model can be considered as a good approximation to an aetiological model of depression, but it is not an exact phenomenon of depression since it is a noncognitive explanation of depression. OB has a strong theoretical rationale (as antidepressants are not effective on normal rats), a face and predictive validity in the identification of antidepressants from some chemical classes. However, there is some question about sensitivity and selectivity as certain antidepressants appear to lack activity in this model. Even if the OB model exhibits a few false positive, only a narrow range of non-antidepressants has actually been tested. However, this remains an interesting model as many antidepressants are only active after sub-chronic or chronic treatment; the duration of treatment is similar to that needed for therapeutic activity to become apparent in depressed patients.

The LH is the most criticised paradigm due to its lack of complete specificity and poor reliability across laboratories. Also many of the depression-like phenomena produced are short-lived, most symptoms dissipating in 48–72 h depending on the shock procedure produced (Weiss and Simson 1989). Anxiolytics can reverse the behaviour (GABA injected into the hippocampus) (Petty and Sherman 1980), and only a few SSRIs (citalopram, fluvoxamine, indalpine and zimelidine) have shown efficacy and then only under particular conditions (Martin et al. 1990). The relevance of this model to depression has been questioned, and Anisman et al. (1980) suggested that the LH model is more a model of stress adaptation than a model of depression.

The CMS model was considered to be the most validated model of depression implicating stress as the aetiological cause of depression (Willner and Papp 1997) but is not selective for antidepressant drugs and it is not used for screening new drugs. The model exhibits poor reliability (D'Aquila et al. 1997) and the behavioural alterations dissipate quickly. The role of chronic stress and anhedonia has been questioned in the aetiology of depression (Breslau and Davis 1986), as an improvement in mood regulation of patients exposed to antidepressants is observed before any improvement in anhedonia. This test presents with the advantage of the chronicity, it looks more of the treatment of depression which takes several weeks to be active. Yet it is difficult to compare time in rat's life with humans. On the other hand, there are a lot of false positive results because CMS is built mainly on anhedonia which is present as well in schizophrenia; as a result some antipsychotic drugs induce positive results on the test.

The TST is a rapid and convenient test to perform; however, results obtained show variations in the same strain, and for the same treatment (David et al. 2003), it is very important to be careful regarding strain, weight of animals as well as the operating conditions. Hascoët et al. (1991) suggested that the TST is closer to a spontaneous activity model like actimetry than an antidepressant model.

The FST model is extensively utilised to screen drugs to define an antidepressant effect, as it is quick, inexpensive and easy to perform and has proven to be an easy reproducible screening test for pharmacological activity. These qualities allow the possibility of investigating various factors such as age, gender, and strain difference, which bear significant relevance to human depression (David et al. 2001a, b). Modification of the test to look at chronic rather than acute drug treatment and prolongation of the stress has been reported to improve the specificity. In a study Detke et al. (1997) showed that antidepressants chronically administered at lower doses

produced a significant decrease of immobility duration in the mouse FST. The value of this test is quite high because it is able to predict very often the dose-response effect in humans.

It is sensitive to all of the major classes of antidepressant drugs presenting with different mechanisms of action. It is necessary to use actimetry to measure the locomotor activity preventing the false positives which are mainly amphetamine drugs. In addition, the mouse FST permits exploration of the possible mechanisms of action of different classes of antidepressants through the use of specific ligands (Redrobe and Bourin 1997; Redrobe et al. 1996, 1998a, b).

For 30 years in our research laboratory, we have invested a lot of efforts in daily use of TST and FST in mice, not only to detect possible antidepressants but also to better understand their mechanisms of action. The use of different ligands, whether they are agonists or antagonists specific for serotonin receptors, allowed us to show the involvement of 5-HT1A and 5-HT1B receptors in the mechanism of SSRIs. Two research papers clearly show the impact of various strains of mice on the response of antidepressants on these two models, these considerations can lead to a pharmacogenomic impact on the efficacy of antidepressants (David et al. 2003; Ripoll et al. 2003). The best effect/size obtained on all the models envisaged is that of the Swiss strain mice on the TST. As the C57BL/6 and the DBA/2 mice attempted to redress their position (i.e. climbing up their tails previously reported by Mayorga and Lucki 2001 and Ripoll et al. 2003), it was difficult to conclude on their activity in the TST. It is necessary to use different strains of mice to demonstrate the antidepressants acting on noradrenaline or serotonin or dopamine although it is believed that the latter is the common final route of all antidepressants. Swiss mice are the most sensitive strain to detect serotonin and/or noradrenalin antidepressants, whereas C57BL/6 Rj was the only strain sensitive to bupropion (dopaminergic agent) using the FST. In the TST, all antidepressants studied decreased the immobility time in Swiss and C57BL/6 Rj strains. In order to evaluate the mechanism of action of a substance that may be clinically shown to be an antidepressant, the use of TST and FST in mice may be useful provided that three strains of mice (Swiss, NMRI and C57Bl/6 Rj) were used concomitantly. Some antidepressants with different mechanisms of action such as tricyclics or SSRIs induce a neighbouring behavioural response (with the exception of some small, difficult to quantify differences) that can be identified by the eye of an experienced experimenter. This is comparable to a psychiatrist with a confirmed clinical experience who can detect rough clinical signs of depression. For these antidepressants, in order to clarify more precisely their mechanism of action, it is useful to associate them with more or less specific compounds at sub-active doses and to practise the FST (Redrobe and Bourin 1999a). According to all results, a decision tree was established to help the screening and to give an indication on the mechanism of action (Bourin et al. 2005a). In the same research, it could be simple to discover new antidepressants as well as to have an idea about their mechanism of action.

20.4 Role of the FST in Evaluating Mood Stabilisers

It is difficult to model bipolar disorder animal models because of the complexity to have in the same animal very different syndromes as mania and depression. Bipolarity is a restrictive disease, affecting everyday life. It can affect different domains such as cognitive faculties (by disturbing the memory, attention or the executive functions of the patients) and sleeping (insomnia without fatigue can be the sign of a manic episode) or manifest through excessive fatigue. It is also characterised by the impossibility of being able to manage its emotions, and this emotional hyperreactivity is incarnated in irritable, angry behaviour. It can also give rise to anxiety disorders. Yet some animal models are used but they are very far from the clinic complexity of the disorder. The amphetamine-induced behaviour is the pivotal test of the disorder (Machado-Viera et al. 2004). Under these conditions, it was interesting to use the FST to better understand their

antidepressive activity (Bourin and Prica 2007). This is all the more important since antidepressants are not recommended in the treatment of bipolar disorder; some mood stabilisers are fortunately poor antidepressants, the reason why they escape to switch to mania or hypomania. Lithium is considered an antimanic more than an antidepressant; however, our team was able to show some antidepressant-like effects in the FST in mice (Hascoet et al. 1994). Moreover, it was possible to potentiate the action of some SSRIs (Nixon et al. 1994; Bourin et al. 1996a); these results match with clinical reports. On the other hand, combination studies of SSRI antidepressants using different drugs as clonidine, lithium and quinine précised the role of 5HT receptor subtypes in the effects of antidepressant action (Redrobe and Bourin 1999b). Lithium did not show antidepressant activity in the rat on FST, sometimes it showed contrary effects (Mague et al. 2003; Carlezon et al. 2006; O'Donnell and Gould 2007), it is very often in behavioural research that rats respond differently with mice, so we must be careful when comparing the interspecies results. 5-HT1A receptors are involved in the mechanism of action of sodium valproate and carbamazepine, yet both drugs are inactive alone on the FST. That suggests that other neurotransmitters than 5HT are involved. Carbamazepine and sodium valproate have complex mechanism of action regarding their anticonvulsive activity, and we know that they affect GABA, dopamine (DA) and noradrenalin (NA) (Post et al. 1992). Interesting results were obtained with lamotrigine, topiramate and phenytoin (Bourin et al. 2005b). Lamotrigine which is an atypical antiepileptic is now for years used as mood stabiliser mainly in depressed bipolar patients, decreasing immobility time in the mice FST. Topiramate and phenytoin as well decrease immobility time in the FST following i.p. administration (unpublished data). We can conclude that lamotrigine, topiramate and phenytoin have a marked activity on FST. Lamotrigine was designed at the early stage of development to become an antidepressant, but its poor antidepressant action leads researchers to move to look at an anticonvulsant action. This antiepileptic action has been suggested because of its action on the inhibition of glutamate release, by an effect on voltage-sensitive sodium channels (Leach et al. 1986; Kuo and Lu 1997). Veratrin, a Na^+ channel activator that increases glutamate release was used to study the role of ion channels in the mechanism of action of drugs on the FST (Lizasoain et al. 1995). The co-administration of veratrin, with lamotrigine, topiramate and phenytoin mice, was studied compared with "true" antidepressants of different mechanisms of action as paroxetine, imipramine and desipramine. Veratrin was antagonising the effect of phenytoin, lamotrigine and topiramate suggesting that sodium channels underlie their action in the forced swimming test. In contrast, veratrin did not affect antidepressant activity of the studied antidepressant drugs (Prica et al. 2008). Thus, the neurobiological mechanisms underlying the processes of swimming or immobility are more complex than envisaged by the discoverers of the FST. So the core idea is that the mechanism underlying the anti-immobility effect of mood stabilisers on their "antidepressant activity" is related to sodium channel and that FST is sensible to sodium channel mechanism and in a way to glutamatergic mechanism (van Enkhuizen et al. 2015).

Conclusion

It is difficult to compare all the animal models of depression as they vary widely in the manner of inducing abnormal behaviour, in the aspects of behaviour chosen for study and in the time course of antidepressant action. This difficulty can be problematic in exporting data from the various laboratories. Other factors hinder the comparison of these models such as strain, age, seasonal variations, light cycles utilised, etc. (Bourin et al. 1998; David et al. 2001a, b). These different parameters can lead to observational differences between laboratories for the same drugs.

The perfect animal model of depression as yet does not exist. No single animal model reviewed here is a precise paragon of depression as seen in humans and questions concerning the utilisation of a battery of tests and/or instead of a single model to determine antide-

pressant activity have been raised. As different aspects of depression are measured in each model and the different models possibly represent a different category of depression, the question remains whether a true comparison between models of a compound's antidepressant activity is possible (Bourin et al. 1996b). However, the screening of drugs in these paradigms allows for a better understanding of the mode of action of antidepressants, the neurobiology of depression (Remus and Dantzer 2016) as well as the discovery of new and more effective antidepressants (Wang et al. 2017). The progress in knowledge of these animal models is a way leading to translational psychopharmacology (Bourin 2010). That means the researchers are able to understand over the models the clinical features and make the synthesis we need to discover new drugs and even to understand better the mood disorders. Animal models of depression have probably not expressed their full capacity, mainly because there are not enough intellectual links between the preclinical and clinical researchers. They can still be very useful in the understanding of depressive illness (Wong and Licinio 2002).

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Part V

Individual-, Age-, Gender-, and Culture-Specific Aspects of Depression

Precision Psychiatry: Personalized Clinical Approach to Depression

21

Giampaolo Perna, Raffaele Balletta, and Charles B. Nemeroff

21.1 Personalized Medicine in Major Depressive Disorder

Personalized medicine is a valuable approach to disease prevention and treatment. It proposes tailoring health care by integrating genetics and epigenetic factors, brain imaging findings, clinical aspects, and environmental factors (Perna and Nemeroff 2017). The aim of personalized medicine in major depressive disorder (MDD) is to predict more accurately disease susceptibility and to tailor the most effective treatment for each individual (Prendes-Alvarez and Nemeroff 2016).

This strategy is important in the treatment of patients with MDD, one of the most prevalent and severe of the major psychiatric disorders. Indeed, MDD affects more than one hundred million people worldwide and increases the risk of suicide by 20 times (Korte et al. 2015). It is among the leading causes of disability, lost workdays, and income.

Although some patients with MDD only suffer from a single depressive episode, many, if not most, experience multiple episodes and, for others, a progressive and chronic illness. As initially observed by Kraepelin (Jablensky 1999), clinical features suggestive of progression include reduced inter-episode duration as a function of increasing number and length of episodes over time. Clinical, neurochemical, and structural and functional neuroimaging studies support the idea that the progressive course of MDD is related to a pathological reorganization of the central nervous system (CNS) during the course of the illness, defined as "neuroprogression" (Moylan et al. 2013). This reorganization is characterized by structural and functional brain abnormalities posited to be due to neural apoptosis, neurodegeneration, and decreased neuroplasticity. Such neuroprogression may arise from several sources including the activation of immuno-inflammatory and oxidative and nitrosative stress pathways as well as hypercortisolism.

G. Perna
Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa San Benedetto Menni Hospital, FoRiPsi, Albese con Cassano, Como, Italy

Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, Miami University, Miami, USA

Research Institute of Mental Health and Neuroscience and Department of Psychiatry and Neuropsychology, Faculty of Health, Medicine and Life Sciences, University of Maastricht, Maastricht, The Netherlands

R. Balletta
Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa San Benedetto Menni Hospital, FoRiPsi, Albese con Cassano, Como, Italy

Villa Elisa Hospital, Casamarciano, Naples, Italy

C.B. Nemeroff (✉)
Department of Psychiatry and Behavioral Sciences, Leonard Miller School of Medicine, Miami University, Miami, USA
e-mail: cnemeroff@med.miami.edu

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A myriad of studies have revealed that substantially fewer than 50% of patients with MDD achieve remission following treatment with antidepressants and/or psychotherapy. This may be explained by, in part, the heterogeneity of depression. Indeed, depression is now conceptualized as a systemic disease influencing several biological processes, such as inflammation, neuroendocrine function, platelet activity, autonomic nervous system activity, and cardiovascular and bone metabolism (Sotelo and Nemeroff 2017). As an example, remission of clinical depression has been reported to be accompanied by a normalization of inflammatory markers; in contrast lack of response is associated with persistently elevated levels of pro-inflammatory cytokines (Eller et al. 2008), a factor that may contribute to neuroprogression and to a negative clinical outcome. Similarly, child maltreatment, a documented vulnerability factor for adult MDD, is associated with increased levels of C-reactive protein (CRP), an inflammatory biomarker that is indicative of systemic inflammation (Coelho et al. 2014). The personalized medicine approach, which is able to integrate biological and environmental factors, can likely contribute not only to improved remission rates but also to ameliorate the longitudinal course of the illness.

The present chapter summarizes different factors that may serve as possible indicators of susceptibility to MDD and predictors of treatment response.

21.2 Major Depressive Disorder and Symptom-Based Subtypes

The fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (American Psychiatric Association 2013) describes MDD as a condition characterized by at least 2 weeks of depressed mood (i.e., hopeless, feeling sad or empty) and/or loss of interest and pleasure (anhedonia) accompanied by at least four additional depressive symptoms, present almost every day and for most of the day. Additional symptoms include increased or decreased appetite and/or significant changes in body weight, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy (fatigue), feelings of guilt or worthlessness, impaired concentration or indecisiveness, recurrent thoughts of death, and suicidal ideation or any attempt. Different specifiers are given to diagnose symptom-based subcategories of MDD, in particular MDD with melancholic features, MDD with atypical features, and, newly introduced by DSM-5, MDD with anxious distress, characterized by additional anxiety symptoms (American Psychiatric Association 2013).

Some of the symptoms listed in the DSM-5 description, in particular those relating to appetite/body weight, sleep, and psychomotor activation, differ in the various subtypes of MDD (Lamers et al. 2010; Korte et al. 2015). Patients with melancholic features experience loss of appetite and weight loss, insomnia, and psychomotor agitation whereas atypical depression is associated with increased appetite/weight gain, fatigue, hypersomnia, and psychomotor retardation (Baldwin and Papakostas 2006). Contrasts emerge from neuro-immuno-neuroendocrinological findings. In melancholic depression, there is a hyperactivity of the corticotropin-releasing hormone (CRH) system and the hypothalamic-pituitary-adrenal (HPA) axis (Stewart et al. 2005; Wong et al. 2000), whereas in atypical depression a CRH deficiency and a reduction of HPA axis activity have been reported (Lamers et al. 2010). Although MDD with melancholic features and with atypical features are different in several clinical and biological aspects, the International Study to Predict Optimized Treatment in Depression (iSPOT-D) showed that remission rates and symptom reduction did not differ among the melancholic, atypical, and anxiety subtypes at least not in the first 1000 subjects (Arnow et al. 2015). The three depression subtypes did not differ in response to three frequently used antidepressants: escitalopram, sertraline, and venlafaxine extended release. More than one third of the participants with MDD met the criteria for two or more subtypes, with no evidence that the mixed subtypes selectively predicted outcome (Uher et al. 2011). These results are consistent with data from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Trivedi et al. 2006), the largest trial

enrolling patients with MDD seeking routine medical or psychiatric care. Overall, these findings do not currently support the clinical utility of symptom-based subtypes of MDD in selecting the best antidepressant treatment for each patient. One clear exception is MDD with psychotic features, which absolutely requires treatment with combination antidepressant-antipsychotic medications or electroconvulsive therapy (American Psychiatric Association (APA) 2010).

In order to improve the management of patients with MDD, clinical symptoms will likely need to be integrated with other factors contributing to each patient's profile, such as genetic, epigenetic, endophenotypes/biomarkers, and environmental influences.

21.3 Endophenotypes/ Biomarkers

Because psychiatric disorders are currently primarily defined on the basis of sign and symptoms, often shared by several disorders, one major goal of psychiatric research is to identify more defined and quantifiable endophenotypes with associated biomarkers.

Criteria defining endophenotypes include being heritable and more prevalent in affected families than in unaffected ones, segregating with the illness in the population and co-segregating with the illness within families, not depending on whether the illness is clinically manifested, being specific to the illness, and being reliably measurable (Gottesman and Gould 2003). Biomarkers are measurable characteristics reflecting biological function or dysfunction, response to therapeutic interventions, and natural progression of the illness (Biomarker Definition Working Group 2001; Ozomaro et al. 2013). The distinctions between endophenotypes and biomarkers are subtle with a partial overlap between these two concepts. Endophenotypes are trait markers, whereas biomarkers may be either state or trait markers.

The identification of endophenotypes/biomarkers would help to identify individuals at risk of developing a disease, and more likely to predict the response to treatments in a less heterogeneous disease population (Alhajji and Nemeroff 2015). To date, available data do not allow the identification of clear endophenotypes/biomarkers able to predict the development of subsequent MDD in at-risk populations and the prediction of antidepressant treatment outcomes. However, there are several promising candidates that need to be tested in longitudinal studies.

21.3.1 Prediction of Disease Vulnerability

21.3.1.1 Clinical Features

Negative mood and anhedonia have been proposed as endophenotypes.

The relationship between daily life negative mood bias and the lifetime diagnosis of MDD was investigated in a population of 259 female twin pairs. Probands with co-twins meeting a diagnosis for lifetime depression exhibited greater negative affect responsiveness to daily life stressors, after controlling for past or current depression in probands (Wichers et al. 2007).

Anhedonia often precedes the onset of MDD and is associated with a family history of depression in unaffected relatives (Hecht et al. 1998). It predicts depression 2 years later (Wardenaar et al. 2012), poor outcomes (McMakin et al. 2012), and chronic course of depression over a 10-year period.

Functional magnetic resonance imaging (fMRI) was used to evaluate whether deficits in brain reward systems, which are posited to be the neural basis of anhedonia, are present in those at risk for developing MDD. Compared with healthy controls, recovered MDD patients showed a decreased neural response in the ventral striatum to pleasant stimuli and an increased response in the caudate nucleus to aversive stimuli, suggesting that even MDD remitted patients may have deficits in the neural basis of reward (McCabe et al. 2009).

21.3.1.2 Blood-Based and Cerebrospinal Fluid Biomarkers

Studies of monoaminergic biomarkers such as peripheral and cerebrospinal fluid (CSF) concentrations of serotonin, dopamine, and noradrenaline

and their metabolites reported inconsistent results (Kunugi et al. 2015), though there is general agreement that reduced CSF 5-hydroxyindoleacetic acid (5-HIAA) concentrations are associated with increased suicidality.

