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 (Prenades-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 illness, defined as "neuropreservation" (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 neuropreservation may arise from several sources including the activation of immune-inflammatory and oxidative and nitrosative stress pathways as well as hypercortisolism.
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, in part, by 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 (Sotoel 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 (Ellert et al. 2008), a factor that may contribute to neuroprogression and 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 (Cortel 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., hopelessness, 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. Differentiation of depression is 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 related 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, hypersonia, and psychomotor retardation (Baldwin and Papakostas 2006). Contrasts emerge from neuroimmuno-neuroendocrinological findings. In melancholic depression, there is a hyperactivity of the corticotropin-releasing hormone (CRH) system and the hypotalamic-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 (SPOT-D) showed that remission rates and symptom reduction did not differ among the melancholic, atypical, and anxiety subtypes at least not in the first 100 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 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 excluding 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 psychiatic disorders are currently primarily defined on the basis of signs 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; Ormoraro 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 (Alhaji 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. Proband with co-twins meeting a diagnosis for lifetime depression exhibited greater negative affect responsivity 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

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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, of the 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 (Soetel 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 improve remission rates but also to ameliorate the longitudinal course of the illness.

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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 noradrenergic
and their metabolites reported inconsistent results (Kunugi et al. 2015), though there is general agreement that reduced CSF 5-hydroxy-indoleacetic acid (5-HIAA) concentrations are associated with increased suicidality. A meta-analysis of longitudinal studies (Valkanova et al. 2015) 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 (Lamer 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 Hees 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).

A second 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 interact 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 70% of patients with MDD (Vreeburg et al. 2009) especially in severe/melancholic MDD. Several studies have reported that SRSs 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) (Howen 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) depressive 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 Schindt 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; Moelich 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 (Mikkit 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 (Bayer et al. 2009). A recent meta-analysis (Poljakova et al. 2015) concluded that antidepressant treatment increases serum BDNF levels in MDD and 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 (ATRI), 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 1080 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-
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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; Kon et al. 2017). More recently, however, SPSTT-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 (ATRI) 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 (BRUTE-MD) (Louchby et al. 2009), patients with ATRI values above the threshold value were 2.4 times more likely to respond to escitalopram than those with ATRI values below threshold.

ERP's 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 N100, 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 no response to the selective serotonin reuptake inhibitor (SSRI) 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 (Khodayeri-Rostamabad et al. 2015). Moreover, significant wavelet coefficients extracted from frontal and temporal pre-treatment EEG data were able to predict antidepressant treatment outcomes (Munter et al. 2017).

Overall, the possibility to predict treatment response using EEG markers needs further studies because the data is 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 subcortical circuitry (SCC) connectivity appeared to predict the response to antidepressants and, more consistently, to responsive transcranial magnetic stimulation (rTMS) to 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 hypermetabolism in the insula is correlated with a good response to CBT and poor response to escitalopram, while hypometabolism 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 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% (Pendleton-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 modulating the monoaminergic 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 some antidepressant effects. A polygenic polymorphism in the SERT gene promoter region (3-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 (L) 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) allele 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 find any significant association or found contrasting results.

Tryptophan, hydroxylation (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 (Girauldi et al. 2010). 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 (Pittman et al. 2013). Several gene coding for components of this system have been scrutinized, in particular the FK506 binding protein 5 (FKBPs) and the corticotropin-releasing hormone receptor 1 (CRHR1) genes (Myers and Nemeroff 2010). FKBPs codes for a co-chaperone protein that modulates the glucocorticoid receptor. Individually homoygous for the minor alleles of the FKB5 SNPs are more likely to express depression after trauma exposure (Zimmermann et al. 2011). FKBPs 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 CRHR1 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 (Arabé et al. 1989; Nemeroff et al. 1994), 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. 2009) and moderate effect of child abuse on the risk for adult MDD (Bradley et al. 2008) as well as suicidal 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 (Garcia-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 biologically predictive 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 (Nijman et al. 2006) and was associated with antidepressant response (Lemmermaier et al. 2013).
Overall, the possibility to predict treatment response using EEG measures remains a subject for 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 responses 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 these regions with the SCC in the left anterior ventral premotor cortex/inisula, the dorsal midbrain, and the left ventromedial prefrontal cortex was differentially associated with outcomes of remission and response to CBT and antidepressant treatment in never treated MDD patients (Donnelly et al. 2017).

