Depression and Personality

Juan Pablo Jiménez
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Etiopathogenic Theories and Models in Depression

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Depression and Personality

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ISSN 2662-3587 ISSN 2662-3595 (electronic)
Depression and Personality
ISBN 978-3-030-77328-1 ISBN 978-3-030-77329-8 (eBook)
https://doi.org/10.1007/978-3-030-77329-8

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

We would like to begin this preface by recalling the parable of the wise blind men and the elephant, which is very well suited to introducing a book of this nature. This well-known story, which originated in ancient times in India, is often used to highlight the difficulties of dialogue between different perspectives in the face of reality. In the various versions of the story, a group of blind men who have never come across an elephant before are invited to touch the body of the animal to grasp what it looks like. Each of them touches a different part, but only one part, such as a leg or a tusk. Then, they compare their observations and realize that they do not agree at all. The blind men argue heatedly trying to impose their own version, until the king who summons them says, "You are all right. The reason each of you is saying different things is that each of you touched a different part of the elephant. Therefore, the elephant has all the characteristics you mentioned". Grasping our point, the sagacious reader will already have substituted the word "elephant" with "depression".

Indeed, depression is a polymorphous heterogeneous condition, with varied clinical presentations. Moreover, there is a broad scientific consensus about the fact that what we call depression probably includes very different groups in terms of aetiology and mechanisms of production. To further complicate matters, in the last few decades, social scientists have pointed out that the term "depression" is used colloquially, at least in the Western world, to refer to the social malaise derived mainly from the model of society that governs us. Thus, we understand depression as a heterogeneous and complex phenomenon that needs to be addressed not only by the natural and medical sciences but also by the social sciences and the hermeneutics of cultural manifestations.

In this book on theories and etiopathogenic models in depression, we have invited different authors from various disciplines of brain/mind research to collaborate so that, as in the parable of the elephant and the blind wise men, they can share what they understand, from their particular disciplinary point of view, about the depressive condition. In a twist on the ending of the parable, we want the blind men (and women) to continue talking to each other, with the aim of finding, among all of them, certain invariant qualities common to their multiple perspectives, beyond the incommensurabilities. The authors of the chapters were asked to critically review

the state of the art in their field of expertise and to present their views without losing sight of the fact that depression is a complex phenomenon, that is, one where no single theory or model can offer a fully comprehensive explanation and, eventually, to explain the weak points of their own theories and their possible openness or attachment to alternative theories or models. This was intended to reinforce the interdisciplinary perspective of the book. We think that such an integrated perspective is of great translational value for clinical practice and for the construction of public policies that can be applied by government agencies. This is an ambitious book in the sense that it aims not only to juxtapose theories with variable degrees of incommensurability between them, but to go further, collaborating in the construction of a pluralistic and integrated model that can be used by clinicians and policy makers in the design of public policies. Certainly, the book that readers have in their hands falls short of this goal, but we expect it to be a step in the right direction. We subscribe to the idea that the present and future of Mental Health research should be guided by the principles of explanatory pluralism. In Chap. 1, we address the difficulties that impede this integration.

As a matter of fact, in our work we face a general scientific problem of our times, namely the realization that the relevant problems afflicting humanity are complex in their presentation and causes and must be tackled in a transdisciplinary way. The current crisis caused by anthropogenic climate change teaches us that the various scientific disciplines, the natural and the social sciences, must work together, because if a complex phenomenon is addressed in a partial manner, without simultaneously considering the multi-level interaction of the various concurrent etiological factors, it is not unlikely for the problem being addressed to end up getting worse, i.e. to produce what in medicine we call iatrogenesis. This book, then, is also an exercise in inter- and transdisciplinary collaboration.

Various studies, using different methodologies, confirm that Chile has around 20% more depressive disorders than the world average. Even more shocking is the fact that, according to the latest National Health Survey (2017), Chilean women report 5 times more depressive symptoms than Chilean men, while in the rest of the world the female/male ratio is between 2:1 and 3:1. This is a striking difference that needs further scientific explanation.

In 2014, a group of researchers from 6 Chilean universities, coming from a variety of disciplines such as Psychiatry and Public Health, Psychology, Sociology, Genetics, and Anthropology, got together to apply for funding from the *Millennium Scientific Initiative*, which the Chilean State makes available to natural and social scientists to investigate problems relevant to the development of the country and the welfare of its population, and to propose public policies that can be subsequently implemented. After an international competition, our group was awarded funding in 2015, and in 2019 the funds were renewed for five more years.

This is not the place to report the numerous goals accomplished in these years by some 160 researchers from every level within MIDAP's hierarchy, together with undergraduate and postgraduate students, global collaboration network members, and visiting foreign researchers. However, given that MIDAP's multiple research projects –which have so far yielded over 200 publications in indexed journals– have

enabled us to delineate several central features of depression, we feel that it is worth mentioning a few of them.

Our studies confirm that depression is a clinical condition of heterogeneous presentation and complex aetiology. Although this is a well-known fact, we have been struck by the enormous aetiological weight that environmental variables have in the onset and maintenance of depressive symptoms and disorders. In contrast to the biomedical model that continues to predominate in psychiatry, we have been surprised by the weight of what have been called the "social determinants of mental health". One factor that stands out in multiple studies is the importance of early trauma for the onset and course of adult depression. The association between depression and social malaise, which reflects the huge inequality gap in Chilean society (like in all the Latin-American region), and which led to a social and political explosion at the end of 2019, has been confirmed by many scientific studies. The Covid-19 pandemic has highlighted structural social inequality and the weight of social determinants in epidemiological figures.

The chapters of the book are grouped according to a thematic logic. The first four chapters are introductory and touch on epistemological, methodological, diagnostic (clinical), and sociological problems of the scientific study of depression. These are followed by two chapters devoted to the field of psychological aetiology. Chapters 7, 8, 9, and 10 are devoted to the genetics, neurobiology, and psychophysiology of depression. Chapter 11 deals with the influence of labour laws and psychiatric culture on the diagnosis of depression. Chapter 12 looks directly at the impact of poverty and social inequality on depression. Chapter 13 approaches depression from the perspective of developmental psychopathology. Chapter 14 explores the complex relationship between personality and depression. Chapter 15 looks at the hot topic of women, transgender, and gender non-conforming depression. The book ends with a chapter that asks how different etiopathogenic models can be applied in the diagnosis and treatment of a particular patient.

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Part I
Epistemology, Epidemiology, Psychopathology and History of Depression

Chapter 1
The Study of Depression in the Frame of the New Research Paradigm in Psychiatry

Juan Pablo Jiménez, Alberto Botto, and Peter Fonagy

1.1 Introduction. Toward an Integrated Research Paradigm for Psychiatry

During the twentieth century, the field of psychiatry and mental health disciplines experienced what Kenneth Kendler (2005) rightly called the *battle of paradigms*. At the start of the last century, psychiatry was just establishing itself as a medical branch and as a discipline, especially in the German-speaking world. Among others, Kraepelin, Bleuler, and even Freud were discussing which etiopathogenic principles should organize the nascent psychiatry. As George Makari convincingly shown in his book *Revolution in Mind: The Creation of Psychoanalysis* (2008), psychoanalysis was, among other things, the proposal that Freud and his group made to the academic world in response to the question of what mental disease is, what causes it, what its mechanisms of production are, and how it should be treated. The story that followed is well-known. During the twentieth century, the rejection by academia of unconscious mental processes and of the notion that it is also possible to become ill due to biographical reasons led to the development of psychoanalysis as an independent hermeneutic discipline, which sought to become epistemologically autonomous. However, the illusion of autarky has resulted in a psychoanalysis that is isolated from natural science and the rest of the disciplines of the mind. This situation may have been inevitable, given that even though Freud never abandoned the idea that the mind and brain are two sides of the same coin and that at some point we would eventually discover drugs that could modify pathological behavior, the

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_1

knowledge about the brain that academia had in the early twentieth century was not on a level with the central discovery of psychoanalysis: a dynamic mind with unconscious motivations. The neurology of the time had yet to finish describing the macroscopic anatomy of the brain; neurons and synapses were just being discovered. In this context, the main intellectual framework of psychiatry could not go beyond the anatomo-functional paradigm advanced by the German neuropsychiatrist Wilhelm Griesinger (1817–1868) some decades before: *mental illnesses are brain diseases*. By the way, taking advantage of current knowledge, we do not object to the assertion that mental disorders are brain disorders, with the difference that the definition of brain has changed radically. Evolutionary neuroscience (Burns, 2006; Dunbar, 2009; Dunbar & Shultz, 2007) has hypothesized that the most relevant brain for mental disorders is the so-called social brain, which only develops within the context of personal relationships; thus, we speak about mind/brain as two sides of the same coin. Thus, authors like David Taylor have proposed that "psychoanalysis is best understood as a highly specialized branch of human biology" (Taylor, 2009, p. 263).

The problem with twentieth-century psychiatry then seems to have been that each orientation defended its own paradigm as the only valid explanation and disregarded all others as mistaken or irrelevant. There was a mainstream psychiatry, the biomedical, and others more or less marginal psychiatries, like a psychoanalytical or psychodynamic psychiatry, a phenomenological psychiatry, a behavioral and social psychiatry, etc., without epistemological and methodological interconnections making constructive dialog between them possible.

Just as in the twentieth century various psychiatries were founded that responded to unique etiopathogenic theories and that did not converse with each other, we believe that the twenty-first century offers the possibility for the various etiopathogenic theories and models to interact with each other, in order to move toward an integrated paradigm in mental health. Just as hysteria was the psychopathological model around which Freud built psychoanalysis, the interdisciplinary study of depression offers the possibility that the different etiopathogenic orientations interact with each other. In depression, we have theories and models with a sufficiently developed empirical basis that range from genetics to culture, including biochemical, brain, psychological, and sociocultural models. Such integration of models can only favor patients as it would promote a personalized treatment appropriate to the different groups of depressed patients. Thus, in the scientific study of depression, we have enormous challenges. Not only building a paradigm that allows theories and models of disparate levels of organization to converse with each other but also relating these to the architecture, functions, and connectivity of the brain.

1.2 Depression Is a Highly Prevalent and Heterogeneous Condition

Depression constitutes a recurrent, frequently chronic, condition requiring long-term clinical management (Hardeveld et al., 2013). Its prevalence among the general population varies from less than 10% and up to 25%, is higher in women than men (Bromet et al., 2011), and, by 2030, is estimated to top the ranking of burden of disease, as measured in disability-adjusted life years (W.H.O, 2008). Both genetic and environmental factors have been implicated in developmental pathways to depression (Saveanu & Nemeroff, 2012; Sullivan, Neale, & Kendler, 2000). In relation to diagnosis, it has been seen that depression is not only misdiagnosed but also frequently overdiagnosed and also underdiagnosed, depending on the population studied and the professionals in charge of diagnosis (Cepoiu et al., 2008). Furthermore, despite the unquestionable progress in the understanding the biological bases and etiopathogeny of depressive disorder (Krishnan & Nestler, 2010), current available treatments have not proven to be effective enough. Regarding pharmacological interventions, naturalistic studies such as Star*D have shown low remission rates, under 30%, at least at initial stages (Insel, 2006). Even though long-term preventive results seem to be more effective both for relapse and recurrences, psychotherapy has rendered similar short-term results compared to medication for mild to moderate cases (Moras, 2006).

According to the World Federation of Societies of Biological Psychiatry, the future of the psychopathology lies in the so-called integrative psychopathology, which depends on the close collaboration with other branches of science concerned with the study of psychiatric phenomena, thus linking theoretical and conceptual knowledge with the findings of empirical research. The main tasks pursued by this approach are the following: to record and describe experimental and behavioral abnormalities within the intersubjective context, to explain their origin from an objective scientific perspective, and to make an effort to understand these abnormalities based on the subjective experience of the patient (Musalek et al., 2010). Berrios (2011) also states that every discipline requires periodical calibration, understood as the adaptation of descriptive language to remain accurate as regards the field of study. Consequently, given the current development of scientific knowledge, and in order to avoid reductionism, understanding depressive disorders requires a multidisciplinary approach that examines depression within the context of the complex mind/brain system (Kendler, 2008).

1.3 Historical and Clinical Considerations About Depression

Affective states present the first obvious feature: in almost all the cases, they represent, independently of its intensity, experiences in some way already known by the sufferer. In contrast, it is out of our habitual experience to feel – as in phenomena

associated with psychosis – that a mysterious evil force controls our thoughts or that anonymous internal voices are commenting on our actions. However, who has not felt anguish at some point in life or suffered pain and deep sadness as a result of some disappointment in love or the loss of a loved person? In other words, what we name as the affective states, no matter how deep or long-lasting they might be, are intuitively grasped. The "affects" have the same quality even when they are not connected with discrete circumstances. If we were to pursue this thought further, the question arises: what do we mean when we talk about affective experiences and use words like mood, emotions, or feelings? Although, as we have said, affective states constitute experiences that we all have had at some point, it is not easy to describe them clearly.

Although there are records of mood disturbances since Egyptian civilization, in Old Testament passages and Plato's *Timaeus*, these disturbances began to be considered as possible "medical" diseases from the first descriptions of the school of Hippocrates 25 centuries ago. It was thought that the principles of life were "humor" that in health were perfectly balanced. The excess, the fault, the migration to body regions different of their natural locus, produced illnesses. Melancholy, etymologically, means "black bile," thus indicating the alteration of one of the fundamental humors: the *atrabilis*. Areteo de Cappadocia (150 AD) is considered to be the first to observe in the same person alternation of mood exaltation and melancholy. He described such fluctuations as a disease of males, adolescents, and young people. Later, Galen (130–200 AD), a Greek physician, described melancholy as a chronic and recurrent disease. For him, mania (exaltation of mood that strictly means "fury") could correspond to primary brain disease or be secondary to other diseases. His observations remained influential through much of the Middle Ages. In a recent paper, Kendler (2020) outlines the process by which European Psychiatry between 1780 and 1880 changed the conception of melancholy as primarily a disorder of the intellect, with or without sadness, to one where it is conceived as a mood disorder, in turn causing cognitive disorders such as delusions. In Kendler's narrative, the first decisive movement away from the cognitive paradigm was made by the Belgian psychiatrist Joseph Guislain (1852) who, writing just after the mid-nineteenth century, defined elementary melancholia as a disorder of mood and then focused on the neglected but illustrative category of non-delusional melancholia. Such patients demonstrated no abnormalities of intellect or judgment. This form of melancholia was, he suggested, a disorder primarily of mood. At the end of the nineteenth century, many authors (Griesinger, Sankey, Maudsley, Krafft-Ebing, and Kraepelin) accepted the primacy of mood in the cause of melancholy and proposed that delusions arise understandably from a deeply altered affective state of mind. Delusion is not the cause of misery, but it engenders it in the mind's attempt to seek an explanation.

Emil Kraepelin (1856–1926) systematized much contemporary psychiatric knowledge in his psychiatry textbook (*Lehrbuch der Psychiatrie*). There, he used the expression *manic-depressive illness* (MDI), which he characterized as periodic and circular mood disturbances, simple mania, melancholy, some cases of amentia, and certain personal constitutions considered as pathological dispositions of humor, which he called *fundamental states* (Kraepelin, 2012). For Kraepelin, all these

pictures represented diverse manifestations of a single pathological process (with types or subgroups more or less differentiated from each other). The contribution of the German psychopathologist can be summarized in three fundamental observations: (1) no reactivity, that is, a lack of association with some external triggers (hence, its "endogenous" character); (2) a similar prognosis that never led to psychic deterioration (as was the case with the *dementia praecox,* group later called *schizophrenia* by Eugen Bleuler); and (3) a marked family aggregation, i.e., a hereditary pattern.

Contrary to what might be thought, the classification proposed by Kraepelin considered a series of clinical pictures which, under the current diagnostic criteria, are far from what is strictly known as bipolar disease. In fact, Kraepelin's ultimate aim was to achieve a correlation between etiopathogenesis, pathological anatomy, clinical description, evolution, and prognosis, ahead of what many years later would be the five criteria – also called *phases* – proposed by Robins and Guze (1970) as requirements for establishing the validity of a diagnosis in psychiatry: (1) clinical description, (2) laboratory studies, (3) differentiation with other disorders, (4) follow-up studies, and (5) family studies.

In 1980, the term bipolar disorder (BD) was incorporated into the American Psychiatric Association's (DSM-III) classification system for mental illness. Since then, research has expanded considerably, to encompass what is now known as the *affective spectrum* and *bipolar spectrum* (Akiskal, 1996; Akiskal et al., 1977; Akiskal & Pinto, 1999; Angst, 2007; Angst et al., 2018; Cassano et al., 2002) (see Chap. 2). Thus, it has been suggested that there should not be a categorical distinction between bipolar and unipolar disorders; on the contrary, it is thought that some fluctuations (to a different degree) would be present in both entities. This perspective facilitates an understanding of disorders such as recurrent brief depression, the "soft" bipolar spectrum, and cyclothymia. In the case of unipolar depression, Ghaemi et al. (2012) has proposed a dimensional classification of the depressive spectrum disorders. In addition to questioning the scientific validity of the construct, Ghaemi suggests that "major depressive disorder" represents a broad spectrum of depressive conditions (from the most chronic and mild pole to the most episodic and severe pole). Regarding melancholy – a term used to refer to the old "endogenous depression" – there is currently enough evidence to consider it an autonomous clinical category with both psychopathological (environmental reactivity, marked anhedonia, high recurrence, psychomotor alteration, cognitive alterations, and specific vegetative alterations, such as insomnia, low appetite, decreased sexual desire, and a daytime variation with morning worsening and evening improvement) and biological specificities (hypercortisolemia, altered sleep pattern, with decreased REM latency, increased REM time, and decreased deep sleep). In addition, melancholic patients respond better to biological treatments (drugs or electroconvulsive therapy) than to placebo or psychotherapy (Parker et al., 2010; Taylor & Fink, 2008).

As we noted, mood disorders form a heterogeneous clinical group that tend to involve a marked family aggregation, an episodic nature (with variable periods of interepisodic normality), and more or less serious alterations of behavior and psychic processes. Its essential phenomenon is recurrent mood disturbance. According

to Jaspers (1996), in abnormal affective states, it is necessary to distinguish two situations: (1) abnormally increased affective states, which can be understood in terms of origins in life circumstances, and (2) altered affective states, whose origin are not caused by external events or conscious causes ("feelings without object"), that is, it is endogenously determined. Therefore, disregarding for the moment the symptoms and attending only to their structure, mood disorders are best defined not by their polarity but by the recurrence of episodes. These episodes are presented to the clinician either by the alteration (increase or decrease) of known psychic phenomena (usually experienced) or by the appearance of such phenomena without a clearly identifiable motivation. However, as we saw, mood disorders can be characterized by their relationship to the polarities represented by mania and depression. In fact, Kraepelin is responsible for the designation of "manic-depressive psychosis" to the whole of what is now called mood disorders and not just the group of bipolar disorders.

1.3.1 Affective Temperaments

The relationship between temperament as a manifestation of personality and mood alterations comes from Greek antiquity (Berrios & Porter, 1995). Throughout history, the relationship between personality and depression has been conceptualized in at least four ways (Hirschfeld, 2013): (1) personality is a predisposing or vulnerability factor for the development of depression; (2) personality changes are a consequence of mood swings resulting from depression; (3) personality is a subclinical manifestation of depression (affective temperaments); and (4) personality characteristics influence the way depression clinically manifests itself (pathoplastic model).

At the beginning of the last century, Kraepelin (2012) distinguished between affective episodes that disrupted normal functioning (and that generally came as a result of external influences), from those manifestations – the so-called fundamental states – that chronically persisted, independently of such episodes. These alterations consisted of certain characteristics, which he called "constitutions." He classified these into depressive ("constitutional depression"), manic ("constitutional excitement"), irritable, and cyclothymic (successive alternation of depression and excitement). According to Kraepelin, the "depressive constitution" is characterized by a gloomy and insecure attitude, often accompanied by doubts and worries, with a tendency to sterile cavillations, especially of the hypochondriac type. Often the person feels overwhelmed and desperate, saying that "he has always felt this way." Everything seems serious to them, full of fears, feelings of guilt, and self-reproach. Each task is transformed into an unattainable enterprise; they devote themselves to their duties with abnegation but are unable to enjoy them. Many of these characteristics are present from youth in a more or less constant way, but it can also be the case that they are imperceptibly transformed into affective episodes, which – Kraepelin says – reveals the intimate kinship that unites the manic-depressive illness with the depressive constitution, the latter corresponding to a preliminary state

of the illness. Something similar was described by Kretschmer – with the picnic type in 1925 – and Sheldon – with the endomorphic constitution in 1940 – linking affective psychosis with the cycloid temperament and a particular form of physical constitution characterized by an increase in volume in the visceral cavities, tendency to fat deposits in the lower part of the trunk, rather fine thorax, and thin limbs, with small hands and feet. However, at present no clear evidence has been found regarding the association between bipolarity and body mass index (Ikeda et al., 2018).

Several decades later, in his text of 1946, Kurt Schneider referred to psychopathic personalities as "those personalities who suffer because of their abnormality or because of whose abnormality society suffers" and included in this group depressive psychopaths (Schneider, 1997). The fundamental state of mind of these subjects does not have such a direct relationship with temperament as is the case of hyperthymic psychopaths; however, they also suffer from a constantly oppressed state of mind and a pessimistic and skeptical view of life. They are insecure, anxious, lacking in self-confidence, flooded by multiple doubts and ponderings, and incapable of enjoying themselves, as if they were immersed in deep, grave, and heavy grief.

Later, Hubertus Tellenbach (1976) developed the concept of *typus melancholicus* to refer to a set of character traits that determine premorbid personality in melancholic depression. For Tellenbach, the essential constituent trait of the depressive is the fixation on a quest for order. This is characterized by its meticulousness, scrupulosity, hypernomy (excessively rigid adaptation to social norms and established practices, leading to a stereotyped application of rules regardless of context), heteronomy (exaggerated influence of usual external practices, where each action of the subject is guided by impersonal motivations referred to socially established criteria), and intolerance to ambiguity, in addition to a permanent interest in the fulfillment of work tasks and an excessive concern for performance, especially compared to others. However, these temperamental dispositions only constitute the premorbid personality of depression. In current thinking, there is a tendency to revisit the concept of *affective temperaments* (depressive, hyperthymic, cyclothymic, irritable, and anxious), considering them as subclinical manifestations of some disorder within the affective spectrum (Akiskal & Akiskal, 2005). These temperaments have been shown to be universal, with distinctive characteristics and without gender differences (Vazquez et al., 2012).

Throughout life, people face two fundamental psychological challenges: (1) to maintain close, reciprocal, and meaningful interpersonal relationships and (2) to maintain a differentiated, coherent, realistic, and integrated sense of self. Based on these polarities of relationality and self-definition, Blatt (2008) has developed a theoretical model for understanding psychological development, personality organization, sources of psychopathology, and mechanisms of change in psychotherapy. This model is based on a conception of nonlinear, dialectical, and complex psychobiological development in which the progress of certain domains allows the parallel advance of others, such as occurs with the development of the sense of self and interpersonal relations. Its main assumption is that the quality of the depressive experience depends on the personality whose development occurs in a dialectical

and synergic interaction between the tendency toward self-definition (identity) and interpersonal relatedness (Blatt & Luyten, 2009). These dimensions have been called, respectively, introjective (autonomy/perfectionism) and anaclitic (dependence/sociotropy). Both dimensions are associated with different personality structures, different relational and attachment styles, a vulnerability to specific environmental events (failure versus loss), a certain clinical presentation, and a characteristic response to pharmacological or psychotherapeutic treatments (Blatt, 2015).

As we have seen, the historical analysis shows that it has not been easy to distinguish and classify depressive states. Current classification manuals such as the DSM-5 have multiple weaknesses when it comes to capturing the full complexity of symptoms typical of depressive experiences (K. S. Kendler, 2016).

1.4 Depression as a Common Disorder: Depression and General Health

For over 100 years, psychiatry has tried to bring order to the heterogeneity of mental diseases. The synthesis we have made of the history of the psychopathology of depression in the spectrum of affective disorders may give the impression that most depressive conditions are severe or psychotic conditions. However, as pointed out by Glen Gabbard (2000), depression covers the entire spectrum of pathology and health and can be present in mild forms at certain times of stress even in basically healthy people. Individuals with minor depression, i.e., those who fail to meet the DSM criteria for major depression or dysthymia, are responsible for more days of disability than people with major depression. In addition, physicians in the healthcare system see more patients with depressive symptoms than with clearly defined depressive disorders.

We already know that depression is the world's leading cause of disability and contributes significantly to the overall global burden of disease (WHO, 2008). But that's not all, because nearly a third of all people with long-term physical conditions have a comorbid mental health problem such as depression or anxiety disorders. These mental health conditions increase the cost of healthcare by at least 45% for a wide range of conditions including cardiovascular disease, diabetes, and chronic obstructive pulmonary disease at each level of severity. Moreover, half of all patients referred for first consultant appointments in primary care level have medically unexplained symptoms, such as back pain, chest pain, and headache (Nimnuan et al., 2001).

There is another important issue: the social gradient of mental illness. Rates of depression, anxiety, and psychosis combined are much higher in the lower quintiles of incomes. Reducing health inequalities clearly requires a much more vigorous approach to mental illness, especially common disorders such as depression and anxiety (Layard, 2012). Several studies have shown the causal impact of environmental and psychosocial factors on the etiology of depression, especially its moderate and subclinical forms (see Chaps. 3, 4 and 12).

1.5 DSM in the Spotlight

The "battle of paradigms" between different currents and orientations in psychiatry has its origin in the different etiopathogenic theories that support them. Medicine took a giant step when it began to connect symptoms with underlying physiological mechanisms, i.e., semiology with pathophysiology. What would become of medicine if we did not yet know the different mechanisms of production of different types of fever? The pathophysiological knowledge facilitates the application of treatments based on the mechanism of production of symptoms and conditions. This is also the premise behind the psychodynamic theory of pathogenesis: if the symptoms and disorders are produced by unconscious conflictive motivations, making those motivational conflicts conscious will allow patients to resolve the conflicts in the light of conscious reason and considering the dictates of reality. Thus, in *Mourning and Melancholia*, Freud (2000) advanced the idea that behind depressive symptomatology there is an unconscious mourning process with special characteristics. If normal grief is a conscious reaction to the loss of a loved one or object, in melancholy the subject does not know what he or she has lost and all reproaches for the lost object turn against him or herself. Every psychotherapist, beyond the psychodynamic orientation, knows the therapeutic power of this theory of grief to understand and explain depression to patients. However, clinicians, no matter the range of causal theories they use, also know that not all in depression can be understood by the analogy with grief. Meanwhile, pharmacological research has given us an arsenal of drugs that act at the level of neurotransmitters to treat depressive patients. The model of pathogenesis underpinning drug treatment is diametrically opposed to that proposed by Freud. However, at the time of consultation, most psychiatrists use combined treatments based on both theories of the pathogenesis of depression.