A meta-analysis of longitudinal studies (Valkanova et al. 2013) revealed that an increase in the inflammatory markers C-reactive protein (CRP) and interleukin (IL)-6 has a small but significant association with the subsequent development of depressive symptoms, supporting the hypothesis of a causal pathway from inflammation to depression. Different inflammatory markers in MDD patients appear to be linked to different depression subtypes. Two studies (Lamers et al. 2013; Rudolf et al. 2014) found that increased inflammatory marker levels, in particular IL-6, were associated with atypical depression as compared to typical or melancholic depression.

Lipids, which have a central role in neuronal function, have been proposed as a potential family of peripheral biomarkers (Van Heesch et al. 2014). The main finding, when comparing MDD patients with controls, is an altered lipid profile. In particular an increase of low-density lipoproteins (LDL) and omega-6 levels and a decrease of high-density lipoproteins (HDL) and omega-3 levels have been reported (Parekh et al. 2017).

Brain-derived neurotrophic factor (BDNF) is the most common neurotrophin in the human brain and shows promising features as a MDD biomarker. In line with the neurotrophin hypothesis of depression, which posits that a scarcity of BDNF contributes to the pathophysiology of depression by decreasing neuronal plasticity, low BDNF blood levels have been consistently reported in patients with MDD (Neto et al. 2011). The relationship of blood to CNS levels of BDNF remains obscure.

21.3.1.3 Neuroimaging

Both structural and functional neuroimaging are potentially useful methods to identify phenotypes indicative of vulnerability to MDD. Patients with MDD showed significantly smaller hippocampal volumes, though it remains unclear whether this is a consequence of the disorder, a consequence of early life trauma (Rao et al. 2010), or if it precedes the onset of the disease (Rao et al. 2010; Schmaal et al. 2016). Decades of task-based fMRI have identified brain circuits with altered functional activity, e.g., the increased amygdala reactivity in patients with MDD while processing negative stimuli (Siegle et al. 2002). More recently, resting-state fMRI, which allows the identification of spontaneous activity of brain networks, i.e., brain areas that increase or decrease their activity synchronically, has been investigated in MDD. The hyperactivity of the default mode network (DMN), which is active during internally directed mental states, such as introspective states, has been reported in MDD patients (Sheline et al. 2010).

21.3.2 Prediction of Antidepressant Treatment Outcome

21.3.2.1 Blood or Other Peripheral Measures

Efforts in the identification of predictors of differential antidepressants treatment response based on blood or other peripheral measures date back several decades.

Evidence of HPA axis hyperactivity, including but not limited to increased blood/CSF/urinary cortisol levels and CSF concentrations of CRH (Nemeroff et al. 1984), non-suppression of cortisol in the dexamethasone suppression test (DST), and the dexamethasone-CRH (DEX/CRH) test, have been observed in up to than 70% of patients with MDD (Vreeburg et al. 2009) especially in severe/melancholic MDD. Several studies have reported that SSRIs decrease HPA axis hyperactivity (Nikisch et al. 2005), though contradictory findings exist (Deuschle et al. 2003). Because effects of antidepressants on the HPA axis seem to occur mainly in MDD patients responsive to treatment (Deuschle et al. 2003; Nikisch et al. 2005), it has been suggested that resolving HPA axis abnormalities during MDD treatment is indicative of SSRI response.

Changes in response to the DST in MDD patients receiving antidepressants might represent a laboratory marker of treatment outcome. Most non-suppressors had progressive normalization of DST responses in conjunction with

clinical improvement, and failure to normalize was often associated with poorer clinical outcome (Greden et al. 1983).

After CRH became available for clinical studies, the DST was combined with CRH administration and the resulting combined DEX/CRH test proved to be more sensitive in detecting HPA system changes than the original DST. Elevated cortisol release after the DEX/CRH test has been consistently observed in patients in an acute major depressive episode, and normalization of the DEX/CRH test was shown to precede or parallel response to antidepressant treatment. Sustained non-suppression of the HPA axis in MDD patients undergoing the DEX/CRH test predicts a poorer outcome of treatment response (Binder et al. 2009) and may be associated with depressive relapse (Aubry et al. 2007).

There is evidence of an interaction between inflammatory processes and antidepressant response (Miller and Raison 2016). MDD is characterized by low-grade inflammation, revealed by higher concentrations of inflammatory biomarkers such as C-reactive protein (CRP), tumor necrosis factor (TNFα), and interleukin 6 (IL-6) (Howren et al. 2009). A meta-analysis (Strawbridge et al. 2015) supports the view that heightened levels of inflammation may contribute to treatment refractoriness. Non-steroidal anti-inflammatory drugs might be beneficial as adjunctive treatments in unipolar (Akhondzadeh et al. 2009) and bipolar (Nery et al. 2008) depressed patients. Although the levels of IL-6 decreased with antidepressant treatment regardless of outcome, persistently elevated levels of TNFα were associated with prospectively determined treatment resistance (Strawbridge et al. 2015). This last result is strengthened by the findings that a TNFα antagonist, infliximab, can improve depression in treatment-resistant patients with higher basal levels of inflammation as defined by elevations in CRP (Raison et al. 2013).

The putative role of IL-6 plasma concentrations as a reliable marker of antidepressant response is still highly debated. Higher serum levels of IL-6 predicted response to ketamine, an *N*-methyl-D-aspartate receptor antagonist that produces a rapid antidepressant effect in patients with treatment-resistant MDD (Yang et al. 2015).

CRP levels have been used to differentially evaluate treatment efficacy in response to antidepressants and the results are discordant. A recent meta-analysis (Strawbridge et al. 2015) and a study by Schmidt et al. (2016) did not find an association between baseline CRP levels and response to antidepressants; in contrast others reported a positive association (Uher et al. 2014; Jha et al. 2017; Mocling et al. 2017).

The role of peripheral BDNF concentrations in the prediction of antidepressant efficacy is also unclear. Higher baseline serum BDNF levels were reported to predict antidepressant treatment response (Mikoteit et al. 2014), but low baseline levels were as well (Nase et al. 2016). Clinical response has also been reported in the absence of a BDNF increase (Başterzi et al. 2009). A recent meta-analysis (Polyakova et al. 2015) concluded that antidepressant treatment increases serum BDNF levels in MDD in responders and remitters significantly more than in non-responders.

21.3.2.2 Electroencephalogram

A number of different electroencephalography (EEG)-derived biomarkers, mainly change in frequency band (alpha and theta) measures, antidepressant treatment response index (ATR), and event-related potentials (ERPs), have been the focus of investigations as potential biomarkers of antidepressant response in MDD.

Early studies reported that pretreatment changes in the alpha band differentiate responders from non-responders to the tricyclic antidepressant imipramine and the SSRIs (Knott et al. 1996; Knott et al. 2000; Bruder et al. 2008). However, data derived from iSPOT-D, a multicenter, randomized, prospective trial, in which 1008 MDD participants were randomized to escitalopram, sertraline, or venlafaxine-XR, concluded that alpha in the occipital and frontal cortex was not associated with treatment outcome (Arns et al. 2016).

Early studies investigating pretreatment changes in the theta band reported conflicting results. When a more sensitive method to localize cerebral sources from where EEG signals generate, the low-resolution electromagnetic tomo-

graphic analysis (LORETA), was applied, studies found more consistently an association between elevated pretreatment theta current density in rostral anterior cingulate cortex (rACC) and response to a variety of antidepressants in MDD (Pizzagalli 2011; Koo et al. 2017). More recently, however, iSPOT-D data was unable to replicate the high frontal and rACC theta association with treatment response (Arns et al. 2015).

In quantitative EEG (QEEG), electrical signals from the brain are converted to digital form, which allows patterns undetectable by the naked eye to be revealed. The antidepressant treatment response index (ATR) is a QEEG measure that integrates frontal alpha and theta power extracted at pretreatment baseline and at 1-week posttreatment. In the biomarkers for rapid identification of treatment effectiveness in major depression study (BRITE-MD) (Leuchter et al. 2009), patients with ATR values above the threshold value were 2.4 times more likely to respond to escitalopram than those with ATR values below threshold.

ERPs are a measure of change in voltage, which represent brain activity elicited in response to visual or auditory stimulation. Among them, loudness dependence of auditory evoked potential (LDAEP), a measure of the ERP component N1/P2, taken 100–200 ms after presentation of an auditory stimulus, is a promising biomarker of response to antidepressants. A larger slope of the P2 amplitude in response to stimulus intensity (strong LDAEP) at baseline was associated with response to SSRIs, such as fluoxetine, paroxetine, and citalopram, while weak LDAEP (lower slope) was found to be associated with response to the norepinephrine reuptake inhibitor (NRI) reboxetine (Juckel et al. 2007; Lee et al. 2015).

Some recent methodological advances in analysis of EEG data seem to be promising. Analysis of a list of discriminating EEG features with a machine learning methodology has allowed an overall prediction accuracy of 87.9% of response to treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants in subjects with MDD (Khodayari-Rostamabad et al. 2013). Moreover, significant wavelet coefficients extracted from frontal and temporal pretreatment EEG data were able to predict antidepressant treatment outcomes (Mumtaz et al. 2017).

Overall, the possibility to predict treatment response using EEG markers need further studies because the extant data are not yet consistent and their clinical relevance still questionable.

21.3.2.3 Neuroimaging

Resting state fMRI studies suggest an association between response to antidepressant medications and increased connectivity between frontal and limbic brain regions, possibly resulting in greater inhibitory control over neural circuits that process emotions (Dichter et al. 2014). The subcallosal cingulate cortex (SCC) connectivity appeared to predict the response to antidepressants and, more consistently, to repetitive transcranial magnetic stimulation (rTMS) in patients with MDD. The resting-state functional connectivity of three regions with the SCC (the left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex) was differentially associated with outcomes of remission and treatment failure to CBT and antidepressant treatment in never treated MDD patients (Dunlop et al. 2017).

Measures of cerebral glucose metabolism by brain PET scan at baseline and after treatment found that hypometabolism in the insula is correlated with a good response to CBT and poor response to escitalopram, while hypermetabolism is associated with a better therapeutic response to escitalopram compared to CBT (McGrath et al. 2013).

21.4 Genetics

The pathophysiology of MDD and the mechanism of action of the antidepressant treatments remain largely obscure. Family, twin and, to a lesser extent, adoption studies provide evidence that genetic factors are involved both in susceptibility to MDD and in response to ADs.

21.4.1 Prediction of Disease Vulnerability

Studies estimate that the genetic risk for developing MDD is approximately 40% (Prendes-Alvarez and Nemeroff 2016). In the past few decades, genetic research on the susceptibility to

MDD has uncovered several so-called candidate genes, primarily chosen on the basis of their role in presumed pathophysiologic mechanisms.

The serotonin transporter (SERT or SLC6A4), through removal of serotonin at the synapse, plays an important role in determining the extent and duration of serotonergic signaling. A polymorphism in the SERT gene promoter region (5-HTTLPR) produces a variation in SERT gene transcription rates such that the short (S) allele, both the homozygote and heterozygote, is less transcriptionally efficient than the homozygotes long (LL) genotype.

In a pioneering study, Caspi and coworkers (2003) reported S-allele-carriers were more likely to develop depression in relation to stressful early life events than the LL-homozygotes. Recently, a meta-analysis confirmed a link between the short (S) form of 5-HTTLPR and stressful life events, resulting in depression (Sharpley et al. 2014). However, approximately 35% of the studies included in the meta-analysis failed to show any significant association or found contrasting results.

Tryptophan hydroxylase (TPH), the rate-limiting step in serotonin synthesis, has been implicated in susceptibility for MDD in a number of reports, with mixed results (Gao et al. 2012). Although TPH1 is primarily found in peripheral tissues, a study identified an association between six haplotypes of this gene and MDD (Gizatullin et al. 2006). In contrast, TPH2 is expressed in CNS and is considered to exert effects on sleep, aggression, food intake, and mood. The identification of single nucleotide polymorphisms (SNPs) (Zill et al. 2004) and loss of function mutations for this gene (Zhang et al. 2005) have been reported to be more common in patients with MDD than controls, suggesting that defects in brain serotonin synthesis can be an important contributor to MDD susceptibility (Zhang et al. 2005).

As noted above, hyperactivity of the HPA axis has been frequently reported in individuals with MDD (Ozomaro et al. 2013). Several gene codings for components of this system have been scrutinized, in particular the FK506 binding protein 5 (FKBP5) and the corticotropin-releasing hormone receptor 1 (CRHR1) genes (Myers and Nemeroff 2010). FKBP5 codes for a co-chaperone protein that modulates the glucocorticoid receptor. Individuals homozygous for the minor alleles of the FKBP5 SNPs were more likely to express depression after trauma exposure (Zimmermann et al. 2011). FKBP5 polymorphisms were associated with an increased recurrence of MDD episodes, poor antidepressant response (Binder et al. 2004), and with suicidal events (Brent et al. 2010). The CRH type 1 receptor mediates the majority of the CNS effects of CRH. Findings of increased concentrations of CRH both in specific brain areas and in cerebrospinal fluid have been consistently replicated in MDD, as well as in suicide victims (Aratò et al. 1989; Nemeroff et al. 1984), and a corresponding downregulation of CRHR1 mRNA expression and binding. Genetic variations in the CRHR1 gene have been associated with increased susceptibility to MDD in a Chinese population (Liu et al. 2006) and moderate the effect of child abuse on the risk for adult MDD (Bradley et al. 2008) as well as suicide risk (Roy et al. 2012).

Genome-wide association studies (GWAS), a powerful tool to probe a molecular phenotype of a disease without requiring an a priori hypothesis, have had only limited success in identifying genetic variants that predispose or protect from MDD, even with relatively large samples (García-González et al. 2017).

21.4.2 Prediction of Antidepressant Treatment Outcome

Approximately 60% of patients with MDD exhibit only a partial response to antidepressants and up to 30% do not respond at all. It is likely that genetic factors and polymorphism contribute to the variability in antidepressant response (Kato and Serretti 2010). In this regard, the definition of biological predictors of treatment response, i.e., "treatment biomarkers," would contribute to the personalized approach driving the selection of the most suitable medication for each individual patient with MDD. One relatively new approach is the microarray analysis of peripheral gene expression in blood cells. The gene expression level in blood has been reported to be comparable to prefrontal cortex (Sullivan et al. 2006) and has been associated with antidepressant response (Labermaier et al. 2013).

A set of candidate genes has been widely investigated as predictors of antidepressant response. The most studied genetic variant is the serotonin transporter (SERT) gene in its promoter region (5-HTTLPR). There is evidence (Porcelli et al. 2012) pointing to a better SSRI response in Caucasian patients carrying the 5-HTTLPR L-allele, though negative findings have been reported as well. Investigations of the relationship between norepinephrine and dopamine transporter genetic polymorphisms and response to antidepressant treatments in MDD have not yielded unequivocal results.

It has been suggested that the HPA axis plays some role in the mechanism of action of antidepressant drugs, because a normalization of HPA axis activity has been reported after successful antidepressant treatment. Polymorphisms of the CRH type 1 receptor (CRHR1) gene, which plays a key role in mediating the CRH effects in depression and anxiety, were found to be associated with response to both fluoxetine (Liu et al. 2006) and citalopram (Lekman et al. 2008). Allele G carriers of rs2270007 of the CRHR2 gene showed a poorer response to citalopram with a threefold increased risk for non-responding after 4 weeks of treatment (Papiol et al. 2007). One single nucleotide polymorphism (SNP) (rs10473984) within the CRHBP gene encoding the CRH-binding protein, which binds CRH with subnanomolar affinity to modulate CRH receptor activity, affects response to citalopram in African American and Hispanic patients (Binder et al. 2010). As noted above, polymorphisms in FKBP5 are associated with rapid response to AD treatment (Binder et al. 2004) and also with remission over 14 weeks of citalopram treatment (Lekman et al. 2008).

Studies on the influence of BDNF polymorphisms in antidepressant response resulted in mixed results with some studies reporting the Met allele polymorphism associated with better response (Licinio et al. 2009) and others showing the Val/Val genotype to have a better outcome (Zou et al. 2010).

Genome-wide association studies (GWAS), performed to identify SNPs associated with antidepressant response, have reported several findings, but most of them have been inconclusive and remain not replicated. In a recent study, 32 differentially expressed probe sets were associated with response to citalopram treatment in MDD (Mamdani et al. 2011). Another study revealed the association of four mRNAs and two microRNAs (miRNAs) with antidepressant treatment response in MDD (Belzeaux et al. 2012). Another microarray study aiming to identify peripheral gene expression profiles reported how responders and treatment-resistant patients with MDD to the SSRI escitalopram could be predicted at the beginning of treatment by expression levels of NLGN2 gene (Pettai et al. 2016).

One possible explanation is that antidepressant response is polygenic and each individual SNP is only responsible for a small fraction of heritability hardly detectable in statistical analyses. However, a polygenic approach (differently from GWAS analysis where a single SNP can reach significance level) that captured the additive effect of multiple SNP alleles across the genome failed to predict antidepressant response analyzing results of two large pharmacogenetic trials (GENDEP, MARS, STAR*D) (García-González et al. 2017; GENDEP Investigators, MARS Investigators, STAR*D Investigators 2013; Lekman et al. 2008).

21.4.3 Pharmacogenetic-Based Decision Support Tools

Genetic variants explain about 50% of individual differences in antidepressant response and adverse effects (Crisafulli et al. 2011). To optimize the individual patient's responses to a prescribed antidepressant, one emerging strategy is to consider the patient's pharmacokinetic and pharmacodynamic genetic profile. Currently, several second-generation tools that offer combinatorial polygenic testing are commercially available. They analyze polymorphisms in genes for cytochrome P450 (CYP) liver enzymes that metabolize antidepressant drugs in addition to genes which encode brain response proteins that purportedly contribute to their efficacy and/or side effects. Moreover, combinatorial pharmacogenomics is able to identify synergies

between genes and provide drug-drug interaction information.

Less than 20% of current available pharmacogenetic tools have been empirically evaluated, and it is not clear if these tools can, indeed, shorten the time to remission, sustain the duration of remission, and improve adherence to antidepressant treatment (Bousman and Hopwood 2016). In treatment-resistant depressed patients, three prospective studies have evaluated the clinical validity and utility of a combinatorial pharmacogenomic test (GeneSight test) compared to a treatment as usual (TAU). The analysis of data from these combined studies demonstrates that GeneSight-guided treatment is associated with a greater reduction in overall depression symptoms and increases in response rates compared to TAU (Altar et al. 2015). However, there are serious methodological concerns in these studies including lack of blindness and very small sample sizes. Pharmacogenetic testing is potentially useful in particular clinical situations but the widespread adoption of these tools in practice is premature relative to the extant data. In the next several years, data derived from ongoing randomized clinical trials in the USA and Canada will allow a better understanding of the role of antidepressant pharmacogenetic tools in real-world practice.

21.5 Epigenetics in MDD

Epigenetics may play an important role in the etiology of complex diseases such as MDD. The term "epigenetics" refers to potentially heritable and functionally relevant changes in gene expression obtained without modification of nucleotide sequence. DNA methylation is one of the major forms of epigenetic modifications. It consists of the addition of a methyl group to cytosine at cytosine-phosphate-guanine dinucleotides (CpG) sites which results in a reduced access of transcription factors into regulatory elements, with consequent reduction in transcription. A second epigenetic mechanism involves histone modification with change of the DNA-histone interaction. Enzymes known as histone deacetylases (HDACs) remove the acetyl group from the histone tail, cause chromatin condensation, and prevent transcription factors access to DNA resulting in a decreased gene expression. Epigenetic modifications in response to early life traumatic experiences have provided new insight into pathophysiology of MDD and may yield novel biomarkers for diagnosis and treatment response.

21.5.1 Prediction of Disease Vulnerability

The role of epigenetic modifications in personalized medicine of MDD has been hypothesized to impact illness vulnerability.