Measures of cerebral glucose metabolism by brain PET scan at baseline and after treatment found that hypermetabolism 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 (McCracken et al. 2013).

21.4 Genetics

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21.4.1 Prediction of Disease Vulnerability

Studies estimate that the genetic risk for developing MDD is approximately 40% (Purcell et al. and Nemeroff 2016). In the past few decades, genetic research on the susceptibility to MDD has uncovered several so-called candidate genes, generally based on their role in presumed pathophysiological mechanisms. The serotonin transporter (SERT or SLCA6A4), 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 (−3-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 homozygote long (L) genotype.

In a pioneering study, Caspi and coworkers (2003) reported S-allele carriers were more likely to develop depression in response to stressful early life events than the LL-homozygotes. Recent evidence confirmed a link between the short (S) form of 5-HTTLPR and stressful life events, resulting in depression (Sharpley et al. 2014). However, approximately 39% of the studies included in the meta-analysis failed to show any significant association or found contrasting results. TFT/TPH hydroxyamine (TPIH), 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 (Guzman 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) (Zhang 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 hypothesized to be involved in individuals with MDD (Ozurano et al. 2013). Several gene codings for components of this system have been scrutinized, in particular the FK506 binding protein 5 (FKB5) 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 (GR). The individual genotypes 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 suicidal behavior (Breton et al. 2010). The CRH1 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 (Aragi et al. 1989; Nemeroff et al. 1984), and a corresponding down-regulation 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. 2022).

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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 polymorphisms contribute to the variability in antidepressant response (Kato et al. 2010). In this regard, the definition of biological predictors of treatment response, i.e., “treatment biomarkers,” would contribute to the personalized approach of prescribing the most suitable medication for an antidepressant 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 (Lubermaier 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 (5-HTT) gene in its promoter region (5-HTTLPR). The 5-HTTLPR polymorphism has been associated with response to citalopram treatment in MDD (Mamdani et al. 2011). Another study of antidepressant response suggested that the 5-HTTLPR L allele, though negative findings have been reported as well. Investigations of the relationship between noradrenergic and dopaminergic 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 Carriers of rs2270006 in the CRHR1 gene showed a stronger response to citalopram with a threefold increased risk for non-responding after 4 weeks of treatment (Petajisto et al. 2007). One single nucleotide polymorphism (SNP) in 5HTTLPR gene encoding the CRHR1-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. 2011). As noted above, 5-HTTLPR is 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 varied results with some studies reporting the Met allele polymorphism associated with better response (Biundo et al. 2009) and others showing the Val/Val genotype to have a better outcome (Zou et al. 2010).

Genotype-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 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 (Petasis 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 differing from GWAS analysis where a single SNP can reach significance levels that captured the additive effect of multiple SNPs alleles across the genome failed to predict antidepressant response analyzing results of two large pharmacogenetic trials (GENDEP, MARS, STAR*D). (Garcia-Gonzalez 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 MDD. The most well-known and studied in the context of antidepressants is the CYP2C19 polymorphism. CYP2C19 is a cytochrome P450 enzyme that metabolizes antidepressants. CYP2C19 polymorphisms can reduce the effectiveness of antidepressants and increase the risk of adverse effects. Therefore, genetic testing can help identify individuals who may benefit more from certain antidepressants. This personalized approach can lead to more effective treatment and reduced side effects.

21.5 Epigenetics in MDD

Epigenetics may play an important role in the efficacy of antidepressant treatments. 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 observed epigenetic modifications. It involves the addition of a methyl group to cytosines in the DNA sequence, which can alter the expression of genes. DNA methylation is influenced by lifestyle factors, environmental factors, and genetic factors. Understanding the role of epigenetics in MDD can help in the development of more personalized treatment strategies.