Until DSM II (1968), American psychiatry applied a nosological system based on etiology. From DSM III (1980) onward, American psychiatry broke with this tradition and tried to develop an "atheoretical" and "descriptive" nosology. With this turn, it was hoped to bring order to the existing diagnostic chaos in world psychiatry – with this change, psychiatry moved away from the rest of medicine, which continues to develop diagnoses based on etiopathogenesis. Among many problems and criticisms of the DSM system, a major one is that research in psychiatry has targeted mental disorders defined according to the criteria of DSM (and/or ICD). The central criticism points to the fact that DSM is a diagnostic system based upon clinical presentation of sign and symptom, with reasonable reliability but with a dubious validity. For example, the DSM-IV diagnosis of major depression (the diagnosis of major depression in DSM 5 is basically the same), a highly prevalent disorder, does not meet any of the commonly accepted standards of validity (Maj, 2012). So, research in psychiatry faces the major challenge of the enormous clinical pleomorphism (Mann, 2010). Conversely, it is highly likely that heterogeneous syndromes grouped into one disorder include different pathophysiological mechanisms.

Although there seems to be no other way of making a reliable diagnosis than by defining certain criteria, the real danger is that in practice the criteria are easily

Table 1.1 Depression in DSM 5

The individual must be experiencing five or more symptoms during the same 2-week period, and at least one of the symptoms should be either (1) depressed mood or (2) loss of interest or pleasure.
1. Depressed mood most of the day, nearly every day
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
3. Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day.
4. A slowing down of thought and a reduction of physical movement (observable by others, not merely subjective feelings of restlessness or being slowed down)
5. Fatigue or loss of energy nearly every day
6. Feelings of worthlessness or excessive or inappropriate guilt nearly every day
7. Diminished ability to think or concentrate, or indecisiveness, nearly every day
8. Recurrent thoughts of death, recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
To receive a diagnosis of depression, these symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning. The symptoms must also not be a result of substance abuse or another medical condition.

confused with reality. Diagnoses become ontological entities, existing beyond their definition. The DSM-5 outlines the criteria presented in Table 1.1 to make a diagnosis of depression.

1.6 The Heterogeneity of Depression

Along with the psychiatric development of the concept of melancholy and depression, during the second half of the twentieth century, the term depression became a significant part of colloquial language. Even if we don't know exactly how to respond when someone says "I'm depressed," everyone seems to understand immediately what they mean. Moreover, sociologists have shown that depression has become an "idiom of distress," an expression of malaise in culture and life in society (Ehrenberg, 2010; see Chap. 4 in this book).

From a clinical point of view, depression presents itself in an extremely varied way, where the clinician can assume different causes and origins, even in cases of similar clinical presentations. Depression can refer to many different conditions: It can be a psychiatric diagnosis according to DSM/ICD criteria (MDD; bipolar disorder; dysthymia; cyclothymia); it can be the mourning response to a tragedy, such as the death of a family member. It can also be an expression of a pessimistic way of looking at life (depressive personality); it can be a transitory emotional state (adjustment disorder) or a state underlying complaint such as fatigue, weakness, lack of energy, insomnia, back pain, or headache. Finally, depression may be the response to, or expression of, an underlying medical illness.

However, from the point of view of research requirements, the heterogeneity and imprecision in the diagnosis of depression has important consequences (Mann, 2010). Research results associating biological, psychological, and environmental variables with depression have been repeatedly evaluated as disappointing. One of the most accepted hypotheses is that these results are due to the fact that the diagnosis of depression groups patients with similar clinical presentations, but with different pathogenetic mechanisms. At least three sources of heterogeneity in depression have been described (see Chap. 15).

1. *Theoretical heterogeneity*: Diagnostic heterogeneity across depression is a structural result of the polythetic diagnostic system of DSM – a given clinical diagnosis can be arrived at by using different combinations of symptoms. As a result, there are 227 different symptom combinations that follow diagnostic rules for depression (Olbert et al., 2014; Zimmerman et al., 2015); resulting combinations can be quite different and even contradictory at the phenotypic level.
2. *Empirical heterogeneity,* which requires collecting patient-level data, typically using symptoms described in diagnostic systems. Using this method, Fried and Nesse (2015) found 1030 unique symptom patterns emerging from a sample of 3703 outpatients diagnosed with depression from the STAR*D trial. An overwhelming majority of these profiles (84%) were present in only a handful of individuals, and half of the profiles were exclusively exhibited by one individual.
3. *Instrumental heterogeneity*. Whatever method is used to analyze patient-level data, symptoms need to be collected using specific instrumentation. These instruments can be interview schedules, used by clinicians, or self-report questionnaires. The underlying assumption is that all these instruments map on the same set of symptoms that constitute a prototype for depression. However, many of the widely used screeners for depression are rather idiosyncratic, that is, there is scarce content overlap between items. According to Fried (2017), all in all, the most common measures used for research in depression map on 52 distinct symptoms, and some of them are compound symptoms that can be disaggregated in such a way that even more symptoms are available. Many of these symptoms are idiosyncratic, that is, they are present in only one or two measures. According to his results, only 12% of all symptoms were present in the seven most used depression schedules or questionnaires.

1.7 The Research Domain Criteria (RDoC) Enters the Scene

Considering this situation, the National Institute of Mental Health has launched the Research Domain Criteria Initiative (RDoC) with the aim to “develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures” (Cuthbert & Insel, 2013, p. 4). The RDoC Project proposes that future psychiatric (and psychotherapeutic) research should focus on systems underlying basic psychological capacities (such as reward

neurocircuitry and the neural systems implicated in self-representation, theory of mind, attachment/separation fear, and positive and negative valence systems), rather than on discrete DSM disorders. "Rather than starting with symptom-based definitions of disorders and working toward their pathophysiology, RDoC inverts this process. Basic science – in genetics, other areas of neuroscience and behavioral science – serves as the starting point, and disorders are considered in terms of disruptions of the normal-range operation of these systems, with an emphasis on the mechanisms that serve to result in dysfunctions of varying degrees" (Cuthbert & Insel, 2013, p. 4). Therefore, RDoC is a transdiagnostic approach.

In a much-quoted commentary, Thomas Insel, when director of the NIMH, and his team, published the *Manifesto* of the RDoC scientific initiative: "RDoC classification rests on three assumptions. First, the *RDoC framework conceptualizes mental illnesses as brain disorders*. In contrast to neurological disorders with identifiable lesions, mental disorders can be addressed as disorders of brain circuits. Second, RDoC classification assumes that the dysfunction in neural circuits can be identified with the tools of clinical neuroscience, including electrophysiology, functional neuroimaging, and new methods for quantifying connections in vivo. Third, the RDoC framework assumes that data from genetics and clinical neuroscience will yield biosignatures that will augment clinical symptoms and signs for clinical management." (T. Insel et al., 2010, p. 749; italics added).

The difficulty we have in accepting this formulation is the biological reductionism it seems to establish. Such strong assumptions about the importance of biology not only presume that complex phenomena are ultimately derived from a single primary principle but also a mind-body dualism, the doctrine that separates the mental from the somatic (Engel, 1977). Biological reductionism minimizes the importance of subjective structures, the sphere of intrapsychic representational systems as moderators between the environment and the brain. *"Intrapsychic representational processes are not just consequences of environmental and genetic effects – they may be critical moderators*. […] For Fonagy, the primary evolutionary function of attachment may be the contribution it makes to the creation in the individual of a mental mechanism that could serve to moderate psychosocial experiences relevant to gene expression" (Fonagy, 2003 p. 108; italics in original). Human genomics, an emerging field of research, is demonstrating that external social conditions, especially our subjective perceptions of those conditions, can influence our most basic internal biological processes – namely, the expression of our genes (Slavich & Cole, 2013).

However, despite its initial impression of reductionism, a more careful look shows that RDoC takes a more sophisticated approach. In fact, RDoC does "not suppose that neural dysfunctions are the only causes of mental disorders, but rather recognize developments in mental health sciences showing that causes or risks of mental disorders may operate at many levels, including the genetic and the neural, the individual, the family environment, and the social context. Crucially, this view of multifactorial or multilevel view of causation (or risk) acknowledges and is intended to accommodate the fact that interventions at these various levels may affect onset and course, playing parts in primary prevention and management and

treatment after" (Bolton, 2013, p. 24). In this sense, RDoC is a transdiagnostic and multilevel approach that recognizes "bottom-up" causation, as well as "top-down" causation. If we consider the intrapsychic representational processes as intermediate phenotypes (see Chap. 9 and 15), RDoC opens, in our view, a window of opportunity for collaboration between neuroscience and different "psychiatries" including a research-minded psychoanalysis; the twenty-first century may represent a new opportunity for an integrated psychiatric paradigm that embraces natural science and hermeneutics.

1.8 Depression as Part of a Complex System

One of the oldest questions in psychiatry – and one that is still very alive – concerns how the brain and mind interact and, thus, the possibility of integrating the different approaches that attempt to explain mental disorders. Kendler (2005) considers psychiatric disorders to be etiologically complex phenomena where brain → mind causality is as real as mind → brain causality; therefore, in opposition to a biological explanatory reductionism, and without abandoning conceptual and empirical rigor, he presents a model he calls *integrative pluralism.*

Depending on their organizational level, complex biological systems such as the human mind/brain are characterized by self-regulation, a function based on internal and external environmental aspects (where the behavior of the parties involved results from the system as a whole), and by their recursive nature, that is, by the fact that both the genetic component and the regulatory systems, determining their expression, are both influenced and affected by the environment surrounding the subject (Mitchell, 2008).

Mood disorders, as a manifestation of an alteration of a complex system like central nervous system, probably constitute the most frequent psychiatric illnesses to be reviewed and classified. From a neurobiological perspective, depression belongs in a heterogeneous group of disorders produced by abnormalities rooted somewhere in the circuitry of emotion (prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala), where the specific subtype of symptoms depends on the localization and nature of the abnormality (Davidson et al., 2002). According to Mayberg (2007), a major depressive episode can be defined as a pattern of dysfunctional interactions between specific brain regions, such as the cingulate, paralimbic, subcortical, and frontal regions, which are fundamental to maintain emotional homeostasis under conditions of endogenous or exogenous stress.

In this way, complexity is a combination of clinical (e.g., diagnostic), biological, socioeconomic, cultural, environmental, and behavioral factors that are statistically associated with clinical prognosis (Safford et al., 2007; Schaink et al., 2012). Individual patients may have protective or risk factors across these domains, and their overall complexity level results from the sum of risks. Clinical, socioeconomic, and cultural risk factors complicate healthcare outcomes by disrupting the balance between *patient workload* (i.e., number and difficulty of daily life demands

Table 1.2 MDD risk factors

Childhood – Genetic risk factors, disturbed family environment, childhood sexual abuse, and childhood parental loss
Early adolescence – Neuroticism, low self-esteem, early onset anxiety, and conduct disorder
Late adolescence – Low educational attainment, lifetime traumas, low social support, and substance misuse
Adulthood – Ever divorced and history of MD
Past year – Past-year marital problems, total difficulties, and two types of stressful life events (SLE): Dependent and independent

including self-care) and *patient capacity* (i.e., resources and limitations affecting ability to meet demands).

The concept of *cumulative complexity* attempts to explain how risk factors accumulate and interact to influence healthcare outcomes (Shippee et al., 2012). In two seminal papers, Kendler, with Gardner and Prescott (2002) and with Prescott, Myers, and Neale 2003), based on studies of twins of both sexes, found a long list of predictors (risk factors) of MDD in adulthood (using DSM-III-R criteria) that grouped into five developmental tiers (see Table 1.2):

Depression is a complex behavior of a complex system that depends on multiple causes and multiple levels of organization. Nevertheless, what remains to be known are the relationships between the properties and behaviors at the different levels.

This is however a problem for the study of all psychiatric disorders. Recent studies on the structure of psychopathology have identified a general psychopathology (or "p") factor underlying common psychopathologies. Models with such a higher-order "p" factor provide a better fit to the data than models with three high-order factors (internalizing, externalizing, and thought disorder). Since Caspi et al.' (2014) seminal study in this area, several studies have replicated this higher-order factor (Del Giudice, 2016; Laceulle et al., 2015; Lahey et al., 2018; Murray et al., 2016) and have found that this "p" factor increases the chance of most types of common mental health problems and negatively influences the course of these problems, much as (complex) trauma (Nanni et al., 2012; Scott et al., 2012; Teicher & Samson, 2013). The "p" factor appears to be a transdiagnostic vulnerability factor that is also associated with "more life impairment, greater familiarity, worse developmental histories, and more compromised early-life brain function" (Caspi et al., 2014, p. 131). But what is this "p" factor and what are the mechanism underpinning it association with all these factors, and more specifically, how does it relate to depression?

There is increasing evidence for "p" being underpinned by a common genetic risk. A major UK study recently found genetic support for the "p" factor by comparing correlations from four different methods used to estimate genetic correlations: family study, genome-wide complex trait analysis, linkage disequilibrium score regression, and on a matrix of polygenic score correlations constructed for each individual in a UK-representative sample of 7026 unrelated individuals. All the major psychiatric disorder loaded positively on the first unrotated principal component, which accounted for 57, 43, 35, and 22% of the variance, respectively, for the

four methods. Schizophrenia, bipolar disorder, and depression were consistently among the highest-loading disorders on this genetic p factor (Selzam et al., 2018).

For our purposes in here, the question then is how can we think about the nature of the trajectory for an individual who moves from being at risk through a genetic vulnerability to developing depressive disorder. Here, Cicchetti and Rogosch's developmental psychopathology concepts of equifinality and multifinality are, as ever, relevant (Cicchetti & Rogosch, 1996). It appears that executive function and emotion dysregulation are the consistently implicated contenders for the functional difficulties that are commonly associated with most disorders (Beauchaine & Cicchetti, 2019; Macdonald et al., 2016; Martel et al., 2017). We would suggest that phenomenology of depression suggests that MDD is associated with an often serious disruption of the feeling of self and self-experience. Mentalization – the capacity to think about one's own or other's thoughts – becomes disrupted, often, misleadingly, replaced by concrete thinking (psychic equivalence), enactment (teleological thinking), and abstract thought unanchored in reality (pretend mode or hypermentalizing), all of which generate ruminations and increasingly unhelpful ways of thinking that become entrenched (as Aaron Beck has carefully documented). We have recently speculated that distorted mentalizing associated with psychopathology may be the "evolutionary flipside" of human social complexity, in particular the capacity for social imagination. Imagination after all is key to social understanding – we have to imagine what may be going on in the mind of a conspecific in order to engage with them in a collaborative task. Individuals whose difficulties with executive function and emotional regulation distort this key social cognitive function generate problematic outcomes from this social imaginative process and will be more likely to develop severe, persistent, and/or comorbid psychological disorder (and they come to be identified as having a high "p factor" because they experience a wide range of symptoms of mental disorder) (Fonagy et al. 2019a). We have further suggested that individuals experiencing such mentalizing difficulties will struggle to gain the regulatory benefits provided by other people's minds – the necessary social calibration we all depend upon to maintain a balance between being socially imaginative (being open to thinking about minds and their contents) and keeping these cognitions adaptively in check. These regulatory relationships between an individual and surrounding minds are also dependent upon the presence of a sufficiently mentalizing social environment: as a result, we have placed increased emphasis on the role of community, social structures, and mentalizing systems in thinking about mental disorder and prospects for effective treatment (Fonagy & Campbell, 2019; Fonagy et al. 2019b). The role of social support in the causation and maintenance of depression has been a central part of our understanding of the disorder for the past 50 years at least (Brown & Harris, 1978).

To further complicate matters, Markova and Berrios (2012) claim that one of the reasons why many aspects within the definition of mood disorders remain elusive is that psychiatry, one of whose bases is descriptive psychopathology, constitutes a hybrid discipline combining natural science epistemology (biology) with human social sciences (semantics). For this reason, the symptoms of mental disorders can be understood as biological-semantic complexes of variable stability and, therefore,

difficult to classify, requiring a new approach to systematize and interpret the knowledge gained about the said disorders.

1.9 Challenges in the Study of Depression

1.9.1 The Transdiagnostic Interactive Dynamic Model

Despite its high prevalence, the diagnosis of depression remains problematic. Over the last 30 years, the taxonomy of affective symptoms has not undergone major changes, but regardless (or perhaps because) of the amount of scientific evidence available, there is still some confusion in this area (Cole et al., 2008). We see in practice that the clinical presentation of depression not only varies among patients but also across different episodes in the life of the same patient. This clinical "pleomorphism" of depression (Mann, 2010) poses a challenge to the study of its etiopathogeny.

Currently, the medical causal model, focused on simple biological essences, has proven to be insufficient in capturing the nature of the mental disorder heuristically; it is dependent on multiple explanatory perspectives that, in addition, requires the consideration of the interaction of these elements at different levels (Kendler, 2012). Depression is a complex, clinically heterogeneous disease which can develop as a consequence of a number of factors and whose psychopathologic manifestations are related to personality and depend on the interaction of genetic and environmental factors. Hence, future psychiatric nosology should incorporate an approach integrating clinical observation and causal hypotheses (Luyten & Blatt, 2007).

As a way to solve the problems posed by the diagnostic approach to depression, Luyten et al. (2005) have developed and labelled the "transdiagnostic interactive dynamic model." Useful across multiple clinical symptoms (transdiagnostic), this model considers the vulnerability/stress paradigm as a source of psychopathy (dynamic) and is interactive; that is, the model considers that the mental illness appears within the context of a permanent interrelation between the genes, early adverse events, vital current stressors, and the various dimensions of the personality (stable cognitive-affective schemes). Besides, it is a model based on the causes (etiologically based) and founded on theory (theoretically founded). Using this model, the authors suggest performing an assessment of depression considering the following: (1) detailed analysis of symptoms and their severity; (2) understanding depression within a dimensional context from the perspective of the vital cycle, i.e., as a deviation from natural development; (3) dynamic (vulnerability/stress) and interactive factors (genes, environment, development, and personality); and (4) a differential indication for treatment.

1.9.2 From "Vulnerability" to "Differential Sensibility"

The diathesis-stress model has been considered the etiopathogenic paradigm of most mental disorders. According to this model (Monroe & Simons, 1991; Patten, 2013), psychopathology originates in the interaction of premorbid constitutional vulnerability (diathesis) and environmental aggressions (stress). Nevertheless, in the past few years, it has been suggested that, rather than diathesis (understood as an organic predisposition), individuals have a differential susceptibility to environmental influences (Belsky & Pluess, 2009); this means that they are not only more vulnerable to the negative effects of an adverse environment but are also extremely sensitive to the beneficial effects of a positive and nourishing environment or even to the absence of adversity. According to evolutionary models of "biological sensitivity to context" (Boyce & Ellis, 2005; Ellis, Essex, & Boyce, 2005) and of "differentiated susceptibility" (Belsky et al., 2007), the differential effect of any given polymorphism can be seen as supporting the notion of plasticity more than of vulnerability to environmental stress (Brune, 2012). This model proposes that the same allelic variation that involves a predisposition to a psychiatric disorder when linked to adverse vital events could lead to an even better than average response in the same domain when faced with favorable environmental conditions. Therefore, although individuals who are more "sensitive" to environmental stimuli are likely to be the most affected by stressors, they are also likely to be better prepared to respond to positive stimuli (Belsky et al., 2007). Furthermore, considering that genetic polymorphism differentially renders individuals "susceptible to plasticity" in the face of environmental stimuli depending on how adverse or favorable their early experiences have been (Brune, 2012), it would be possible to state that, from an evolutionary perspective, allelic variation poses a selective advantage if external contingencies have been beneficial (Wurzman & Giordano, 2012).

1.9.3 The Stress-Reward-Mentalizing Model of Depression

According to the stress-reward-mentalizing model of depression proposed by Luyten and Fonagy (Luyten & Fonagy, 2018), depression – particularly when it emerges in childhood and adolescence – results from a series of three-pronged interactions among impairments in three basic biobehavioral systems. It is suggested that three systems evolved in response to the continuing need to adapt to the ever-changing circumstances and the growing complexity of human interpersonal relationships in particular. They are (a) a system that deals with distress following threat (the stress/threat system); (b) a system that produces rewarding features associated with positive environmental features, including the formation of interpersonal relationships involved in infant–mother, mother–infant, pair-bonding, and other attachment relationships, and experiences of agency and autonomy (the reward system); and (c) a mentalizing or social cognition system, which subserves the capacity to

understand oneself and others in terms of intentional mental states such as feelings, desires, wishes, attitudes, and values, and delivers the necessary computational power human beings need to navigate their complex interpersonal world and to acquire a sense of agency and autonomy.

While these systems are adaptive, both internal and contextual threats may disrupt their highly interrelated functioning, and the nature of such disruptions may reflect what we have come to see as different forms of depression. These interacting impairments can in turn obstruct the achievement of developmental tasks that rely on capacities associated with these domains, increasing the risk for depression and associated conditions, particularly during developmental transitions (e.g., from childhood to adolescence and from adolescence to early adulthood). In adolescence and early adulthood, in particular, the establishment of new and more complex relationships and an emerging sense of agency and autonomy rely heavily on the stress regulation, reward, and mentalizing systems, which may explain the increased prevalence of depression during these developmental transitions.

The model argues that excessive and/or age-inappropriate stress, most probably in combination with increased stress sensitivity, typically sets in motion a developmental cascade effect. Both biological and environmental factors and their interactions are likely to be involved in the negative development cascade, which may originate in any of these three domains. The negative cascade may lead to a reward deficiency syndrome at a time of increased stress and decreased mentalizing capacities, leading to a state commonly referred to as subclinical or clinical depression, which further interferes with negotiating normative developmental tasks and challenges.

1.10 Conclusion

In this chapter, we have defined depression as a highly heterogeneous clinical phenomenon that can have different causes and pathogenetic mechanisms, ranging from genes to culture. Thus, depression is a complex condition that belongs to the mind/brain complex system, with different levels of pathogenetic explanation; however, little is known about the interaction between the different levels of organization. One of the properties of complex systems is the recursion between different levels of organization. This makes it necessary to study the system as a whole, since it is not possible to disaggregate its components, due to the multiple loops between levels that constitute it.

In the case of psychopathological phenomena such as depression, when we refer to etiopathogenic models, we are talking not only about the causes and the mechanisms that allow us to *explain* the origin of the symptoms using the methods of natural-scientific knowledge but also about the reasons, that is, about *understanding* the psychological motives behind the symptoms. It seems to us that this distinction is fundamental since inevitably the notion that the clinician has about the origin of the mentally ill will condition the way of understanding psychic suffering and, consequently, of implementing the therapeutic indications. In this sense, beyond the

"battle of paradigms," it is necessary to consider that the knowledge of the different etiopathogenic models should be at the service of understanding how and why a certain patient became depressed in order to establish a treatment plan that is as personalized as possible. To achieve this, it is necessary to understand the biological basis of the inheritance of mood disorders and their close relationship with the influences of the psychosocial environment as well as the various paths that emotional development can take, considering the effects of early trauma and adverse life events as well as personality influences.

There is probably no disease that has been subjected to as many classifications as depression. One of the difficulties in its diagnosis is the definition of the clinical picture. Thus, for example, one study showed that if the medical criteria used to define depressive illness are reviewed, it is possible to obtain 227 types of possible combinations of symptoms (van Loo et al., 2012). Therefore, the first problem is to determine the validity of the clinical diagnosis. At this point, we can find at least two aspects that diagnostic manuals such as the DSM-5 do not know about: the relevance of clinical phenomenology as a basis for psychopathological diagnosis and the fact that mental symptoms can change over time. In this sense, it is possible that the "clinical pleomorphism" or "phenotypic heterogeneity" that depression presents is due to our inability to incorporate into the diagnostic process a series of variables that can influence the way depression presents itself, such as personality characteristics and culture.

Depressive feelings can be experienced by all people and are part of the normal affective manifestations of grief and loss. However, how depression is understood, interpreted, discussed, communicated, and treated varies from culture to culture. For example, in some Southeast Asian languages, there is no equivalent to the word "depressed," while in regions such as Nigeria, only one word is used for depression, anxiety, and anger (Thakker & Ward, 1998). It is known that in Western societies, depression is more commonly viewed as an "illness" with both hereditary and biological components, while a "situational" view that encompasses symptoms in the context of psychosocial stress and interpersonal difficulties is often associated with traditional societies and minority communities. Thus, those who interpret problems as "emotional reactions" to environmental adversities – as opposed to a "pathological" interpretation – are less likely to seek professional help in the field of mental health (Karasz, 2005). Others, on the other hand, will feel more comfortable when a directive and hierarchical relationship is established, much closer to the classic medical model. In Chinese society, for example, the experience of depression is more "physical" than "psychological"; patients rarely report feelings of sadness or discouragement; instead, they present discomfort such as pain, sleepiness, fatigue, and boredom, evidencing a clear somatoform pattern (Kleinman, 2004). This would be explained because in these societies the expression of feelings, especially of negative affections, is considered something unacceptable.

Another difficulty has to do with the very concept of "depressive episode." There is increasing evidence that the course and natural history of depression is far more complex than a mere "episode." Research in the field of attachment theory and developmental psychopathology, especially in relation to traumatic events during

childhood, supports the notion that depression can be considered not only as an alteration of psychobiological development (Luyten, 2012) that manifests itself throughout the life cycle but also that it can be inherited by the offspring, which has been seen in both animal (Dietz & Nestler, 2012) and human (Fossion et al., 2015; Starr et al., 2014) models. Likewise, the role of social interactions and interpersonal relationships in the origin and maintenance of depressive symptoms has given rise to a series of studies that relate certain aspects of personality with involvement in potentially stressful situations in what has been called "stress generation theory." According to this model, certain personality traits and some interpersonal styles are capable of exposing the individual to a situation of increased risk of psychosocial stress and are one of the reasons that would explain the recurrence of mood disorders (Liu, 2013). Consequently, depression must be understood as (1) a developmental disorder, (2) occurring in a cultural and interpersonal context (both in origin and recurrence), and (3) which can be transmitted transgenerationally. This approach allows us to consider not only the effect that the environment can have on depressive symptomatology but also the impact that the depressed subject (and his personality characteristics) has on his social environment.