In the first genome-wide DNA methylation scan in MDD, the comparison of 39 postmortem frontal cortex samples of patients with 26 controls identified 224 candidate regions having DNA methylation differences >10% (Sabunciyan et al. 2012). Several other studies have explored these findings and overall support the idea that SLC6A4 methylation and demethylation of CpGs in the functional glucocorticoid response elements in intron 7 of the FKBP5 gene may be related to childhood maltreatment and thus might be a useful marker of MDD susceptibility. Higher methylation status of the BDNF promoter, repeatedly associated with MDD, might also represent another epigenetic marker of disease vulnerability (Fabbri et al. 2017).

Although brain tissue is an ideal sample for DNA methylation analyses, it is restricted to postmortem tissue sampling. Fortunately, peripheral blood samples have provided a noninvasive model for DNA methylation status, and the results are correlated in some studies to those observed in postmortem brain tissue, as, for example, the Stenz et al. (2015) study, in which the promoter methylation of the BDNF gene was measured both in blood and postmortem brain tissue from depressed patients. Januar et al. (2015) proposed the detection of BDNF hypermethylation in oral tissue as a potential biomarker of depression. Finally, two studies (Hobara et al. 2010; Iga et al. 2007) evaluated gene expression of the histone deacetylases (HDACs) in peripheral blood cells of depressed patients as potential

biomarkers and found that HDAC2 and HDAC5 expression were significantly increased in MDD patients compared to healthy controls.

21.5.2 Prediction of Antidepressant Treatment Outcome

The most studied epigenetic modification, DNA methylation, has been evaluated in the context of AD treatment response.

Investigations focused on baseline levels of DNA methylation of specific genes, in particular SERT (SLC6A4), BDNF, and interleukin-11 (IL-11) genes in the prediction of antidepressant response with some promising results (Lisoway et al. 2017).

Domschke et al. (2014) reported that DNA hypomethylation of the SERT region was associated with impaired antidepressant treatment response to escitalopram in a Caucasian population. Okada et al. (2014) reported that higher pretreatment methylation rate of SLC6A4 is associated with better therapeutic responses to antidepressants in a Japanese population sample. Kang et al. (2013), however, did not confirm this finding using a series of different antidepressants. Lower baseline methylation status of the BDNF promoter region predicted non-response to antidepressant medication (Tadić et al. 2014). Higher levels of DNA methylation at IL-11CpG unit 4 were associated with better response in individuals treated with escitalopram, but with worse response in those treated with nortriptyline (Powell et al. 2013).

21.6 Childhood Adversity

21.6.1 Prediction of Disease Vulnerability

A large body of evidence has confirmed and extended the finding that childhood adversities, such as sexual, physical or emotional abuse, emotional or physical neglect, or parental loss, are significant contributors to the subsequent development of MDD and predict a more severe course of illness and greater chronicity (Nemeroff 2016). Physically abused (odds ratio, OR = 1.54), emotionally abused (OR = 3.06), and neglected (OR = 2.11) individuals were found to have a higher risk of developing depressive disorders than non-abused individuals (Norman et al. 2012). A meta-analysis of 16 epidemiological studies (more than 20,000 participants) suggested that childhood maltreatment was associated with an elevated risk of developing recurrent and persistent depressive episodes (OR = 2.27) (Nanni et al. 2012).

21.6.2 Prediction of Antidepressant Treatment Outcome

Several studies suggest that a history of early life childhood trauma predicts poorer response to antidepressant and psychotherapy. A meta-analysis of ten clinical trials (more than 3000 participants) concluded that childhood maltreatment was associated with lack of response/remission to treatments for depression (OR = 1.43) (Nanni et al. 2012).

Patients with chronic depression without a history of childhood trauma had an equivalent response to nefazodone, when compared with a form of CBT designed for chronic depression, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), and a better response to the combination of treatments (Keller et al. 2000). Among patients with a history of early childhood trauma, CBASP alone was superior to antidepressant monotherapy, and the combination of psychotherapy and pharmacotherapy was only slightly superior to CBASP alone (Nemeroff et al. 2003).

Lewis et al. (2010) compared the efficacy of a 12-week treatment with fluoxetine, CBT, their combination, and placebo in 427 adolescents with MDD. The no-trauma group responded to fluoxetine, while CBT was not superior to placebo. In individuals with a history of trauma or physical abuse, no treatment was more effective than placebo. In sexually abused patients, placebo was more effective than CBT (Lewis et al. 2010).

In patients with MDD in the iSPOT trial, the incidence of childhood abuse was fourfold higher than in their healthy peers. Abuse occurring before the age of 7 years predicted poorer

response and remission following treatment with escitalopram, sertraline, or venlafaxine extended release (XR) (Williams et al. 2016). Finally, childhood abuse was associated with poorer treatment response to "low serotonin affinity" medications than to "high serotonin affinity" ones (Quilty et al. 2017).

Conclusions

The personalized or precision medicine approach to MDD is a very active avenue of investigation. This approach is relatively novel yet there are several promising findings that need to be explored further with studies of large samples before being considered for translation in clinical practice.

Genetic and epigenetic factors clearly play a role both in the prediction of disease vulnerability and treatment outcome. However, in studies that evaluated the association of candidate genes with MDD and responses to treatment, candidate genes were selected on the basis of existing knowledge on MDD and the supposed mechanisms of action of antidepressants. Because the gene selection is done a priori, this approach rarely opens new fields of investigation. Until now, candidate gene studies have failed to find a strong genetic impact on MDD, but rather they have confirmed or denied the influence of the selected genes. It was expected that a GWAS strategy, which evaluates all known genes without any a priori hypotheses, could identify genetic variants associated with MDD and treatment response. Despite this great technical advancement, genes or biomarkers predictive of susceptibility to MDD or of response to antidepressant have not yet been reliably identified. Because studies have revealed that common genetic variants and biomarkers are unlikely to have widespread predictive value as single predictors, a strategy that integrates several types of genetic clinical and neurobiological markers should be considered. Polygenic risk factor scores represent one promising new direction. In the near future, multi-omics including transcriptomics, metabolomics, and proteomics will also surely be scrutinized as potential markers as well. The development of biosignatures profiling clinical phenotypes, neuroimaging and EEG data, a diverse array of peripheral/serum growth factors, cytokines, hormones and metabolic markers, genetic makeup, and environmental factors (e.g., childhood early experiences) is clearly an alternative to the single-biomarker approach. Personality features in patients with depression might disentangle depression heterogeneity and help to tailor treatments (Berg et al. 2017). Moreover, there is some evidence that pretreatment information on sex, height, weight, and BMI may help medication selection in depressed patients. Venlafaxine XR was more effective than escitalopram in patients with comorbid obesity and MDD, and the association between adiposity and remission was greater in females than in males (Green et al. 2017). Finally, it has been observed that socioeconomic measures, including education, income, and employment status, were better predictors of treatment response than clinical factors, such as past medication response, severity of MDD, and comorbid psychiatric diagnoses (Jakubovski and Bloch 2014). More studies are needed to foster the development of new methodological and statistical means to better capture the complex world of depression and to allow a concrete move from the hope of a personalized approach toward the reality of widespread clinical practice.

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22 Risk Factors and Prevention Strategies for Depression in Childhood and Adolescence

Jun Won Kim and Jae-Won Kim

22.1 Introduction

With a high prevalence, depression is chronic and is associated with impairments related to increased psychosocial and medical morbidity and mortality (Lewinsohn et al. 1998). The World Health Organization determined that depression has the third greatest burden of all diseases and that it will be the second greatest by 2020 and the greatest by 2030 in higher-income countries (Mathers and Loncar 2006). Child and adolescent depression has a negative impact on schooling, educational attainment, and interpersonal relationships, resulting in negative long-term consequences in adulthood (Lewinsohn et al. 1998). In addition, an early-onset and long-standing course of depression is related to poor treatment response (Klein et al. 1999). Therefore, it is certain that depression is a major public health problem that requires effective strategies to prevent its onset and recurrence from medical and socioeconomic viewpoints.

One-fourth of the population is affected with depression during their lifetime. Of note, half of occurrences of depression onset happen during adolescence, leading to a high risk of recurrence for the rest of a person's life (Kessler et al. 2005; Avenevoli et al. 2008). This means that intervention during childhood or adolescence is important to effectively prevent depression. However, existing prospective community studies report that adolescent depression is underdiagnosed and undertreated compared to adult depression (Leaf et al. 1996). Incidences of depression increase rapidly during teenage years, especially for women, and there is a 10–17% prevalence rate reported for people during early adulthood (Moffitt et al. 2010). However, according to previous epidemiologic studies, adolescents report depression that is nine times greater than their parents' notice (Cho et al. 2006). Again, this means that adolescent depression is not recognized and treated as it should be. Depression is one of the most common adolescent psychiatric illnesses, with a 1-year prevalence of 4–5% (Jane Costello et al. 2006). Given its high prevalence and serious social and educational impairment (Fletcher 2010) and given that it is a major risk factor for suicide, proper knowledge of an active intervention for depression is necessary (Windfuhr et al. 2008). For instance, appropriate and active intervention targeting high-risk children

J.W. Kim
Department of Psychiatry,
Catholic University of Daegu School of Medicine,
Daegu, South Korea

J.-W. Kim (✉)
Department of Psychiatry and Behavioral Sciences,
Division of Child and Adolescent Psychiatry,
Seoul National University College of Medicine,
Seoul, South Korea
e-mail: kimjw412@snu.ac.kr

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and adolescents for depression could prevent possible serious problems related to the emotion, cognition, and social skills of subjects and their relationships with peers and family members (Thapar et al. 2012). Therefore, we must evaluate the risk factors for depression and establish prevention strategies based on the risk factors identified.

It is important to distinguish the risk factors and causal mechanism. The causal mechanism is the process of how the course that the disease takes, while risk factors precede and increase the incidence of the disease (Garber 2006). Risk factors may be divided into fixed (e.g., gender, genotype) and modifiable factors depending on whether the depression is changeable or controllable. Previous studies have revealed risk factors such as gender, genes, parental depression, anxiety independent from mood symptoms, subsyndromal depressive symptoms, traits and characteristics, negative cognition, inappropriate coping skills, stressful life events, and difficulties in interpersonal relationships. The limitation of previous studies regarding risk factors in depression is that these factors have mostly been reported in adult depression studies. It is known that child and adolescent depression has different etiology and risk factors from those of adult depression (Kaufman et al. 2001). Perinatal insult, motor skill deficit, unstable caregivers, psychopathology and criminal risks in the family, and social-emotional problems are examples differentiating child and adolescent from adult depression (Jaffee et al. 2002). Thus, different periods of depression may have different risk factors. However, we do not know whether the risk factors identified for child and adolescent depression are incorporated into the respective preventive strategies and measures. In this chapter, we will first introduce and summarize the genetic, social-environmental, and biological factors for child and adolescent depression. Second, we will summarize prevention strategies for child and adolescent depression based on the characteristics of target population groups or delivery modalities. Furthermore, we will investigate whether the existing prevention strategies are linked with identified risk factors for depression.

22.2 Risk Factors

Depression is a complicated disease with many risk factors and etiologies contributing to and affecting each other. Previous studies have shown genetic and psychosocial risks, while recent studies focus on neurocognitive and neuroendocrine mechanisms. We will describe each risk factor depending on its characteristics.

22.2.1 Familial Risks

Children whose parents have depression are at greater risk of suffering from depression. Offspring of depressed parents have a risk of depression that is three times higher than children of non-depressed parents (Weissman et al. 2016). This increased risk is the result of both genetics and environmental influences (Tully et al. 2008). A recent long-term follow-up study of the offspring of depressed parents for 30 years revealed their characteristics as follows: first onset between 15 and 25 years of age, deterioration of overall function, difficulties due to emotional problems lasting longer than in offspring of non-depressed parents, higher mortality due to unnatural causes, and a life expectancy 8 years shorter than the control group (Weissman et al. 2016). Rice and colleagues conducted a study to determine the pathogenesis of first-onset major depressive disorders (MDD) in children and adolescents aged 9–17 years. In this study, the parents had at least two MDD episodes. Parental depression turned out to be the highest risk factor independent of poverty, also known to be a serious risk factor (Rice et al. 2016). Whelan and colleagues explained that postnatal maternal depressive symptoms were associated with adolescent irritability, which is connected to adolescent depressive symptoms (Ahlen et al. 2015). Many twin studies report that although the heritability of depression is low during childhood compared to the adolescent period, heritability increases with age. The heritability rate during late adolescence is 30–50%, which is similar to the rate in adults (Thapar and Rice 2006).

Recent studies suggest that not only genetic factors but also psychosocial mechanisms play an important role in familial transmission. Although many studies explain that being exposed to maternal depression during prenatal and postnatal periods is important for depression onset, timing does not matter that much (Goodman and Gotlib 1999). One adoption study proved that offspring of depressed mothers in biologically unrelated mother-child pairs have a higher prevalence of depression (Tully et al. 2008). Other studies of children who are genetically unrelated to maternal depression suggest that the risk effect of maternal depression is mediated by exposure to later and sustained maternal depressive symptoms or associated adversity experiences (Foster et al. 2008).

Clearly, offspring of depressed parents seem to be the most vulnerable group, and parents' depression should be treated to prevent offspring from becoming depressed. Depressive symptoms of offspring improve if remission of parents' depression occurred, and this change is related to the improvement of familial function.

22.2.2 Genetic Risks

Many studies have been performed to establish genetic associations with child and adolescent depression, but consistent and powerful risk factors have yet to be discovered. A specific depression gene needed for an animal model has not yet been found. Therefore, it is thought that genetic factors interact with environmental risk factors to determine the onset of depression (Caspi and Moffitt 2006). This interplay can occur in two ways. First, a gene-environment interaction suggests that genes and environments combine to increase the subject's susceptibility to psychosocial stress (Uher and McGuffin 2010). Second, a gene-environment correlation suggests that genes and environments combine to increase the subject's vulnerability. In other words, genetic characteristics may influence the subject's behavior tendency, which increases the risk of stressful environments (Lau and Eley 2008).

The serotonin-transporter-linked polymorphic region (5-HTTLPR) has received attention related to gene-environment interaction. Adolescents who have this variant and are exposed to stressful life events or childhood maltreatment may develop depression (Caspi et al. 2005). A study of 337 adolescents, divided into 4 groups by their severity of depressive symptoms and environmental risks, was conducted to identify serotonin-related genes such as 5-HTTLPR serotonin receptor 2A (HTR2A), serotonin receptor 2C, monoamine oxidase type A (MAOA), and tryptophan hydroxylase (TPH). The results showed that HTR2A and TPH significantly predicted the depression group independent of the effects of sex, environmental risk group, and their interaction. Interestingly, there was a significant genotype-environmental risk interaction for 5-HTTLPR in female subjects only, while environmental factors were not significant factors for depression (Eley et al. 2004). Another study reported that adolescent depression following negative life experiences was related to the 5-HTTLPR genotype (Kaufman et al. 2004). These results may reflect variations in gene-environment interactions by age and/or gender, markedly shown in postpubertal females (Uher and McGuffin 2010).

A study of brain-derived neurotrophic factors (BDNF) and 5-HTTLPR genotypes compared 109 children with abuse history to 87 without and included additional information of psychiatric symptoms and social support. There was a significant three-way interaction among BDNF genotype, 5-HTTLPR genotype, and maltreatment history in predicting depression. Children with the met allele of the BDNF gene and two short alleles of 5-HTTLPR had the highest depression scores, but the vulnerability associated with these two genotypes was evident only in the maltreated children. With social support added as a covariate, children with a maltreatment history had similar depression scores to the control group when social support was appropriate but higher depression scores when genetic variation existed with poor social support. This study demonstrated a gene-by-gene interaction conveying vulnerability to depression and showed a protective effect of social support in ameliorating genetic

and environmental risks for psychopathology (Kaufman et al. 2006).

Although reported in many studies, it is unclear whether specific genes increase susceptibility for unipolar depression. The reason for this uncertainty is that depression has a more complicated interaction of gene and environment than is found in other mental illnesses, such as schizophrenia and bipolar disorder (Thapar et al. 2012).

22.2.3 Psychosocial Risks

Previous studies have demonstrated that social-environmental factors contribute to child and adolescent depression. These studies have shown that adolescents exposed to social-environmental stress experience more depressive symptoms and are more strongly associated with the first onset than recurrence of depression (Lewinsohn et al. 1999a). This is especially noticeable in female adolescents (Thapar et al. 2012). With 95% of adolescent depression involving at least 12 months of chronic psychosocial problems (Goodyer 2008), multiple life events and chronic psychosocial risks should be considered (Lewinsohn et al. 1999a). Psychosocial risks include loss of parents, divorce or marital conflicts, child abuse or neglect, peer bullying, and illness or death of family members (Jaffee et al. 2002). Childhood adversity such as abuse and neglect increases the risk of depression. Childhood adversity has been known to be related to depression in terms of earlier onset, lower treatment response rate, and relapse (Molnar et al. 2001; Barbe et al. 2004). Children deprived of appropriate parental care at a young age have lower central serotonergic function, which results in impulsive aggression, depression, and suicidal behavior (O'Connor and Cameron 2006). Low birth weight and early maternal age are also risk factors for depression (Costello et al. 2007). Childhood adversity increases the risk of not only depression but also substance abuse, posttraumatic stress disorder (PTSD), suicidal behavior, and disruptive behavior (Brown et al. 1999).

Although psychosocial risks are factors for depression across all ages, differences have been found. First, several twin studies report relatively low heritability estimates in childhood depression compared to adolescent depression (Thapar and Rice 2006). Next, adolescent- and adult-onset depression has different psychosocial risk profiles. Adolescent-onset depression seems to have a closer relationship with problematic peer relationships, parental neglect, and childhood family adversity (Hill et al. 2004). Other researchers argue such risk factors may look different depending on the time of onset. When potentially genuine risk differences among the depression-onset groups were separated from differences due to the recency of risk, there was no difference between child- and young adult-onset depression in terms of psychosocial risk profiles (Shanahan et al. 2011).

On the other hand, children and adolescents exposed to chronic, multiple, and serious stressors do not always become depressed. It seems there are various confounding factors that are not yet found and are difficult to measure; however, research has confirmed the relationship between psychosocial risk factors and depression. Further studies should focus on the contribution of certain psychosocial risks to the onset of depression.

22.2.4 Neural and Neuroendocrine Risks

Genetic and psychosocial factors are distal risk factors, while changes in the neural circuits and endocrine system are considered proximal risk factors, yielding a direct effect (Pine et al. 2010). It has been shown that genetic and environmental factors have stronger influences on the brain in adolescents than in adults (Lenroot et al. 2009). Previous studies suggest two neural circuit and related systems that increase the risk of depression.

The first neural circuit connects the amygdala, hippocampus, and prefrontal cortical regions and is associated with hypothalamic-pituitary-adrenal (HPA) axis activity, which is related to emotional

processing of threats (Maughan et al. 2013). Activity in this neural circuit seems to increase in depression patients and decrease after treatment (Brody et al. 1999). A study comparing depressive disorder, anxiety disorder, and normal adolescents showed different amygdala responses to fearful faces in anxious and depressed children. Those with anxiety disorder had increased activity, while those with depressive disorder had decreased activity (Thomas et al. 2001). Children and adolescents at risk for major depression showed increased activity of the amygdala and nucleus accumbens during emotional facial expression (Monk et al. 2008). Perturbations in this neural circuit activate the stress-managing HPA system and increase the cortisol level within our body influencing the serotonergic system (Lopez-Duran et al. 2009). Genetic factors, psychosocial stress, sex hormones, and developmental plasticity have also been associated with activity in this circuit (Pine 2003).

The second neural circuit connects the striatum, prefrontal cortex, and ventral dopamine-based system, which is related to reward processing (Maughan et al. 2013). A decrease in right-sided ventral striatal activity was observed when adolescents with depressed parents were given tasks related to the reward system (Sharp et al. 2014). In addition, depressed adolescents had lower left-sided caudate nucleus activity and higher dorsolateral prefrontal cortex activity than the comparison group during a monetary reward task (Forbes et al. 2009). These changes are considered pathophysiological mechanisms leading to an abnormal reward circuit in depression, which is specifically related to low positive affect and anhedonia of depression.