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% (Sabuncu et al. 2012). Several other studies have explored these findings and overall support the idea that SLCA4A4 methylation and demethylation of CRE in the functional glucocorticoid response elements in intron 7 may be related to childhood maltreatment and thus might be a marker of MDD susceptibility. Higher methylation status of the BDNF promoter, especially associated with MDD, might also represent another epigenetic marker of disease vulnerability (Fabbi 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. For example, the Stenz et al. (2015) study, in which the promoter methylation of the BDNF gene was measured in both blood and postmortem brain samples in a sample of depressed patients. Interestingly, the authors showed reduced access of transglutaminase to regulatory elements, with consequent reduction in transcription. This 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, causing 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 novel insights into pathophysiology of MDD and may yield novel biomarkers for diagnosis and treatment response.
A set of candidate genes has been widely investigated as predictors of antidepressant response. The most studied genetic variant is the serotonin transporter (5-HTTLPR). There is evidence (Porcelli et al. 2002) pointing to a better SSR1 response in Caucasian patients carrying the 5-HTTLPR L-allele, although negative findings have been reported as well. Investigations of the relationship between noradrenaline 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 antidepressants, because a normalization of HPA axis activity has been reported after successful antidepressant treatment. Polymorphisms of the CRH type 1 (CRHRI) 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 (Li et al. 2006) and citalopram (Leckman et al. 2008). Allelic G-carriers of rs22077 of the CRHR2 gene showed a poorer response to citalopram with a threefold increased risk for non-responding after 4 weeks of treatment (Papillo et al. 2007). One single nucleotide polymorphism (SNP) (rs1799853) within the CRHR2 gene encoding the CRH-binding protein, which binds CRH with subnanomolar affinity to modulate CRH receptor activity, affects responsivity 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 (LeKam 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 (Lucintio et al. 2009) and others showing the Val/Val genotype to have a better outcome (Zen 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 (Mandani et al. 2011). Another study revealed the association of four miRNAs and two microRNAs (miRNAs) with antidepressant treatment response in MDD (Belcaux et al. 2016). Another microarray study aiming to identify peripheral gene expression profiles reported how responders and treatment-resistant patients with MDD to the SSR1 escitalopram could be predicted at the beginning of treatment by expression levels of NLGN2 gene (Peitai 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 polygenetic approach (differently from GWAS analysis where a single SNP can reach significance levels 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) (Garcia-Gonzalez et al. 2017; GENDEP Investigators, MARS Investigators, STAR*D Investigators 2013; LeKam 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 (Cristaulli et al. 2011). To optimize the individual patient's response 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 responsive 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 10% of currently 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 (Brown and Hopwood 2016). In treatment-resistant depressed patients, three prospective studies have evaluated the clinical validity and utility of a combinatorial pharmacogenomic test (GeneGibnh test) compared to a treatment as usual (TAU). The analysis of data from these combined studies demonstrates that GeneGibnh-guided treatment is associated with a greater reduction of 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 vast 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 modifications 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 CpG islands (CpG islands are sites where in a reduced access of transcription factors into regulatory elements, with consequences 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.

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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% (Subramanian et al. 2012). Several other studies have explored these findings and overall support the idea that SLC6A4 methylation and demethylation of CGIs 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 (Fabret 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 Suenz et al. (2015) study, in which the DNA 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 serum as a potential biomarker of depression. Finally, two studies (Hebarra 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-1 (IL-1) genes in the prediction of antidepressant response with some promising results (Linoway et al. 2017).

Domchek 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 pre-treatment methylation rate of SLC6A4 is associated with better therapeutic responses to antidepressants in a Japanese population sample. Kang et al. (2015), however, did not confirm this finding in 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-1β/C67 and associated with better response in individuals treated with escitalopram, but with worse response in those treated with norripitoline (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).

21.4.2 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-treatment 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 SIFOT trial, the incidence of childhood abuse was four-fold 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 big-data

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Acknowledgements The authors thank Alessandra Aica, MD, for her help in the preparation of the chapter.

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References


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