The way in which we approach the various objects of study and, therefore, the conditions in which it is possible to know are determined by the world and the culture in which we live. This condition of knowledge in the most developed societies has been called "postmodern" and finds its expression in a basic disbelief with respect to the meta-narratives (Lyotard, 2008). From the publication of The Structure of Scientific Revolutions by Thomas Kuhn (2007) arises the notion of "paradigm" understood as the achievements that a particular scientific community recognizes for some time as the foundation of its subsequent practice. Such achievements are characterized by the absence of precedents and by being open enough to leave a significant number of problems unsolved for the group. Paradigms are, therefore, frames of reference adopted by a scientific community at a given time and from which the phenomena studied are understood. The development of scientific knowledge occurs in cycles made up of phases of "normal science" (where a certain basic paradigm is accepted) and times of crisis that make new paradigms emerge and then return to a period of "normality." The problem, Kuhn argues, is that the paradigms that come into conflict are often irreconcilable, and it is impossible to find a common language that will bring them together, so to resolve them, one must often resort to irrational methods that are based on "subjective" or even "aesthetic" motivations. As a way of confronting the hegemony of the "simplification paradigm," Morin (2011) proposes the need for a new model that he calls "complex thought." Complexity is the fabric of events, actions, interactions, retroactions, determinations, and fates that constitute our phenomenal world. However, our understanding has historically made an effort to order, systematize, and clarify, rejecting the uncertain and ambiguous, thus depriving the observed phenomena of an essential aspect: their own complexity.

It is likely that, paradoxically, the development of empirical research and theoretical advances around the depressive phenomenon have led us to a kind of dead end represented by the concept of "depressive episode." It is also likely that today

we are witnessing not only a change in the way we understand depression but also in how it presents itself clinically. Our hypothesis is that we are facing a new paradigm in the way of understanding the depressive phenomenon that requires the incorporation of the notion of complexity in its study, through a multidimensional approach that considers the interaction of the different levels of analysis from genes to behavior, including personality and culture.

Kendler (2014) proposes three research goals for the twenty-first century psychiatry: "The first one is to continue the current work and populate the major levels and sublevels of our field with validated risk factors. Critical to this effort are a reliance on an interventionist model in which quality of causal inference is the only relevant criterion and a willingness to use our imaginative understanding to explore risk factors first understood in mental space. This is the best way to deal with our pluralistic values, our debates about the importance of mental, social, and biological causes… The second goal follows on the heels of the first and moves from a descriptive mode to a mechanistic one" (p. 937). This is a scientific effort that has already begun, but there are still few papers that investigate risk factors simultaneously on more than one level of organization. "The third goal is to take these mechanisms understood in a third-person objective perspective and attempt to move them into a first-person perspective – that is, to move from explanation to understanding." Patients do not consult for a third-person explanation of their subjective suffering: abandonment, loneliness, low self-esteem, or feeling threatened by a hostile world. They seek first of all to be understood by their therapist empathetically. "Here we are seeking first-person understanding for our patients and enlarged powers of empathy for us. The story begins with individual causal risk factors, connected together through mechanistic cross-level processes that can then be re-expressed in comprehensible mental language. This is closing the circle. We begin our investigations with patients displaying symptoms. We categorize and study them. We clarify the nature of their underlying disorders. Our efforts are not complete until we have returned to where we started and can explain to our patients how their symptoms arose" (p. 937; see Chap. 17).

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Chapter 2
Psychopathology of Depression in the Spectrum of Mood Disorders

Paul A. Vöhringer, Pablo Martinez, and José Manuel Arancibia

2.1 Introduction

Mood diseases encompass a diversity of clinical entities. Nosological systems have classified them in multiple ways. An extended denomination of depression in psychiatric practice is major depressive disorder (MDD), proposed by the Diagnostic and Statistical Manual of Mental Illness, since its third edition (DSM-III) (American Psychiatric Association, 1980). A relevant issue about MDD is that depressive illness do not correspond to a single diagnostic unit but there are different types of it (Ghaemi et al., 2012). The misleading major depressive episode is a heterogeneous hybrid that gives rise to a wide spectrum of depressive states. As a result, multiple affective episodes satisfy the major depressive episode criteria. Notwithstanding whether a major depressive episode has manic or anxious symptoms is a critical psychopathological distinction both at nosological and therapeutic level. To understand depression, we need to understand much beyond MDD. This chapter revises relevant concepts about the clinical approach to the depressive spectrum.

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2.2 Nosological Issues

2.2.1 Background

Historically, mood conditions have been seen as a set of entities. The first known to describe both melancholia and mania as two aspects of the same condition was Areteo from Cappadocia in the first century B.C. (Angst & Marneros, 2001). He claimed that both presentations had biological explanations (following the idea that Hippocrates already proposed, i.e., diseases were caused naturally, not because of superstition and gods). His main postulates were as follows: mania and melancholia had brain alterations, and melancholia was the phenomenological counterpart of mania.

When considering mood pathology as a dimensional spectrum, bipolar disorder (BD) comprises an important group of patients with mood conditions that usually tend to have a more complex course than unipolar ones. The modern concept of bipolar disorder was initially described in France with works by Farlet about folie circulaire (1851, 1854) and Baillarger (1854) about "folie de double forme" (Angst & Marneros, 2001). In Germany, in turn, Emil Kraepelin (1896) ended up gathering together all distressed disorders in the "manic-depressive insanity" (MDI) concept (Goodwin & Jamison, 2007a; Kraepelin, 1899, 1921), distinguishing it from dementia praecox. Inside this entity, there was room for several different clinical presentations (ranging from euphoric manic phases to melancholic depressive phases). Kraepelin offered a dimensional approach to mood conditions with no clear bounds between all of them. This unitary concept developed by Kraepelin was initially widely agreed worldwide. On the other hand, closer to the late 1950s, German psychiatrist Karl Leonhard made a division of MDI into bipolar and unipolar recurrent psychoses (Leonhard & Robins, 1979). This approach was leaning toward a more "cut and clear" categorical differentiation between these conditions. In the 1960s and 1970s, the Washington University of St. Louis researchers made an attempt to bring the more scientifically based Kraepelin's work to American nosology, which was broadly influenced by psychoanalytic thinking before that. The *neo-Kraepelinian* (Klerman, 1986) Washington group rephrased Leonhard's approach into bipolar illness and unipolar depressive illness, in order to expand affective disease to nonpsychotic mood presentations (Ghaemi, 2013a, b; Kendell, 1975). This definition was the basis for the Research Diagnostic Criteria (RDC) of the 1970s (Spitzer, 1978), which in turn became transformed in the DSM-III by the American Psychiatric Association (APA). DSM-III divided MDI into bipolar disorder and major depressive disorder, a nomenclature which is still kept in contemporary DSM-5 (American Psychiatric Association, 2013) and ICD-10 (World Health Organization, 1992) nosology.

DSM-III division of MDI into bipolar disorder and MDD was fundamented on the accepted validators of psychiatric diagnosis (Robins & Guze, 1970), which were introduced by the Washington University researchers as fivefold: clinical description, laboratory studies, delimitation from other disorders, follow-up study, and

family study. Briefly, the first validator referred primarily to the clinical picture of patients (i.e., mainly, but not exclusively, the *symptom* profile). Secondly, laboratory studies may be thought of as objective evidence of disease (i.e., *biological markers*) or results from well-established clinical assessment tools. Regarding delimitation from other disorders, Robins and Guze substantiate the necessity of fundamental exclusion criteria; in the next paragraph, we will see that such standard may be met by the *course* of illness. On the other hand, the authors agree that outcomes and prognostic differences between patients would be evident after a thoroughly conducted follow-up study, underlining the importance of *treatment response*. Finally, family study or *history* is related to the clustering of psychiatric illnesses within families. It was claimed that bipolar disorder and MDD differed in all forms (Ghaemi, 2013a, b):

1. Symptoms: depression is present in both entities, but mania is present only in bipolar disorder (Leonhard & Robins, 1979).
2. Family history: early genetic studies suggested that if a patient presents mania, it is also present in family members; but if the patient presents only depression, mania is not present in family members (Angst, 1966; Perris, 1966).
3. Course: unipolar recurrent depression was described with fewer and longer episodes than recurrent mania plus depression, where episodes were shorter and more frequent. Patients were older in recurrent depression (around age 30) and younger in recurrent mania plus depression (around age 20) (Angst, 1966; Perris, 1966).
4. Treatment response: recurrent depression responded to tricyclic antidepressants; recurrent mania plus depression responded better with lithium (Shorter, 2007).
5. Biological markers: recurrent depression was seen as having norepinephrine and possibly serotonin function alterations; recurrent mania had dopamine abnormalities (Schildkraut, 1965).

Note that the distinction between unipolar and bipolar affective illness seemed to be extensively supported through the publications of Jules Angst, Carlo Perris, and George Winokur, who independently showed that there exist clinical, familial, and course characteristics validating the distinction between unipolar and bipolar disorders (Angst, 1966; Angst & Marneros, 2001; Perris, 1966). They showed data that was interpreted at that time as confirming the Leonhardian categorical approach. Once DSM accepted the bipolar and unipolar dichotomy, it moved toward a *neo-Leonhardian* mood frame (Ghaemi, 2013a, b) and, at the same time, moved away from the original attempt to rescue the Kraepelinian MDI nosology.

2.2.2 The Bipolar/Manic Depressive Spectrum (MDS)

In recent years mood researchers developed the concept of "mood spectrum," (Angst, 2007; Ghaemi et al., 2002). This new development is a way of trying to go back to the Kraepelinian MDI concept. Note that MDI includes any course of mood

disease characterized by recurrence of episodes. Recurrence is the fundamental clinical fact, regardless of a course where episodes are only depressives or a course where depression and mania occur. In the definition of BD, the emphasis is not on recurrence but on polarity, such that the inclusion criterion implies the presence of manic (or hypomanic) episodes. Therefore, MDI in the current conception of the mood pathology corresponds to the bipolar disease defined by the DSM plus a good part of the broad spectrum of MDD. In other words, in MDI, a recurring course of unipolar depressions or a recurring course of bipolar depressions (part of a bipolar disorder) corresponds to the same disease. A central reason why Kraepelin emphasizes recurrence, not polarity, is the observation, in conjunction with other authors, that most states are not purely depressive or manic but a combination of both. In fact, Kraepelin went on to define six types of mixed states (Salvatore et al., 2002). Consequently, approaching mood disease according to polarity (major depression or bipolar disorder) is nosologically insufficient. That's why some authors have proposed the concept of "bipolar spectrum" or "manic-depressive spectrum," to integrate the original vision of manic-depressive illness and the current definition of unipolar and bipolar variants of mood pathology (Ghaemi, 2019). The notion of spectrum emphasizes that mood illness does not behave as categorical entities but rather as clinical presentations inside a dimensional concept. Different studies in the last decades have revisited the conceptual frame of clinical validators given by Robins and Guze (1970), supporting that an entirely dichotomous distinction between MDD and bipolar disorder is not scientifically valid. Instead, by the same criteria, it is possible to make relevant clinical distinctions between mood states within a unique mood spectrum, where a significant group of MDD presentations actually belongs to a highly recurrent episodic mood illness, whether as a bipolar course (along with manic or hypomanic episodes) or not.

2.2.3 Mood and Psychomotor Activity

Classically, mood is the result of the combination of at least three independent domains: feelings (polarity, intensity, reactivity, and emotional stability), thought (quality, quantity, and speed), and volition (energy, drive, and stability underlying a certain behavior). Emil Kraepelin, following Weygandt, argues that the combination of these domains gives rise to the whole range of states that constitute the mood pathology (Marneros, 2001; Salvatore et al., 2002). From the Kraepelin and Weygandt model, a nosological conflict arises: feelings are not central for diagnosis of a mood disorder. Feelings can be diverse and even changeable throughout a depressive or manic episode. A patient can have depression without any sad feeling at all; instead, anhedonia is present. A patient can have mania without any euphoric feeling at all; instead, irritability is present. Consequently, feelings lack sufficient consistency for diagnosis. More consistent and essential in the psychopathology of mood disorders is psychomotor activity (Ghaemi, 2019), a concept that encompasses Kraepelin's domains described above. Analogous to psychomotor activity is

the concept of activation (Barroilhet & Ghaemi, 2020; Scott et al., 2017). Scott et al. (2017) define activation as "a multilevel construct emerging from underlying physiologic change, measurable in objectively observed behavior (motor activity) and the related subjective experience of the overt behavior (energy)." Activation appears closely linked to the production and ideational flow, the state of the impulse or volition, and the evolution of feelings or emotions. Barroilhet and Ghaemi (2020) clarify this concept when comparing it with the notion of voltage. In this way, psychomotor activation will give the power or charge underlying display of affectivity, thought, and volition. For each of these symptomatic domains, psychomotor activity will present in a continuum that goes from over-activation (or excitation) to deactivation (or inhibition). The coincidence in the activation state of these domains will determine pure depressive and manic episodes (40% of the mood episodes (Ghaemi, 2019)), while activation in some of them and deactivation in others will lead to mixed states (60% of the mood episodes (Ghaemi, 2019)). In Italy, researchers have highlighted the distinctive classifying role that psychomotor activity has in dimensional terms. Cassano et al. (2004) showed that a state of psychomotor activation in association with intense irritability and suicidal ideation corresponds with a high degree of certainty to a severe mood disorder with a highly recurrent course. In addition, Benazzi (2002) showed that depressed patients presenting psychomotor agitation and intense distress have frequently a family history of mood disorders and an early debuting disease in their life.

In the next paragraphs, we describe the psychopathological characteristics of the different depressive states grouped into the broad MDD definition. For this purpose, recurrence degree on the illness course and psychomotor activation (or deactivation), already defined in this chapter, must be taken into account.

2.3 MDD Mood Spectrum

There is clinically developed evidence, claiming that at least four different types of depressive episodes can be described using the clinical validators developed by Robins and Guze (1970). These are neurotic, melancholic, mixed, and pure depression (Ghaemi et al., 2012).

2.3.1 Neurotic Depression

A generic approach to the neurotic depression, and of clinical utility for the differential diagnosis with other types of depression, is the disturbance of the affectivity only at a superficial level. This implies a mixture of depressive and anxiety symptoms that do not seriously compromise "vital feelings." The concept of "vital feelings" came from the prominent philosopher Max Scheler and his influence on the work of the psychiatrist Kurt Schneider (Cutting et al., 2016). Scheler proposed a

hierarchy of values and feelings that guide the life of human beings (Scheler et al., 1973). Schneider (1920/2012) then transfers this stratification of emotional life to the very nature of morbid states of affectivity, thus proposing a phenomenological basis to classify depressive disorders. He then develops the concept of "vital depression" as the central element of melancholy (or "endogenous depression"). Vital feelings are experienced as a basic state, according to which we are strong and lively or, instead, weary, slow, and flattened. If melancholy involved the affection of vital feelings and values, "reactive or exogenous depression" implied a disturbance at the level of "psychic (or mental) feelings." They are positive or negative feelings derived from our own personal state, such as anguish, loneliness, helplessness, or insecurity. Neurotic depression is concerned with this latter dimension. This affliction in shallower dimensions of affectivity implies a low level of psychomotor impairment or degree of activation of the patient. This idea keeps consistency with what is proposed in the Mood and Psychomotor Activity section in this chapter. A low level of psychomotor impairment is the most relevant and distinctive qualitative aspect in the psychopathology of neurotic depression.

Neurotic depression covers a wide range of possibilities in clinical practice, from reactions to biographic stressors with a significant burden of affective discomfort, passing for residual affective complications to traumatic experiences, to its more chronic presentation. Regarding the course of neurotic depression, the tendency toward chronification, together with a lower clinical severity, is a relevant clinical fact to advance in the differential diagnosis with the other types of depression, whose course is episodic and more severe (Ghaemi et al., 2012). Consequently, from a conceptual point of view, neurotic depression is not part of the manic-depressive spectrum. In fact, it could be debated whether at least a subgroup of neurotic depressions is definitely outside the frame of mood pathology. Neurotic depressions can pass along with pathoplastic determinants, such as high neuroticism and even depressive character traits, which facilitate chronification (Ghaemi et al., 2012; Ghaemi, 2019).

Neurotic depression, at least in its more chronic course, tends to present prominent anxious symptoms, even greater than depressive feelings (Ghaemi et al., 2012; Ghaemi, 2019), as well as a high degree of sensitivity to psychosocial stressors, more than is usual in episodic forms of depressive disorders. This susceptibility to psychosocial stressors, in association with a moderately anxious-depressed baseline, could facilitate clinical exacerbations, such that the criteria suggested by the DSM for major depressive episodes are met. This presentation tends to remit fairly quickly or to the extent of the resolution of the original stressor. In other words, they have frequent but brief DSM major depressive episodes and with a clear relation to psychosocial stressors. The main problem for such patients is the chronic depressive baseline, not the brief full depressive episodes (Ghaemi et al., 2012).

Neurotic depression does not exist in the nomenclature from DSM-III to DSM-5. It could be said that generalized anxiety disorder (GAD) and dysthymia are the two entities proposed by DSM that encompass chronic mild anxious and depressive symptoms, the core of neurotic depression. However, these two "disorders" are somewhat misleading; first of all their diagnostic criteria present a clear overlap

between them. Actually, the origin of these diagnostic categories responds to more political and professional than scientific reasons. In an attempt to develop a more scientific research-based nosology, *the neo-Kraepelinian* group proposed to replace the broad psychoanalytic concept of neurosis with the diagnoses of major unipolar depression and specific anxiety conditions (i.e., phobias, panic attacks, obsessive-compulsive disorder). The term "major" was used to exclude all mild depressive conditions, and the term unipolar was used to indicate distinct episodes rather than the mild chronic symptoms of neurosis. Nevertheless, the exclusion of the term neurosis from the DSM-III was met with resistance by the American Psychiatric Association's members and observers, most of whom were psychoanalytic practitioners. In fact, the most common diagnosis in psychoanalytic practice was neurotic depression. In order to reach consensus between groups, in addition to major depression, a "minor" depression was proposed as a condition which would cover the mild and chronic anxious-depressive symptoms of neurotic depression. However, the psychoanalytic groups objected to the term "minor," given the impact on health insurance reimbursement that a mildly connoted entity would have. Once "minor depression" was rejected, the milder depressive criterion initially meant for minor depression was folded into the major depression (Roth & Kerr, 1994). Then, the GAD construct was created to specify that clinical presentation marked by chronic anxiety, and the depressive dimension of this chronic course was referred to the category of dysthymia, which, in turn, is part of the wide range of the major depressive disorder. As could be expected, the overlap between MDD and GAD becomes common in clinical practice, being their delimitation scientifically questionable and with low validation among peers. No wonder, then, that twin studies show that there is a complete genetic correlation between the two categories. Thus, it is not possible to argue that there is a genetic/biological distinction between the constructs of major depressive disorder and generalized anxiety disorder (Ghaemi et al., 2012; Kendler, 1992). With all, neurotic depression persists as a less confusing and scientifically more valid entity.

The concept of neurotic depression is not vague. Nassir Ghaemi, based on the work of Martin Roth (Roth & Kerr, 1994), published a set of diagnostic criteria for neurotic depression that could be used to validate the diagnosis in new studies, as well as a clinical guide for its detection (Ghaemi, 2008) (see Table 2.1). The concept of neurotic depression was historically used in the field of psychoanalysis, which otherwise had an important influence on the development of DSM until its second edition. In psychoanalysis neurosis is an anxious-depressive state, resulting from defensive resources coming from the unconscious (Ghaemi et al., 2012). Outside the circle of psychoanalysis, primarily in European psychiatry, the term neurosis was never used in that way. There, neurosis was a merely psychopathological concept, with no connotation of causality: mild anxiety-depressive symptoms. Once DSM-III tended to detach itself from the influence of psychoanalysis and to assume that all depressions were conceived in the broad definition of major depressive episode, the term neurosis (and neurotic depression) fell into disuse. Despite this, Roth argued that neurotic depression was a scientifically valid and clinically useful concept (Shorter, 2007), distinguishable from melancholic depression. Subsequent

Table 2.1 Modified Roth criteria for the diagnosis of chronic neurotic depression (Ghaemi, 2008)

A. Depressed mood leading to severe subjective distress or marked functional impairment
B. Meeting two to four of the following criteria: Decreased or increased sleep, decreased interest in usual activities, decreased self-esteem, decreased energy, decreased concentration, decreased or increased appetite, and suicidal ideation, but not meeting DSM-5 criteria for a major depressive episode (i.e., subsyndromal major depressive episode symptoms)
C. Prolonged or frequent worries or anxiety, nearly daily for most of each day, or sustained or frequently recurring multiple somatic symptoms (e.g., gastrointestinal distress, headaches, paresthesia) with no secondary medical cause
D. Criteria A to C present over at least 6 months, during the majority of early every day
E. Mood or other symptoms apparently reactive to adverse or favorable changes in circumstances or everyday events
F. Absence of severe psychomotor retardation, guilt, anger, agitation, or psychotic features
G. DSM-5 major depressive episode criteria are not met during more than half of the duration of features A to G

research has supported Roth's position regarding the existence of various subtypes of depression, as emphasized in this chapter.

Regarding treatment of neurotic depression, antidepressants seem to be least effective compared with placebo, especially when referring to an anxious-depressive baseline with a chronic course (Fawcett, 1994; Ghaemi et al., 2012; Ghaemi, 2008; Kirsch et al., 2008). In fact, the STAR*D trial also showed lower antidepressant response in MDD with anxiety (as in the case of neurotic depression and mixed depression) versus non-anxious MDD (as in the case of melancholic depression) (Fava et al., 2008). In neurotic depression an antidepressant seems to behave as a transitory "feeling modulator," a kind of anesthetic in the context of clinical exacerbations. On the other hand, the coexistence of temperament with character determinants justifies a poor interference of antidepressants in the chronic course. Therefore, the prolonged use of antidepressants in this profile of patients doesn't have any conceptual support.

2.3.2 Melancholic Depression

Severe form of depression, with a predominance of psychomotor inhibition, intense anhedonia, and usually without anxiety. Cognitions are marked by hopelessness, helplessness, frustration, guilt, or ruin. A fundamental clinical fact of melancholic depression lies in the lack of emotional reactivity, such that patients do not experience greater emotional lability or greater response to psychosocial stressors (Ghaemi et al., 2012). Consequently, events with a negative connotation usually do not trigger greater anxiety, sadness, or irritability. In the same way, events with a positive or stimulating connotation do not bring greater subjective well-being, energization of behavior, or improvement of impulse.

Barroilhet and Ghaemi, in the publication *Psychopathology of Mixed States* (2020), carried out an extensive review of the literature, extracting through factorial and cluster analysis, the main characteristics that define these states. Regarding depression, they find that the available literature suggests two depression clusters: one characterized by psychomotor activation/hyperreactivity and the other characterized by psychomotor retardation/hyporesponsiveness. The psychopathology of the latter reveals main characteristics of melancholic depression: central is psychomotor retardation, including reduced energy, inhibition of thought, motor activities, motivation, and interests. About affectivity, the narrowing of the emotional range and lack of emotional reactivity are core symptoms.

Melancholic depression tends to be more episodic than chronic. It is more frequent in bipolar disorder than in unipolar depression. It constitutes a severe clinical state with a high suicide risk. Episodes are usually of slow evolution, lasting up to a year. Treatment should be provided as soon as possible, usually with tricyclic antidepressants or MAO inhibitors, which have proven useful, not the same for the widely used selective serotonin reuptake inhibitors (SSRIs), which tend to be less efficacious. Electroconvulsive therapy should be considered as well in the treatment of melancholia. The course of this type of depressive episode tends to be recurrent over time (Ghaemi et al., 2012).

2.3.3 Mixed Depression

The mixed depressive episode is characterized by psychomotor or psychic agitation, irritability, and mood lability as core features (Pae et al., 2012). These patients may also have anxiety as with neurotic depression, but the difference is that these symptoms are episodic and severe, unlike those with neurotic depression. This kind of depression presents the highest suicidal risk of all kinds of depressive episodes.

A relevant issue in relation to the wide range of clinical entities covered in the MDD definition is the very narrow definition of mania or hypomania, and particularly in the case of mixed states. In the DSM-5 (American Psychiatric Association, 2013), "with mixed characteristics" is incorporated as a specifier in major depressive episodes; however, arbitrary definitions are still being prominent: three or more manic symptoms concomitantly with the full depression criteria allow to qualify the episode as mixed, but the assumption is that the overlapping symptoms (included in both the definition of pure depression and that of pure mania: irritability, agitation, insomnia, and indecision) do not qualify as being of manic nature (Koukopoulos & Sani, 2013). Actually, some authors argue that mixed depression as defined in the DSM manual corresponds more to mixed hypomania (Barroilhet & Ghaemi, 2020; Koukopoulos et al., 2013), since euphoria and increased intentional activity are acceptable as symptoms of the manic pole, but not to irritability (symptom classified as overlapping). Empirical evidence shows a clear different picture about mixed depressive states, a broad group characterized primarily by psychomotor activation – acceleration of thinking, marked anger or irritability, and impulsivity – in addition to depressive symptoms. This is what we define here as mixed depression

(Ghaemi et al., 2012). Evidence suggests that up to 50% of patients diagnosed with a major depressive episode present between one and three manic symptoms (Angst, 2011; Ghaemi, 2019).

Kraepelin was one of the first authors to provide a comprehensive depiction of mixed affective states. He stayed mixed episodes are the largest proportion of manic-depressive illness (Kraepelin, 1913, Marneros, 2001; Salvatore et al., 2002). As mentioned earlier, he described an inhibition-excitement continuum of three domains of psychic life: thought, volition, and feelings. As a result, Kraepelin defined two mixed depressive syndromes (among six forms of mixed states): depression with flight of ideas and anxious (or excited) depression (Kraepelin, 1913, Koukopoulos et al., 2007). In the first one, the flight of ideas predominates but with inhibition of motor activity, including language, to the extreme of rigidity and silence; in the second one, an increase in anxiety and restlessness coexists with inhibition of thinking. Kraepelin argued that these presentations were frequently in the transition between depression and mania, such that they should be understood as "mixed states between depression and manic excitability" (Koukopoulos et al., 2007).