Recent studies focus on the increased negative affect and diminished positive affect shown from depression. This is useful to understand mechanisms underlying mood and subjective experiences (Forbes and Dahl 2012). Positive affect is defined as an ability to experience expectations, happiness, and pleasure with rewards. Depressed children and adolescents do not react to rewards and have a lower level of positive affect than other children (Silk et al. 2007). Depressed children and adolescents also have a tendency to choose the tasks with lower possibilities of reward and have decreased activity in brain regions related to the reward system (Forbes et al. 2007). Depressed adolescents exhibit reduced reactivity in the striatum in response to decision-making, anticipation, and monetary reward (Forbes et al. 2009). Some studies have reported that depressed adults and adolescents exhibit high reactivity in the medial prefrontal cortex, which is thought to play a role in regulating reward response (Knutson et al. 2008; Forbes et al. 2009). Meanwhile, there are reports that age was negatively correlated with striatal activation to happy faces (Lindstrom et al. 2009). This finding means that striatal response from different rewards can change with age and age-related variations in this brain function can result in adolescent depression. In conclusion, a lower level of positive affect and decreased activity in a reward-related system are known to be predictors of depression onset and relapse (Forbes et al. 2006a).

Emotional regulation is also considered a risk factor for child and adolescent depression. Emotional regulation consists of two meanings: the degree and duration of physiological arousal and strategies for emotional response. The amygdala response for facial expressions is found to be different for depressed children than for normal children (Roberson-Nay et al. 2006). Offspring of mothers with early-onset depression were found to have a lower base respiratory sinus arrhythmia and faster heartbeat rate after experiencing frustration (Forbes et al. 2006b). Offspring of depressed parents have a decreased ability to switch attention, to use distraction, to engage in cognitive shifting, and to use positive memories as strategies for emotional response (Forbes et al. 2006b). Although emotional regulation is a very complicated process consisting of unconscious, cognitive, and self-regulatory components, it can be adaptive or maladaptive. Maladaptive emotion regulation has a correlation with depression and is a risk factor for depression recurrence during adulthood (Joormann and D'Avanzato 2010). Some specific maladaptive emotion regulation strategies such as rumination, catastrophizing, and self-blame are associated with increased depressive symptoms in adolescents. On

the other hand, adaptive strategies such as positive reappraisal, positive refocusing, and putting into perspective are associated with decreased depressive symptoms (Garnefski et al. 2003; Kraaij et al. 2003).

22.3 Prevention Strategies

22.3.1 Introduction

The purpose of prevention is to decrease relevant risk factors or promote relevant protective factors to reduce the possibility of negative outcomes in the future (Coie et al. 1993). Preventing depression can increase opportunities for healthy development across multiple domains. Long-term emotional and physical outcomes may improve by preventing depression. Preventing or delaying depression occurrence during adolescence and young adulthood allows for healthy social and emotional development tasks. Both mental health problems and comorbid physical problems related to depression can be prevented, which is a positive factor for multiple domains throughout life (Moussavi et al. 2007). In addition, preventing depression reduces lifetime mental healthcare needs and likely yields medical care cost savings. Appropriate prevention strategies can provide cost savings for patients and family members. This can increase opportunities not only for treatment cost savings but also for education and occupation, ultimately creating social benefits (Zechmeister et al. 2008).

Meta-analytic studies report that strategies for preventing child and adolescent depression have modest effects, even among high-risk samples (Brunwasser et al. 2009; Stice et al. 2009). High-risk samples include having parents with depression history, adolescents having depression history, and the experience of subthreshold depressive symptoms (Lewinsohn et al. 1999b; Beardslee et al. 2011). The main outcomes and measures of prevention strategies are reducing depressive symptoms and preventing depressive episodes. However, few studies confirm significant effects of preventing and reducing episodes of adolescent depression, and only one study conducted by Beardslee et al. reports a sustained effect lasting several years (Beardslee et al. 2013). Most studies of prevention strategies focus on reducing depressive symptoms; high-risk adolescents are associated with a larger effect size ($r = 0.23$, $P < 0.001$) than normal adolescents, especially for negative cognition and anhedonia of depressive symptoms (Stice et al. 2009).

22.3.2 Types of Prevention

Preventive interventions are classified into three categories based on the characteristics of the target group (Abela and Hankin 2008). Universal intervention strategies are provided to everyone without targeting subgroups, such as a school-wide depression prevention program, therefore eliminating the possibility of labeling. Selective prevention strategies involve identifying a group of children at risk who have known factors that increase susceptibility but who have not developed the disorder, such as a depression prevention program for offspring of depressed parents. Indicated strategies involve detecting signs and symptoms of the disorder in a population, such as by screening, and then directing the intervention to the targeted sample. Target individuals are at the highest risk for developing the disorder based on subclinical symptoms or signs that do not yet meet full diagnostic criteria, such as a depression prevention program for adolescents with subthreshold depressive symptoms. Although universal programs have advantages including lower dropout rates, the ability of subjects to avoid stigma, or the opportunity to intervene with at-risk adolescents not targeted via screening instruments, previous studies have taught us that universal intervention has a smaller effect size than selective and indicated intervention (Stice et al. 2009). Therefore, in this chapter, we will focus on selective and indicated programs and introduce studies based on the positive results given priority to randomized controlled trials (RCTs). The following programs were selected based on the positive findings in meta-analytic studies of depression

prevention programs for children and adolescents published between 2006 and 2015 (Stice et al. 2009; Teubert and Pinquart 2011; Ahlen et al. 2015). Programs that were not included in meta-analyses but were worth mentioning were included based on the positive results from at least two RCTs published after 1995.

22.3.3 Selective Programs

22.3.3.1 Penn Resiliency Program

The Penn Resiliency Program (PRP) is a cognitive behavioral and social problem-solving intervention designed to reduce and prevent depressive symptoms in children and adolescents; the PRP is one of the most studied and best-known depression prevention programs (Gillham et al. 2000). The cognitive behavioral component (five sessions) is based on cognitive theories of depression. It focuses on teaching adolescents to identify and evaluate pessimistic thoughts by considering alternatives and examining evidence. The social problem-solving component (seven sessions) addresses the interpersonal and conduct problems that often co-occur with depression in adolescence. It also teaches skills for assertiveness, decision-making, and coping with conflict. Advantages of the program are that it can be used not only in school settings but also in primary care and juvenile detention settings (Brunwasser et al. 2009).

Cardemil et al. (2007) performed a randomized controlled trial on the efficacy of the PRP with low-income, racial/ethnic minority children. The PRP program can be categorized as selective prevention because low-income and ethnic minority status have been reported as risk factors for depression (Vega et al. 1998; Najman et al. 2010). A total of 168 Latino and African American middle school children who were at risk for developing depressive symptoms by virtue of their low-income status participated in the trial. Latino students showed a significant decrease in depressive symptoms compared to the control groups after 6 months and 2 years, respectively. However, no beneficial effect for the African American children was found at any point.

Cutuli et al. (2006) performed a randomized controlled trial on the efficacy of the PRP with adolescents who exhibited high levels of conduct problems but not depression symptoms. Childhood disruptive behavior was reported as a key domain of lowering functions, such as academic achievement and interaction with parents. Under this model, children have more negative experiences and encounter repeated failures in adolescence. These repeated failures in multiple domains are associated with later depression symptoms (Capaldi 1992). A total of 294 students (mean age of 12 years) were randomly assigned to either the intervention or control condition. Longitudinal analyses demonstrate that the program successfully prevented elevation in depression symptoms in adolescents compared to the no-intervention control group. However, the effect size of the intervention was not reported in the study.

Gillham et al. (2007) designed a randomized controlled trial investigating the effectiveness and specificity of the PRP. The PRP was used as a universal prevention program in this study. Children (N = 697) from three middle schools were randomly assigned to the PRP, control, or Penn Enhancement Program (PEP). Children's depressive symptoms were assessed through 3 years of follow-up. The findings varied by school. The PRP prevented onset of depressive symptoms compared to the control in two schools but not in the third school. In two schools, the PRP significantly reduced depressive symptoms at follow-up compared to the control and PEP groups. However, intervention effect sizes at posttest and follow-up were 0.02 and 0.01, respectively, in the meta-analysis (Ahlen et al. 2015). On the other hand, some studies using the PRP as a selective strategy rather than a universal strategy reported relatively larger effect sizes (0.40 by Pattison and Lynd-Stevenson and 1.24 by Cardemil et al.). Thus, the PRP is expected to be more effective when used as a selective strategy.

Chaplin et al. (2006) examined whether a depression prevention program, the PRP, was more effective for girls in all-girl groups than for those in coeducation groups. Girls were assigned

to all-girl groups, coeducation groups, or a control group. In the result, the all-girl groups were better than coeducation groups in reducing hopelessness and for session attendance rates but were similar to coeducation groups in reducing depressive symptoms. The intervention effect size at posttest was 0.42 in the meta-analysis (Ahlen et al. 2015). Although the effect size was larger than in other studies, the absence of a follow-up assessment and the limitation of the sample containing only girls as subjects are limitations for interpretation.

22.3.3.2 Cognitive Behavioral Prevention Program

The Cognitive Behavioral Prevention (CBP) program was a modification of the intervention developed by Clarke et al. (2001), who demonstrated significant prevention of depressive episodes with CBP compared to usual community care (UC) for adolescents of parents with depression. The CBP program aims to help high-risk adolescents gain control over negative moods, resolve conflicts with family or friends, and alter maladaptive thought patterns. The CBP program is designed to be delivered by at least master's level trained clinicians and trained mental health professionals (e.g., social workers and psychologists).

Clarke et al. (1995) examined the effectiveness of the CBP program compared to a UC group in a randomized controlled trial of 94 adolescent offspring of parents treated for depression. Eligible adolescents had to have subthreshold depressive symptoms and/or a history of mood disorder and a parent with depression. The CBP group reported fewer depressive symptoms, fewer symptoms of suicide, and better overall functioning. At 12-month follow-up, 9.3% of the adolescents in the CBP program met diagnostic criteria for major depressive disorder compared with 28.8% of the adolescents in the UC program. In addition, a significant preventive effect persisted across a 24-month follow-up interval.

Garber et al. (2007) examined the four-site effectiveness of the CBP program compared to a UC group in a RCT of 316 adolescents. They modified the CBP program to include 8 weekly and 6 monthly continuation sessions. The results indicate that at 9-month follow-up, adolescents randomized to the CBP condition had significantly fewer episodes of depression (21.4%) compared with those in UC (32.7%). Moreover, this main intervention effect was moderated by a current parental depressive symptom at baseline. The CBP program was significantly more effective in preventing subsequent depressive episodes compared to UC for adolescents whose parents were not depressed at baseline.

Beardslee et al. (2013) conducted a multisite randomized clinical trial to examine the effectiveness of the CBP program for 316 adolescent offspring of depressed parents. This study also aimed to determine whether the positive effects of the CBP program extended to longer-term follow-up. The CBP program consisted of 8 weekly 90-min group sessions followed by 6 monthly continuation sessions. Adolescents were at high risk because of their parents with depression history (selective prevention) and the adolescents' own history of a prior depressive disorder or current depressive symptoms (indicated prevention). The results indicate that the CBP program showed significant sustained effects compared with UC in preventing the onset of depressive episodes in high-risk adolescents over a nearly 3-year period. Weersing et al. (2016) examined predictors and moderators of a CBP program for the same sample mentioned above. The results indicate that depression onset was predicted by lower functioning and greater hopelessness. The superior effect of CBP was decreased when parents had current depressive symptoms at baseline or a history of hypomania. In addition, adolescents' psychiatric symptoms (e.g., depressive symptoms, anxiety, and hopelessness) also reduce the superior effect of CBP. Thus, the CBP program may have superior results when high-risk families are in a relatively good state of mental health.

22.3.3.3 Aussie Optimism Program

The Aussie Optimism Program (AOP) was developed as a school-based intervention and used to prevent depression and anxiety symptoms. The AOP has two components. The social life skills component was developed to over-

come interpersonal risks, such as social problem solving, poor social skills, lack of social support, and friendship difficulties (Roberts et al. 2003b). The optimistic thinking skills component targets cognitive vulnerabilities including pessimistic attribution style, negative self-perceptions, and future expectations (Roberts et al. 2003a). These components each contained ten 60-min lessons to be taught by teachers. The lessons included didactic information; interactive activities such as role-play, games, and cooperative learning tasks; cross-curriculum applications; worksheets; and homework activities to integrate skills into the home setting. The reason why the AOP is categorized as a selective program is that schools implementing the program are in low socioeconomic areas. Students are more likely to be exposed to risks such as low family income, broken families, conflict, and other stressful life events, which increase the probability of depression occurrence.

Roberts et al. (2010) designed a randomized controlled trial with 7th grade students ($N = 496$) from disadvantaged government schools in Perth, Western Australia. Six schools were randomly assigned to the AOP, and six schools received their usual health education lessons. Students in the intervention group showed significant improvement in parent-rated internalizing symptoms at posttest. No significant group effects were found for the student-reported data. Follow-up group effects were not significant. Intervention effect sizes at posttest and the follow-up point were −0.14 and −0.05, respectively, in the meta-analysis (Ahlen et al. 2015). However, the implementation, fidelity, and student attendance associated with the AOP were high. Hence, it is unlikely that the program was ineffective because of poor implementation or low student participation rates.

22.3.4 Indicated Programs

22.3.4.1 The Feeling Club

The Feeling Club is a manual-based, 12-week group cognitive behavioral therapy (CBT) program focused on recognizing and managing negative feelings and maladaptive thoughts. It utilizes cognitive restructuring and is adapted from the earlier evaluated "Coping Bear" manual for child anxiety disorders. This program encourages children to "choose a feeling" and allows them to apply strategies to all forms of negative affect. In addition, three psychoeducational parent evenings about internalizing symptoms and CBT principles were offered. Activities consisted of the following two distinct conditions: a structured, supervised after-school activity and parent evenings of general child-rearing discussion group that did not concentrate on CBT or symptoms (Manassis et al. 2002).

Manassis et al. (2010) evaluated a preventive CBT program targeting internalizing symptoms relative to an activity contrast condition in a randomized 12-week trial. A total of 1139 participants from 3rd to 6th grade from many cities across Canada were screened with the Multidimensional Anxiety Scale for Children and Children's Depression Inventory. The study included 148 subjects, all having T scores over 60 through the screening tests. They were randomized either to the Feeling Club group or to a structured after-school activity group of equal duration. The study results showed improved internalizing symptoms in all participants, but no significant difference between the groups was found. Therefore, the authors reported that adolescents with internalizing symptoms could obtain help through both the Feeling Club and the structured activity program.

22.3.4.2 Friends for Life

The Friends for Life program is a protocolled preventive intervention for childhood anxiety and depression based on cognitive behavioral therapy. The program teaches children how to recognize symptoms of anxiety or depression, how to relax, how to act when a problem arises, and how to engage in positive self-talk; provides graded exposure to feared situations; and teaches them to reward themselves after trying rather than focusing on succeeding. This program consists of ten group sessions and one booster session 1 month

after the program has finished. Each session lasts 90 min. Schools conducted one to two parent sessions (Shortt et al. 2001).

Lowry-Webster et al. (2003) designed a randomized controlled trial investigating universal and indicated strategies for preventing anxiety and depressive symptoms using the group CBT program Friends for Life. Participants were 594 children aged 10–13 years from seven schools in Brisbane, Australia. Participants were randomly assigned to an intervention or control group on a school-by-school basis. The results were examined for all children (universal strategy) and for children who scored above the clinical cutoff point at pretest (indicated strategy). A rate of 31.2% of the control group achieved scores below the cutoff point, while 85% of the intervention group achieved scores below the cutoff point. Improvements in clinical symptoms were evaluated via self-reports and diagnostic interviews that were maintained until the 12-month follow-up assessment.

Kösters and colleagues investigated whether the intervention effects of Friends for Life were maintained over a period of 12 months after the intervention in a naturalistic setting. Participants included 339 children in the intervention group and 157 in the control group (aged 8–13 years) at schools in Amsterdam, the Netherlands. There was a continued and significant decrease in anxiety and depression scores for the intervention-group children compared with the control group. Anxiety and depression symptoms did not worsen after 12 months. The authors contended that the program has a long-term effect in reducing anxiety and depression problems (Kösters et al. 2015).

22.3.5 Other Types of Prevention

Existing preventive interventions for child and adolescent depression are mostly based on schools because schools are easy contexts for gathering data from subjects and have a low dropout rate. However, other prevention strategies for children who do not attend school are needed since these children may also be vulnerable to depression. The first one is a family-based intervention. The risk of depression is 3–4 times higher in children with depressed parents, making them targets for active intervention (Weissman et al. 2006).

Beardslee et al. (2003) included not only depressed children but also parents themselves, unlike in other intervention programs. A total of 121 children in 93 families participated in the study and were randomly assigned to either a lecture or a clinician-facilitated intervention. The lecture condition consisted of two separate meetings delivered in a group format without children present. The clinician-facilitated condition consisted of 6–11 sessions, including separate meetings with parents and children. Information about depression, communicating skills, and depression symptoms of parents was discussed through family meetings. Both interventions increased the understanding of depression and decreased internalizing symptoms. Parents' behavior and attitude changes and their connection to children's changes in understanding were identified as an important mediating variable for family change. Compas et al. (2009) also improved the parenting skills of depressed parents and taught methods to handle stress related to parental depression using the Family Group Cognitive Behavioral program. RCT trials showed that this program is effective and can be maintained for 12 months. A systematic review based on 15 studies of family-based parent training and social skills training for preventing depression suggested significant reductions in depressive symptom at follow-up (Waddell et al. 2007).

A new delivery modality is the implementation of digital platforms as a prevention strategy using internet and computer technology. In recent years, there has been increasing interest in the use of digital platforms for the delivery of mental health interventions. The advantage of online mental health intervention is that it allows individuals to have direct and convenient access to resources. Interventions of this kind also offer individuals increased privacy and anonymity and provide a cost-effective means of accessing services for those with poor geographical accessibility (Barak and Grohol

2011). Therefore, digital platforms using internet and computer technology are commonly used for the delivery of mental health programs. A systematic review showed that internet and computerized interventions for depression were successful in reducing depressive symptoms among adolescents and young adults but not younger children (aged 5–11 years). Another study resulted in improvements in depressive symptoms via internet-based intervention and motivational interviewing or brief advice provided by a primary care physician (Saulsberry et al. 2013). The most recent systematic review based on 20 studies of online intervention indicated a significant effect of computerized CBT on reducing adolescents' anxiety and depression (Clarke et al. 2015). However, there are several studies that report nonsignificant effects, and no meta-analysis has been conducted due to the heterogeneity among studies. Therefore, more extensive and rigorous research is warranted to further establish the conditions that enhance effectiveness.

Conclusion

The purpose of this review was to identify the genetic, social-environmental, and biological risk factors for child and adolescent depression and the existing strategies known to be effective for preventing depression. Child and adolescent depression not only is a current mental health problem but also causes negative long-term consequences in adulthood. In addition, adolescence is a key window for preventive interventions because the prevalence of depression significantly increases during this developmental period. Thus, the need for efficacious preventive interventions for the childhood and adolescent period is widely recognized.

Many epidemiologic and clinical studies have helped to identify who is at risk for developing depression and what should be the target of interventions to prevent depression. Risk factors associated with an increased likelihood of child and adolescent depression include familial risks (e.g., offspring of depressed parents), genetic risks (e.g., 5-HTTLPR, TPH, and BDNF genotype), psychosocial risks (e.g., childhood adversity), and neural and neuroendocrine risks (e.g., neural circuit associated with HPA axis or reward processing, positive affect, and emotional dysregulation). Some researchers have suggested that a specific single risk factor alone can induce depression and have tried to measure the extent of the influence single risk factors on developing depression (Lewinsohn et al. 1994). However, it is difficult to distinguish one particular causal mechanism from others because cognitive, psychosocial, and biological changes occur rapidly in adolescence. Therefore, most researchers have suggested that complex interactions between various risk factors and mechanisms increase the likelihood of depression. In general, based on the integrated multilevel models (Garber 2007), individuals with a particular fixed risk factor (e.g., gender, genetic phenotype) have an increased likelihood of depression when confronted with stressful life events. Moreover, these individuals' vulnerability both increases the risk of exposure to stressful environments and decreases the ability to cope with psychosocial stress.