A modern exponent of the concept of mixed depression was Athanasios Koukopoulos, who points out that the fundamental aspect that distinguishes the types of depression is the predominantly inhibited character of some and those with marked symptoms of an excitatory nature, that is, internal and psychomotor agitation, acceleration of thinking, talkativeness, intense irritability, and affective lability, among others (Koukopoulos et al., 2007). Remember that, in melancholic depression, agitation is absent by definition.

Koukopoulos suggests that a fundamental psychopathological problem in mixed depression is related to the excitatory nature of the causal process of psychic pain, anxiety, suicidal ideation, anhedonia, functional impairment, and other symptoms usually associated and caused by a depressive process. W. Griesinger, as early as 1861, proposed that the basic nature of "psychic depressive states" was not necessarily the weakening or suppression of the underlying psychic or brain processes. The author argued that "states of brain irritation and excitement of psychic processes frequently give rise to depressive states or psychic pain" (Griesinger, 1861). Based on the above, Koukopoulos argues that a relevant proportion of depressions are the effect of maniacal states ("Supremacy of Mania" (Ghaemi & Vohringer, 2017)). One of the clinical presentations that account to a greater extent for this relationship corresponds to mixed depression, a scenario in which depressive symptoms cannot be separated from maniacal symptoms, presenting a common pathophysiological basis. This model questions the delimitation of mental illness based on polarity criteria.

In addition to agitated depression associated with psychomotor exaltation, Koukopoulos describes mixed depression associated with psychic agitation, both being the (nonpsychotic) presentations of mixed depression (melancholia agitata) (Koukopoulos et al., 2007). The fundamental clinical fact lies in the usual criteria that define a depressive episode in addition to an experience of internal tension or restlessness. The presence of motor agitation confirms the presence of psychic agitation; however, in the absence of motor excitement, the difficulty lies in the

distinction between anxiety and frank agitated depression. For this, the author proposes as a distinctive criterion the presence of at least three of the following symptoms (always in the presence of the elements that define a major depressive episode):

A. Racing or crowded thoughts.
B. Irritability or unprovoked feelings of rage.
C. Absence of signs of retardation.
D. Talkativeness.
E. Dramatic descriptions of suffering or frequent spells of weeping.
F. Mood lability and marked emotional reactivity.
G. Early insomnia.

Such symptoms are of excitatory, not depressive, nature and indicate the absence of inhibition. Later, Pae et al. (2012) in a prospective study found that the most common presentation of mixed depression includes the triad of irritability, acceleration of thinking, and distractibility. Barroilhet and Ghaemi, in their review of the *Psychopathology of Mixed States* (2020), obtained that the fundamental characteristic of mixed states is psychomotor activation, independent of polarity, being irritability or dysphoric hostility the second most relevant symptom. Specifically, they observed that the mixed depressive cluster is characterized by psychomotor agitation, irritability, emotional lability, distractibility, and emotional hyperreactivity. The high frequency and great intensity of affects, such as irritability, anger, panic, and exaltation, stand out. They also describe the presence of somatic symptoms such as alterations in appetite and exalted sensory perception. Psychomotor agitation favors suicidality. The authors conclude that the conceptual models of Kraepelin and Koukopoulos fit adequately to the empirical results obtained.

Using the proposed criteria for mixed depression, Koukopoulos et al. (2007) observed that 51% of depressions are mixed. Angst (2011), based on the definition suggested by Benazzi (2008), obtained a similar proportion. Subsequently, based on the criteria developed by Koukopoulos, Sani et al. developed the Koukopoulos mixed depression scoring scale, validating it psychometrically. By factor analysis, they found that anger and psychomotor exaltation determine the greatest variability of the scale (80% of the variance) (Sani et al., 2018).

The therapeutic implications of the recognition of mixed depression are important: if the excitatory/manic nature of depression is accepted, the use of antidepressants as first-line treatment could be ineffective (Angst, 2011) and even worsen the clinical picture, as they do in manias (Goldberg et al., 2007). Sani et al. (2018) observed that around 50% of the patients who presented a mixed depression were using antidepressants. Additionally, suicide attempts were 2.5 times more frequent, if the mixed episode was associated with the use of antidepressants, compared to those of spontaneous origin. Later, treating mixed depression with mood stabilizers, neuroleptics, or electroconvulsive therapy led to a better clinical response (Patkar et al., 2012; Suppes et al., 2014), consistent with treating the underlying excitatory mechanism (and the resulting psychomotor exaltation and irritability) and not just its effect (depression).

Mixed depression, like melancholic depression, is episodic and more common in bipolar disorder than in major depression (but it is frequently present in MDD), again revealing the nosological conflict behind the distinction between unipolar and bipolar illness (Ghaemi et al., 2012).

2.3.4 Pure or Simple Depression

This category, common in clinical practice, is defined by the absence of the psychopathological elements that give rise to the other types of depression already described (Ghaemi et al., 2012). Patients tend to maintain a certain emotional reactivity and interests, as opposed to the frank lack of reactivity and anhedonia typical of melancholic depression. In turn, they maintain some functional capacity, being able to even sustain work or academic tasks, unlike a severely weakened and inhibited patient. In these cases, the criteria defined by the DSM manual for major depression are usually met but without any specifier, such that manic symptoms or prominent anxiety are absent. In other words, they are not melancholic patients nor are mixed or neurotic, but they are depressed.

The pure-non-melancholic depression we describe here is quite similar to the so-called "typical" depression. The problem with distinguishing a "typical" form of depression is that by default there is an "atypical" depression (DSM-5. American Psychiatric Association, 2013), whose validity as a subtype of depression is scarce. The essential of an atypical presentation is the emotional reactivity; however, this is frequently present in neurotic depression or mixed depression too. The same occurs with the atypical criteria of marked anxiety and a persistent pattern of "interpersonal sensitivity," characteristics which are also present in neurotic and mixed depression. Regarding the classical association of increased appetite (usually type "craving" for carbohydrates) and sleep, as opposed to insomnia and anorexia of the "typical" presentation, there is no consistent empirical evidence to suggest that, most of the time, these symptoms occur together (Ghaemi et al., 2012). It is common for a patient to have hypersomnia and anorexia, or insomnia and hyperphagia. In addition, hypersomnia and hyperphagia attributed to "atypical" depression are common in anergic bipolar depression; however, this description is not too far from melancholic anergic depression with a severe psychomotor inhibition and lack of emotional reactivity. In fact, melancholic depression is more common in bipolar than unipolar depression. Consequently, it seems more likely that the symptoms of "atypical" depression can occur in the range of the different subtypes of depression already described, rather than forming a valid nosological entity. This does not mean that the symptoms attributable to "atypical" depression have no semiological value. Actually, the association of hyperphagia, hypersomnia, and anergy is more common in depressions of episodic course. An example of this symptomatic conjunction is seen in winter depression (Magnusson & Boivin, 2003). This does not constitute a subtype of depression but rather the seasonal exacerbation (implies episodicity by definition) of a mental illness, due to a chronobiological distortion

caused by a change in the photoperiod (Lewy et al., 2007), and is much more frequent in bipolar disorder (Geoffroy et al., 2014; Ghaemi, 2019). In turn, if maintenance insomnia and early awakening attributable to "typical" depression are usually associated with an advance of the circadian phase with respect to the sleep-wake cycle, daytime hypersomnia and lethargy (i.e., "atypical" presentation), sometimes in conjunction with early insomnia, are more frequently associated with a circadian phase delay, a fact that has important therapeutic implications, in addition to being more frequent in bipolar depression (Takaesu, 2018). Therefore, it is recommended not to disregard due to their non-specificity these "atypical" semiological elements, since they contribute to doubt that we are facing a pure-non-melancholic depression, in addition to suggesting pathophysiological differences that could be relevant in therapeutic decisions.

Pure depression tends to be episodic but without the recurrence or severity of the other forms of episodic depressions (Ghaemi et al., 2012). It tends to appear in the third or fourth decade of life and has little genetic familial background. Conceptually, pure depression would be located on the frontier of the manic-depressive spectrum. Regarding the pharmacological approach, it is not entirely clear if antidepressants could be particularly more effective in pure-non-melancholic depression compared to the mixed (episodic and with high recurrence) or neurotic (tending to chronicity) forms (Ghaemi et al., 2012). This is because studies of antidepressants efficaciously operate with the definition of major depressive episode, such that they include a heterogeneous range of depressive conditions. Based on the evidence, it can be argued that the episodic evolution and chronicity of depressive symptoms, suggestive of illness in the manic-depressive spectrum in the first case and a temperamental substrate in the second one, are associated with a lower response to antidepressants (Ghaemi, 2008). On the other hand, it has been described that around one-third of patients diagnosed with unipolar major depression present a course characterized by one or a few episodes (Goodwin & Jamison, 2007b). Precisely, antidepressants seem to be more effective in this group of patients with a non-chronic and highly recurrent course, typical of pure-non-melancholic depression (Ghaemi, 2008; Ghaemi et al., 2012). Some authors suggest that pure-non-melancholic depression is the "true unipolar depression," such that it constitutes the niche where selective serotonin reuptake inhibitors would acquire greater therapeutic value.

2.4 Final

It has been argued in this chapter that the distinction between different types of depression is scientifically supported and is possible to carry out in routine clinical practice. It could be argued that MDD is an operationally useful definition; however, it has been shown that it does not adequately guide therapeutic strategies as has been observed in reports of the long-term antidepressant effect from STAR*D protocol (Ghaemi, 2008; Rush et al., 2006). The wide use of antidepressants is ineffective, especially in the long term, and even more so, it can be deleterious in a significant

group of patients. No class of biological drug is capable of being highly effective across such a heterogeneous clinical spectrum as depressive disorder (Ghaemi et al., 2012).

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Chapter 3
Epidemiology of Depression: Burden of Disease, Trends, and the Contributions of Social Epidemiology to the Study of Its Causes

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3.1 Burden of Disease Due to Depression

3.1.1 Introduction

Depressive disorders are an urgent problem for health systems around the world, not only due to their high frequency and their contribution to the global burden of disease but also because of their impact on other physical diseases that cause disability and mortality, their negative effect on the quality of life of those affected by them and their families, and their economic consequences. In the first part of this chapter, we attempt to outline these aspects, which support the decision to prioritize depressive disorders when implementing policies and initiatives at a national level (OMS, 2004; Cassano & Fava, 2002).

To conduct epidemiological research on a given health problem, authors require an operational definition of it to be able to differentiate between affected and unaffected subjects (Gustafson & Greenland, 2014). This makes it possible to estimate the rate of incidence (new cases), prevalence (total cases), and associated mortality. In the case of depressive disorders — and for the rest of psychiatric problems — it is not easy to arrive at an adequate classification because diagnostic criteria have changed over time, because there are no objective and precise diagnostic indicators (such as imaging or histopathology procedures), and because depressive cases can

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_3

be strongly shaped by cultural factors in terms of their clinical and linguistic expression (Patel, 2001).

In this context, the description of operational criteria for the identification of mental disorders — through the International Classification of Diseases and the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association — constituted a major step forward. These tools made it possible to construct standardized interviews for population studies, the most common of which is the Composite International Diagnostic Interview (CIDI), which has been shown to have good validity and reliability indicators (Kessler et al., 2004; Kessler & Üstün, 2004). This instrument has changed over time, as its authors have expanded the types of mental disorder that can be diagnosed and the number of specific categories within each disorder.

Therefore, to perform a comparative analysis of multiple population prevalence figures, it is necessary to take into account the type of instrument employed, the version used (which considers the DSM and ICD criteria current at the time), and the inclusion criteria of specific disorders in each category. In the specific case of depressive disorders, it is important to differentiate when studies refer to a major depressive episode (MDE) and major depressive disorder (MDD). Likewise, a MDE can occur during a bipolar disorder (BD) but are not always included in prevalence studies. In studies that employ the CIDI, a MDE taking place during a BD is not regarded as part of MDD because the BD category exists. This is noted by Kessler and Bromet (2013) in their review of the epidemiology of depression:

> MDE includes depressive episodes that occur as part of a bipolar disorder while MDD excludes bipolar depression. As the vast majority of lifetime MDE is MDD, the difference between the two is not of great importance when examining lifetime prevalence estimates. However, as bipolar depression is considerably more persistent than non-bipolar depression, the proportion of MDE cases due to bipolar depression increases as the time frame of assessment decreases, making it important to distinguish MDE from MDD in examining current prevalence and correlates. We consequently distinguish between MDD and MDE in summarizing the literature (p.2)

3.1.2 Prevalence of Depressive Disorders in the General Population

The first report, based on interviews conducted in ten countries using a standardized instrument (the DIS — Diagnostic Interview Schedule — a preliminary version of the CIDI) and the DSM-III criteria, was compiled by Weissman et al. (1996). Its results are summarized in Table 3.1.

These results revealed significant differences in MDD prevalences and informed an important debate on potential explanations. Regarding the 12-month prevalence rate (calculated for only eight of ten countries), the highest values were reported for New Zealand (5.8%), Canada (5.2%), and West Germany (5.0%), in stark contrast with Taiwan (0.8%) and Korea (2.3%). As for the lifetime prevalence, a rather

Table 3.1 Lifetime and 12-month prevalence for major depressive disorder in people aged 18–64 years, in 10 countries

Country, city	12-month prevalence[a] (%, SE)[b]	Lifetime prevalence[c]		
		Women (%, SE)	Men (%, SE)	Total (%, SE)
United States	3.0 (0.18)	7.4 (0.39)	2.8 (0.26)	5.2 (0.24)
Canada, Edmonton (Alberta)	5.2 (0.45)	12.3 (0.93)	6.6 (0.73)	9.6 (0.60)
Puerto Rico	3.0 (0.49)	5.5 (0.91)	3.1 (0.72)	4.3 (0.59)
France, Paris	4.5 (0.65)	21.9 (1.80)	10.5 (1.39)	16.4 (1.16)
West Germany	5.0 (1.13)	13.5 (2.46)	4.4 (1.56)	9.2 (1.50)
Italy, Florence	–	18.1 (2.16)	6.1 (1.40)	12.4 (1.33)
Lebanon, Beirut	–	23.1 (2.63)	14.7 (2.25)	19.0 (1.76)
Taiwan	0.8 (0.09)	1.8 (0.19)	1.1 (0.16)	1.5 (0.12)
Korea	2.3 (0.22)	3.8 (0.38)	1.9 (0.29)	2.9 (0.24)
New Zealand, Christchurch	5.8 (0.70)	15.5 (1.51)	7.5 (1.14)	11.6 (0.96)

[a]12-month prevalence: the number of people who experience at least one MDD in the 12 months prior to the interview, as a percentage of the total number of people in that age and sec group
[b]SE: standard error
[c]Lifetime prevalence: the number of people who have experienced at least one MDD in their life, as a percentage of the total number of people in that age and sec group

similar pattern was observed, with the highest rates being found in Lebanon (19.0%), France (16.4%), and Italy (12.4%), followed by New Zealand (11.6%), Canada (9.6%), and West Germany (9.2%). The lowest values were again found in Taiwan (1.5%) and Korea (2.9%).

Are the differences found produced by the instrument and the method employed? This doubt will inspire subsequent studies and the further development of the CIDI, although it cannot be fully elucidated at present. Whether these dissimilarities are produced by macrosocial, economic, and/or cultural factors that determine how people live is a question that remains unanswered and that researchers continue to explore (Guinsberg, 2001; Talarn, 2007; WHO, 2017).

Weissman et al. (1996) also provided highly relevant information about sex differences, the age of onset of the first MDE, symptom profiles, and comorbidities. Regarding sex differences, Table 3.1 indicates that women display 12-month prevalence rates that are always higher than those of men: the woman/man ratio is highest in West Germany (3.1) and Italy (3.0) and lowest in Lebanon (1.6) and Taiwan (1.6). This greater prevalence in women relative to men has encouraged the search for differential neuroendocrine mechanisms; however, the cause may also lie in social determinants of health, as will be explored in a later section.

Regarding the age of the first MDE, it ranged from 24.8 years (Canada) to 34.8 years (Italy), with a median value of 29.3 years. With respect to the symptom profile, the authors report those found in at least 60% of cases, for each country. *Insomnia and low energy*, the most common symptoms, are present in all ten countries. They are followed by *thoughts of death and suicide* (seven out of ten

countries), *concentration problems* (six out of ten), and *feelings of guilt and uselessness* (five out of ten). Results indicate that some symptoms are common to all cultures, while others differ among countries. This aspect must be taken into account when conducting clinical and epidemiological studies. Lastly, the study revealed that people who had experienced MDD were at a higher risk for comorbidity with: alcohol abuse/dependence (in all seven countries where it was studied), drug abuse/dependence (in four of the six countries where it was studied), panic disorder (in all eight countries where it was studied), and obsessive-compulsive disorder (in all seven countries where it was studied).

More recently, the WHO developed the World Mental Health Survey Initiative, intended to generate more valid and accurate measurements of the prevalence of MDD by perfecting the instrument (CIDI 3.0) and the methods used in cross-sectional studies. Table 3.2 shows the most relevant data extracted from Kessler and Bromet (2013, p.22).

The figures reported here yield a more up-to-date picture of the prevalence of MDD. Regarding lifetime prevalence, major differences can be observed, with the highest values being reported for France (21.0%), the United States (19.2%), and

Table 3.2 Lifetime and 12-month prevalence for major depressive disorder in 18 countries, as part of the WHO World Mental Health Survey Initiative

Country	Lifetime prevalence % (SE)	12-month prevalence % (SE)
I. High-income countries (HIC)		
Belgium	14.1 (1.0)	5.0 (0.5)
France	21.0 (1.1)	5.9 (0.6)
Germany	9.9 (0.6)	3.0 (0.3)
Israel	10.2 (0.5)	6.1 (0.4)
Italy	9.9 (0.5)	3.0 (0.2)
Japan	6.6 (0.5)	2.2 (0.4)
Netherlands	17.9 (1.0)	4.9 (0.5)
New Zealand	17.8 (0.4)	6.6 (0.3)
Spain	10.6 (0.5)	4.0 (0.3)
United States	19.2 (0.5)	8.3 (0.3)
Total	14.6 (0.2)	5.5 (0.1)
II. Low- to middle-income countries (LMIC)		
Brazil (Sao Paulo)	18.4 (0.8)	10.4 (0.6)
Colombia	13.3 (0.6)	6.2 (0.4)
India (Pondicherry)	9.0 (0.5)	4.5 (0.4)
Lebanon	10.9 (0.9)	5.5 (0.7)
Mexico	8.0 (0.5)	4.0 (0.3)
People's Republic of China	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)
Total	11.1 (0.2)	5.9 (0.2)

Brazil (18.4%) and the lowest for the People's Republic of China (6.5%), Japan (6.6%), and Mexico (8.0%). As for the 12-month prevalence, the differences are less stark, with the highest values being found in Brazil (10.4%), Ukraine (8.4%), and the United States (8.3%) and the lowest in Japan (2.2%), Italy (3.0%), and Germany (3.0%). Overall, it can be observed that clear differences remain among the lifetime and 12-month prevalence rates of the countries studied. Previously, Simon et al. (2002) had conducted a study to compare symptom structure and differential sensitivity to diagnosis through interviews in 14 countries, concluding that there is a latent symptom structure that is similar across all countries. This makes it possible to reject the possibility that differences may be due to the use of this interview and encourages us to seek causes in each individual population.

Importantly, Table 3.2 shows a higher lifetime prevalence for MDD in high-income countries (14.6%) compared to low- and middle-income ones (11.1%), with no significant differences being observed in the 12-month prevalence. Although the role of methodological aspects cannot be wholly ruled out, these findings suggest that explanations may be linked to the lifestyles and the socioeconomic structure of these high-income countries.

3.1.3 Sociodemographic Correlates of Depressive Disorders

Three sociodemographic characteristics have been linked to MDD in community epidemiological studies: sex, age, and marital status (Bromet et al., 2011). Nevertheless, since almost all studies have been conducted in Western countries, their results should be interpreted considering this limitation.

Sex The analysis reported by Bromet et al. (2011) reveals that, in nearly all the countries where the analysis was performed, women were twice as likely as men to have experienced MDD. The odds ratios by sex were estimated for each country, with the values ranging from 1.6 in Israel to 2.7 in Spain. No significant differences were found between high-income countries and low- and middle-income countries.[1]

Age The association between belonging to a certain age group and experiencing MDE or suffering from MDD is observed in most countries and is stronger in high-income ones (Kessler & Bromet, 2013). The most at-risk age group varies: in France, Germany, Japan, and the United States, it is young people (between 18 and 34 years old); in Brazil, it is the group between 35 and 49 years of age; and in Spain, it is the group aged 50–64 years. In nearly all the countries analyzed, the group over 64 years of age displayed the lowest prevalence rates for MDE compared to the rest of the age groups. However, Kessler et al. (2010) reported that in some LMICs this pattern could be different: for instance, they found that prevalence rates might

[1] The odds ratio (OR) is an estimator of the relative risk of a group with respect to another in cross-sectional studies.

increase with age (e.g., in Ukraine). It is necessary to pay closer attention to the roles played and the kinds of stress experienced by each age group in these countries.

Marital Status In most countries, separated or divorced people displayed higher prevalence rates for MDE than those who were married. An association with being widowed was only found in some countries, with a more modest odds ratio. In countries such as Lebanon (OR = 19.3), Japan (OR = 10.8), and India (OR = 8.2), the risk was noticeably higher for separated people, but in others it was not a risk factor (e.g., Colombia, OR = 0.9). This variability reminds us of the need to examine in more depth how — or whether — marital status operates as a risk factor in each culture.

Income The report by Bromet et al. (2011) also identifies income level as a possible risk factor for MDE, considering four categories relative to each country's income: low, mid-low, mid-high, and high. High-income status is regarded as the least risky. Taking countries separately, low income is associated with the development of MDE in four of the HICs studied (France, Germany, New Zealand, and the United States) and in one of the LMICs studied (Mexico). However, when countries are considered separately and grouped by income, the HICs display a risk gradient associated with income: the lower a person's income, the higher the likelihood of experiencing MDE. This gradient is not observed in the LMICs studied. Again, this prompts hypotheses linked to the lifestyles and the socioeconomic and cultural structures of HICs.

Educational Level The report by Bromet et al. (2011) also analyzed educational level as a risk factor, revealing a weak association. It was only observed that low educational level was linked to the presence of MDE in two of the HICs (Israel and the United States) and three of the LMICs (India, Mexico, and Ukraine). In China, an inverse association was found: MDE risk increased with educational level.

3.1.4 Incidence of Depressive Episodes in the General Population

Incidence studies are difficult to conduct because they require a well-constructed cohort that can be followed up with a high retention rate. For this reason, studies on MDE incidence are scarce and hard to compare with one another. In addition, a variety of methods have been used to identify MDE.

Waraich et al. (2004) conducted a review of four incidence studies based on population cohorts that used similar instruments (DIS and CIDI) in Canada (Alberta), the United States, Norway, and Russia (Udmurtia). Among women, incidence rates ranged from 2.0% to 10.1%, surpassing those of men (0.4%–4.1%) in all four countries. The overall incidence rate ranged from 1.6% (USA) to 7.5%

(Udmurtia), with an aggregate value of 2.9% (95% CI[2], 1.3–4.8) being calculated for the four sites.

More recently, Ferrari et al. (2013b) performed a new systematic review that included four studies (only one of which was included in the previous review) conducted in the United States, Canada, and Ethiopia. Their findings were similar, with an aggregate incidence rate of 3.4% (95% CI, 1.9–6.3) for women and 2.7% (95% CI, 2.0–3.7) for men. The aggregate annual incidence was estimated at 3.0% (95% CI, 2.4–3.8), not much different from the values reported by Waraich et al. (2004).

Cohort studies have shown that people with MDE report suffering from subclinical depressive symptoms before the start of their case. An early systematic review conducted by Cuijpers and Smit (2004), which included 23 studies based on community samples, primary care patients, and high-risk subjects, consistently revealed that people who displayed a subclinical case of depression had a much higher incidence of MDD than those without such symptoms.

More recently, Bertha and Balázs (2013) confirmed this observation in adolescents through a systematic review of 27 studies. They found that the prevalence of subclinical depression in community samples of adolescents could be quite high, affecting 22% of the subjects. Their risk of developing MDD was high and had a negative impact on their quality of life.

Importantly, these findings make it possible to identify groups of people with cases of subclinical depression and conduct interventions aimed at reducing the likelihood of or preventing MDD in the future. This will enable us to make progress in the development of strategies for the prevention and timely detection of MDE.

3.1.5 Burden of Disease Due to Depressive Disorders

Burden of disease is measured with an aggregate indicator of mortality and morbidity known as DALYs (disability-adjusted life years) in English and AVAD (*años de vida ajustados por discapacidad*)[3] in Spanish. This is calculated by measuring the number of years lost due to premature death (difference between life expectancy and age of death) and the years lost due to disability (the period during which the person is unable to perform his/her normal activities, adjusted for a disability index). The calculation is made for individual diseases (including accidents and other types of injuries) or groups of diseases, within a certain territory and over a specific period (Murray & Acharya, 1997). Other adjustments can be made according to the sex of the person and his/her age when the disease or death occurs; also, a discount rate can be applied. However, it is not our aim to examine these methodological details or their associated ethical controversies (see Arnesen & Nord, 1999).

[2] CI 95%: 95% confidence interval

[3] In Chile, the acronym AVISA (*años de vida saludable* [years of healthy life]) is used, but not extensively.

Since the first estimations made, depressive disorders have topped the global lists of specific causes of DALYs (alongside HIV/AIDS, perinatal conditions, and ischemic heart disease). By the year 2000, MDD ranked fourth among the specific causes of loss of DALYs, explaining 4.4% of them. If we consider only the disability component, MDD is responsible for 12% of all the years lost due to disability in the world. These figures differ among the world's macrozones: in the Americas, MDD ranks first among the specific causes of loss of DALYs (8.0%), ranking second in the West Pacific (6.0%) and third in Europe (6.1%) (Üstün et al., 2004).

Ferrari et al. (2013a) performed a comparative analysis of the loss of DALYs as a result of depressive disorders in studies conducted in 1990, 2000, and 2010. In their latest study, they made a separate calculation of the DALYs lost due to suicide and ischemic cardiopathy attributable to depressive disorders; however, these issues continued to top the list of specific causes. MDD was responsible for 2.5% of the DALYs lost globally and for all causes, with estimates being higher for women and working-age adults. Likewise, globally, it accounted for 8.2% of the years lost due to disability. If we added the DALYs lost due to suicide and ischemic heart disease attributable to depressive disorders, the percentage would go up by one third.