Prevention strategies for depression are intended to enhance the protective factors or decrease the modifiable risks of high-risk children (e.g., those experiencing adversity or having a genetic vulnerability to depression). Several recent systematic reviews and meta-analyses concluded that prevention interventions are beneficial in preventing child and adolescent depression (Stice et al. 2009; Corrieri et al. 2014). Although a small effect size was a major limitation for most of the prevention studies, prevention programs should be actively developed and utilized, considering the positive results consistently reported and the benefits related to finance and public health.

The strategies can be categorized into three types of intervention methods, as previously mentioned. From recent meta-analyses, it is argued that a selective and indicated prevention strategy is effective in preventing the occurrence

of depression in children and adolescents, whereas universal prevention is not (O'Connell et al. 2009; Stice et al. 2009). Although the efficacy of selective and indicated prevention programs turned out to be statistically significant, the effect size of the selective and indicated prevention was not large enough. This limitation arises because only a few studies exist; few subjects participated in the studies, and heterogeneity in characteristics was observed with respect to current symptoms of depression. For more significant results, there is a need for future studies with adequate statistical power, with homogenous samples, and with a common template used among various research groups to consistently study child and adolescent depression. It is also important to develop a new prevention program targeting low positive affect, reward processing, and emotional dysregulation. Previous studies have repeatedly reported that a lower level of positive affect and decreased activity in the reward-related system are associated with child and adolescent depression. Emotional regulation has also been shown to be related to biological correlates of depression, such as amygdala reactivity and cortisol hypersecretion (Joormann and D'Avanzato 2010; Forbes and Dahl 2012). Therefore, better outcomes may be obtained by carefully assessing these risk factors and by applying targeted preventive strategies in accordance with the risk factors identified.

In conclusion, the complexity and costs associated with the treatment of child and adolescent depression are the reason for the development of various prevention strategies. However, the key components for preventive intervention have not been precisely identified, and cost-effectiveness is a major concern, thus serving as targets for future research. Finally, future studies should demonstrate not only the effectiveness of programs but also their generalizability with different ethnic and cultural groups.

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Neurobiology and Risk Factors of Late-Life Depression

23

Neha Jain and David C. Steffens

23.1 Introduction

Depression is one of the most common and disabling psychiatric illnesses in the elderly. Prevalence rates of geriatric depression vary depending on the definition of depression, the population being studied, and the instruments used. In community-dwelling elders, the prevalence of major depressive disorder appears to be between 1 and 4% (Mulsant and Ganguli 1998; Steffens et al. 2000). Subsyndromal depressive symptoms are more common in the elderly, with prevalence rates up to 15% (Hendrie et al. 1995). Combining all measures, prevalence of clinically significant depressive symptoms in the USA has been reported to be 11.19% among individuals aged over 70 (Steffens et al. 2009). All depressive disorders are associated with significant morbidity and impaired quality of life. In the elderly, depression leads to an increased risk of both dementia and death (Schoevers et al. 2000b; Ownby et al. 2006; Diniz et al. 2013).

Recent technological advances have led to an improved understanding of the neurobiological basis of mood disorders. New models have moved beyond the traditional monoamine systems theory to include altered neurotrophins, immune system dysfunction, inflammation, and altered gene expression to explain the various phenotypes of geriatric depression (Drevets et al. 2008; Krishnan and Nestler 2010). This chapter will review these findings and highlight important new advances in our understanding of the biological underpinnings of late-life depression (LLD), which we define as depression occurring later in life regardless of age of onset.

23.2 Neural Pathways of Depression

Neuropathological and neuroimaging studies have led to the identification of neuroanatomical circuits that regulate various aspects of emotions and behavior. While some studies specifically examined the neural circuitry of depression in younger adults, the models described are likely helpful in understanding the neuropathology of LLD as well. Drevets et al. described several pathways relevant to depression among adults (Drevets 2000; Drevets et al. 2008). The limbic-cortical-striatal-pallidal-thalamic (LCSPT) circuit is formed by connections between the orbital prefrontal cortex (OPFC), medial prefrontal cortex (MPFC), amygdala, hippocampus, ventromedial striatum, thalamic nuclei, and ventral pallidum. Any disruption through this circuit, for example, in degenerative diseases of the basal ganglia, can produce the symptoms of major depression (Drevets

N. Jain (✉) • D.C. Steffens
Department of Psychiatry, University of Connecticut Health Center, Farmington, CT, USA
e-mail: njain@uchc.edu

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et al. 2008). Microstructural changes in the white matter of the right superior frontal gyrus have been associated with late-life depression (Taylor et al. 2004).

Philips et al. described two neural systems that may be implicated in the neuropathology of depression: a ventral/affective circuit, including the amygdala, insula, ventral striatum, and ventral regions of the anterior cingulate gyrus and prefrontal cortex, involved in the identification of the emotional significance of a stimulus and production of an affective state in response, along with automatic regulation of emotional responses. The second circuit is best described as a dorsal/cognitive network, including the hippocampus and dorsal regions of anterior cingulate gyrus and prefrontal cortex, predominantly important for the regulation of the affective state (Phillips et al. 2003) (Fig. 23.1).

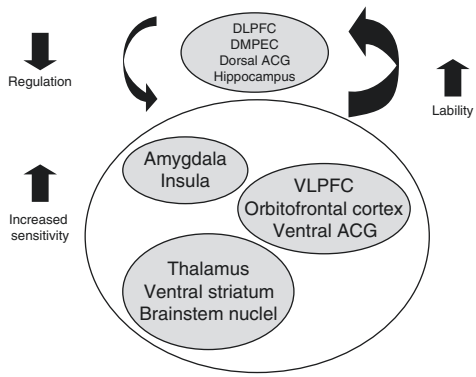

Fig. 23.1 Schematic diagram depicting neural structures involved in the three processes underlying emotion perception. A predominantly ventral system is important for the identification of the emotional significance of a stimulus, the production of an emotional response, and the autonomic response regulation (depicted in dark gray), whereas a predominantly dorsal system (depicted in pale gray) is important for the regulation of the resulting emotional states. A reciprocal functional relationship may exist between these two neural systems. VLPFC, ventrolateral prefrontal cortex; DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ACG, anterior cingulate gyrus. Reprinted from "Biological Psychiatry", Vol 54, Issue 5, Authors Mary L. Phillips, Wayne C. Drevets, Scott L. Rauch, Richard Lane, "Neurobiology of emotion perception I: the neural basis of normal emotion perception", 504–514, Copyright (2003) Society of Biological Psychiatry, with permission from Elsevier

It has been suggested that the clinical expression of LLD may be mediated by hypometabolism of dorsal cognitive regions and hypermetabolism of ventral affective structures (Alexopoulos 2005). Studies demonstrate that LLD is associated with greater white matter lesion (WML) severity in specific tracts including the cingulum bundle, uncinate fasciculus, and superior longitudinal fasciculus (Sheline et al. 2008; Taylor et al. 2011). Greater WML severity in the uncinate and superior longitudinal fasciculi is also associated with executive dysfunction (Smith et al. 2011) and greater depression severity (Dalby et al. 2010b). In a review of the "vascular depression" hypothesis, the authors proposed three complimentary, interconnected mechanistic pathways to LLD: disconnection, hypoperfusion, and inflammation (Taylor et al. 2013).

Several studies have examined the role of the hippocampus in mood disorders. In a study comparing hippocampal volumes of ten older adults with a history of recurrent depression with matched controls, the authors reported significant smaller hippocampal volumes with no loss of cerebral volume in the depressed group. The degree of hippocampal volume reduction correlated with the total duration of depression. The authors suggested that hippocampal atrophy in depression may be mediated by glucocorticoid neurotoxicity (Sheline et al. 1996). The hippocampus is also implicated in the memory deficits frequently seen in LLD (Steffens et al. 2011b). In a sample of elderly patients with depression, Krishnan et al. (1993) reported smaller putamen and caudate volumes relative to controls.

Multiple neurotransmitter systems have been implicated in the pathogenesis of depression. Researchers have focused on serotonergic, noradrenergic, dopaminergic, and more recently glutamatergic neurotransmission and their roles in LLD (Ressler and Nemeroff 2000).

Extensive evidence supports the construct of a deficit in serotonergic neurotransmission in the development of major depression (Meltzer 1989). In LLD, a lack of alteration in 5-HT1A binding sites in frontal, temporal, and parietal lobes has been reported (Bowen et al. 1989). In the elderly,

age-related changes in 5-HT neurons may lead to a vulnerability to depression. Evidence suggests that a combination of disturbances in cholinergic and serotonergic function may play a role in cognitive impairment in Alzheimer's disease, with serotonergic dysfunction potentially responsible for some of the neuropsychiatric symptoms of the disease (Meltzer et al. 1998). In a study using PET imaging to evaluate 5-HT2A receptor binding among elderly patients with depression and dementia, no significant abnormalities in altanserin binding were observed in the patients with LLD, and no effect of depression on binding potential was present within the Alzheimer's disease group. However, patients with Alzheimer's disease had significantly lower binding than the normal subjects in several brain regions (Meltzer et al. 1999). Serotonin is important in the regulation of N-methyl-D-aspartate receptor activity, which in turn modulates synaptic plasticity (Bennett 2010). Functional imaging in LLD patients treated with the selective serotonin reuptake inhibitor (SSRI) citalopram implicates an interaction between subcortical dopamine and serotonin systems with cortical glutamatergic function (Diaconescu et al. 2011).

Dopamine has both inhibitory and excitatory effects on fronto-subcortical functioning. Dopamine cells from the ventral tegmentum and the substantia nigra project to three principal areas: (1) the neostriatum, mainly to the caudate and the putamen, (2) the limbic cortex, and (3) other limbic structures. Dopaminergic connections between the substantia nigra and limbic system are involved in the integration of emotional input, motor activity, cognition, and motivation.

Neuroimaging studies in depressed non-geriatric adult patients show reduced dopaminergic neurotransmission (Nutt 2005). Degeneration of dopaminergic neurons in Parkinson's disease is associated with increased vulnerability for developing depression (Santamaria et al. 1986). Studies have shown that alterations in mesolimbic dopaminergic neurotransmission may be critical to at least some aspects of antidepressant action (Alexopoulos 2001). In elderly patients with "vascular depression," dopaminergic agents may be more useful than other antidepressants (Andreescu and Reynolds 2011).

Multiple animal models and human studies provide evidence for a role of glutamate and GABA in the pathophysiology of LLD (Frisardi et al. 2011). In a review of clinical trials implicating glutamate in mood disorders in adults, Sanacora et al. (2004) suggested that dysregulation of glutamate transmission seen in depression may be a result of glial dysfunction. Decreased uptake of glutamate by astrocytes would increase glutamatergic neurotransmission, and the antidepressant effect of NMDA antagonists would be a result of increased activation of AMPA and kainate receptors. In a study of depressed elderly patients, the authors reported significantly reduced glutamate/glutamine levels in the dorsolateral prefrontal cortex and left anterior cingulum compared to age-matched controls, which then returned to normal in those who responded to electroconvulsive therapy (Michael et al. 2003).

Parallel to findings of glutamatergic dysfunction, there is also growing evidence for dysregulation of GABA in depression. Non-geriatric studies have reported reduced GABA levels in both the dorsomedial/dorsal anterolateral PFC and the occipital cortex (Sanacora et al. 1999; Hasler et al. 2007), but there is a paucity of research on GABAergic neurotransmission in LLD. In one postmortem study examining two calcium binding proteins that bind to GABAergic interneurons in the DLPFC of elderly depressed patients, authors reported significant reductions in parvalbumin immunostaining in layer 6 of the DLPFC (Khundakar et al. 2011a).

The hypothalamic-pituitary-adrenal (HPA) axis is the primary regulator of the physiological stress reaction. Overactivity of the HPA axis, together with an overactive glutamatergic system and a hypoactive GABAergic neurotransmission, has been associated with depression in younger adults (Thomson and Craighead 2008). In an interesting population-based study, Bremmer et al. (2007) reported a U-shaped association between cortisol and major depression in older adults. Hypocortisolemic depression was associated with female sex, joint diseases, and smok-

ing. Hypercortisolemic depression was associated with older age, male sex, cardiovascular diseases, nonsteroidal anti-inflammatory drug use, and cognitive impairment. This indicates that LLD may have multiple subtypes.

23.3 Vascular Depression

Depression in the elderly may be related to multiple underlying pathologies reflected in the heterogeneity of age of onset, clinical presentation, and presence of comorbidities such as cognitive impairment (Naismith et al. 2012) (Table 23.1).

One approach to disentangling this heterogeneity led to the development of the "vascular depression hypothesis," which stated that "cerebrovascular disease may predispose, precipitate, or perpetuate some geriatric depressive syndromes" (Alexopoulos et al. 1997).

The vascular depression hypothesis has been well studied, with a focus on white and gray matter lesions seen on neuroimaging, vascular risk factors (Steffens and Krishnan 1998), and the formulation of a depression-dysexecutive syndrome

Table 23.1 Clinical, etiological, and prognostic features of early-onset and late-onset depression

	Early-onset depression	Late-onset depression	
		"Vascular" depression	Neurodegenerative
Description	• Development of depressive and/or anxiety symptoms early in life, typically before age 25 • Profile generally indicative of frontotemporal and amygdala change	• Development of depression after age 50 or 60 years • Profile indicative of fronto-subcortical dysfunction	• May include more pronounced hippocampal and temporal lobe change, particularly with underlying Alzheimer's pathology
Clinical features	• Anxiety features • Prominent heritability • Development of awareness to social cues	• Psychomotor change • Executive dysfunction • Apathy • Treatment resistance • Absence of family history	• May additionally include emerging changes in memory consolidation and language
Relationship to cardiovascular disease	• Depression is a risk factor for cardiovascular disease and adverse outcomes including stroke and myocardial infarction	• Increased rates of: – Cerebrovascular disease – Hypertension – Diabetes – Heart disease – Hypercholesterolemia – White matter lesions on neuroimaging	• Cerebrovascular disease may play a role in risk for depression, cognitive decline, and more rapid progression of Alzheimer's pathology
Genetic vulnerabilities	• Gene susceptibility most operative early in development, with vulnerability emerging in childhood and adolescence	• Genetic susceptibility relates to systemic vascular risk, associated with methylenetetrahydrofolate and serotonin transporter genes	• For those whose depression occurs in the context of incipient underlying neurodegenerative change, genetic associations between BDNF and ApoE and volumetric reductions in key brain regions may be important
Prognosis	• Possibly longer time to remission after treatment with antidepressants	• Poorer treatment outcomes • Associated with increased mortality and progression to de mentia • Presence of white matter lesions and cognitive impairment, particularly executive functioning, may predict poor prognosis	

Table 23.1 (continued)

	Early-onset depression	Late-onset depression	
		"Vascular" depression	Neurodegenerative
Treatment	• Possible preferential response to serotonergic agents • High rate of non-response to initial antidepressant • May require lithium augmentation • Non-pharmacological therapy (e.g., cognitive behavioral therapy) useful in targeting anxiety or dysfunctional thoughts	• Management and reduction of vascular risk • Possible preferential response to therapies increasing dopamine and/or noradrenaline • Consider antidepressant augmentation with Ca channel blockers • Additional clinical features such as melancholia and psychosis may require consideration of tricyclics, lithium, antipsychotics, and electroconvulsive therapy • Non-pharmacological therapies (e.g., cognitive training, problem-solving therapy) may be useful when cognitive dysfunction is present	• Consider the role of acetylcholinesterase inhibitors • Non-pharmacological therapies (e.g., cognitive training, problem-solving therapy) may be useful when cognitive dysfunction is present

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(Alexopoulos et al. 2002). Vascular depression typically is associated with a later age of onset, less family history, more treatment resistance, poorer cognitive functioning, and greater progression to dementia (Hickie and Scott 1998; Steffens et al. 2007).

There is extensive research into risk factors for vascular depression, including coronary artery disease (CAD) and stroke (Thomas et al. 2004). In a large case-control study of elderly subjects, the authors reported that 20% of those with CAD also had depression compared with 12% of the controls and that the odds ratio of depression after the onset of CAD was about 2 in both men and women (Hippisley-Cox et al. 1998). A large population-based study showed that depression scores were significantly associated with hypertension (Steffens et al. 1999). Diabetes, hypercholesterolemia, heart disease, obesity, and smoking are other known risk factors. Less studied cardiovascular disease markers include carotid intimal-media thickness (Chen et al. 2006) and retinal venule diameters (Ikram et al. 2010). Research has also examined depression related to stroke, with up to 40% patients developing poststroke depression (Robinson and Spalletta 2010). Newer studies have found LLD to be associated with cortical thinning, which is associated with age at depression onset, gender, and level of cognitive functioning (Lebedeva et al. 2015).

While the significance of white matter lesions in late-life mood disorders is well accepted, the construct of vascular depression is not yet robustly established. Many older people with cardiovascular disease do not develop LLD, leading to further investigation into other neurobiological and neuropsychological factors (Aziz and Steffens 2013).

23.4 Stress Hypothesis of Late-Life Depression

In 1978, Brown and Harris proposed a social stress model of depression in adults, suggesting that depression may be the result of stress factors such as life events or long-term difficulties, combined with vulnerability factors such as social disadvantage, lack of intimate relationships, early traumatic life events, lower education, and family history (Brown and Harris 1978). In several cross-sectional reports based upon the Amsterdam Study of the Elderly (AMSTEL), van Ojen et al.

suggested three different subtypes of LLD based on etiologic determinants. One was recurrent depression starting early in life, which was associated with increased vulnerability due to sensitization or "kindling." The second was late-onset depression with cognitive impairment, often associated with the presence of organic vulnerability factors. Finally, late-onset depression without cognitive impairment was found to be associated with factors related to current life stresses (van Ojen et al. 1995a, b, c).

In a prospective study of 1940 community living elderly that tested this model, the authors reported that higher age, personal history of depression, death of spouse, and health-related factors showed significant associations with depression incidence. The effect of stress factors on incident depression was not modified by a genetic/familial vulnerability nor by an organic vulnerability. Effect modification by environmental factors was however evident (Schoevers et al. 2000a).

In another prospective case-control community study of elderly subjects, researchers compared 83 survey participants who subsequently developed a depressive episode with depression-free comparison participants. The authors determined dates of onset, history, and severity of episodes and dates of occurrence and severity of stressful life events and difficulties. More than 50% of the subjects with depression and about 25% of the normal comparison subjects had had at least one stressful life event within a 3-month period. More than 60% of the depressed subjects had either high levels of neuroticism or long-term difficulties such as poverty, chronic illness in the family, or caregiver burden. Without both high neuroticism and difficulties, stressful life events did not increase risk. High neuroticism and difficulties increased risk, even without a stressful life event. In the presence of high neuroticism and/or difficulties, the depressogenic effect of stressful life events was substantial.

The effect of neuroticism was stronger in individuals with a prior history of depression. This study demonstrated the usefulness of a dynamic stress-vulnerability model for understanding late-life depression (Ormel et al. 2001).

Higher levels of neuroticism in older adults with major depression are associated with reduced treatment response over time (Hayward et al. 2013). In a study investigating the relationship between neuroticism and depression in the elderly (Steffens et al. 2015), older depressed adults showed higher scores on neuroticism and lower scores on extraversion, agreeableness, and conscientiousness. The depressed cohort also showed less resilience and optimism. In a recent study of older depressed adults, higher neuroticism traits of vulnerability to stress, impulsivity, anger-hostility, and anxiety were associated with worse treatment response over time. High vulnerability to stress negatively influenced the rate of global cognitive decline over time (Manning et al. 2017).

23.5 Neuropsychology of Late-Life Depression

Neurocognitive deficits in LLD have been well studied, especially the core deficits of slowed processing speed, difficulties with attention, and executive function, along with aspects of memory (Sheline et al. 2006; McDermott and Ebmeier 2009). Executive deficits are associated with greater severity of depression and poorer clinical outcomes (Boone et al. 1995; Sneed et al. 2007). Alexopoulos et al. used the term depression-executive dysfunction syndrome to describe LLD with key features of psychomotor retardation, apathy, impaired insight, pronounced behavioral disability, and poor response to treatment. Slowed processing speed has also been associated with poor treatment response (Sheline et al. 2010). There is evidence linking the hippocampus to memory deficits in depression. In a 2-year study period, older adults with depression had smaller left hippocampal volumes, which in turn predicted greater cognitive decline (Steffens et al. 2011a).