All the above supports the notion that depressive disorders (including MDD) must be prioritized in public health at a global level, stressing the urgency of taking action to reduce the burden of disease attributed directly or indirectly to these disorders. This necessity has been highlighted by multilateral health organizations (Ferrari et al., 2013a; WHO, 2017; OPS, 2018).

3.2 Negative Effects of Depression on the Life of People and Their Communities

Depressive disorders have been linked to various negative consequences for the people who suffer from them, as well as for their families and communities. These impacts include the development of physical diseases and excess mortality, difficulties in the performance of various social roles, and associated social and economic costs.

3.2.1 Physical Diseases and Excess Mortality

MDD has been linked to a wide range of chronic physical diseases. Initially, several cross-sectional studies showed this association, but it was only when studies based on large population cohorts were conducted that it became possible to confirm this association and its strength.

One such study was conducted by Patten et al. (2008), who worked with a population cohort of people over 12 years of age, representative of Canada. The initial

evaluation was conducted in 1994, with 15,254 subjects who were included in a follow-up program until 2002 (for this report) and evaluated every 2 years. Data were collected from interviews with the participants and their medical records. Using a survival analysis technique, the authors calculated the risks (HR[4], hazard ratio) for several chronic physical diseases. Their findings were greatly interesting, since they revealed that MDD was a risk condition for a number of chronic diseases: chronic bronchitis and/or emphysema (HR = 2.2), asthma (HR = 2.1), arthritis (HR = 1.9), migraine (HR = 1.9), and heart disease and high blood pressure (HR = 1.7).

More specifically, authors have studied the link between MDD and cardiovascular and cerebrovascular diseases, cancer, and other conditions, with extensive and recent systematic reviews showing that depressive disorders are an independent risk condition. Below, we look at some of the most relevant systematic reviews.

- ***High blood pressure.*** Meng et al. (2012) reviewed 9 cohort studies that met the inclusion criteria, with a total of 22,367 participants, and estimated an RR[5] of 1.45 (95% CI, 1.09-1.86; p-value = 0.009).
- ***Coronary disease and acute myocardial infarction.*** Gan et al. (2014) conducted a systematic review of 30 cohort studies with follow-up periods of 2–37 years. The authors estimated RR at 1.30 (95% CI, 1.22–1.40) for coronary disease and 1.30 (95% CI, 1.18–1.44) for acute myocardial infarction. In addition, Wu and Kling (2016), also based on cohort studies, reported an RR of 1.22 (95% CI, 1.09–1.57) for the joint risk of acute myocardial infarction and death in people with a depressive disorder.
- ***Cerebrovascular disease.*** Pan et al. (2011) examined 28 cohort studies with follow-up periods of 2–29 years and 317,540 participants in total. The authors estimated an HR of 1.45 (95% CI, 1.29–1.63) for vascular encephalic accident (VEA), 1.55 (95% CI, 1.25–1.93) for VEA with death, and 1.25 (95% CI, 1.11–1.40) for ischemic VEA.
- ***Cancer.*** The systematic review conducted by Wang et al. (2019) included 51 cohort studies with 2,611,907 participants and an average follow-up period of 10.3 years. The authors estimated the effect of anxiety and depression (measured through scales or clinical diagnosis) on a variety of cancer types. They found increased risk for the incidence of all types of cancer, with an RR of 1.13 (95% CI, 1.06–1.19); for specific mortality due to cancer, with an RR of 1.21 (95% CI, 1.16–1.26); and for mortality due to any cause in patients with cancer, with an RR of 1.24 (95% CI, 1.13–1.35). When they only considered studies with a clinical diagnosis of depressive disorders and anxiety, they again confirmed the increased risk of incidence of all types of cancer, mortality, and shorter survival

[4] HR is an estimator of relative risk for survival studies, indicating how many more times the outcome is present in the group that displays the condition (in this case, MDD) compared to those without it.

[5] RR: relative risk, used in cohort studies to estimate how many more times the outcome is present in the group that displays the condition (in this case, depressive disorders) compared to those without it

for people undergoing cancer treatment. The authors conclude that, once cancer has been detected, depressive and anxiety disorders may have an etiological effect on survival. The mechanisms of this association are unclear and need to be examined in more detail.

- ***Dementia.*** The early evidence linking depression to dementia was obtained through case-control studies, as cohort studies have only been conducted in the last few decades. Da Silva et al. (2013) summarized most of these studies, concluding that people with a depressive disorder are at increased risk for developing dementia and that this risk is greater when depressive episodes are more intense and frequent. Entering a debate that remains undecided, these authors suggest that the case of depression may be a forerunner of the cognitive disorder, noting that both clinical conditions may have a bidirectional association and be expressions of the same morbid process (Brzezinska et al., 2020).
- ***Diabetes mellitus.*** Over several decades, studies had reported that depressive disorders were more prevalent among people diagnosed with diabetes mellitus. However, the direction of this link was unclear. Nowadays, authors agree that a bidirectional relationship exists: depressive disorders increase the risk of developing diabetes mellitus, operating either directly or indirectly (reduction of physical activity, increased BMI, and unhealthy behaviors), while the presence of diabetes mellitus and its complications increases the risk of developing a depressive disorder (Renn et al., 2011). The evidence also shows that people with diabetes mellitus who also suffer from a depressive disorder are 1.5 times more likely to die from various causes (e.g., cardiovascular problems) (van Dooren et al., 2013).

As we have shown, there is a large body of evidence from systematic reviews of cohort studies that consistently indicates that depressive disorders may be a causal factor of various chronic diseases and accidents (Shi et al., 2019). Similarly, the appearance of a depressive disorder over the course of a physical disease can reduce the effect of treatments, deteriorate the patient's clinical evolution, and increase the risk of death. For all these reasons, it is clear that a close association exists between depression and physical diseases, strengthening the negative impact of the former and making it crucial for it be diagnosed and treated in a timely manner. All the findings described suggest that people who experience MDE or MDD should display a higher mortality rate than those without these problems. What do we know about this?

In this regard, one of the first meta-analyses was conducted by Cuijpers and Smit (2002), who examined 25 community-based studies with 106,628 participants in total. The authors found that depressive subjects had a relative risk (RR) of dying of 1.81 (95% CI, 1.58–2.07). Interestingly, people with a subclinical case of depression also displayed excess mortality, similar to that of people with a depressive disorder.

A more recent systematic review and meta-analysis, which included many more studies and analyzed excess mortality in people with various mental disorders, confirmed that people with depression had a significantly higher relative risk of dying,

with a value of 1.71 (95% CI, 1.54–1.90) [Walker et al., 2015]. This additional mortality is greater in people with psychosis (RR = 2.54, 95% CI, 2.35–2.95) and bipolar disorders (RR = 2.00, 95% CI, 1.70–2.34) and similar for other affective disorders (RR = 2.08, 95% CI, 1.89–2.30) and anxiety-related disorders (RR = 1.43, 95% CI, 1.24–1.64).

3.2.2 Difficulties in the Performance of Social Roles

A wide range of studies have demonstrated that people with a depressive disorder experience a deterioration of their roles as family members and workers while also undergoing the impoverishment of their financial achievements. In this subsection, we will follow the review conducted by Kessler and Bromet (2013).

A strong association has been reported between conflict and distress in the couple and the presence of depressive symptoms, at a similar level for men and women. Longitudinal studies show that the association is bidirectional, but dissatisfaction in the couple more strongly predicts the emergence of depressive symptoms (Proulx et al., 2007. Whisman & Uebelacker, 2009). Conflicts in the couple are another risk condition for the development of a depressive disorder in the postpartum period, with a strong and independent effect (Alvarado et al., 2000).

Similarly, there is a link between the presence of depressive symptoms and couple violence. Trevillion et al. (2012), in a meta-analysis of 41 studies, reported an OR of 2.77 (95% CI, 1.96–3.92) of increased risk of suffering intimate partner violence in adult life for women with depressive disorders. However, since other studies show a bidirectional association, it is necessary to continue studying how violence in the couple interacts with depressive symptoms in its members (Kessler & Bromet, 2013).

3.2.3 Parental Role Functioning

Several studies have shown that the presence of a depressive disorder in the mother and/or the father has a negative impact on the child's development, affecting the physical, emotional, and social domains.

A meta-analysis of 17 studies conducted in 11 countries, with a total of 13,923 mother-child dyads, showed that the presence of depressive symptoms or a clinical condition increased the likelihood of having a baby affected by underweight (OR = 1.5, 95% CI, 1.2–1.8) or growth retardation (OR = 1.4, 95% CI, 1.2–1.7) (Surkan et al., 2011). This is consistent with our findings in Chile, where women with postpartum depression significantly reduced their breastfeeding frequency in the first 3 months after childbirth relative to those without depression (Alvarado et al., 1993). This is a potentially significant factor. Likewise, breastfeeding and growth

retardation might result from an attachment issue, as shown in the systematic review conducted by Śliwerski et al. (2020).

In addition, several studies and reviews have shown that a depressive disorder that affects the mother or the father can be associated with negative parenting, poor care, and affective detachment, leading to negative effects on growth, learning, and adaptation to school settings. Although this negative effect is observed in all age groups, results seem to indicate that it is stronger in younger children. Also, the impact is stronger on male children when the mother is affected by a depressive disorder. Most studies indicate that certain factors can strengthen this effect, especially parental age and poverty, which result in a lack of support and aid for these parents from state services and the community (Lovejoy et al., 2000; Tronick & Reck, 2009; Wilson & Durbin, 2010).

3.2.4 Occupational Role Functioning and Productivity

Several studies have shown that MDD reduces work performance, increases absenteeism, decreases the time spent working, and reduces productivity. The WHO initiative known as World Mental Health conducted an interview with 62,971 participants from 24 countries, evaluating chronic physical health and mental health problems by measuring the number of days that these disorders had prevented them from fulfilling their duties at work or in their daily life during the 30 days prior to the interview (Alonso et al., 2011). The authors found that MDD was associated with 5.1% of all nonoperational days, ranking fourth among all the physical and mental conditions included (only surpassed by migraine, other chronic pain conditions, and cardiovascular disorders) and first among mental disorders.

3.2.5 Costs of Depression

Most studies on the cost of depression should serve as a point of reference for estimating the economic relevance that a health problem can have, since these costs vary greatly depending on the countries, institutions, and parameters considered. Most researchers seek to estimate the direct costs (due to healthcare expenses such as hospitalization, medications, and human resources) and indirect costs (which can include production losses and reduced tax revenue, among other consequences). For this reason, cost studies must always be analyzed taking into account the context where they were conducted.

Regarding depressive disorders (including MDD and MDE), two studies conducted in the United States reveal the major economic impact of this disease. Stewart et al. (2003) estimated productive losses by comparing workers with a depressive disorder with nondepressed ones and evaluating the costs associated with the loss of productive time (due to absenteeism and reduced productivity) in

these groups. The authors found that people with MDD lost 5.6 h/week compared to 1.5 h/week for other workers, with most of these costs being explained by reduced work performance. Extrapolating these figures to the total number of workers in the United States, the authors estimated a yearly cost of USD $44 billion due to workers with a depressive disorder and additional yearly costs of USD $31 billion compared with their nondepressed peers.

3.3 Has the Number of Cases of Depression Increased Over Time?

Much scholarly discussion has been devoted to this topic, which is difficult to elucidate because of the changes in the diagnostic criteria, classifications, and instruments used to define a case. Nevertheless, we will attempt to evaluate the progress made in this regard. The first reports about possible changes in the characteristics and tendencies of depressive disorders were made by clinicians, who noted that their patients were increasingly younger, more neurotic, and with less intense symptoms compared to prior decades (Paykel et al., 1970).

Klerman and Weissman (1989) performed an extensive review of multiple epidemiological and family studies conducted in the United States, Sweden, Germany, Canada, New Zealand, Korea, and Puerto Rico. The authors observed an increase in the rates of prevalence in the cohorts born after World War II and a reduction in the age of onset. They found that, between 1960 and 1975, the rates of depressive disorders increased for all age groups, with risks remaining greater for women (2–3 times), although this sex-based difference is lower in younger people. This increase is clear in the United States, Sweden, Germany, Canada, and New Zealand, but it is not present in Korea or Puerto Rico nor in Mexican-Americans living in the United States, which prompts the need to study the social, economic, and cultural conditions that affect lifestyles in the first group of countries relative to the other two.

Another relevant body of evidence was provided by the studies conducted in Stirling County, Canada. This research project is based on two cohorts: between 1952 and 1970 and later between 1970 and 1992. A report by Murphy et al. (2000) analyzes the trends in the annual incidence of depressive disorders, using similar criteria in all evaluations. No significant differences were found in the first evaluations, but the most recent one (1992) revealed an increase in the incidence of depressive disorders in women under 45 years of age.

Similar results were reported by Eaton et al. (2007), based on a cohort from eastern Baltimore (United States), which is part of the Epidemiological Catchment Area (ECA) Program. This cohort had a follow-up period of 23 years, with evaluations in 1981, 1993, and 2004. Interestingly, the prevalence rates increased progressively for women in these three evaluations. However, the incidence rates between 1993 and 2004 were lower than between 1981 and 1993, which prompted the authors to suggest that greater prevalence is due to increased chronicity.

Another useful element for answering this question is the Global Burden of Disease (GBD) Study. This study is based on the best available evidence, employs an equivalent methodology, and features multiple evaluations over time. James et al. (2018) reported a comprehensive evaluation of the incidence, prevalence, and years lived with disability (YLD) for 354 causes in 195 countries and territories between 1990 and 2017. This study shows that YLDs as a result of depressive disorders increased by 33.4% between 1990 and 2007, with a 14.3% increase (13.1% to 15.6%) between 2007 and 2017. As previously noted, World Health Organization estimates (WHO, 2017) indicate that 4.4% of the DALYs were lost due to MDD in 2015, with the rate being higher in women (5.1%) than men (3.6%), with regional and age group variations.

Ferrari et al. (2013b), in their systematic review of variations in prevalence and incidence, show that the region where a study is conducted and its methodology have an impact on the prevalence of MDD, which must be considered in the GBD. In addition, the authors note that MDD incidence data are scarce.

In brief, to date it is not possible to give a satisfactory answer to the question of whether depressive disorders are on the rise. The evidence seems to indicate that prevalence rates have increased, but that incidence has not (although few studies have focused on the latter phenomenon), that this situation tends to affect women and not men, and that it may be due to an increase in chronicity.

It is worth remembering the words of Frances (2013) and Hidaka (2012), who identify several theories for the apparent increase in the prevalence and chronicity of depressive disorders over time. The first theory is that this occurs because we are subjected to extreme pressures by a hectic and stressful society, leading to a reduction in social capital and a more solitary life. Another theory — related to the first — makes reference to factors such as a sedentary lifestyle, overweight and obesity, and reduced exposure to sunlight, which are linked to the rise in chronic diseases. A third theory suggests that this increase is due to pollutants and environmental changes. A fourth theory proposes that we are now better equipped to detect depressive disorders, which can in turn be attributed to an improvement in doctors' specific diagnostic competences or to the fact that health professionals diagnose these disorders in an attempt to help these people. Lastly, the final hypothesis is that the pharmaceutical industry has used its influence to transform normal problems into pathological conditions (Frances, 2013).

3.4 Social Determinants of Depression

3.4.1 Conceptual History. The Social Determinants of Health

The study of environmental effects on human health has a long history, even being discussed the chapter "on airs, waters, and places" of the Hippocratic Corpus. Since the nineteenth century, and especially in the twentieth, concerns grew over the

impact of unhealthy living conditions and poverty on the development of diseases and premature death, which resulted in public policies aimed at alleviating these negative effects. In the 1960s and 1970s, several epidemiologists — e.g., Mervyn Susser and John Cassel — made conceptual and methodological contributions that made it possible to incorporate the insights of the social sciences into studies on the greater risks of developing diseases and dying that affected certain populations. These efforts resulted in the creation of the discipline of social epidemiology, featuring an ecological, multilevel perspective that considered environmental, macrosocial, and microsocial determinants. Likewise, researchers developed the perspectives of life trajectory, the differential impact of determinants by age, risk accumulation, and resiliency processes. All this converges on a search for mechanisms connecting the social and the biological: the ways in which the body and its subjectivity are shaped by the social conditions of life (Berkman et al., 2014).

Although the study of the social determinants of health focused on the impact of poverty, which affected specific populations living in these conditions, authors over the last decades have emphasized the impact of living in unequal and inequitable societies (Wilkinson, 2002) and on the multiple mechanisms, whereby living in a certain social stratum negatively impacts on one's risk of becoming sick and dying (Marmot & Wilkinson, 2006). The evidence for their importance has increased enormously; thus, multilateral agencies — e.g., WHO, World Bank — and many countries have begun to develop health policies that take social determinants into account (WHO, 2007; Blas et al., 2008).

The social determinants approach has also influenced the field of mental health, where a large body of evidence has been well summarized in a collaborative effort led by Compton and Shim (2015). The transition from understanding social determinants to the development of public policies across all the levels of governments, as well as the influence of psychiatry on this phenomenon, has been brilliantly outlined by these authors (Shim & Compton, 2018).

> "Treating" the social determinants of mental health involves focusing more on policies than on medication, therapy, and neurobiological innovation. It entails creating public policies that improve these issues and changing social norms to place greater value on giving everyone an equal chance at living a fulfilling and healthy life. Local, state, and federal governments set policies, and the psychiatric field has considerable power in influencing those policies and shaping the social norms that inform them. (p.844)

3.4.2 What Do We Know About the Social Determinants of Health in Depression?

The latest evidence tends to suggest that the social determinants of health have a strong impact on the risk of experiencing depressive disorders.

Poverty It has been well established that, globally, low socioeconomic status correlates with higher psychiatric morbidity — with greater chronicity and disability—

as well as with access to poorer healthcare. A meta-analysis conducted by Lorant et al. (2003), which examined 51 prevalence studies, 5 incidence studies, and 4 case follow-up studies, all of which concerned depressive disorders, found that low SES was associated with a greater likelihood of being depressed (OR = 1.81, $p < 0.001$), a higher incidence of new depression cases (OR = 1.24, $p < 0.004$), and greater depressive disorder chronicity (OR = 2.06, $p < 0.001$).

Being born, growing up, and living in poverty entail several mechanisms through which depressive disorder risk may increase: low housing quality, crime, food scarcity, poor access to health services and education, more unsafe and low-paying jobs, and loss of social capital in neighborhoods and towns (Compton & Shim, 2015).

Social Inequity Patel et al. (2018) have recently conducted a review and meta-analysis of the association between social inequity and depression, as well as of its possible underlying mechanisms. To measure income inequality, the studies employed the Gini coefficient (the most commonly used indicator in this regard). Most of the studies reviewed reported an association between higher-income inequality and higher prevalence of depressive disorders. Some of them (23.1%) did not find a significant association, while only one (3.8%) found the opposite association.

Although living in a less equitable society affects the whole of its members and increases risk across all social strata, the studies examined show that the risk is greater for low-SES people. Likewise, low-SES women, adolescents, and older adults display even higher levels of risk, which suggests that gender and age strengthen the negative effect of social status. Andersen et al. (2009) had described a strong association (very high ORs) between low income and joblessness and the presence of a depressive disorder in a high-income country with a good social protection system.

Also, it is well-known that people diagnosed with a mental disorder can be affected by social stigmatization, which entails discrimination and exclusion. Although this situation has been adequately described for people diagnosed with schizophrenia and severe mental disorders, a depression diagnosis also carries a stigma (Cook & Wang, 2010; McLoughlin, 2013; Sickel et al., 2014). In this context, stigma can increase isolation and social exclusion, reducing people's chances to access social benefits, better employment, and greater social capital. Thus, depressive disorder affects the person's social position and can deteriorate his/her living conditions (Compton & Shim, 2015). This shows that social causation and drift are two mechanisms that are present, have been empirically demonstrated, and reinforce the cycle of poverty and depression (Lund & Cois, 2018. Compton & Shim, 2015).

Social Support Social support, in its multiple dimensions (information, affective support, instrumental support), has been extensively documented as a protective factor of general health, as well as a specific protective factor of mental health and depression (Turner & Brown, 2010). Evidence shows that the most important element for mental health protection is the subjective perception that one has a social

network that will provide support whenever necessary. The effects of such a network operate in two ways: the perception of having this support is in itself a source of well-being, self-esteem, and self-efficacy; also, at the same time, it has a "buffer effect" regarding the stress and psychological distress produced by adverse events. For all these reasons, increasing social support has become one of the main aims of interventions focused on promoting mental health and well-being. In our own research, we have demonstrated that social support plays a relevant role in the appearance of depressive disorders during the postpartum period (Alvarado et al., 1994), interacting with variables such as age (Alvarado et al., 2000). Likewise, we have observed that, in rural areas — a scarcely researched context — social support buffers the effect of adverse events, preventing the development of a depressive disorder (Alvarado et al., 2008).

Perceived social support vary greatly according by social position and cultural setting: in Western countries, gender, marital status, and socioeconomic status determine the level of perceived social support (Turner & Brown, 2010).

Neighborhood, Home, and Physical Surroundings The condition of a person's home as well as the characteristics of the neighborhood, where it is located and its surroundings, are relevant and have a connection with the aspects discussed previously. Although the studies that seek to associate neighborhood characteristics and physical surroundings with depression are heterogeneous, employ dissimilar measurements, and have generally been conducted in HICs, there is a growing consensus that they must be incorporated into the model of social determinants of depression (Kim, 2008).

The systematic review carried out by Rautio et al. (2018), which examined 57 articles, showed that most of the studies identified a significant association between a feature of the subjects' physical and material surroundings and depressive mood. The most strongly associated factors were characteristics of the home where one lives (poor quality, does not work well, fails to protect its dwellers from the cold or the rain), neighborhoods that lack green spaces, excessive noise, and environmental pollution. The authors also found other factors, although the strength of the link was less consistent across studies: population density, the aesthetic characteristics of the neighborhood, and the availability of social services.

Lastly, another neighborhood-level element that must be mentioned is the ability of neighbors to regulate the behavior of other residents through informal social control, exerted through community networks. Haines et al. (2011) observe that the social capital of the community network mediates the contextual effect of the neighborhood on depressive symptoms. Thus, research demonstrates the value of social capital, bonds that exceed neighborhood boundaries, and formal and informal community support (Diez-Roux & Mair, 2010; Mair et al., 2008).

Job Characteristics It is not only joblessness that has been linked to depressive disorders, as pointed out before, but also the characteristics of a person's occupation, its setting, and its psychosocial conditions. Several theoretical perspectives have been empirically tested, among which the "effort-reward imbalance" model is

the most extensively studied (Karasek & Theorell, 1990). This model states that, when the worker's increased efforts are connected with a poor reward (of various types), the risk of stress and psychological distress grows. The systematic review and meta-analysis conducted by Rugulies et al. (2017), who examined 8 cohort studies that met strict inclusion criteria and sampled 84,963 employees — 2,897 of whom developed a depressive disorder in the follow-up period (3.4%) — estimated that effort-reward imbalance increased the risk for the onset of a depressive disorder (RR = 1.49, 95% CI, 1.23–1.80, P <0.001). This finding is relevant because, through the effort-reward imbalance model and others, it can inform public policies aimed at controlling the psychosocial conditions that increase workers' risk. In this context, Kristensen et al. (2005) developed a questionnaire for assessing these psychosocial risks, which has gradually expanded throughout several countries with locally adapted versions. Chile is a good example of this expansion, as the questionnaire is routinely administered in all companies and institutions as part of a public policy (Alvarado et al., 2012).

Early Adverse Experiences In the field of social epidemiology, authors have identified adversity during pregnancy and the first years of life as one of the most important factors in the development of physical and mental diseases in later stages of life (Berkman et al., 2014; Marmot & Wilkinson, 2006). The underlying mechanisms of this phenomenon have been extensively analyzed and involve biological and psychosocial aspects that operate together to increase subjects' biopsychosocial vulnerability to premature disease and death (Cohen et al., 2010; McEwen & Gianaros, 2010). Adverse events can accumulate during a person's life, generating a biological fingerprint through stress response, inflammatory processes, and cellular oxidation, even modifying genetic transcription activity and accelerating cellular aging (Brisson et al., 2020).

In Chile, we have confirmed the association between traumatic childhood experiences — especially child abuse and domestic violence — and depressive disorders (Numhauser et al., 2004). Even more so, Vitriol et al. (2017) have identified a special subtype of depressive disorders linked to traumatic childhood events, which are frequent among primary care patients and require specific therapeutic management.

However, most studies are cross-sectional and depend on recall for the assessment of childhood violence and abuse, which may lead to a memory bias. For this reason, Li et al. (2016) conducted a systematic review that only considered cohort studies with a good evaluation of experiences of abuse in childhood — including physical abuse, sexual abuse, and caregiver negligence — and concluded that the OR for depressive disorders reached 2.03 (95% CI, 1.37-3.01). The authors estimated the attributable fraction of risk, concluding that more than half of depression cases can be ascribed to these types of childhood mistreatment. In consequence, this finding cements the role of abuse in childhood as one of the most relevant factors for the development of depressive disorders.

Gender and Depression We have saved for the end one of the most interesting discussions from the perspective of social epidemiology: gender as a social

determinant. Since population studies have systematically shown that depressive disorders are more frequent among women, the first hypotheses prioritized biologicist explanations. However, as the social sciences gradually defined a specific field for gender studies, this conceptual framework was incorporated into public health research, being specifically applied to the study of mental health issues. The core idea of this approach is that differences can be interpreted upon the basis of how we construct femininity, masculinity, or any other forms of gender in a specific culture such as ours (Hoagland & Frye, 2005).

The social construction of gender begins early on — since the unborn baby's sex is determined. Experiences, roles, play, and expressions of affection, among other elements, are forms of learning through which sex-based gender identity is constructed; then, this identity becomes a social stratification mechanism for a specific society. Forms of subordination, inequality, and discrimination against women and other types of gender are established, which operate within the historical and sociopolitical context during the life cycle. Thus, trajectories are constructed and vulnerabilities are accumulated which differ among men, women, and other gender choices, in such a way that corporality and emotionality are expressions of this inequality (Krieger, 2001).