In a study of depressed elders, greater volume of white matter lesions (WMLs) was associated with decline in both BADLs (basic activities of daily living) and IADLs (instrumental activities of daily living). White matter

lesions remained significantly associated with decline in IADLs after controlling for age, gender, medical comorbidities, and depression severity (Steffens et al. 2002c). In a study following depressed elders over 2 years of treatment, the depressed subgroup that did not achieve or sustain remission had greater increases in WML volume compared with the subgroup that achieved or sustained remission (Taylor et al. 2003). Other predictors of cognitive decline include apathy, age of onset of anxiety, memory deficits, and executive dysfunction (Bartolini et al. 2005; DeLuca et al. 2005).

23.6 Structural Neuroimaging

There have been many qualitative and quantitative studies examining volumetric measurements of key regions as well as volumes of white matter lesions in LLD (Steffens and Krishnan 1998). In this section, we will review studies examining structural neuroimaging findings in late-life depression and their implications.

While whole-brain volumes do not seem to be significantly different in depressed elderly and controls (Andreescu et al. 2008), individuals with LLD often present with increased ventricular sizes (Alexopoulos et al. 1992). Several studies have noted the association between LLD and reduced frontal lobe volume (Kumar et al. 2000). In a study examining the prefrontal cortex, authors reported reduced sizes of OFC, ACC, and gyrus rectus in LLD as compared to controls (Lavretsky et al. 2007). A study by (Elderkin-Thompson et al. 2009) demonstrated the association between the smaller OFC, ACC, and gyrus rectus with impaired executive function in the elderly.

Other structures have also been examined. Multiple studies have commented on the association of reduced hippocampal volume and depression, both in young adults and the elderly (Sheline et al. 1996). Smaller hippocampal volumes are also associated with increased cognitive decline in the elderly, increasing the risk of dementia in non-demented depressed elderly (Steffens et al. 2011a). This ties in neatly with the known role of hippocampus in memory and cognitive functioning. The hippocampus has become an area of renewed interest since several studies have shown that antidepressants may increase levels of neuroprotective neurotrophins such as BDNF (brain-derived neurotrophic factor) in the hippocampus (Wang et al. 2008). In a recent study examining the relationship between hippocampal volume loss and amyloid uptake in depressed elderly, authors found no differences in cortical amyloid uptake between depressed subjects and controls (De Winter et al. 2016).

There has been little research into the volume of the amygdala in LLD; however, there is some evidence of reduced volume in late-onset depression (Hickie et al. 2007). A meta-analysis by Hamilton et al. in 2008 found that medicated depressed subjects had larger amygdala volumes compared with healthy controls but the amygdala volume of unmedicated depressed individuals was lower than controls. The authors postulated that antidepressants exert a neuroprotective effect and that the observed volumetric reduction among unmedicated subjects may be a result of stress-induced glucocorticoid toxicity.

Several important studies have looked at white matter lesions in LLD, including those reported in the previous section. LLD, in particular late-onset depression, is associated with increased number and intensity of WMLs (de Groot et al. 2000; Steffens et al. 2002a). Multiple authors have highlighted the link between age, WMLs, vascular risk factors, and late-onset depression (Alexopoulos et al. 1997; Hickie et al. 1995). Studies have also explored the importance of lesion location and lesion burden in LLD, with mixed results. In a latent class analysis of two independent samples, the authors found that severity of deep white matter lesions was highly sensitive and specific for the vascular depression subtype (Sneed et al. 2008). In a small but innovative study using diffusion tensor imaging, Dalby et al. reported that there was no significant difference in the number or volume of deep WMLs between groups. However, in the patient group, there was a significant positive association between the severity of depression and lesion density in the opercular part of the left superior

longitudinal fasciculus and the right superior temporal gyrus (Dalby et al. 2010a). Recent data from the prospective LADIS (Leukoaraiosis and Disability in the Elderly Study) show that WML volume predicts depressive burden at 2- and 3-year follow-ups as well as functional disability (Teodorczuk et al. 2010). Subcortical gray matter disease burden is linked with greater MADRS scores over a 5-year period (Steffens et al. 2005).

23.7 Functional Neuroimaging

Functional neuroimaging methods include positron-emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI).

PET is a noninvasive functional imaging technique that uses radionuclides, which are positron-emitting isotopes. When these positrons decay, the photons emitted are sensed by radiation detectors and used to produce three-dimensional images of the brain. PET studies initially focused on the investigation of cerebral blood flow and cerebral metabolism. Several studies have shown cerebral blood flow and metabolism abnormalities in the frontal and subcortical regions of the brain in depressed elderly, with metabolic abnormalities often corrected with antidepressants (Drevets 1998; Soares and Mann 1997). As expected, metabolic and blood flow findings suggest reduced serotonergic binding in the PFC, ACC, hippocampus, and dorsal raphe nucleus (de Asis et al. 2001; Diaconescu et al. 2011). Others have found hypermetabolism in anterior and posterior cortical regions (Smith et al. 2009).

With the development of selective radionuclides, researchers are able to examine specific neurotransmitter systems, focusing particularly on dopaminergic and serotonergic systems. In a study of 16 depressed elderly patients, researchers demonstrated significantly reduced hippocampal receptor binding (Sheline et al. 2004). In another study of late-life depression, authors found reduced 5-HT1A receptor binding in the dorsal raphe nucleus (Meltzer et al. 2004). PET studies have also been used to measure the response to SSRI treatment in LLD. The authors reported that a subcortical-limbic-frontal network was associated with improvement in depressive symptoms, while cognitive improvements were related to a medial temporal-parietal-frontal network (Diaconescu et al. 2011).

Similar to PET studies, several small SPECT studies have also demonstrated cortical cerebral blood flow reductions in frontal, temporal, parietal areas as well as the basal ganglia of depressed elders (Awata et al. 1998). There are limited data specifically looking at clinical corrections and treatment responses (Ishizaki et al. 2008).

Functional MRI (fMRI) is based upon changes in the concentrations of oxygenated hemoglobin in different regions of the brain during periods of rest or activity. Studies using fMRI have examined brain responses to emotion- or memory-based tasks in depressed and non-depressed subjects. Depressed subjects showed reduced activation in the PFC during tasks of emotional evaluation of words (Brassen et al. 2008). Aizenstein et al. (2005) have reported that frontal rather than striatal changes are at the root of executive deficits in LLD.

In a study comparing 33 elderly depressed patients with 27 non-depressed comparison subjects, structural and functional MRI were used to assess white matter lesion burden and functional magnetic resonance imaging (fMRI) blood-oxygen-level-dependent (BOLD) response on a facial expression affective-reactivity task. The subgenual cingulate region showed greater task-related activity associated with a greater white matter lesion burden in the depressed group. Compared to the non-depressed group, the depressed group showed a greater interaction of WML by fMRI activity effect (Aizenstein et al. 2011).

In an fMRI study investigating executive deficits in LLD, depressed patients showed diminished activity in the dorsolateral prefrontal cortex (DLPFC) and diminished functional connectivity between the DLPFC and the dorsal anterior cingulate cortex (DACC). Moreover, right DLPFC showed increased activity after treatment. The authors suggested that LLD has both episodic and persistent neurobiologic components. While

the altered functional connectivity appeared to be persistent, perhaps because of vascular etiology, prefrontal hypoactivity might be an episodic characteristic of acute depression responsive to treatment (Aizenstein et al. 2009).

Recent studies have explored functional connectivity between various brain networks using the technique of resting-state fMRI. In a recent study examining the relationship between the uncinate fasciculus, a key frontotemporal tract, and resting-state functional connectivity between the ventral prefrontal cortex (PFC) and limbic and striatal areas, the authors found positive correlations between left uncinate fasciculus structural integrity and resting-state functional connectivity between the left ventrolateral PFC and left amygdala and between the left ventrolateral PFC and the left hippocampus (Steffens et al. 2011a). These results support the notion that resting-state functional connectivity reflects underlying structural integrity. Other studies have confirmed altered functional connectivity in LLD, which may provide a new target for the treatment of late-life depression (Kenny et al. 2010; Alexopoulos et al. 2012).

23.8 Genetics

Depression is a multifactorial, heterogeneous disease, with genetic vulnerability coupled with environmental influences playing a role in its pathogenesis. Genetic factors are of less significance in patients presenting with depression for the first time in late life (Krishnan 2002). However, several genetic polymorphisms have been identified that coupled with environmental influences predispose the vulnerable elderly to depression (Taylor et al. 2008; Karg et al. 2011).

23.9 Serotonin Transporter Gene (5HTTLPR)

Serotonin transporter gene polymorphisms have been long associated with depression, both in young adults and later in life. The most common *5HTTLPR* polymorphisms are the long allele (a 44-base pair insertion) and the short allele (deletion of the same base pair). The L allele is associated with increased serotonin uptake, while the S allele is associated with poor transcription of the serotonin transporter (Heils et al. 1995).

In a study of 289 older depressed adults, Steffens et al. found no significant association between the short variant of the *5HTTLPR* gene and depression (Steffens et al., 2002b). There was a nonsignificant trend for more short-allele homozygotes among the entire group that was more prominent among men. There was also an association between the short allele and recurrent depression as well as family history of depression in women. Several studies suggest that individuals with short-allele homozygotes are more susceptible to depression as a result of early childhood stress, increased medical burden, and acute stressful life events (Caspi et al. 2003; Kendler et al. 2005). Studies have also looked at the serotonin polymorphisms in the context of cardiovascular disease in the elderly with mixed results (Nakatani et al. 2005).

Another important consideration is the association between *5HTTLPR* and vascular burden in the elderly. Older depressed adults who are heterozygous for the serotonin transporter gene seem to have greater WML burden (Steffens et al. 2008). In another study of depressed elderly, S-allele carriers had both microstructural white matter abnormalities in frontolimbic networks and a lower remission rate than L homozygotes (Alexopoulos et al. 2009).

23.10 Brain-Derived Neurotrophic Factor (BDNF)

There is substantial evidence that *BDNF* (the gene associated with brain-derived neurotrophic factor) is involved in hippocampal learning and memory. A common *BDNF* polymorphism results in an amino acid substitution of valine to methionine at codon 66. This Met allele is associated with abnormal intracellular packaging and altered BDNF distribution (Egan et al. 2003). In a study, (Taylor et al. 2007) reported that Met66 allele carriers have almost double the odds of having geriatric depres-

sion than do Val66 allele homozygotes. This polymorphism was unrelated to other clinical characteristics of depression in later life such as age of onset, family history, or recurrent episodes. In a larger population-based study of older adults the year before, Surtees et al. did not find such an association (Surtees et al. 2006).

There have been more consistent results regarding the effects of *BDNF* polymorphisms in treatment responsiveness in LLD. The Met allele has been associated with increased odds of remission after treatment (Alexopoulos et al. 2010).

In an important study in 2009, Gatt et al. examined the interactions between the *BDNF* Val66Met gene and early life stress. They found that *BDNF* Met carriers exposed to greater early life stress have smaller hippocampal and amygdala volumes and a decline in working memory. The combination of Met carrier status and exposure to early life stress predicted reduced gray matter in hippocampus and, in turn, more severe depression. The *BDNF* Met-stress interaction also predicted elevated neuroticism and more severe depression. These effects were specific to the *BDNF* gene and were not evident for the related *5HTTLPR* polymorphism (Gatt et al. 2009).

23.11 Apolipoprotein E Gene (APOE)

The *APOE* gene encodes the lipid transport protein apolipoprotein E and is an important risk factor in the development of Alzheimer's disease (AD). In particular, the *APOE* epsilon-4 (ε4) allele is considered a risk factor for the development of AD (Corder et al. 1993), with some association with vascular dementia as well (Frisoni et al. 1994). Several studies have examined the association between ε4 allele and LLD, with mixed results (Krishnan et al. 1996; Steffens et al. 2003). Researchers have studied neurostructural changes in LLD and the *APOE* ε4 allele, reporting greater reductions in hippocampal volume and greater cognitive decline in depressed subjects with ε4 genotype (Sachs-Ericsson et al. 2011). In a longitudinal MRI study of older depressed adults, Steffens et al. (2007) reported that *APOE* genotype was not associated with onset of dementia. This is consistent with a study of 45 depressed elders, where the *APOE* ε4 allele was not found to be associated with depression or cognitive impairment. Interestingly, authors did find an association between the ε4 allele and psychotic depression (Zubenko et al. 1996).

23.12 5-Methylenetetrahydrofolate Reductase (*MTHFR*) Gene

The *MTHFR* gene is involved in homocysteine metabolism. A common *MTHFR* polymorphism (C677T) leads to reduced enzymatic activity and increased homocysteine levels. Studies have linked increased homocysteine levels to cerebrovascular disease and white matter lesions (Hogervorst et al. 2002).

Studies exploring the association between C677T genotype, LLD, and neurocognition have found mixed results (Naismith et al. 2002; Almeida et al. 2005). In a study examining the relationship between *MTHFR* polymorphism, LLD, WML volumes on MRI, and neurocognitive testing, the authors reported that *MTHFR* C677T polymorphism was associated with greater WML by age, but not with gray matter lesions, depression, or performance on neurocognitive testing (Hong et al. 2009).

In addition to *MTHFR* polymorphisms, recent studies have examined other single nucleotide polymorphisms in the folate metabolism pathway. In an interesting study exploring ten of these genes and outcomes, the investigators reported that methionine synthase reductase *(MTRR)* A66G was a significant predictor of remission, especially in those taking antidepressants. A borderline association was also found between *MTHFR* A1298C polymorphism and remission status, with those with AC genotype 2.5 times more likely to be in remission than those with AA genotype (Jamerson et al. 2013).

23.13 Role of Inflammation

There is growing evidence that links chronic low-grade inflammation and depression (Thomas et al. 2005; Bremmer et al. 2008). The most common inflammatory markers that have been implicated include interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP). Multiple studies have looked at the association between interleukin-1 and interleukin-6, CRP, and major depression. Some found positive associations, but others did not (Penninx et al. 2003; Hemingway et al. 2003). In a large population-based study, Bremmer et al. reported that high levels of IL-6 were associated with major depression, both in recurrent and first episodes. The association of CRP elevation with depression scores was lost after correction for the effect of age and chronic diseases (Bremmer et al. 2008).

The association of stress, inflammatory markers, and depression has been explored as well. Chronic stress is associated with depression in older adults (Marin et al. 2011). Early-life adversity, such as physical or sexual abuse during childhood, results in long-lasting changes in the CRF-mediated stress response and a greatly increased risk of depression in genetically predisposed persons (Nemeroff 2003).

There is new research into the role of glia in the neurobiology of geriatric depression. While neurohistological studies in young adults with depression have shown a reduction in both number and density of glial cells (Rajkowska and Miguel-Hidalgo 2007), the findings in LLD have been more mixed (Bowley et al. 2002; Khundakar et al. 2011b).

In a 2013 study of depression in older adults, Naudé et al. introduced neutrophil gelatinase-associated lipocalin (NGAL) as a novel inflammatory marker associated with late-life depression. Depressed patients had significantly higher NGAL plasma levels compared to non-depressed comparison group. Subjects with a recurrent depression had higher plasma NGAL levels compared to those with a first episode. NGAL levels were related neither with specific symptom profiles nor with antidepressant drug use (Naudé et al. 2013).

Finally, most studies investigating LLD have explored single or few biomarkers in isolation. With the development of large biomarker panels using multiplex technology, Diniz et al. sought to determine neurobiological abnormalities related to LLD through a multimodal biomarker approach combining a large, unbiased peripheral proteomic panel and structural brain imaging. A panel of three proteins (C-peptide, FABP-liver, ApoA-IV) discriminated LLD and control participants with 100% accuracy. The peripheral biosignature of LLD has predictive power and may suggest novel therapeutic targets for the treatment of LLD (Diniz et al. 2016).

Conclusion

This chapter has attempted to review the key neurobiological factors that underpin late-life depression. LLD plays an important role in the emergence of neurodegenerative disorders. Treatment paradigms for LLD must address prevention of risk factors that form a common pathway to both depression and dementia. Future models of LLD should be able to examine not just subcortical/hippocampal pathways, genetic polymorphisms, and inflammatory and glial markers but also how these complex systems interact with one another.

There are limited efficacy data related to the treatment of depression that are specific to age of onset and subsyndromal characteristics (Nelson 2008; Taylor and Doraiswamy 2004). Further research is needed to clarify the links between syndrome subtypes and course and outcomes of LLD (Sheline et al. 2010). The elderly face multiple role transitions, as well as stressors including bereavement, social isolation, concurrent physical illness, and disability. These factors make it important to evaluate the role of educational, social, and psychological therapies in the treatment of LLD (Huang et al. 2015).

Intervention strategies must focus on prevention of depression as well as protecting brain function (Naismith and Mowszowski 2016). Focusing on cognitive and emotional resilience of the population may lead to new directions of intervention development that are oriented more toward wellness and resilience (Lavretsky 2014).

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Gender Differences in Depression

24

Seoyoung Yoon and Yong-Ku Kim

24.1 Introduction

Female predominance in depression is a consistent finding across various nations, ethnicities, and cultural backgrounds. Additionally, gender differences in clinical manifestations have been reported, such as symptom characteristics, comorbid conditions, and suicidality. Female-specific depression-related syndromes, such as premenstrual dysphoric disorder (PMDD), major depressive disorder with peripartum onset, and perimenopausal depression, occur at specific stages of the female life cycle.

Psychosocial factors and biological factors have been suggested to explain gender differences in depression. Expected social role and threatened life stress are different between males and females. Biological differences, such as gonadal hormones and their effects on endocrinology and neurobiology, also lead to gender differences.

In this chapter, we present an overview of gender differences in the clinical manifestations of depression and the possible contributors to psychosocial and biological factors. We then present the clinical implications, including the need for special consideration of gender in the management of depression.

24.2 Clinical Characteristics: Prevalence, Symptom Manifestation, and Comorbidity

The prevalence of depression in females is almost double that in males (Kessler et al. 1993; Weissman et al. 1993). According to a US national comorbidity survey, the lifetime prevalence of major depressive episode was 21.3% in females and 12.7% in males (Kessler et al. 1993). This female predominance seems to appear after the pubertal stage. In prepubertal children, there is no gender difference in depression prevalence, and male predominance is even observed in some studies (Angold et al. 1998). Further, the gender difference in prevalence seems to be related more with pubertal status than with age (Angold et al. 1998; Wang et al. 2016). This suggests the possibility that the maturating of the hypothalamic-pituitary-gonadal axis or the changes in androgen and estrogen contribute to this phenomenon (Angold and Costello 2006; Angold et al. 1999). Dramatic body morphology changes occur in this period, and related psychosocial stressors, such as peer stress according to puberty-related factors

S. Yoon
Department of Psychiatry, Daegu Catholic University College of Medicine, Dague, Korea

Y.-K. Kim (✉)
Department of Psychiatry, Korea University College of Medicine, Seoul, Korea

Department of Psychiatry, Korea University College of Medicine, Ansan Hospital, Ansan, Korea
e-mail: yongku@korea.edu

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(e.g., earlier maturation) and sexual harassment, can increase the likelihood of depression in adolescent girls (Conley et al. 2012; Galvao et al. 2014; Skoog et al. 2016).