Most of the aspects of life examined in previous paragraphs are connected with gender, and they indicate that women in a society like ours are exposed to more risks and adversities in nearly all the domains mentioned. Therefore, in the model of social determinants, gender is a structural factor that affects the whole of a person's life cycle, providing the clearest illustration of how the social, the psychological, and the biological are dialectically integrated.

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Chapter 4
Idioms of Depression in Contemporary Individualistic Societies: The United States and Chile

Claudio Maino Orrego

4.1 Introduction

Despite the evident improvement in economic comfort expressed by individuals with respect to previous generations in Chile, "delving into the issue of depression among Chileans and, in particular, the inhabitants of large cities is, to say the least, Depressing" (Rossel and cols, 1999). In this way, a psychiatrist and editor of a collective work on depression introduces one of the many works circulating on the treatment of depression as a public health problem, which would have begun to proliferate since the 1990s in Chile. He draws attention to the scale that this disease has reached to the extent of becoming a "generalized epidemic" over the last decade. In his opinion, the Chilean depression had its roots, on the one hand, in what the United Nations Development Programme in Chile (UNDP) called "fear of the other", as the emotional expression of a social malaise and decline that persisted after the civil-military dictatorship (1973–1990) (PNUD, 1998). He recognizes "fear, uncertainty, lack of confidence, confinement in small worlds without communication with anyone, not even with one's neighbours" as expressions of this fear in everyday local life. On the other hand, depression would also be rooted in "stress" (the active face of depression), which would had penetrated all aspects of urban life: from family life to work and from school to social life (Rossel and cols, 1999).

Just as in the Western societies developed in the last century, depression has multiplied to such an extent in Chile that it has currently gone from being a circumscribed object at the level of the clinic and public health, at the end of the twentieth

Chapter edited and translated from Spanish into English by Amelia Orrego and Filomena Orrego.

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*,
Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_4

century, to being at our present times a precious indicator of a disturbed intimacy and proper functioning of our society. However, up until the 1980s, depression had remained totally outside the common experience and the ordinary language of distress of the twentieth century malaise. How has this particular mental "epidemic" been transmitted from one latitude to another? What is the principle behind the spread and multiplication of the symptoms of inadequacy, deflation of desire, inhibition of action, emotional disconnection and despair in the face of a bleak future? In short, what interests us here is to examine how this clinical category has imposed itself as the paradigmatic language of intimate and collective discontent in contemporary individualistic societies.

Based on the work of Alain Ehrenberg, our starting point lies in this true paradigm of American society which stems from Western democracies and in the spread of psychiatry in our everyday life as well. Nevertheless, our point of arrival lies in the Chilean society, where depression took on an air of sudden and urgent explosion. Since so little has been developed from a socio-historical point of view, this work aims precisely to contribute with some pioneering ideas. The purpose is to make the reader sensitive to the customs, local controversies and social rules at play in the adoption of this medical category. Such customs seem to silently define how depression is spoken and acted upon in the United States and in Chile.

4.2 Depression and Individualism: Beyond the Scientific and Political Perspective

In order to draw a practical lesson from the location of depression considered to be an individual and collective affliction in contemporary societies, two major epistemological obstacles must be overcome: *scientific* causality and *political* causality. Among promoters of scientific reductionism, depression is often understood in terms of internal biochemical imbalance. Psychiatrists, based on this causal hypothesis, are convinced that they are doing nothing more than manipulating notions defined by meticulous procedures which arise from the best quality psychological objectification (Castel, 2011; 9). On a practical level, however, the recurrent complaint has to deal with notions – such as depression – contaminated by informal and contingent practices and uses. The promoters of political reductionism, in turn, interpret the spread of depression as the destructive effect of global neoliberal personal well-being on individual action and their social bonds. According to some scholars, the increase of medical and psychological concerns into daily life is nothing more than the expression of a new form of government in which psychiatry, in the name of scientific neutrality, stands as a key piece of social control. Outside the hospital walls, psychiatry oppresses more than normalizes, and it creates a subject rather than silencing it by locating the cause of mental symptoms in the psychological/biological individuality rather than in social contradictions (Kitanaka, 2012).

As Pierre-Henri Castel states, these two great trends have dominated mental health research and have imposed themselves on a cultivated public as scientific conquests or as moral political evidence, respectively. Ultimately, however, they always end up referring to their premises and stirring up an irreconcilable conflict. Some of these reduce mental illness to a pure description that leaves us with another one encapsulated in its internal dysfunction. The other ones reduce these mental disorders into a mere description of the one that we suffer from (Castel, 2011: 23). In both cases, we can see a reduction in the reasons that intertwine action and passion today: both in terms of our *ways of being affected by our ways of acting,* as *in our ways of acting in relation to these afflictions* (Ehrenberg, 2015: 62). Both of these approaches, the scientific and the political one, have in common – as we shall see – the fact that they are atomistic and individualistic, based on the opposition between the individual and society, between biology and society and the objective and subjective. While the scientific theses believe that depression can be cut back from the social realm, the latter conceives the social exclusively in terms of domination and relations of power. In other words, this perspective conceives the individual as only a vis-à-vis, thus completely devaluing the description of the individual "with respect" to the other (Ehrenberg, 2012). It neglects the irreducible place that "social interdependence" has in the value that "independence" and – in conformity – the disturbed intimacy in individualistic societies have acquired.

In the same way, the history of depression has also been examined, either from the immoderate evolution of psychiatry, and even beyond what it could reassure as a science, or from the penetration of the neoliberal doctrine in the world via pharmaceutical globalization. For the psychiatrists such as Allan V. Horwitz and Jerome C. Wakefield, these affective evils multiply after the change of focus of psychiatry from the asylum to the community and the success of epidemiological surveys, statistical classifications and antidepressants such as Prozac, which redraw the borders between what is considered to be a psychiatric problem or normal life's problems (Horwitz & Wakefield, 2007). For the latter, sociologists such as Nikolas Rose view the success of depression as the result of the globalization of the "Prozac narratives" that would inculcate "the singularized vision of the 'neurochemical self' that fits with the new economic order" (Rose, 2007).

According to Alain Ehrenberg, we analyse the place of depression as an individual and common suffering in light of our ideals, values and norms of autonomy inherent in individualistic societies. Depression, among all medical ills, embodies like no other an obstacle to the demonstration of motivation, personal initiative and the ability to progress in life on one's own. Attitudes are as appreciated (values) as they are expected and demanded (standards) in these societies. This sociological perspective makes it possible to describe how our ways of acting and suffering in society change in an interdependent manner and become impregnated with collective representations of autonomy, such as competitiveness, consumer expectations and cooperation at work (Ehrenberg, 2015). The concept of *impregnation*, according to French scholars such as Pierre-Henri Castel and Bruno Karsenti, would be in this case the appropriate notion insofar as these collective representations do not constrain us "from outside"; they are expectations that determine or rather

constitute us by affecting us in a *total manner* (Karsenti, 1998; Castel, 2014; Ehrenberg, 2015). Today, the experience of depression, however intimate it may be in each case, draws its language from these representations of autonomy, an accent which varies from one society to another, just as the expression and treatment of this "social aliment". As the anthropologist Marcel Mauss would say, the nature of affects (pathological or not) and their expression occur in conformity with social norms and the spirit of our institutions. Moreover, the fact that it affects us in a *total manner* (according to the anthropologist) means that it is through the "physiological effect" that one identifies the "social expectation" (Mauss, 1924/1971: 284). In short, as Wittgenstein states, there is an *intimate* relationship between categories, concepts, words and the (emotional) life of those who use them (Wittgenstein, 1953/2004). These representations, common to individualistic societies, also open a horizon of comparison within the language that depression acquires in each context, as well as in particular actions – at the level of public health, education and work management – that are undertaken in conformity in each case. This point of view, on the one hand, does not disregard the analysis of the relations of force in the new capitalist era, but it rather allows them to be better posed, in accordance to the social spirit of each society. On the other hand, it displaces the *causality* accent of depression to rather describe the *restlessness* that mobilizes this illness in each one of these societies, where the autonomous action has become the most valued action style.

4.3 The Loss of Self-Confidence: The American Way of Depression

As it happened with neurasthenia in the late nineteenth century ever since the second half of the twentieth century, in industrial societies a paradox associated with modernity has often been raised. Although progress has brought greater comfort to the masses, this has occurred at a high price: the multiplication of neuropsychiatric diseases and the destruction of life in common.

The Second World War marks an unprecedented turn of interest in the psychological sequels of war, which drive into population studies about minor emotional disorders. The stressful effect of wars, the dizzying pace of cities and work plus a hard life in popular districts have become the privileged objective of these surveys. According to the historians Christopher M. Callahan and Germán E. Berríos, the possibility of increasing productivity at work, including productivity in combat, has given credibility to the study and treatment of emotional disorders in the United States and in the United Kingdom (Berríos & Callahan, 2004). On the other hand, since the 1950s, the antidepressants and in particular the "minor tranquilizers were presented on American soil as "lifestyle drugs". In other words, beyond their therapeutic value, they were expected to facilitate the self-realization and performance expectations of a modern nation (Tone, 2009). A few years later, however, the media and the WHO itself, in the framework of World Health Day, announced the

psychological nightmare of such modernity: "guys who were exalted or depressed by credit cards", "workers who were subjected to the stress of chain work" and "employees who were submerged in economic worries" (Lavín Valenzuela, 1959). The other side of this American dystopia (as was illustrated by the New Yorker magazine years later) was the mass production of anonymized and over-adapted individuals absorbed by tranquilizers and perplexed by the daily dilemma of whether they would need to be stimulated in order to function more effectively or whether they would instead need to be sedated in order to forget and calm down (Romero, 1965). Until the 1960s, anxiety disorders were imposed as the century's evil. Since the 1970s, however, there has been talk of a rise of the so-called pathologies of ideals (in which depressive symptoms become the model), usually associated with a society that has lost authority over individuals.

At a sociopolitical level, in the United States the arise of these new troubles coincide with the crisis of the welfare state that predominated during the progressive period known as the New Deal (1930–1960). The moral liberation and the new expectations of well-being of the 1960s, even though they might lift the locks of repression, might also open up a new grammar of malaise: that of the individual who does not feel up to the expectations of autonomy (Ehrenberg, 2010a, 2010b). On a clinical level, the feeling of depression insufficiency relegates intrapsychic conflict and neurotic guilt to the background. According to analysts and psychologists, we move from a clinic of "repressed subjectivity" of transference neuroses to a clinic of a "freed subjectivity" from narcissistic pathologies. On this second track, it is not a matter of freeing the individual from the "constraints" and demands but of subtracting him from the morbid seductions of the "ideals" that force him to be himself and even better than himself.

In the 1960s, Philip Rieff had already described profusely how the "restlessness of private life", "impulsive life" and the "relaxation of community ties" had become a trend in popular and specialized literature. He pointed out that psychotherapy was no longer just "a way of healing", among Americans, but that it had become a "world view", for the "psychological man", who had displaced a social and religious man who used to move between guilt and expectation of salvation (Rieff, 1966). In his opinion, the decline of the old communities and the correlative "therapeutic triumph" (in particular analytic therapeutics) carry an unprecedented lesson for civilization: to show how the "modern individual can use the community to optimize himself" without paying the costs (of guilt and transgression) of yesteryear. Contrarily, it preserves the individual from the risks of the "ideology of a good choice" embodied by the "adaptive attitude" promoted by the post-Freudians and the uncontrollable market for tranquilizers.

However, a decade later, "the triumph of therapeutic" is placed on the same side of the medicalization nightmare, embodied by the first American anti-hero: the narcissistic man. Based on the same social portrait made by Philipp Rieff (starting with the fact that public life would have taken on a more personal tint), Richard Sennett and Christopher Lasch popularized the thesis of the corrosive effects of individualism in social bonds and on "the public man", whose indicators were the rise of depression symptoms and narcissistic personalities. This kind of analyses would

then become a commonplace in the United States and, years later, everywhere (Ehrenberg, 2010a, 2010b). At this time, Sennett advanced some of the major concerns that depression still raises in individualistic societies. For him, "the liberation from the bonds of authority" is inseparable from the fact that "the self of each individual has become his main burden". As the psyche becomes privatized – claims this author – it becomes less alive, turning out to be increasingly difficult [for the individual] to both feel and express a feeling (Sennett, 1974/1979). According to Lasch, the Americans are trapped like Narcissus in this position that makes the whole thing a mirror of itself. The new individualistic morality would not give the individual "the freedom to be autonomous nor the possibility to enjoy his individuality". On the contrary, it would contribute to a personal insecurity that the individual "can only control by seeing upon himself the attention directed to him by the other" (Lasch, 1979/1981:141).

In such a scenario, according to psychologists and analysts, the vague and shapeless existential dissatisfaction centred on self-image, typical of character neuroses described in the 1940s, becomes the predominant symptom of a psychological distress. Among these patients, the malaise oscillates between a feeling of inner emptiness and a search for sensations to fill this void between a depressive emptiness and addictions plus fantasies of omnipotence as well. For both authors, the complement to this narcissistic tragedy is the "therapeutic culture" described by Rieff, where the ideal of knowing oneself would have become in the society of the 1970s an end in itself and not a means of action to know and dominate the world. As a result, justice, children's education and even hierarchical relations in companies are "therapized". As Lasch sees it, whether therapeutic culture "relieves the individual of his guilt" and "legitimizes deviations as diseases", in either case it "considers the patient to be unfit to lead his own life, and thus, it puts him in the hands of a specialist" (Lasch, 1979/1981: 310). At the same time, beyond the clinical level, the rise of this therapeutic culture in America becomes the indicator: that individuals begin to conceive community life solely in terms of identity, to the detriment of collective action (Sennett, 1974:1979: 173)); that the healthy would have become "a fight of all against all"; and that the "search for well-being" would have become the impasse of "the individual's narcissistic obsession with himself" (Lasch, 1979/1981: 10).

In this era, both moral liberation and the welfare state are placed at the base of the weakening of moral responsibility, cornerstone of the pursuit of individual and common welfare. The wave of narcissistic pathologies in this decade reveals the crisis of "self-confidence" that would coincide – in the local myth – with the loss of confidence in America. As Alain Ehrenberg states, "the 'self' among Americans is more than a state of mind". It is a collective representation that unites the individual and the common. This is expressed in "self-government", referring to the capacity of the community and the individual to govern themselves, and in "equality of opportunity", based on giving the weakest the ability to enter the competition to get ahead on their own. Finally, it is revealed in "self-confidence", referring to the confidence to cope by oneself in the face of adversity and the ability to cooperate with others. Conversely, "the crisis of the self" reveals itself to be a constant in American history. On the one hand, it is shown in a pendulum swing between "individualism"

and "community" and, on the other hand, in a permanent tension between "individual fulfilment" and "equality" (Ehrenberg 2010b: 35).

The history of depression in this country, which is inseparable from the fantasies that antidepressants awaken, has been part of this "celebration and crisis of the self" since the 1980s, which is inherent to the dilemmas and expectations of moral responsibility in this society. In the name of the sacred value of autonomy and pluralism, DSM-III (rightly called by Steeves Demazeux, the "American *bible* of Psychiatry") defined in 1980 the multiplicity of syndromes as a disease that one "has", not that one "is" (Ehrenberg, 2010a; Demazeux, 2013). In this way, it honours psychiatry's fight against the stigma of mental illness and personality theories. However, soon after that, "biological reductionism" appeared – especially in depression – as the disturbing face of this statistical classification based on emotional intensity. A few years earlier, in 1975 the Austrian intellectual Ivan Illich published *The medicalization of life*, a classic text in North America, in which he presents the "medicalization" as a means to silence dissidence and the ability to reflect on the social and political roots of distress (Illich, 1975). Decades later with the publication of the third edition of the DSM, an increased use of antidepressants was conceived in terms of "loss of sadness". This evoked the American fear that people would lose the capacity for tolerance, patience, suffering and pain that is necessary for an active and mature life (Horwitz & Wakefield, 2007). In fact, when Prozac was introduced during the period of the economic expansion in the United States, it aroused great expectations among Americans, like being "happy without pain", "discovering oneself" and even "becoming a kind of superman" (Rose, 2007). However, critical theories wondered whether the rampant prescription of antidepressants might not have produced two serious problems: the erroneous feeling of having to control everything by oneself and the lesser attention paid to the social causes of one's distress (Illich, 1975).

At the turn of the twentieth century, while the depressed person personifies individual inadequacy with respect to the norms of autonomous action, the controversy over antidepressants touches on the spirit in which one acts: by being oneself or someone else, increasing or not increasing the flexibility of action, uniting or not uniting competitiveness and cooperation, and enabling the ability to act on one's own behalf or plunging the individual into the deepest dependence. "Dependence", "subjection" and "loss of moral responsibility" are the terms in vogue associated with narcissistic personalities in the 1970s and the rise of depression in the late twentieth century (Ehrenberg 2010b: 160). Such terms are evoked either in regard to the "nurturing state", aimed at increasingly protecting the individual, or to evoke dependence on social assistance, experts or psychotropics. At various adverse moments in the twentieth century, politicians and psychologists alike evoked the betrayal of the "American way" centred in self-confidence. In short, the boom and the successive controversies about tranquilizers and antidepressants, while evoking freedom and self-realization, arouse the tragedy of an individual with poor self-esteem, incapable of self-direction, which amounts to a society in corduroy.

4.4 The Chilean Depression: The Malaise of Popular Disarray

The Sennett and Lasch-style theses, which link the emergence of a hedonistic self to the corrosion of common and intimate life, echo in the Chilean psychiatric reflection after the return to democracy, since 1990. In this decade and at the height of the economic boom, local and international epidemiological surveys (including the well-known epidemiological WHO multicentre study that examines the rates of mental disorders in healthcare services in 15 cities of the world) announce the psychiatric index of the paradoxes of progress: Chilean society – to the great surprise of many – is emerging as the world capital of depression (OMS, 2001a, 2001b). What is truly intriguing is that, unlike the United States, depression (from sad neuroses to manic-depressive psychoses) led to a common opinion among psychiatrists during the twentieth century: either it was a rare disease (especially among the popular classes) or it had raised little interest (Matte-Blanco, 1950; Roa, 1952; Kernberg, 1959; Varela, 1971). At the level of public health, one of the arguments for dismissing the importance of affective ills was the hierarchy of "social ills", such as infectious diseases and infant mortality linked to the country's poverty. On the other hand, however, alcoholism (as the most mental face of social ills) was a subject for permanent public concern. Since the so-called pacification of the Araucania, ever since the end of the nineteenth century, until the Pinochet dictatorship (1973–1990), this evil represented a great national "scourge": "degrading monster" for families and "saboteur" of work and industries. In short, the alcoholic was the anti-hero of a declining modernity for over a century.

The radical opposition between the "developed" North and the "underdeveloped" South was often evoked as a way of understanding the ubiquity of alcoholic disorders and the weak spread of depression in the population over the last century. In the psychiatric language, from the bottom-up representation of Chilean society, this opposition resulted into two expressions of intimate discomfort. On the one hand, that of the individual from a mixed origin and an alcoholic pathological destiny, associated with weak self-control and, on the other hand, that malaise of the white elite of European origin and its depressive pathological fate, associated with the excess of self-control, according to the North-Western rules of conduct focused on responsibility for themselves. For the popular Chilean man, according to psychiatrist Otto Dörr – Hubert Tellebach's disciple – while group "alcohol consumption" "is a legitimate form of recognition", work absenteeism and lack of personal responsibility do not bring discredit to this subject, upon which "the feeling of self, of individuality and of one's own" does not prevail on those who live in the temporary (Dörr and cols., 1972: 30).

Until late in the twentieth century, alcoholism was examined and treated from the foundational myth of order in the nation, which unites the weak self-control of the ordinary individual with the need for virtuous elite and strong authority as a condition of order and progress. At the beginning of the last century, it was at the hacienda where this narrative stood out clearly. Throughout the National Agricultural

Society Bulletins, we see how, while some employers decided to pay part of the salary in alcohol in order to keep the worker within the farm's premises, others opposed criticism of the poor semi-salary conditions of the peasantry in force until the 1960s, on the pretext that such increase would only contribute to the alcoholization of workers. In this same period, under the so-called the Mapuche's question, the inalienable character of Mapuche lands was discussed under the same argument: "for the indigenous people the most important factor in work is to obtain a fruit that allows them to cultivate their dominant vice, drunkenness, in its most depressing expression" (Serrano Montaner, 1912:195).

After the explosion of the debate on the "social question" (1880–1920), firstly, and definitely after the nationalist turn of the state in the era of "inward capitalism" (1930–1970), in which the economy depended both on the strength of the urban labour force and its capacity to consume: alcoholism was approaching depression. In the opinion of doctors and psychiatrists, behind the weak self-control of the alcoholic man, there was a tired and suffering man, relegated to the bottom of the social scale. Alcohol, in turn, was "necessary for the depressed subject to improve mood, for the weak to feel strong, for the shy to arm themselves with courage and for the loser to forget" (Muñoz, 1957). After World War II, when psychoanalysis acquires – under the guidance of Ignacio Matte-Blanco – the greatest influence in Chile, according to psychiatrists, the psychological terrain in which alcohol works is in low self-esteem, depressive affections, inferiority complexes and dependent character of oral type, originated in childhood. If these complexes are more entrenched among men of lower classes, it is because these individuals would not have found in their education or work neither the recognition nor the assessment of an encouraging future. Instead of this, drinking appeared as the way to exalt their masculinity and affirm their personal image in front of others. This period saw a proliferation of discourses on mental hygiene, public education, psychological therapies, the improvement of living conditions and the invigoration of workforce through the development of qualifications. Sublimation is identified in this period as the spring to master destructive passions of the working class in the name of higher ideals of personal and national improvement (Romero, 1969: 156).

The debate on the role of alcohol consumption is inseparable from the dilemmas relating to the afflictions of the working-class men during the twentieth century, linked by some to his refractory attitude in the face of adversity and obligations and by others to the psychosocial effects of material adversity. The question was whether this evil underscored a long-standing lack of self-control in this man or rather highlighted the fatigue and lack of self-esteem of this individual who found in alcohol an antidepressant and a means of asserting his self-image which he did not find at work. Likewise, the call for strong – civilizing – authority as a counterpart necessary to the expectation of lack of control of the working-class men, as well as the expectation of freeing this man from authoritarian dependencies of class (in the revolutionary 1960s), formed the backdrop that accompanied both discussions as social-medical measures to act on the nature of the evil behind popular alcoholism. However, during the Pinochet dictatorship (1973–1990), the repression and the so-called "laboratory" of ultraliberal reforms (also in labour, education, pensions and

health) is justified on the representations of the evils of the Chilean common man. The excess of military authority and the virtue of the business elite, on the one hand, were judged as the condition of order and progress in the face of the overflow and "whim of the masses" of the 1960s. The popular sovereignty was suspended for almost two decades in the name of the "sovereignty of centuries", based on strong authority (Correa, 2004: 276). The norms and values of meritocracy and competition, on the other hand, are presented as the antidote to mediocrity and weak congenital self-control. Since then, especially in conservative sectors, while the state is presented as a means of undermining personal responsibility (considered deficient in the Chilean people), it adds to the American criticism of the ineffectiveness of the state, that of the people – inefficient – who would lead it.

Such were the main dilemmas and controversies that made of alcoholism (closer to depression or laziness) the hegemonic language of Chilean disturbed intimacy for -at least- a century and a half.

Hence, in the 1990s, the ubiquity of depression called for a rethinking of the common suffering in the light of the value that individualism acquires in Chile. At the return of democracy, there is a dramatic reduction in poverty and a substantial economic boom (Moulian, 1998). While credit is open to the population with minimal restrictions, consumer goods, previously reserved for privileged groups, are now legitimately accessible to everyone. Far from the restlessness of work absenteeism, whose ghost stimulated alcoholic disorders, the country is rising in this decade at the top of the world ranking of hours worked (PNUD, 2009:131). The change in habits and the renewal of the individual's self-image – starting from consumerism and meritocracy – become a common topic among sociologists. The Chilean people would have gone from shyness, pessimism and low self-confidence [typical of the Spanish and indigenous heritage] to "having a proud and optimistic attitude towards the future, in the image of the Anglo-Saxon spirit" (Véliz, 1994; Tironi, 1999:15). At the end of the decade, however, hit by the "Asian" crisis, the "paradise" of consumption, as claimed by the sociologist Tomás Moulian, is transformed into the "purgatory" of over-indebtedness. That goes hand in hand with increased work commitment and the common perception of "having lost control of their time" (Araujo & Martucelli, 2012). At the same time, if consumption alleviates mistrust of others and the uncertainty of a future haunted by debt, the medicalization of depression and anxiety – in the image of the United States, according to the Chilean philosopher Carlos Pérez – has become one of the main mechanisms for containing the Chilean malaise and preventing such malaise from becoming a social protest (Pérez, 2016).

In this vein, reversal to the new national anti-hero – the hedonistic and vulnerable common individual – a local depression begins to be portrayed. Such an individual departs from the misery of the old low classes because he accesses the welfare of consumption, and through it, he magnifies his personal image. However, at the same time, the only new means available for him to progress is credit, which subjects him to the pressing temporality of debts, the excessive labour that is imposed on family impermanence and the growing feeling of powerlessness in the face of disparity of

opportunities. Around these coordinates, the explosion of depression in Chile is understood, which until then had considered it as a rare disease and had reserved it for elite individuals who were supposed to assume higher levels of responsibility. Terms like "learned helplessness", "stressful life", "bitter depression" and "culture of self-medication" begin to abound in the mouth of specialists and lay people. However, although depression is routinely recognized in that individual who suffers from the least effort, the dilemma sets in if the feeling of popular insufficiency is due to a "psychosocial" reason linked to the accumulation of demands and expectations of personal fulfilment (which would mostly affect the disadvantaged groups who are unable to satisfy these but who think they deserve them) or, conversely, would be due to an attitude – a personality rooted in their culture – disarranged and overactive (hence concerning the body) with regard to suffering (Florenzano and cols, 1993; Lolas, 2000; Heerlein and cols., 2000).

From the first perspective, a social psychiatrist, such as Mario Vidal, understands the popular depression associated with bitterness that is brought about by deprivation of something (recognition of merit, access to opportunities) that they never had but that they believe they deserve. Hence, the destruction of self-esteem, instead of referring to oneself (typical of "melancholic" depression), is articulated in resentment and rage against others (in positions of authority and to deny recognition), which can take on violent overtones (Vidal, 1999). From the cultural perspective, on the other hand, the stress and the low self-esteem **associated with depression would be rather associated to a short-sighted personality** and a disorganized disposition in the face of adversity and effort, by working badly, more than working too much, and by not knowing how to balance consumption and credit, more than the hardships of credit in a low-wage society (Roa, 1997; Araujo & Martucelli, 2012).