Frequently, symptom manifestations also differ by gender. Atypical depression symptoms, such as increased appetite or weight, interpersonal sensitivity and mood reactivity, and somatic complaints, are more common in females, whereas psychomotor agitation is more common in males (Marcus et al. 2005; Schuch et al. 2014). Commitment of parasuicide is three times more frequent in females than in males, although commitment of suicide is three times more frequent in males than in females (Diekstra and Gulbinat 1993). Rutz et al. suggested this male predominance in suicide despite female predominance in depression is due to the characteristics of male depressive syndrome. This syndrome includes lowered stress tolerance, acting out, aggressiveness, low impulse control, feeling burned out, emptiness, chronic fatigue, irritability, restlessness, dissatisfaction, indecision, sleep disturbance, morning anxiety, uneasiness, abuse, transitional sociopathic or personality disorder, negativism, and hereditary factors (e.g., suicide, depression, abuse) (Rutz et al. 1995, 1997; Zierau et al. 2002). After this suggestion by Rutz et al., the Gotland male depression scale was developed, used, and validated for multiple countries and languages (Chu et al. 2014; Innamorati et al. 2011).

Anxiety disorder is frequent in both genders, but the prevalence is higher in females than in males. Depressive males suffer more frequently from alcohol or substance abuse (de Graaf et al. 2003; Marcus et al. 2005; Schuch et al. 2014). The higher prevalence of somatic symptoms in females may be explained by the higher comorbidity of anxiety disorder in female depressed patients (Haug et al. 2004). Physical and sexual abuses have also been suggested as a reason for somatic symptoms in females (Drossman et al. 1995; McCauley et al. 1995). Given that almost half of the cases of adult suicide ideation or attempts were reported to involve over-drinking alcohol, the greater prevalence of alcohol abuse in males may partly explain the higher rate of suicides in males (De Leo et al. 2005).

24.3 Explanatory Factors Associated with Gender Differences in Depression (Fig. 24.1)

24.3.1 Psychosocial Factors

24.3.1.1 Sociocultural Factors

Expected social roles and norms differ greatly by gender, largely dependent on cultural background, and this affects individual lifestyles and

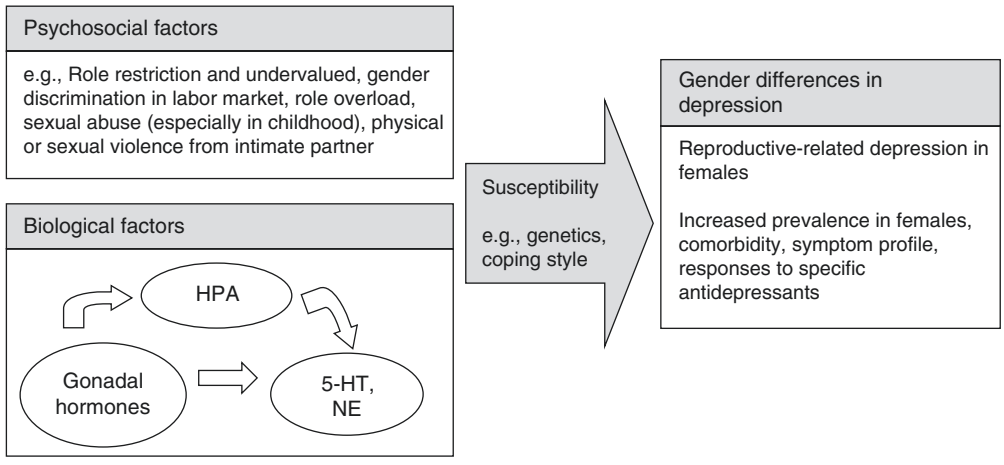

Fig. 24.1 Suggested explanatory factors for gender differences in depression. *HPA axis* hypothalamic-pituitary-adrenal axis, *5-HT* serotonin (5-hydroxytryptamine), *NE* norepinephrine

psychological conditions. Chronic strain, low mastery, and rumination are higher in women and interact with each other (Nolen-Hoeksema et al. 1999). A previous case register study showed that married females had a higher rate of affective disorder than their single counterparts, whereas the opposite tendency was seen in males (Bebbington and Tansella 1989). In the elderly, an increased risk for depression has been reported in divorced and widowed males, compared to married males, but no such difference was seen among females (Jang et al. 2009). Although these findings are not always consistent, the literature generally reports marriage has an advantageous effect for men (Rendall et al. 2011). Traditionally, for both Eastern and Western countries, homemaking and caring for children and the elderly were considered to be the duty of females. This role expectation led to females' having fewer chances to hold money-making jobs. In modern society, economic strength has become more valued, and the role of the housewife has become less valued, which in turn, can cause women to feel frustrated (Piccinelli and Wilkinson 2000).

For women with full-time or part-time jobs, job inequality and role overload can also be problems. Gender discrimination in the labor market with lower payments for women has been studied and fully supported (Wright and Ermisch 1991). Full-time female workers are frequently responsible for the majority of child and elderly care and the domestic work of the home, which can result in burn out and increased risk of depression. And when the domestic loading is increased, women are more likely to be asked to give up their paying jobs (Yee and Schulz 2000). A WHO study conducted in 14 countries concluded that, when the effects of social role variables, such as marital status, children and occupational status, are accounted for, female predominance in depression prevalence decreases about 50% across all countries (Maier et al. 1999). Chronic strain due to occupation and role restriction and being undervalued partially explain the female predominance for depression.

24.3.1.2 Adverse Life Events

Psychosocial stressors, such as negative life events, show greater contributions in the first episode of major affective disorder than in consecutive episodes. Stressors and mood episodes are known to result in vulnerability to further occurrences of mood episodes via modulation of gene expression (Post 1992). Childhood trauma can have long-lasting effects on the hypothalamic-pituitary-adrenal (HPA) axis response to stress and may result in chronic and recurrent mood disorders (Juruena 2014). Females are more likely than males to experience some specific kinds of major trauma, such as sexual assault. Childhood sexual abuse increases the risk of adult-onset depression in both genders, and these adverse events occur more frequently in girls than in boys (Weiss et al. 1999). A study estimated that about 35% of gender differences in adult depression could be explained by the higher incidence of assault in girls than in boys (Nolen-Hoeksema 2001). Physical or sexual violence from an intimate partner has physical and psychological sequelae, including headaches, gastrointestinal disorders, and depression. Such events occur more frequently in females than in males (Campbell 2002; Sugg 2015).

There are also stressors related to reproductive events that only women experience. Reproductive traumas, including infertility, miscarriage, and perinatal loss, occur in up to 15% of women, and they are frequently associated with psychiatric consequences like depression (Bhat and Byatt 2016). Unwanted pregnancy is also a risk factor for depression, although findings are not conclusive about the effect on maternal mental health depending on whether a pregnancy ended in an abortion or live birth (Iranfar et al. 2005; Schmiege and Russo 2005).

However, overall, adverse life events are not experienced more frequently by women than men. But some studies have explained that the higher prevalence of depression in females is due to differences in the actual impact of the adverse events rather than their frequency. Rather, it is more likely related to having a few highly valued goals along with low perceived power of choice, due to role restriction and strain, such that women have increased risk of depression when major adverse events threaten their main goals (Piccinelli and Wilkinson 2000).

24.3.1.3 Self-Concept and Coping Style

It has been suggested that women may have lower self-concepts than men, but study findings have been inconsistent. A relatively consistent difference in self-concepts between men and women is their interpersonal orientations. Women tend to be more interpersonally oriented than men, from childhood, and they are more prone to develop depression when conflict occurs or a relationship ends (Nolen-Hoeksema 2001). Regarding coping style, *rumination*, which is an inward focus on feelings of distress and personal concerns, may contribute to female predominance in depression. According to Nolen-Hoeksema, women tend to use rumination more than men as a stress response, and this tendency increases the risk of depression when distress occurs (Nolen-Hoeksema et al. 1999).

24.3.2 Biological Factors

24.3.2.1 Gonadal Hormones

Female predominance for depression seems to emerge at the pubertal stage and decrease at the postmenopausal stage. Reproductive stage-specific depressive syndrome is well documented; thus, cycling levels of gonadal hormones may be explanatory factors for increased vulnerability to depression in women. Hormone supplement therapy is a treatment option for midlife depression for both women and men. Gonadal hormones are steroid hormones, and most of their effects are mediated by intracytoplasmic steroid receptors, which serve as transcription factors. In addition to genomic pathways, gonadal hormones can exert fast effects via membrane-localized receptors that act through secondary messenger pathways. Among the gonadal hormones, estrogen has been widely studied as a key contributor in mood regulation. Estrogen affects the central nervous system in various manners, with fluctuation of estrogen levels seeming to be more important than their absolute levels in mood regulation.

Estrogen seems to modulate the monoamine neurotransmitter system, which plays a critical role in the pathogenesis of depression. According to animal and human studies, estrogen regulates the serotonergic system via increased serotonin synthesis, decreased serotonin breakdown and modulation of serotonin receptors. Estrogen inhibits monoamine oxidase activity in several brain regions, according to some animal studies. Tryptophan hydroxylase mRNA, which is an enzyme for serotonin synthesis, is increased by estrogen. Acute estrogen administration is related to increased serotonin transporter density in the forebrain. Estrogen acts differently on different subtypes of serotonergic receptors, resulting in overall increases of serotonin neurotransmission via downregulation of 5-HT1A autoreceptors and upregulation of 5-HT2A receptors, respectively (Lokuge et al. 2011). Estrogen also plays a role in modulating norepinephrine synthesis, breakdown, and receptor activity. In an animal study, the level of norepinephrine increased with higher estrogen levels. Estrogen administration in ovariectomized rats increased norepinephrine in the ventral hippocampus, cortex, and hypothalamus. Estrogen induces increased tyrosine hydroxylase for norepinephrine biosynthesis, but this effect is limited to short-term not chronic administration, mimicking the preovulatory surge. Catechol-*O*-methyltransferase (COMT) is an enzyme that degrades norepinephrine. In a human postmortem study, prefrontal catechol-*O*-methyltransferase activity was higher in men than women. And preclinical studies suggest that estrogen may decrease this enzyme activity, inhibiting norepinephrine degradation. Adrenergic receptors are also modulated by estrogen. Estrogen decreases postsynaptic adrenergic receptor expression, and this may be compensatory, but more studies are needed to add evidence supporting this hypothesis (Bangasser et al. 2016).

Estrogen also modulates the activity of specific brain regions and functional connectivity. Estrogen receptor β exists in human brain regions, such as the hippocampus, entorhinal cortex, and thalamus. Membrane-localized estrogen receptors, such as G protein-coupled estrogen receptors, also exist in the hippocampus, hypothalamus, and midbrain. According to the menstrual cycle and estrogen level, a signifi-

cant difference in cortical activation for adverse stimuli was seen in functional neuroimaging studies. High-estrogen states seem to be related to improved top-down modulation of limbic activity, such as cortical control of the amygdala, compared to low-estrogen states, when arousal is increased (Goldstein et al. 2005). In a high-estrogen state, improved fear extinction recall with modulated ventromedial prefrontal cortex and amygdala reactivity was also reported (Zeidan et al. 2011). Further, excess amygdala activation due to stress may impair hippocampal functioning, resulting in more adverse psychological effects of stress and negative bias on emotional memory. But estrogen may ameliorate this process by protecting hippocampal activity. These findings suggest that, when stressful events happen, women in high-estrogen-level phases may have enhanced activity of higher level structures that modulate negative emotions which is related to better reappraisal and reduced negative affective state (Newhouse and Albert 2015).

Estrogen also exerts neuroprotective effects via various mechanisms, such as increased brain-derived neurotrophic factor (BDNF), which is important to neuronal plasticity, attenuating excitotoxic glutamate-induced neurotoxicity, antioxidative effects, and anti-inflammatory effects (Borrow and Cameron 2014; Liu et al. 2005; Luine and Frankfurt 2013; Tskitishvili et al. 2017; Zhao and Brinton 2007). Although most studies suggest that estrogen exerts an antidepressant effect, the cycling of gonadal hormone levels, rather than the absolute levels, seems to be more strongly related to the reproductive stage-specific depressive syndrome in women, which may contribute to the female predominance in depression. In studies of depression during the menopausal transition, greater variability in levels of follicular stimulating hormone (FSH) or estrogen were associated with higher risk of depressive symptoms (Freeman et al. 2006; Ryan et al. 2009).

Allopregnanolone, a metabolite of progesterone, also seems to be related to mood disorders. The major target of allopregnanolone is gamma-aminobutyric acid (GABA) A receptors, which exert anxiolytic, sedative/anesthetic properties. Since the levels of gonadal hormones vary by the menstrual cycle or reproductive stage, GABA A receptor plasticity over those physiological conditions is important to maintain to obtain the ideal level of GABA-based inhibition. And when there are deficits in this compensatory change in vulnerable subjects, GABAergic alterations by gonadal hormones, especially allopregnanolone withdrawal, can cause PMDD or postpartum depression (MacKenzie and Maguire 2014).

Vulnerability in some women may affect these mood syndromes with regular hormonal cycling, but it is less likely that the hormonal cycling itself is abnormal in affected subjects. Studies of PMDD have found no consistent differences in gonadal hormone levels between affected subjects and healthy controls. Medical reduction of gonadal steroids via a gonadotropin-releasing hormone (GnRH) agonist was effective in the management of PMDD and in clinical trials, GnRH agonist reduced symptoms of PMDD induced by add back of estrogen and progesterone; this effect was seen only in subjects with a prior history of PMDD and not in subjects without a PMDD history (Rubinow and Schmidt 2006). Similarly, when introducing and withdrawing supraphysiological gonadal steroids in GnRH-agonist-induced hypogonadism subjects, only subjects with histories of postpartum depression experienced mood symptoms during the withdrawal period, whereas none of the subjects without history of postpartum depression experienced mood symptoms (Bloch et al. 2000). These findings indicate that it is not abnormal levels or cycling of gonadal hormones but rather preexisting susceptibilities that produce mood syndromes during the naturally cycling of gonadal hormones. This susceptibility can be due to specific personality traits, past psychiatric illness, environmental factors, or genetic factors. A twin study revealed that additive genetic influences accounting for 44% of total variance were identified for PMDD, and they seemed to be related to neuroticism and lifetime depression, but these factors could not fully explain the genetic influences (Treloar et al. 2002). A genetic study reported that an estrogen receptor α gene (ESR1)

occurring with a specific COMT genotype was associated with PMDD (Huo et al. 2007).

In addition to the possible effects of estrogen and a metabolite of progesterone on depression, we consider androgen levels. Unlike those two hormones, the levels of androgens (testosterone, DHT, DHEA) are relatively stable and decrease gradually during midlife in both genders. Testosterone deficiency is a contributor to depression in elderly men. Lower levels of testosterone have been found in depressed patients than in non-depressed patients in previous studies, especially in men with severe and treatment-resistant depression and in the elderly population (Zarrouf et al. 2009). Interaction between the HPA axis and the HPG axis are possible mechanisms underlying the association between testosterone level and depression. A study reported improved cerebral interhemispheric coherence after testosterone administration and suggested this phenomenon as the biological basis underlying the relationship between testosterone and depression (Schutter et al. 2005). An animal study reported testosterone-dependent extracellular signal-regulated kinase 2 (ERK2) expression in the hippocampus. Given that reduced hippocampal ERK2 activity induced anhedonia in gonadectomized male rats and that overexpression of ERK2 rescued this symptom, ERK2 signaling may help explain the antidepressant-like effects of testosterone (Carrier and Kabbaj 2012). Although clinical studies of testosterone administration for depressed men have shown somewhat negative and inconsistent results, a current meta-analysis concluded that testosterone may have an antidepressant effect, especially in depressed patients with hypogonadism or HIV/AIDS (Zarrouf et al. 2009). In studies of perimenopausal or postmenopausal women, depression was related to lower levels of plasma DHEA (Laughlin and Barrett-Connor 2000; Schmidt and Rubinow 2009). In clinical trials with postmenopausal women, although the results were heterogeneous and inconclusive, some studies showed that supplemental or increased levels of androgens, including testosterone, were associated with improved sexual satisfaction, general well-being, and mood (Garefalakis and Hickey 2008).

24.3.2.2 Hypothalamic-Pituitary Axis (HPA Axis)

HPA axis activity is responsive to stress. Dysregulation and increases in HPA activity are known to be related to depression. So gender differences in the HPA axis are thought to contribute to gender differences in depression prevalence and reactivity to stress. Several human studies using the Trier social stress test (TSST) generally found greater HPA axis activation with greater adrenocorticotropic hormone (ACTH) or cortisol responses in men than women after exposure to stress, although the results were somewhat heterogeneous (Allen et al. 2014; Uhart et al. 2006). After pharmacological stimulation using naloxone or ovine corticotropin-releasing hormone (CRH), female subjects generally showed greater activation of the HPA axis than males (Gallucci et al. 1993; Uhart et al. 2006). In animal studies, basal ACTH levels were not different between male and female rodents, but acute stress-induced ACTH and cortisol levels were greater in females than males (Goel et al. 2014). A recent study found that males showed steeper increases in ACTH and cortisol, and their decreases were also steeper and earlier than in females (Stephens et al. 2016). In an animal test, male rodents tended to show better cortisol habituation than females after repeated stress. Habituation to repeated nonthreatening conditions can be beneficial by reducing the risk of hypercortisolemia and conserving energy (Goel et al. 2014). Although, human and animal studies have lacked consistency in their results, it seems that there are differences in HPA axis activation between genders. Acute HPA axis activation can be an adaptable response to stress, but chronic activation can be deleterious; therefore, these gender differences can result in different consequences, such as mood disorder, after exposure to stress.

In females, HPA axis activation seems to be affected by the menstrual cycle and pregnancy. Rodent studies showed that HPA axis activation differed by menstrual cycle, and when estrogen levels were greater, the HPA axis activation became greater. Pregnancy is associated with an elevated basal cortisol level and suppressed HPA

axis activation. These effects seem to be protective of offspring in facilitating their development and care while protecting them from high-stress-induced glucocorticoids (Goel et al. 2014).

24.3.2.3 Neurotransmitter Systems

As mentioned previously, gonadal steroids, especially estrogen, modulate the synthesis, metabolism, and receptor activity of monoamine neurotransmitter systems, usually upregulating these systems. Gender differences in the serotonergic and noradrenergic systems were also studied and suggested as independent explanatory factors for gender differences in depression. Levels of central serotonin and cerebrospinal fluid 5-hydroxyindole-3-acetic acid (5-HIAA) were reported to be higher in female rats than in male rats. In a human current brain positron emission tomography study, being female, rather than male, was related to lower serotonin transporter (5-HTT) levels and higher 5-HT1A binding potentials, which is somewhat different from animal study results (Jovanovic et al. 2008). 5-HT1A is an autoreceptor downregulating the serotonergic system, and its higher level has been reported in depression. Lower 5-HTT levels were also found in depressed subjects. So, although not consistent with animal studies and needing more evidence, the current neuroimaging study's findings may explain some of the female predominance in depression. In depressed females, diencephalon 5-HTT availability decreases with age, but depressed males showed no differences in 5-HTT availability (Staley et al. 2006). Based on a tryptophan (precursor of serotonin) depletion test, plasma tryptophan depletion was greater in females than in males, and further, a higher likelihood of depressive symptom development was observed in females than in males (Booij et al. 2002; Ellenbogen et al. 1996). These findings imply that 5-HT metabolism and the related mood response differ by gender. A positron emission tomography study found that the type-2 serotonin receptor-binding capacity of the frontal and cingulated cortex was higher in males than in females, which in turn, may affect sexual differences for depression (Biver et al. 1996).

As described previously in this chapter, rumination tendency is a possible explanatory factor for female predominance in depression. Rumination is associated with a high arousal state, and so its related biological basis in the locus ceruleus and the increased activity of the norepinephrine system, which differs by gender, may explain the difference in rumination tendency. In some strains of rats, the locus ceruleus is larger in females than males due to continuous neurogenesis in this region during puberty in females, but not in males (Pinos et al. 2001). Further, locus ceruleus dendrites seem to be denser in female rats than in male rats (Bangasser et al. 2011). Stress-induced CRF also activates the locus ceruleus and the norepinephrine system. But the CRF dose-response curve for locus ceruleus activation seems to be shifted to the left in females, compared to males, which means the locus ceruleus is activated more easily by lower CRF levels in females (Curtis et al. 2006). Increased locus ceruleus sensitivity to CRF in females may be mediated by the gender difference in CRF 1 receptors (Bangasser et al. 2010). Overall, females may be more vulnerable than males to stress-related arousal symptoms that lead to depression symptomatology due to gender differences in the locus ceruleus and the noradrenergic system.