As a portrait of social decline, depression is subject to both conservative and progressive representations. On the conservative side, for psychiatrist Armando Roa, the main representative of the psychiatric phenomenology, the rise of this disease is associated with hedonistic individualism, with the "easy pleasure" of **consumption and rights demands** that undermines any sense of sustained effort and duty, of all suffering and conception of sacrifice for the sake of achieving greater individual and collective goals. Out of their hedonist pleasures, says the psychiatrist, the individuals find themselves alone and powerless, unable to sustain any project **in the long term**, hence the depressive omnipresence (Roa, 1994). On the progressive side, Moulian understands depression as the silent partner of Chilean triumphalism and a citizen that is asleep in the "passive pleasure" of consumption, which was the result of a protected democracy (inherited from the dictatorship, in which citizen deliberation was limited by the consensus agreed in advance by experts) and a deregulated market conceived as "natural order". However, the sociologist warns, in a country with a modest income and a labour market adverse to workers, the individual is dependent on credit and must pay for his or her creditworthiness with the loss of "the government of themselves" (Moulian, 1997: 142). Hence, the emergence of feelings of anguish, hopelessness and low self-esteem takes place in the population.

Although from opposite sides, both authors see in the fainting responsibility of the hedonistic individual, the way in which depression (as once alcoholism) is transformed into a key indicator of social collapse. The first, despite the fact that in Chile social rights were strongly limited in dictatorship, it stresses "easy pleasure" that blurs any idea of "must-be" and sustained effort for larger projects. The second one stresses the "passive pleasure" that subordinates' political and citizen responsibility to a tutelary elite. However, these authors refrain from examining how community is built around the value of autonomy consistent with the myth of order: more oriented to "making responsible" than to "making capable". This is not indifferent to the relational and family imprint of Chilean individualism, where the family reveals itself to be a springboard for "conceiving and even dreaming about a personal project" (PNUD, 2002: 20). The sincere affective bond is inseparable from the instrumental bond represented by the family as a nuclear means of self-affirmation in Chile.

This speaks for itself, as the disparate value agreed upon for the treatment of depression at the level of mental health programs and at the workplace, where this issue (**generate working conditions favourable to the acquisition of capabilities and personal assertion**) is virtually absent. At a clinical level, since the National Depression Program implemented in 2001 in the poorest sectors of the country, the well-being of depressive women is located at the centre of the family's well-being. On the other hand, the economic paradigm of health, promoted by the WHO and the World Bank partnership since the 1980s, has been going through the design of this program (Miranda, 2015). Depression, given its presumed disabling effect, acquires a clinical and social interest, since the opening of its treatment to the population reveals to be at the same time a means of stimulating action and a means to alleviate poverty while promoting social reintegration as well. The underlying reasoning is that people living in poverty would have greater difficulty in suffering mental disorders, because of their difficulties to cope. While in reverse, those affected by an illness (particularly one as disabling as depression, in particular among women) would be more susceptible to poverty, because of their incapacity to work (OMS, 2001a, 2001b; OMS, 2008).

At the work level, although the relationship between stress and depression has often been evoked since the 1990s, neither depression nor personal investment came into the equation of flexible work. This is what the sociologist Claudio Ramos notes in his empirical study on "unbalanced modernization" of Chilean companies, in which he researches more than 200 companies from different economic sectors. According to this author, after the Asian crisis, at the same time that the companies drastically reduce the number of workers, they diversify their activity. This represented an intensification of working time in Chile, which was combined with low wages, permanent vertical control and low capacity of the worker to influence his tasks. What surprises this author is that in the "local organizational management", there is a clear border between those who decide and those who obey. However, the post-Fordist working model is supposed to stimulate (due to the variability of demands and activities of the modern companies) cognitive and affective skills, cooperation, commitment and worker's personal motivation. In such an

organizational arrangement, mental health is compromised in "more than 60% of workers [who] report suffering from one or multiple illnesses" and "at least one third have been severely affected, given their deteriorated life, both in their work and in their private life" (Ramos, 2009: 33). According to different international studies, work intensification induces *surmenage* and depressive conditions only when it is coupled with a low recognition of initiative and the worker's involvement in individual and shared tasks (Esping-Andersen and cols, 2006). In the case of Chilean companies, what Ramos calls the "self-fulfilling prophecy of laziness", very rooted in the expectations of the management of companies, it increases the discomfort linked to an autonomy exclusively focused on keeping workers occupied. According to this author, while workers have extended the time of work, the autonomy at work is conditioned by this prophecy that is structured in a managerial discourse such as this: "I don't think the workers know how to participate"; "I don't give them the opportunity to participate"; "they don't know/don't learn to participate"; "I don't trust the worker's participation" (Ramos 2009: 232).

The Chilean depression, in short, is inscribed in an unbalanced plot between responsibility and capacity, which is distributed unequally. Just like in other countries, little has been achieved in pointing the finger at the relationship between neoliberalism and depression, without describing the fine web of expectations, representations and norms that reveal the concrete value that autonomy and its disorders in the social fabric acquire. In the case of Chile, both the particular language of depression and the actions to treat it seem to be inseparable from the national myth of order, which combines the need to "hold accountable" the weak individual self-control, which increasingly clashes in the twenty-first century, with greater expectations of horizontality and personal recognition.

4.5 Conclusion: The Social Coherence of Depressions

Between the 1970s and 1990s, with the decline of the Providence State in Europe and the crisis of the so-called liberal cycle in the United States (1945–1975), the idea of narcissism (characterized by a fragile self-esteem and uncontrolled impulse) prevailed in this society and it became a typical feature of the hedonistic and multitasking individual. At the same time, with the shift in focus from psychiatry to the community and the rise of "Prozac narratives", depression has displaced anxiety disorders as the "disease of the century". Until the 1970s, both evils disputed such a place associated with moral individualism. This occurs when the value accorded to personal choice and comfort, independence and lifestyles gains ground over the values prescribed by tradition. A decade later, beyond the well-known psychiatric mutations and the success of the pharmaceutical industry, depression stands out as the paradigmatic reverse of an individualism rooted in action, shaped by flexible work. Personal initiative, self-motivation, purposiveness and the ability to communicate, among others, emerge as obligations (rather than choices) inherent to business competitiveness. Conversely, impotence, anhedonia, mental fatigue and

emotional disengagement raise depression as the main obstacle to the realization of a new performative individuality.

In short, depression can no longer be cut out of the social sphere as a list of problems to which one must respond, by imposing itself as the obligatory expression of emotions (as Marcel Mauss would say) in the face of new expectations and norms of autonomy. In particular, depression – and mental health problems – comes as a clinical entity through which guilt changes are elaborated in psychopathology (and the reasons for feeling guilty and get sick) in this society (Ehrenberg, 2012). Thus, for half a century, as the sociologist Alain Ehrenberg has investigated, depression and narcissistic pathologies have left the field of clinic to become true sociological categories. Through them, the correlation between symptoms, personality and social life in individualistic societies has mobilized discussion and intervention beyond the strict domain of medicine and psychology. From this perspective, the theses of the weakening of society and the inconsistency of the contemporary individual, to which the new affective "epidemics" would testify, reveal a common concern in individualistic societies. However, as Emile Durkheim states, it is not that social obligations have disappeared but that they have mutated as the sense of obligation has (Durkheim, 1906/2006). Hence, we have tried here to particularize how the concern of social disaffection is posed in light of the respective emphases on values, norms and ideals of autonomy in each place. Finally, we have described the "singular" way in which depression unites personal afflictions with collective difficulties, interdependently to the ways in which autonomy is considered and practiced" in each of these societies (Ehrenberg, 2015).

What Alain Ehrenberg Has Systematized Is That the Particularity of American Individualism Is That It Places the Public and the Private on the Same Level Self-confidence unites the intimate and the common, personal fulfilment and equality as well. Such an individualistic conception draws its principles from the puritanical religious doctrine, according to which "a Christian is a church", the relationship with God is direct, not mediatized by any institution. Likewise, unlike European Protestantism, one becomes a Christian through a pact; such is the American particularity: an act of personal will is required. On the other hand, on the political level, such postulates have taken shape in the idea that public intervention must be subordinated to individual moral responsibility. After the penetration of psychiatry in everyday life, under the model of the diversity of Protestant churches, a plurality of mental syndromes is created in the United States, of which the DSM and the group of patients' associations that identify them around different mental syndromes are a clear reflection (Ehrenberg 2010b; Castel, 2011; Demazeux, 2013). Under these coordinates, the American tragedy of social decline – regarding which the rise in depression has appeared as a sociological test since the 1970s – revolves around the decline of self-confidence, often related to the medicalization and psychologization of moral responsibility. After the conservative turn of American society in the 1980s (which condemned the hedonistic spirit promoted by the welfare state and the institutional bureaucracy on behalf of an energetic individual and a self-confident country), the "crisis of self-confidence" has disguised the role of institutions and social protection in personal assertion and self-reliance.

The Chilean founding myth is built on the Tocquevillian principle that "societies where oligarchies are weakening would be more exposed to the tyranny of the majority" (Jocelyn-Holt, 2014). In local history, the rhetoric of order (guaranteed by a strong authority and cohesive and virtuous elites) is interdependent with the idea of a vicious majority. Chilean individualism, although it has known its current form since the 1990s, inherits some premises from the dictatorship, which updated and deployed the dramaturgy of this national idea of order and progress. Thus, personal responsibility is designed both from the horizon of merit as in that of the limitation of leisure and inherent disorganization of the common Chilean. Accordingly, the elite Catholic religion (such as the Jesuit religion at the beginning of the twentieth century and Opus Dei at the end of the century, which had great influence on the new entrepreneurial spirit) is distinguished from the common religion by the self-control that their faithful have to show (Thumala, 2007). Therefore, on the political and religious level, there is a "model" of elite morality and a popular morality that is supposed to be modelled. Around this rhetoric, the relationship between stress, depression, narcissistic hedonism and social decline since the 1990s is not posed as in the developed West in light of the mutation of neurotic malaise (linked to guilt, repression, renunciation of drives, desire and its psychic costs) but from the mutation of the alcoholic scourge. In this sense, the intimate and common discomfort does not refer to the plurality (American style). Discomfort has been divided into two interrelated intimate idioms of distress, linked to the self-control and psychological problems of the privileged man and to the lack of control and emotional instability of the **common man**. In this vein, a political and medical premise in the twentieth century, which had alcoholism at the centre of social dilemmas, was to transform the people: from the race regeneration and revolution to the repression and demobilization of people during the civic-military dictatorship.

With the return to democracy in the 1990s, the shift from alcoholism to depression represents a renewal in the way of thinking and acting about intimate and social disorders. Individual suffering (in particular of women) takes on greater prominence in the face of the threatening tint to public order, which has always retained the scourge of **man's alcoholism**. If women's depression is gaining notoriety, it's partly because autonomy has been assimilated in the restricted sense of making family the heart of self-affirmation. In this context, the family unites Chileans as the affective and instrumental support of their ability to move forward; at the same time, it divides them, as the main obstacle to personal merit. Likewise, it appears as the main individual refuge, over which the action of the state must remain at a margin, while absorbing the new tensions of the inequality of temporal imbalance, as a result of the interdependence between overwork and over-indebtedness in Chile. However, it is in the workplace where the principle of protection and autonomy (only centred in responsibility) is more clearly subordinated to the myth of national order. In fact, the need for a vertical and pragmatic exercise of authority is often evoked as a necessity in front of the disorganized attitude of subordinates (Araujo, 2016). In this regard, at the beginning of the twenty-first century, on the one hand, Chile rises as one of the Latin American countries with the weakest trade union activity (Cook, 1998). On the other hand, according to the studies of quality of

work, the Chilean flexible company (contrary to the evidence of psychosocial risk studies) has not understood that inherent to the demands of involvement and competitiveness, companies must generate practices that respond to the expectations of personal recognition (Ramos 2009).The cost of a company that does not take this principle into account is the proliferation of new affective and psychosomatic diseases at work. Under such coordinates, the excessive time dedicated to work in Chile, according to Danilo Martuccelli and Kathya Araujo, "would thus have no other reason than the harsh economic reality" and has "no other brake than another imponderable: the illness that incapacitates", "the body that refuses to continue" (Araujo & Martucelli, 2012). This is the background of obligations and social expectations that, most probably, give a psychosomatic imprint to fatigue and a feeling of inadequacy – which comes to be expressed as depression – in the contemporary Chilean individual.

In conclusion, the cases examined here show that the uneasiness that depression has aroused as an indicator of social decline in our individualistic societies gives evidence of a style of passion linked to the attitude towards autonomy. At the same time, by examining the local language of depression and the variety of moral dilemmas that this affective disorder awakes in the light of the ideals of autonomy, we see that what is discussed is so varied and the actions so specific, that one begins to wonder whether we are talking about the same thing in Chile as in the United States.

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Part II
Etiopathogenic Theories and Models

Chapter 5
Contemporary Psychodynamic Theories on Depression

Marianne Leuzinger-Bohleber

5.1 Introduction: Chronic Depression and Trauma: Signatures of Our Time? *Some Societal, Conceptual, and Methodological Considerations*

In recent decades, depressions have increased to such an extent that, according to WHO estimates, depression will become the second most widespread disease worldwide in this decade (see e.g., Moussavi et al., 2007). For a long time, depression was considered a disorder with a relatively good treatment prognosis, but this has changed in recent decades. Results from epidemiological research showed that depression is often a recurrent disorder with a high relapse rate and becomes chronic for 25–30% of those affected (see e.g., Steinert et al., 2014). There is also a high degree of comorbidity between depression and different personality disorders. In addition, pharmacological and short psychotherapeutic cognitive-behavioral as well as short psychotherapeutic treatment approaches have proved to be far less successful than hoped: 50% of the depressed patients suffer a relapse after the first depressive episode, 70% after the second, and 90% after the third episode. Fifty percent of all depressed patients have a relapse after any form of short psychotherapy (see Blatt & Zuroff, 2005). Twenty to thirty percent of all depressed patients do not respond positively to drugs at all (see e.g., Corveleyn et al., 2013, Trivedi et al., 2011, Huhn et al., 2014). Of those with a positive response, one third has a relapse within 1 year, 75% within 5 years (see also Cuipers et al., 2017; Steinert et al., 2014). For these patients, long-term psychoanalytic therapies or psychoanalyses may offer an alternative (see Leichsenring, 2008; Leichsenring & Rabung, 2011; Leuzinger-Bohleber et al., 2019a, b). In the representative DPV (*Deutsche Psychoanalytische Vereinigung*) outcome study, around 80% of all the 402 former psychoanalyses patients or patients of long-term psychoanalytical therapies have

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*,
Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_5

shown sustained improvements in their psychopathological symptoms as well as in their object relations, professional quality, and in life quality. Among them, there were 27% who had been diagnosed as depressed mostly in combination with some personality disorders. To mention just one of the unexpected results of the study, 62% of the patients had been severely traumatized children of the Second World War (cf. Leuzinger-Bohleber et al., 2003a, b).

Although depression can be regarded as one of the psychoanalytically best investigated disorders, the differentiation between its various forms is by no means easy and not yet sufficiently understood. The older definition focused on psychogenic, endogenic, and somatogenic depression, and then DSM IV and ICD 10 started from the descriptive-symptomatic level and arrived at dimensionally different disorders (major depression, dysthymia, etc.). Without excluding the biological factors (see Chaps. 7, 8, & 9 in this volume), in a psychodynamic understanding of depression, the forms are not fanned out categorically or dimensionally (see, e.g., Hill, 2009). Thus, as Sidney Blatt (2004) suggests, the different forms of depression can be located on a continuum ranging from the dysphoric mood of microdepression to severe depression (see Luyten & Fonagy, Chap. 14 in this volume).

According to Bohleber (2005/2010), in *social sciences the depression has advanced to a signature of our time*, in which traditional structures and clear behavioral expectations have largely dissolved. The phenomena of delimitation and the enormous increase of individual's choices of life perspectives result in a loss of social security and make one's own identity the lifelong project of the individual. In his study, the French sociologist Alain Ehrenberg (2016) declares the exhausted self to be the disease of contemporary society, whose behavioral norms are no longer based on guilt and discipline but mainly on responsibility and initiative. The late bourgeois individual seems to be replaced by an individual who has the idea that "everything is possible" and is marked by the fear for his self-realization, which can easily increase to the feeling of exhaustion. The pressure for individualization is reflected in feelings of failure, shame, and insufficiency and finally in depressive symptoms. For Ehrenberg, if neurosis is the illness of the individual torn apart by the conflict between what is allowed and what is forbidden, depression is the illness of the individual inhibited and exhausted by the tension between what is possible and what is impossible. Depression thus becomes a tragedy of inadequacy (for the role of social and cultural factors in depression, see Jiménez, 2019 and Chap. 4 in this volume).

Such epistemological-clinical data and social-scientific analyses also challenge psychoanalysis to reexamine the issue of depression and evaluate the state of its research. Therefore, in 2004, a multicenter research group of psychoanalysts and cognitive behaviorists decided to initiate a comparative psychotherapy study on the outcomes of cognitive-behavioral and psychoanalytic long-term treatments, the so-called LAC study. We conceptualized the study in close collaboration with the research group of Phil Richardson, Peter Fonagy, and David Taylor, who also – at that time – planned a study on the outcome of psychoanalytic long-term psychotherapies in difficult-to-treat depression, the so-called Tavistock Adult Depression Study. We used a number of identical measuring instruments to compare the data

from the two studies. Close collaboration was also established on the psychoanalytic conceptualization of depression. David Taylor had just written the first versions of the Tavistock Treatment Manual for the treatment of difficult-to-treat depressive patients. He agreed to train the psychoanalytic study therapists of the LAC study, a prerequisite for us to include psychoanalysts of various psychoanalytical orientations as study therapists.[1]

In the meantime, both the results of the Tavistock study (Fonagy et al., 2015a, b) and the LAC study (Leuzinger-Bohleber et al., 2019a, b) have been published. These and several other studies show the positive outcomes of long-term psychoanalytic therapies for depressed patients. However, the problem remains: most outcome studies up to date have focused on short-term therapies. The outcomes of psychoanalytic short-term therapies according to evidence-based-medicine criteria have meanwhile been confirmed by many studies (see, e.g., Fonagy, 2015; Shedler, 2010, 2015; Abbass et al., 2009; Driessen et al., 2010; De Maat et al., 2013; Kaechele & Thomä, 2000; Kaechele et al., 2006). Liliengren has collected 272 RCT studies in this field until now (see also 3rd edition of the *Open-Door Review*, Leuzinger-Bohleber et al., 2015/2019). In contrast, still only a few studies are available on the effects of long-term psychotherapies and psychoanalyses (see, e.g., Blomberg 2001; Grande et al., 2009; Huber & Klug, 2016; Knekt et al., 2011; Fonagy et al., 2015a, b; Leichsenring 2008). This is one of the main reasons for planning a kind of a replication study of the LAC study: the *Multi-Level Outcome Study of Psychoanalyses of Chronically Depressed Patients with Early Trauma (MODE)*. It follows on from the results of the *LAC depression study*, which showed that chronically depressed patients can be successfully treated with psychoanalytic (PAT) and cognitive-behavioral long-term therapy (CBT) (high effect sizes in symptom reduction, high remission rates, etc.). It was found that structural changes (measured with

[1] Already in the LAC study, we assumed that we wanted to investigate – in the sense of a naturalistic study – psychoanalytic long-term treatments, as they are really carried out in the private offices in Germany, financed by the health insurance companies. Therefore, we assumed a thorough psychoanalytic training of the therapists and required at least 3 years of experience after completion of their trainings. The additional training in David Taylor's manual then built on this "foundation of psychoanalytic knowledge" and sensitized the study therapists to specific challenges in the treatment technique of this difficult-to-treat group of patients.

It is well-known that for the acceptance of outcome studies in times of evidence-based medicine, it is necessary to use treatment manuals. This also applies to psychoanalytic long-term treatments. However, as we have discussed in various papers, these manuals have a different character from manuals for short-term psychoanalytic therapies. Especially the group of chronically depressed patients requires a lot of creativity, originality, and flexibility from the psychoanalyst to reach the patient emotionally, to initiate a therapeutic process at all, as well as to work through the idiosyncratic unconscious conflicts and fantasies of the chronically depressed in the transference relationship. Nevertheless, the creative psychoanalyst will need to follow specific psychoanalytic treatment techniques that are described in a "manual". The basic treatment principles are elaborated in such manuals (in the MODE study, we speak of a "workbook") – not in the sense of a "cookbook – but of binding basic principles based on a specific psychoanalytic understanding of the psychodynamics of depression. These basic principles are illustrated with concrete anchor examples from psychoanalyses or long-term psychoanalytic therapies.

Operationalized Psychodynamic Diagnostics, OPD) can only be observed in PAT but not in CBT after 3 years of treatment. One unexpected result of the LAC study was that around 80% of chronic depressives suffered from early trauma and responded particularly well to high-frequency psychoanalyses (see also Negele et al., 2015). One of MODE's aims is to investigate this group of difficult-to-treat patients. In other words: the study focuses on the question whether there are certain patient groups that require intensive long-term treatments in order to achieve sustained improvements in their chronic depression. In addition, it will be investigated whether and how symptomatic and structural changes in this patient group can also be investigated with neurobiological instruments. For this reason, MODE considers neurobiological (e.g., fMRI) and clinical psychoanalytical (e.g., changes in dreams) observation methods in addition to the usual (psychological) instruments of comparative psychotherapy research (see Moser & von Zeppelin, 1997; Peterson et al., in prep.)

The following contribution to this volume is based on a draft of a workbook (treatment manual), which was written for training the study therapists of MODE. It is based on the rich clinical experiences of psychoanalytical long-term treatments in the LAC study. Furthermore, the knowledge of four central papers conceptualizing psychoanalytic treatments of chronic depressed patients with early traumatization is integrated (Taylor, 2010; Bleichmar, 1996, 2010; Bohleber & Leuzinger-Bohleber, 2016; Lane et al., 2015) as well as other contemporary psychoanalytic and interdisciplinary knowledge on depression and trauma.

Therefore, in this chapter, I focus on psychoanalytical, interdisciplinary inspired conceptualizations of depression as well as treatment problems in *psychoanalysis and psychoanalytical long-term therapies* based on this knowledge. As is well-known, knowledge gained in these intensive, long-term psychoanalytic treatments still forms the basis for many applications in short psychodynamic and psychoanalytical interventions in different psychiatric and psychological settings, e.g., crisis interventions, various forms of short therapies (e.g., the transference-focused psychotherapy (TFP) of the group around Kernberg and Clarkin (cf. Caligor et al., 2018), mentalized-based treatment (MBT) by Fonagy et al. (cf. contribution by Luyten and Fonagy, Chap. 14 in this volume, focal therapies (cf. Leuzinger-Bohleber et al., 2017) or different forms of psychoanalytical group or family therapies to name but a few.

In the limited context of this contribution, the psychoanalytical knowledge of the psychodynamics of depression is first briefly summarized in today's psychoanalysis, and some of the important historical lines are outlined (Sect. 5.2). In Sect. 5.3, this knowledge is compared with selected interdisciplinary findings on trauma and depression from the field of embodied cognitive science and neuroscientific memory research. The first attempt at integration of psychoanalytical and interdisciplinary knowledge is discussed.

5.2 Some Basic Lines of a Psychoanalytic Understanding of Depression

In this section, I will summarize the major findings of conceptual and clinical psychoanalytical research on depression relatively shortly because I assume that most of this knowledge is well-known in the meantime.

5.2.1 Depression as a Reaction to Loss, Guilt, and Reparation

In contemporary psychoanalysis, depression is still seen as the reaction to a loss, that of a real object in the outside reality of the patient or that of an inner object, a loss of an internal relationship. The focus of the psychoanalytic investigation, however, is not the object loss itself but its mental processing. In "Mourning and Melancholia" (1916–1917g), Sigmund Freud distinguishes mourning from melancholia. Mourning is a feeling "out of tune" with a painful mood, a suspension of interest in the outside world, the loss of the ability to love, and an inhibition of creativity in work and one's leisure time. All this serves the devotion to mourning and the facilitation of mourning work ("Trauerarbeit"). The mourning individual painfully works through his memories of the lost object in order to be able to remove the libidinal cathexis from the object and finally to accept the loss. If the withdrawal of the libido is successful, then the grief comes to an end and the ego is "free and uninhibited again." Metaphorically speaking: The libido can now look for other objects.

The pathological sadness of melancholia may be complicated by the fact that an already existing deep ambivalence toward the object has been intensified by narcissistic insults, setbacks, and disappointments on the part of the object. In contrast to normal grief, the object cannot be abandoned; the attachment is preserved by being incorporated into the ego through narcissistic identification. Now the ego feels the hatred that originally was directed toward the object; the ego is insulted, denigrated, and humiliated.

The love relationship has been taken back to the level of sadism. But at the same time the process of identification establishes a "critical voice" in the ego. The object chosen according to the narcissistic type assumes the role of a kind of judge as (unconscious) part of the ego, and the accusations against the object become self-reproaches. One of Freud's most important insights into melancholia was the discovery of the development of the individual subject, as he formulated it in 1923 in "The Ego and the Id." The replacement of the cathexis of the object by identification becomes its constituent condition. The character of the ego is now formed by the "permanent traces of old object relations." Thus, Freud also revises his strict separation between mourning and melancholia, because early object relationships always shape the personality structure of the self, thanks to the continuous identifications with them.

Accordingly, the cathexis (and the attachment) of the lost object is not simply abandoned but transformed in a restructuring process, whereby the memories can become a permanent component of the inner world (Hagmann, 1995): With the structural theory and his insights into the influence of the superego, Freud can better grasp the conflicts and tensions between superego and the ego. The overpowering superego seizes the consciousness of the depressive and rages against the ego. It has seized the sadism of the individual and turned it destructively against the ego. Freud now calls this mental constellation prevailing in the superego a "pure culture of the death instinct," which often enough succeeds in actually driving the ego to death.

Karl Abraham had already identified hatred as the cause of depression in 1911, which led to repressed self-accusations and feelings of guilt. In 1924, like Freud, he also recognized identification as a fundamental mechanism. If the person predisposed to depression loses his love object, he reacts with hatred and contempt, and the frustrating object is ejected and, in the course of regression to the oral-sadistic stage, is immediately introjected back into the self. Through this narcissistic identification with the devalued object, the ego itself becomes worthless and reacts melancholically.