24.4 Clinical Implications

The mainstay of treating depression is antidepressants, and a plethora of antidepressants acting via different mechanisms have been developed. Previous studies focused on gender differences in treatment responses to specific antidepressants. The most consistent finding is that females before menopause showed poorer responses to tricyclic antidepressants than postmenopausal females and males (Sagud et al. 2002). Higher response rate or tolerability to selective serotonin reuptake inhibitors in females, especially at younger ages, have been reported (Baca et al. 2004; Thase et al. 2005; Young et al. 2009), although some studies did not find gender differences in treatment responses (Hildebrandt et al. 2003; Quitkin et al. 2002). Studies of serotonergic antidepressants and newer noradrenergic antidepressants have had results similar to

those of previous tricycle antidepressants (Berlanga and Flores-Ramos 2006). A study reported that the efficacy advantage of venlafaxine relative to a selective serotonin reuptake inhibitor was lower in younger than older women (Thase et al. 2005). Although the idea that treatment responses to antidepressants differ by gender is still controversial, several explanations have been suggested. As mentioned above, estrogen generally activates the serotonergic system, and this may favorably influence the response to selective serotonin reuptake inhibitors in young women. Further, atypical depression, which preferentially responds to MAOIs or SSRIs, is more common in women (Keers and Aitchison 2010).

Just as fluctuating gonadal hormone levels have been suggested as a biological basis of PMDD, postpartum depression and perimenopausal depression in some susceptible females, hormone-related treatment has been suggested to manage these syndromes. However, the mainstay of pharmacological management is still antidepressants. In perimenopausal depressed women, oral estrogen preparations have shown mixed results, but transdermal estrogen has shown more promising results. Because it is the fluctuation in estrogen, not a low level that is a risk factor for depressive syndrome, it is not surprising that hormone replacement treatment seems to be ineffective in the late postmenopausal period. However, for perimenopausal-onset depression with hot flashes and night sweats, hormone replace monotherapy can be especially worthwhile (Gordon and Girdler 2014). One study suggested that transdermal estrogen was also effective for postpartum depression, but more studies are needed (Gregoire et al. 1996). Anovulation induced by a GnRH agonist, danazol, and oral contraceptives has been a treatment strategy for PMDD (Maharaj and Trevino 2015).

The psychosocial approach is also important for managing depression. As women and men face somewhat different stressors in their sociocultural environments, psychotherapeutic approaches should be performed with these factors taken into consideration. Although findings are not yet conclusive, various coping styles seem to be more frequent by gender, making them effective targets for psychosocial treatment (Shors et al. 2017). Research suggests that the treatment efficacy of psychotherapy is not different between genders (Watson and Nathan 2008). But one study suggested that a type of short-term psychotherapy might be differently beneficial by gender; supportive forms of therapy focusing on external circumstances were more beneficial for women, whereas interpretive therapy focusing on uncomfortable emotions and intrapsychic conflicts was more beneficial for men. They explained that this happened because women tend to prefer to participate in relationships, and diminishing self-blame is helpful for them. For men, generally reared to be independent and often with underdevelopment of affective awareness and expressiveness, interpretive therapy might provide new methods for dealing with problems and expressing emotions (Ogrodniczuk et al. 2001).

Conclusions

Gender differences in depression are seen in its prevalence, clinical manifestations, and comorbidities. Possible explanations based on psychosocial and biological factors have been suggested. For now, most findings are not conclusive or fully explained, but a growing body of evidence provides increased understanding. Interactions among gonadal hormones, the HPA axis, and neurotransmitters seem to show gender differences that affect the manifestations of depression and the treatment responses to specific strategies. More studies are needed to build sufficient evidence to explain the apparent gender differences in depression as well as to develop evidence-based gender-specific depression evaluation and management strategies that would be helpful for developing effective depression treatments.

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An Update on the Epidemiology of Major Depressive Disorder Across Cultures

25

Joao P. De Aquino, Alicia Londono, and André F. Carvalho

25.1 Introduction

Major depressive disorder (MDD) is a psychiatric disorder that encompasses a wide range of symptoms such as sadness, guilt, low self-esteem, reduced capacity to experience pleasure or enjoyment, changes in sleep and appetite, low energy and concentration, as well as a sense of hopelessness and suicidal ideation. According to the last edition of *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (American Psychiatric Association 2013), at least five of these symptoms need to be present for more than 2 weeks to warrant a diagnosis of MDD. It is estimated that, by 2020, depression will be the second leading cause in health disabilities. According to the World Health Organization (WHO), at least 350 million people live with depression worldwide (World Health Organization 2013). There have been multiple epidemiological studies evaluating the prevalence of MDD in different countries and cultures, with wide variety in estimates of prevalence and more consistent findings pertaining to other aspects of descriptive epidemiology.

In this chapter, we summarize the epidemiological literature in relation to the prevalence of depression across cultures. Initially, we critically review commonly encountered challenges in conceptualizing and measuring major depressive disorder symptomatology across cultures. We then proceed to examine the latest international figures on the prevalence of MDD, highlighting other potential factors that may account for the wide variety prevalence estimates. Finally, we summarize other epidemiological findings related to depression across cultures, such as sociodemographic correlates, course, and functional outcomes.

25.2 Methodological Issues

Several challenges arise in exploring the epidemiology of depression across cultures. First, epidemiological data may not be easily available or be suboptimal for many countries, particularly for low-income countries. Second, differences in how the term "depression" is operationalized are encountered in the international epidemiological literature. For instance, some surveys have chosen to focus on single major depressive episodes (MDE), while others have operationalized "depression" as MDD, in accordance to different DSM criteria over the years. This distinction is especially significant because although the majority of

J.P. De Aquino • A. Londono
Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA

A.F. Carvalho (✉)
Department of Psychiatry, University of Toronto, Toronto, ON, Canada

Centre for Addiction & Mental Health (CAMH), Toronto, ON, Canada
e-mail: andrefc7@terra.com.br

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MDE correspond to an underlying diagnosis of MDD, some MDE are experienced by individuals who suffer from bipolar disorder (BD), a disorder with higher chronicity and recurrence rates. This higher chronicity may subsequently affect estimates of the point prevalence of depression. Finally, the conceptualization and the actual symptoms of depression may differ across cultures, which add another layer of complexity to applying validated psychometric instruments designed for individuals from one particular culture to individuals from another. In the section below, we expand this last and particularly significant topic.

25.2.1 Cultural Context and MDD

Responses to stress are embodied not only in genetic predisposition and neurobiological underpinnings but also deeply embedded and profoundly affected by culture. This is exemplified by counterintuitive findings reported in a cross-national study led by the WHO. This study found that among different countries, those with the highest prevalence estimates of MDD also had the lowest levels of functional impairment associated with this disorder. One interpretation is that these variations might be partly explained by the fact that culture shapes both the subjective experience and signs of MDD, which in turn may impose a challenge to assess this illness using descriptive criteria cross-nationally. Another possibility is that while the validity of the concept of depression may be similar, DSM criteria, which are widely used internationally, may define distinct levels of severity in different countries, partly due to indirect cultural influences.

25.2.1.1 The Chinese Context As an Example

In "*Depression in Cultural Context: Chinese Somatization revisited*," Andrew G. Ryder and Yulia E. Chentsova-Dutton (Ryder and Chentsova-Dutton 2012) offer a clinical example of Chinese somatization and use it to illustrate how cultures may be more or less permissive with the expression of physical and emotional discomfort and how this translates into different internal experiences and external manifestations of depressive syndromes. The authors argue that procuring cases that fit into DMS-based MDD criteria does not necessarily indicates that the Western construct of MDD best captures depressive syndromes across disparate cultural groups, as depressive syndromes may not present similarly cross-culturally. Clinical features recognized as ubiquitous in the Western world might facilitate group comparisons but tend to put emphasis on generalizations, having this aim. This imprecision inherent to the current descriptive psychopathology is, for instance, more evident in the case of the DSM criteria for personality disorders.

Differences in symptom presentation, or reporting biases, might in fact have influenced estimates of the prevalence of depression in China. For instance, one of the first reported presumed cultural differences in psychiatric health was a low rate of depression in that country. The 1-year prevalence rate for MDE was found in metropolitan China to be 1.8% (Lee et al. 2009), approximately one fifth of that of the United States in a previous study (Kessler et al. 1994). Similarly, a recent systematic review and meta-analysis found a lifetime prevalence rate for bipolar disorder of 0.11% (Zhang et al. 2017), which is substantially lower than US figures (Merikangas et al. 2007).

The use of the diagnostic construct *shenjing-shuairuo* (SJSR; often translated as "neurasthenia") instead of standard DSM criteria in China seems to support this notion. This construct was used by local psychiatrists after the Second Chinese Civil War and was introduced by Soviet physicians (Liu 1989). SJSR lists symptoms similarly to MDD but has a significantly higher emphasis on somatic aspects, with core symptoms being physical and mental low energy. For several decades, SJSR was the most frequently identified psychiatric disorder in China, with as many as 80% of psychiatric outpatients carrying SJSR diagnoses. Comparatively, the diagnosis of depression was rather sporadically used (Lee 1996). Psychological experiences cannot be separated from a cultural context as each is affected by the other.

Often psychiatric and psychological research employs the term "culture" as a synonym of nationality or ethnicity. Although this approach may have advantages, such as facilitation of research designs and clearer identification of target groups, there are also drawbacks. Among the disadvantages is treating national or ethnic groups as groups with fixed characteristics, overlooking the heterogeneity within group members. This is further exemplified by another study (Di Florio et al. 2016) examining the impact of education, country, race, and ethnicity on the self-report of postpartum depression. The results suggest that education, but not ethnicity/race, influenced the reporting of that disorder.

Working cross-culturally in mental health epidemiology, therefore, faces challenges posed by the need of an expanded view of the global landscape of psychiatric disorders that simultaneously takes into account cultural factors and remains grounded in clearly operationalized criteria.

25.3 Prevalence Across Cultures

Many cross-national studies investigating the prevalence of depression have been carried out, utilizing a variety of different surveys and diagnostic criteria. For instance, the Diagnostic Interview Schedule (DIS), using DSM-III criteria has been used to operationalize depression (defined as MDE, in this case) in representative communities (Weissman et al. 1996). Prevalence estimates for that study are found in Table 25.1.

Another cross-national comparison (Andrade et al. 2003) employed the WHO Composite International Diagnostic Interview (CIDI), according to DSM-III-R and DSM-IV criteria for MDD (Kessler et al. 1998). Prevalence estimates of that comparison study are found in Table 25.2.

Epidemiological findings were pooled (Moussavi et al. 2007) on ICD-10 MDE in the WHO World Health Survey in over 60 countries. The 1-year prevalence average was 3.2% in individuals without medical comorbidities and 9.3–23.0% in participants with chronic medical problems.

Table 25.1 Prevalence estimates of major depressive episodes (MDE)

	Lifetime prevalence/100 (SE)	1-year prevalence (SE)
Taiwan	1.5 (0.12)	0.8 (0.09)
Beirut	19 (1.76)	–
West Germany	9.2 (1.5)	5 (1.3)
Edmond, Canada	9.6 (0.6)	5.2 (0.45)
Christchurch, New Zealand	11.6 (0.96)	5.8 (0.7)
United States	5.2 (0.24)	3 (0.18)
Paris, France	16.4 (1.16)	4.5 (0.65)
Puerto Rico	4.3 (0.59)	3 (0.49)

Note: adapted from Weissman et al. 1996. *SE* standard error

Table 25.2 Prevalence estimates of major depressive disorder (MDD) using DSM-III and DSM-IV criteria

Country	Lifetime prevalence/100 (SE)	1-year prevalence (SE)
Czech Republic	7.8 (0.9)	2 (0.4)
United States	16.9 (0.0)	10 (0.6)
Canada	8.3 (0.6)	4.3 (0.4)
Chile	9 (0.6)	5.6 (0.6)
Mexico	8.1 (1.2)	4.5 (0.8)
Germany	11.5 (0.7)	5.2 (0.5)
Japan	3 (0.5)	1.2 (0.4)
Netherlands	15.7 (0.5)	5.9 (0.3)
Brazil	12.6 (0.9)	5.8 (0.6)

Note: adapted from Andrade et al. 2003. *SE* standard error

The wide variability in the estimated prevalence in these studies is likely due to a combination of genetic, environmental (substantive), measurement, and study design (methodological) factors.

Finally, a cross-national study (Bromet et al. 2011) was conducted evaluating the epidemiology of major depressive episodes across 18 countries employing face-to-face interviews using the WHO CIDI version 3.0, a unified instrument (according to DSM-IV), in an attempt to account for some of the methodological factors in previous studies—the World Mental Health (WMH) Survey. Prevalence estimates are found in Table 25.3.

Table 25.3 Prevalence estimates of major depressive episode (MDE) in the World Mental Health Survey initiative

	Lifetime prevalence/100 (SE)	1-year prevalence (SE)
High-income countries		
Belgium	14.1 (1)	5 (0.5)
France	21 (1.1)	5.9 (0.6)
Germany	9.9 (0.6)	3 (0.3)
Israel	10.2 (0.5)	6.1 (0.4)
Italy	9.9 (0.5)	3 (0.2)
Japan	6.6 (0.5)	2.2 (0.4)
Netherlands	17.9 (1)	4.9 (0.5)
New Zealand	17.8 (0.4)	6.6 (0.3)
Spain	10.6 (0.5)	4 (0.3)
United states	19.2 (0.5)	8.3 (0.3)
Low- to middle-income countries		
Colombia	13.3 (0.6)	6.2 (0.4)
Brazil	18.4 (0.8)	10.4 (0.6)
India	9 (0.5)	4.5 (0.4)
Lebanon	10.9 (0.9)	5.5 (0.7)
Mexico	8 (0.5)	4 (0.3)
China (Shenzhen)	6.5 (0.4)	3.8 (0.3)
South Africa	9.8 (0.7)	4.9 (0.4)
Ukraine	14.6 (0.7)	8.4 (0.6)

Note: adapted from Bromet et al. 2011. *SE* standard error

In this study, the authors found that the average lifetime and 1-month prevalence estimates of MDE, as defined by the DSM-IV, were 14.6 and 5.5% in high-income and 11.1 and 5.9% in the low- to middle-income countries. The lifetime estimated prevalence of MDE was approximately 4.5% higher in high-income, compared to middle-income countries (Table 25.3). One notable exception in the latter group, though, was the southwest region of Brazil, the economic hub, and wealthiest region of that middle-income country. These results are consistent with previous cross-national reports, including the WMH surveys and previous epidemiological studies (Demyttenaere et al. 2004).

The WMH investigators also studied cross-national differences in stem question endorsement, considering the possibility of differences in threshold of diagnostic criteria and symptom scores influencing estimates of prevalence. They argue that significantly smaller cross-national differences should be expected, if that was the case. Stem questions address only if subjects experienced episodes of sadness and loss of interest, compared to diagnoses of MDE, which involve more specific and ample criteria. About half of subjects in both high-income and low- to middle-income countries endorsed at least one stem question, which contrasts with the discrepancies in the estimates of prevalence of MDE between high- and low-income regions. This supports the previously mentioned notion that estimates of prevalence may be affected not only by the validity of the concept of depression but also variations in interpretation of widely distributed diagnostic criteria. It is still unclear which of these factors account mostly for the prevalence estimates. Although structured interview two-way translations, consideration of the influence of culture, and other methodological challenges of studies investigating estimates of prevalence of depression have improved over the last decade, this remains an important limitation of this literature.

The counterintuitive finding that people in wealthier countries experience more depression than those in low- to middle-income countries could be explained by differences in stress exposure and income inequality, which may promote a wide variety of chronic conditions, including depression. Furthermore, it has been suggested that MDD, to a certain extent, tends to affect more affluent populations (Kessler and Bromet 2013).

A discrepancy in the literature that is worthy of mention is that although estimates of prevalence of MDD were higher in wealthier countries, no significant difference was found in 1-year prevalence, which means the ration of 1-year to lifetime prevalence was higher in poorer nations. This could be related to either an accurately lower lifetime prevalence or higher persistence of depression in poorer countries. Of course, recall bias cannot be excluded by nature of these data being cross-sectional. Only a longitudinal methodology would permit asserting if such a difference really exists.

25.3.1 Sociodemographic Correlates

Across cultures, MDD most commonly starts in late adolescence (Kessler et al. 2007), with the median age of onset for a MDE being around the mid-1920s. Also across cultures, the highest risk of developing a MDE was deemed to be from adolescence to the beginning of the fourth decade of life (Table 25.4).

Bromet et al. found that younger age was associated with a higher 1-year prevalence in high-income countries (Bromet et al. 2011). Comparatively, in low- to middle-income countries, older age was associated with greater likelihood of having a MDE. The association between age and MDE was more pronounced in high-income countries (Alonso et al. 2011; Andrade et al. 2003).

Sex and marital status may also modulate the prevalence of depression across cultures. Women have been repeatedly deemed to have an approximate cross-national twofold increased risk of MDE compared with men, and people who are separated or divorced have significantly higher rates of depression than currently married individuals (Kessler and Bromet 2013). The strongest demographic variables associated with MDD in high-income countries is being separated, and in low- to middle-income countries, being divorced or widowed.

Finally, there is significant variability of point prevalence of depression within different socioeconomic groups in the same countries. Subjects from the poorest socioeconomic groups in high-income countries were noted to have a twofold increased odds of a MDE compared with those in the highest socioeconomic strata. Interestingly, in poorer countries there was no clear association between income and MDE.

Table 25.4 Cross-national differences in age of onset of MDD

High-income regions	MDD—age of onset (years)
United States	22.7
Spain	30
Japan	30.1
Israel	25.5
Italy	23.7
Low to middle regions	
Shenzhen, China	18
South Africa	22.3
Ukraine	27.8
Pondicherry region of India	31.9
Sao Paulo, Brazil	24.3
Colombia	23.5
Mexico	23.5
Lebanon	23.8

Note: adapted from Bromet et al. 2011

25.4 Adverse Consequences

The WHO ranks depression as the fourth leading cause of disability worldwide. It is the leading cause of disease burden for women in both high-income and low-income counties according to the 2008 WHO report (Alonso et al. 2011).

Several studies show an association between early onset of depression with premature interruption of education, with a diagnosis of MDD being associated with higher drop-out rates from school. This reported association is stronger in high-income nations (Kessler and Bromet 2013). An earlier age of onset of MDD also predicts a low probability of becoming married and a higher likelihood of experiencing a divorce (Breslau et al. 2011). Maternal depression is also known risk factor for poor growth in children.

Depression is also associated with unemployment and a higher occupational instability cross-culturally. These associations are also stronger in high-income countries compared to lower-income countries, which is thought to be related to higher work complexity in wealthier societies (Kessler and Bromet 2013).

25.5 Summary

MDD is a commonly occurring disorder across cultures. Cross-national reports reveal significant variability in estimates of the prevalence of depression, with the highest prevalence often found in countries with the highest incomes per capita. There is intriguing data indicating an

inverse relationship between high- and low- to middle-income countries in estimates of lifetime prevalence and persistence of MDD. Methodological factors may challenge the characterization of accurate worldwide prevalence of MDD, as sociocultural factors play a role in symptom expression and likelihood of endorsing standard MDD criteria across different cultures. The definition of culture as exclusively national or ethnic groups may facilitate research designs but also has disadvantages, failing to consider within-group heterogeneity. Despite these limitations, the descriptive cross-national epidemiological literature indicates consistency for a wide variation in age of onset, with median age of onset in early adulthood; a recurrent and chronic clinical course; higher prevalence in women compared to men; and association with numerous adverse outcomes. Future epidemiological research on cross-national differences in prevalence of MDD needs to develop a workable strategy to deal with the possibility of differential recall error and cultural context, among other methodological challenges, as plausible contributors to cross-national differences in prevalence estimates. In addition, prospective cross-national data remain limited. The firm establishment of environmental risk factors of depression awaits cross-cultural prospective studies. These initiatives may aid in the identification of vulnerable individuals, who can benefit from targeted preventative strategies (Munoz et al. 2010).

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