This psychodynamic understanding of depression described by Freud and Abraham has been taken up by various psychoanalytic researchers. The decisive determinant for the outbreak of depression is not the loss of the real object itself but a constitutional heightening of ambivalence or aggression that intensifies it, which originates from narcissistic offenses by and disappointments in the object. Sándor Radó, Melanie Klein, and Edith Jacobson further explored the sadistic aggressiveness of the superego as one important factor of depression. In Melanie Klein's work, the archaic severity of the early superego comes from the splitting of the object and self-representations into an "ideal good object" on the one hand and "phantazised evil one" on the other hand. Through the later integration of these splits in the representations, the child becomes aware of his own aggression against the idealized primary object and falls into a depression. Melanie Klein introduces the new concept of reparation in the so-called depressive position. Depression occurs when the libidinal and aggressive impulses, thoughts, and drives can be integrated and reparation associated with it can be achieved. If excessive aggressive impulses are dominating the libidinal ones, such an integration and reparation cannot take place: A depression develops.[2]

Edith Jacobson describes a basic conflict that can be found in all depressive states. If the ego cannot achieve the satisfaction it desires and cannot use its aggression for achieving this satisfaction, then it turns the aggressive impulses against the self-representation. A narcissistic conflict develops between the desired self-image and the image of the failing devalued self. The self-esteem is lost and a depressive mood develops. Severe depressions are found above all in people whose early frustrations and disappointments had such devastating effects because they reacted with

[2] David Taylor (2010) focuses in his manual mainly the Kleinian tradition for understanding and treating severely depressed patients.

unusual hostility. Early frustrations create excessive expectations, love objects are idealized, and ego ideals and desire-determined self-imagines are exaggerated and unattainable. New narcissistic insults lead to a devaluation of the love object. In order to endure these insults and to make up for them, glorified grandiosity fantasies of the love objects are introjected into the superego; the devalued fantasies of a bad parent, on the other hand, are introjected into the ego. Thus, the child can hold on to the hope of love in the future but from now on is exposed to the massive criticism and hostility of these idealized unconscious fantasies and representations. At the same time, the narcissistic self-regulation of the ego is damaged.

5.2.2 Narcissistic and Psychotic Depression

Psychoanalytical authors have repeatedly addressed the fact that in depressive patients, the ego is particularly vulnerable and intolerant of frustration and disappointment. Also, self-representations and object representations do not yet seem to be sufficiently differentiated from each other. Already in 1927, Sándor Radó noticed the special tendency of depressive patients to passive-dependent object relationships, because this was the only way they could maintain their self-esteem. A somewhat different basic understanding of depressive basic conflicts now follows on from this. It places the basic disorder in the narcissistic regulatory system and describes it as the tension between strongly pronounced narcissistic expectations and ideals on the one hand and the inability to meet these ideals or to receive narcissistic support from the object for them on the other. This then results in the depressive affect. In 1952, Edward Bibring was the first to elaborate on this explanatory approach and to separate it from the assumption of aggression directed at the self as the main determining factor of depressions. Depression is "an emotional expression of a state of helplessness of the self." It is a mode of reaction generally available to humans. The ego often finds itself in a state of real or imaginary helplessness in the face of overwhelming difficulties. Others speak of *narcissistic depression*, given the underlying tensions between ego and ego ideal. The dominant feelings here are not feelings of guilt fed by aggression and self-hatred but shame and humiliation and feelings of abandonment and helplessness. In 1965, Sandler and Joffe describe the loss of narcissistic integrity as the central cause of the depressive affective reaction. It is not so much the loss of a love object that is in the foreground as the loss of the well-being that is inseparably linked to it. It is a feeling of having been deprived of an ideal state of the mind. If the individual feels helpless and resigned in the face of the mental pain experienced and cannot resort to an outwardly directed aggression to remedy it, he or she reacts affectively with a depression. Wolfgang Loch (1967) also assumes an imbalance between the ideals of the individuals and its self-esteem. The perception of this discrepancy produces the depressive affect. In the depressive patient, there is no stable connection between the self and the ideal self, because the process of identifying the self with the ideal object is disturbed by aggressive impulses and attitudes. Thus, the connection between the self and the ideal self is

only guaranteed as long as the real presence of an ideal object is given. In *psychotic depression*, the ideal self is lost, forcing the cathexis of the superego as a substitute. This archaic persecutory superego has taken the consciousness function of the ego and robbed the depressive of his self-esteem: the real self-assessment gets lost. Because the libidinal cathexis of the ideal object was already disturbed in early childhood, depressive feeling of emptiness and inhibition of vitality develop later in life.

5.2.3 Integrative Models of Depression

Another group of psychoanalysts does not attempt to describe one central basic conflict but rather to develop an integrative model of depressive states of the mind in view of the diversity of pathogenic conflict constellations in depression. Stavros Mentzos (1995) starts from the narcissistic self-regulation, which is carried by a mature ideal self, ideal object, and superego in a mature self-regulation. A blocking or pathological development of one of these factors of the self-regulation leads to different clinical pictures of depression (e.g., mania, anaclitic depression, and guilt depression). Herbert Will (1994) orders the different types of depression on the basis of leading emotions: superego or guilt depression with guilt and self-accusation, oral-dependent depression with anxious longing and disappointment, ego depression with helplessness and hopelessness, and narcissistic depression with shame and self-denigration.

Based on many empirical studies, Sidney J. Blatt (2004) characterized two different organizations of depression: the anaclitic type, which centers around interpersonal factors such as dependence, helplessness, feelings of loss, and abandonment. In contrast: the introjective type shows a strict, punitive superego, self-criticism, low self-esteem, and basic feelings of failure and guilt (see Luyten und Fonagy Chap 14 in this volume).

Bleichmar (1996) attributes a major role in the outbreak of depression to the feeling of helplessness and hopelessness. In the predepressive individual, there is a fixation on a desire that occupies a central position in the libidinal economy of the subject and cannot be replaced by any other. This desire appears to be unattainable, leading to a sense of deep helplessness and a self-representation of powerlessness. A feeling of hopelessness spreads, which extends not only to the present but also to the future. They lead to an increasing deactivation of the efforts to still fulfill the wish. Depressive affects, apathy and psychomotor inhibition are the result. There are quite different pathways that cause a depressive state and determine it. None is obligatory; each is determined by different factors and psychodynamic constellations. As discussed under 2.1, most authors give aggression a prominent or even universal place in the determination of depression (see dynamics on the left upper part in the graph below). In addition to this, Bleichmar lists the following factors: guilt and feelings of guilt, frustration in the realization of narcissistic aspirations, narcissistic personality disorders (either with a weak narcissistic self-regulation or

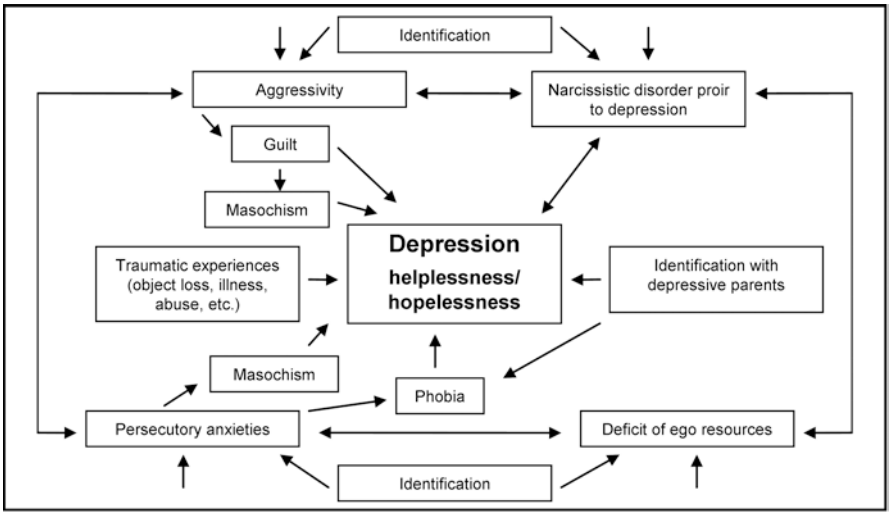

Fig. 5.1 Pathways to depression. (Authorized reproduction from Bleichmar 1996)

with traits of grandiosity and omnipotence collapsing through reality; dynamics on the left upper side of the graph below), persecution fears, ego deficits, and traumatic experiences. These factors can be effective individually but also in combination or in succession as Bleichmar (1996) illustrates this dynamics in three extended case examples (see Fig. 5.1).

5.3 Depression and Trauma: Some Interdisciplinary Findings

5.3.1 Depression and Embodied Memories of Trauma

The extreme feeling of helplessness and hopelessness is not only, as just outlined, a central basic feeling of depression but also characterizes the traumatic experience. As Bohleber (2010/2012) points out, the traumatic situation can result in an extreme sense of helplessness, linked to the overwhelming anxiety often confronted with the danger of death or annihilation as well as an experience of being completely left alone:

"Psychoanalytic trauma theories have evolved on the basis of two models, one psycho-economic, the other hermeneutic and based on object relations theory. In order to grasp the phenomenology and long-term consequences of trauma, we need both models. The psycho-economical model focuses on excessive arousal and on anxiety that cannot be contained by the psyche and that breaks through the shield against stimuli. The model based on object relations focuses on the breakdown of

internal communication which produces an experience of total abandonment, precluding the integration of trauma by narrative means" (Bohleber, 2010/2012, p. xxi; see also Cooper, 1986, p. 44; Leuzinger-Bohleber, 2015). The traumatic experience breaks down both the basic trust of the traumatized individual in a helping object (see Erikson, 1958/1993, see also the concept of epistemic trust by Fonagy et al. (2015b) on the one hand and the basic trust in one's own self-agency on the other hand (see, e.g., Emde & Leuzinger-Bohleber, 2014; Leuzinger-Bohleber, 2015). The traumatized person is unconsciously and firmly convinced that nobody but nobody can help him in a situation of extreme, life-threatening danger and dehumanization, but that he is totally left alone and completely incapable of freeing himself from the unbearable situation.

The psychoanalytic knowledge of short-term and long-term effects of extreme traumatization is mainly based on clinical psychoanalytical experiences with survivors of the Shoa and their children and grandchildren. The kind of experiences that the victims of the Shoa had gone through exceeds our all imagination. The incomprehensibility of the trauma is described in psychoanalytic-scientific general concepts like extreme traumatization (cf., e.g., Krystal, 1988) or sequential (Keilson, 1991) or cumulative traumatizations (Khan, 1964). The survivors of such extreme traumatizations illustrated that such traumatizations are not to be processed psychically but lead to lifelong disturbances such as nightmares, flashbacks, loneliness and depression, dissociation and derealization, disturbances in the sense of time, and a basic feeling of identity, diffused panic, fear and aggression attacks, and emotional encapsulations, breaking down a basic trust in a helping other and self-agency (see above) as well as basic meanings of life. Some of the psychosomatic symptoms include sleeping disturbances, bodily pain that is not easy to localize, etc. The suffering linked to these deep psychic wounds can be relieved in long psychotherapy, but the wounds can never really be (fully) "healed." Besides, the experienced trauma is often transmitted to the second and third generation.

For comprehensible reasons, it took nearly 60 years until psychoanalysts in Germany started to talk about the effects of severe traumatizations in the families of the persecutors and bystanders during the times of National Socialism. The concern about equating the horrifying singularity of the Shoah with the families who had been actively involved in the Nazi crimes is still justified. Regardless, German psychoanalysts tried to make sense of the unexpected results of the DPV Follow-Up study mentioned above: Around 62% of the 402 patients who had undergone psychoanalyses during the 1980ies had been traumatized former children of the war (see, e.g., Leuzinger-Bohleber et al., 2003a, b and in Radebold et al., 2006). Additionally, as already mentioned above, one unexpected finding of LAC depression study was that 84% of the chronically depressed patents had gone through severe childhood trauma (Negele et al., 2015). To make a long story short: Psychoanalysts in Germany (as well as in other European countries) are treating many traumatized patients due to the long (mainly unconscious) shadows of the extreme man-made disasters of the Second World War and the Nationalsozialismus onto the second and third generation. They are still living in traumatized societies!

Hence, many clinical and empirical studies show the short-term and long-term consequences of traumatizations due to the so-called man-made disasters . The traumatic experiences lead to a great vulnerability of the traumatized after the escape of the acute danger (cf. in addition among other things, Bohleber, 2010/2012, see, e.g., Laub, 2005; Bodenstab, 2015). This vulnerability makes them hypersensitive especially to human relationships, in general, and, of course, also to the therapeutic relationship. I have discussed some of the consequences of these findings for the treatment techniques of chronic depressed, early traumatized patients in some extended case studies (e.g., Leuzinger-Bohleber, 2015a).

Bohleber and Leuzinger-Bohleber (2016) discussed the following: In many cases, traumatic experiences can only be fragmentarily recollected, because they are dissociated entirely from current consciousness. In psychoanalyses or psychoanalytic therapy, they repeat themselves in enactments and other manifestations in the transference.

Generations of psychoanalysts since Freud have concerned themselves with the way in which repetition in transference can be rendered a healing process of remembering. This primarily involves symbolically represented and repressed memories or relationship patterns. However, theory and clinical psychoanalysis has focused for quite some time on psychic material present in the analytical relationship in other, *not yet symbolized,* "unrepresented" *ways*. Levine, Reed, and Scarfone entitled their anthology "Unrepresented States and the Construction of Meaning" (2013, in honor of André Green) and focus on the question of the search for meaning in the unrepresented from a contemporary perspective. With his broadly received concept of "dead mother," Green (2007) described the early identification with an absent mother leading to a withdrawal cathexis and thus to a disappearance of the inner representation which, in the transference relationship, can be perceived by the analyst as an empty, negative hallucination of the object, "a representation of the absence of representation" (Green, 1999, p. 196, quoted from Reed, 2013, p. 39). Reed (2013, p. 29 ff.) points out that this negative hallucination of the object leads to an emptiness rather than a representation of the lost object – an empty mirror, which with these patients is always there but which is frequently observed in the analysand's extreme reactions to separation from the analyst. Green is concerned with the process of de-objectification, namely, the obliteration of representation. Other psychoanalysts, by contrast, focused on the psychic material of patients, which had only insufficiently, if at all, gone through the processes of symbolization. Dominique Scarfone (2013) presented a conceptual integration of different forms of psychic representation and their various psychoanalytic conceptualizations. He compared Pierce's sign theory to Freud's conception of primary and secondary processes, Lacan's theory of the real, the imaginary and the symbolic, Wilfred Bion's beta and alpha elements, Jean Laplanche's infantile sexual theories and their decoding in analytic discourse, and Piera Aulagnier's concept of the primary, such as "primary violence," which entered the stage ("mise-en-scène") and that could ultimately open up the discourse on secondary processes: a brilliant example of contemporary concept research.

In many papers, Leuzinger-Bohleber and Pfeifer (e.g., 2002) pursued another path by drawing on several studies in the field of basic research, more specifically, embodied cognitive science and the cognitive neurosciences, so as to show that these disciplines offer first explanations for the clinically important phenomenon, such as the analyst's spontaneous inspiration, his associations to the "unrepresented" which can be an initial central step to understanding hitherto unrepresented psychic material and which is capable of making psychoanalytic processing accessible at all (see also Vivona, 2009). Hence, this should provide new perspectives on familiar concepts, such as "scenic understanding" (Argelander, Lorenzer), "hearing with the third ear" (Reik), "cracking up" (Bollas), or the "now moments" by the *Boston Change Process Study Group*. Furthermore, aspects of current discourse on intersubjective psychoanalysis and on enactment are touched on, as well as further understanding of countertransference around the bodily sensations of the analyst. Their considerations also can be related to works on musicality, dynamically emotional syntax, and performance of the analytic relationship (cf., among others, Gaensbauer, 2011; Knox, 2009; Marshall, 2009; Leuzinger-Bohleber, 2015).

Inspired by biology and the life sciences, embodied cognitive science currently understands memory not as a retrieval of stored knowledge in the brain but as a function of the entire organism, the product of complex, dynamic recategorization and interactive processes that are always embodied (cf. among others, Edelman, 1987, 1989; Lakoff & Johnson, 1999; Damasio, 1994; Pfeifer & Bongard, 2007; Leuzinger-Bohleber & Pfeifer, 2002, Leuzinger-Bohleber, 2015). The human organism – and the human psyche – is in an ongoing (embodied) state of transformation involved in constant dynamic processes of interaction with the environment in which a continuous process of recategorizing experiences occurs. Memories of earlier situations unconsciously determine present thought, feelings, and action, though not in the sense of stored knowledge in analogy to a computer or static memory traces. In contrast, memories are products of dynamic, complex constructions in the here and now. In the sense of embodiment, sensorimotor coordinations in the present always operate in an analogue manner as was the case in earlier situations. The similarities between a current and a past situation are not perceived cognitively, e.g., by cognitive pattern matching but by similar complex information gained by different senses (auditory, visual, olfactory, touch, smell, etc.) and actions of the body (characterized as sensorimotor coordination in embodied cognitive science). Through such sensorimotor coordination, memories, and categories are constructed automatically as self-regulating process of learning by doing (John Dewey), in other words, by means through coordinating information from sensory channels and connected (motor) actions of the body. Memories resulting from sensorimotor coordination thus provide orientation in a new situation.

A brief example may illustrate the processes of building categories involved in learning by doing. If you put a bar of chocolate in one hand of a one-year-old boy and a bar of colored wood in the other, the child will immediately put both bars in his mouth. Only a very few trials are required before he prefers the chocolate: Through sensorimotor coordination, he has developed the categories "chocolate"

and “wooden bar” without having the categories explained to him but solely by learning, by doing, and by sensorimotor coordination.

Another field of research is important for understanding social interaction, in general, and transference relationships, in particular. Recent studies have illustrated the decisive role of the so-called mirror neuron system, which enables human beings to identify immediately with the observed behavior and the mental state of others (see, for instance, 2009, 2013, Shapiro, 2009). In the psychoanalytic treatment, this means that during interaction with the analysand, analogue sensorimotor coordinations take place within the psychoanalyst as in the analysand implying that unconscious processes of immediate identifications are occurring. These processes bring forth categories of understanding – automatically, spontaneously, and unconsciously – which are connected with the analysand’s unconsciously occurring memory processes from earlier, important relationship experiences. In the case of traumatized patients, these are recurring memories of psychically and physiologically unbearable experiences of flooding stimuli, of extreme powerlessness, of desperation, of pain, of panic, and of fear of death. By identifying with the analysand’s ongoing sensorimotor coordination and the construction of memories of the traumatic experiences in his countertransference, the psychoanalyst immediately (unconsciously) understands the traumatic psychic reality of the patient. And yet, at the same time, the extreme quality of traumatic experiences mobilizes his own spontaneous defense, thereby hindering becoming conscious of what he unconsciously has perceived in the interaction with his analysand.

To summarize: Formerly, memories have been explained by way of a model of representation in which, due to excessive arousal, traumatic experiences are not psychically integrated but incompletely represented or not even registered. Contemporary interdisciplinary research results are now available following radical rethinking on the conception of memory and recollection, which are changing the understanding of memories and their relevance for transformation processes in psychoanalyses. This new interdisciplinary knowledge has consequences for the treatment technique of chronically depressed, early traumatized patients, which we have so frequently treated in the LAC study (see Bohleber & Leuzinger-Bohleber, 2016, Leuzinger-Bohleber, 2008, 2015).

5.3.2 Trauma, Depression, and Memory Consolidation

Lane et al. (2015), in his introduction to an important review of current memory research and its implications for various psychotherapies in the journal Brain and Behavioral Sciences, refer to the beginnings of psychoanalysis as a trauma theory. Freud and Breuer (see Freud, 1895) postulated in their first theory that the child's inability to express emotions during the trauma of sexual seduction is the cause of hysterical disease and must therefore be “dissipated” in catharsis. As we know, this thesis proved to be too simplified: the oedipal fantasies replaced the real, traumatic experience. The reexperience of early childhood conflicts and fantasies in the

transference and their elaboration in the analytical relationship took their place. As Bohleber (2010/2012) pointed out, the consequences of early childhood traumatizations in psychoanalysis then receded into the background and, especially in their implications for treatment techniques, were even neglected for a long time (see above).

According to Lane et al. (2015 p. 3 ff), a large number of neurobiological studies on trauma confirm the concept of the dynamic unconscious of psychoanalysis in a new way. Traumatizations are preserved in the unconscious because of their emotionally overwhelming quality, but, metaphorically speaking, they continue to have an effect and determine inadequate pathological thinking, feeling, and action in our patients. Another agreement of the authors with psychoanalytical approaches is that they postulate that the traumatic, emotionally unbearable experience in the therapeutic relationship must be revived – in all forms of psychotherapy – if these lead to real, lasting changes. The research group around Lane et al. (2015) justifies this thesis with the concept of memory consolidation.

In this paper, we propose that change occurs by activating old memories and their associated emotions, and introducing new emotional experiences in therapy enabling new emotional elements to be incorporated into that memory trace via reconsolidation. Moreover, change will be enduring to the extent that this reconsolidation process occurs in a wide variety of environmental settings and contents. This proposed mechanisms may be timely ... We propose an integrated memory model with three associative components – autobiographical (event) memories, semantic structures, and emotional responses – that are inextricably linked and that, combined, lead to maladaptive behaviors (p. 3).

Through the therapeutic activation of old memories and emotional reactions associated with them, new traces of memory are created that also modify the old, “pathological” ones. The corrective relationship experience takes place in a new context, the therapeutic setting itself (i.e., in the transference relationship), which is associated with the old memory, namely, through the process of reactivation, re-encoding, and reconsolidation (see Ryan et al., 2008). Through the "updating" of memories of earlier events through new experiences, the associated knowledge, rules, and schemata are also changed. Therefore, new semantic structures, rules, and schemes are developed that, through therapeutic processing, can lead to a more adequate way of interpreting events and linking them to more appropriate emotional responses. These changes are sustainable if they lead to reconsolidation processes in different contexts, leading to a generalization of the newly developed memory structures and their semantic contents to new situations and environments (see Lane et al., 2015, p. 3)

Lane summarizes two different theories of memory consolidation: The “standard model of memory consolidation” (Squire & Alvarez, 1995) emphasizes that the structures of the brain change from the medial temporal lobe (including the hippocampus) to neocortical structures including the prefrontal cortex. It is important that the content of the memories remains unchanged through this consolidation process. Nadel and Moscovitch (1997) developed an alternative theory of memory consolidation, the so-called multiple trace theory (MTT). Instead of focusing primarily on

the time course of memory consolidation, the theory deals with the question of how repeated memories of earlier events lead to a strengthening of the memory representation of the original event. Analogous to the "standard model of consolidation," the MTT postulates that the development of long-term memories requires a permanent interaction between the hippocampal region of the medial temporal lobe and the neocortical regions. But in contrast to standard theory, MTT postulates that the hippocampal region remains an integral part of memory traces and is therefore always involved when episodic memories are retrieved from long-term memory, no matter how old these memories may be. The evidence for this theory comes from fMRI studies. The classical theory assumes a phase of instability immediately after the event, which is successively replaced by a stabilization of memory in which the memories can no longer be changed. MTT, on the other hand, postulates a much more dynamic understanding of memory, which coincides with the psychoanalytical concept of "Nachträglichkeit."

According to MTT, the old memory contents and the emotions associated with them are therefore activated with each new memory, but they change each time anew – due to the current context of the processing – and thus acquire, as the concept of "Nachträglichkeit" (Freud) describes, a current, "new" meaning, which, as Freud explains in the case of "Emma," can ascribe a traumatic quality to earlier experiences, even through development-specific (adolescent) conflicts and fantasies.

Interestingly, the research group refers in its arguments to the "false memory debate" of the 1990s and the many empirical studies which show that memories are constantly rewritten and therefore never depict the "historical truth" in a "one-to-one" sense. They adapt in a flexible way to the narrative context in which they are told. It is precisely this phenomenon that Lane et al. use as an argument why the new, reliable, professional relationship experiences in psychotherapy hold the chance to change unbearable emotions that have not yet been psychologically integrated, which go hand in hand with the corresponding (implicit) memories and irrational convictions: Since memories are "adaptive," they can use the security of the new relationship experience to adapt inadequate emotions and convictions anew and more adequately to the here and now.

Lane et al. then investigate the different roles which implicit emotions play in different psychotherapies: in behavioral therapy, in cognitive-behavioral therapy, in emotion-focused therapy (EFT, a further development of Roger´s nondirective psychotherapy) and in psychoanalysis. Since emotional reactions, as well as episodic and semantic memory, do not function independently of each other, as was long assumed, but interact with each other in a more complex way, memory structures can use "different entrance gates" in the integrative memory model outlined by Lane (see Fig. 5.2).

The "classical behavioral therapy" (BT) which has proved successful in many studies, e.g., in the treatment of patients with post-traumatic stress disorder, tries, e.g., in exposure therapy, to make inadequate emotions, which are implicitly connected with traumatization, explicit in a safe therapeutic relationship and thus not to "extinguish" them but to change them or adapt them to the current environment (environmental contingencies). According to Lane et al., BT is therefore suitable for

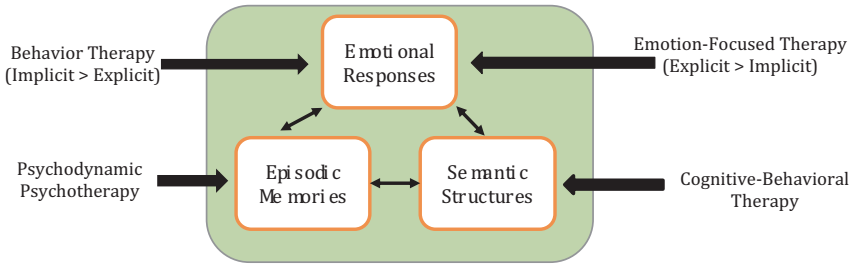

Fig. 5.2 Integrative memory model. (Authorized reproduction from Lane et al., 2015)

the treatment of patients with disorders in specific, identifiable situations with implicit, inadequate emotions, such as patients with phobias.

Cognitive-behavioral therapy (CBT) starts with pathological beliefs (irrational thoughts) (i.e., semantic memory structures) associated with traumatic emotions and attempts to correct them through psychoeducation, exercises, and homework, i.e., to change the semantic memory.

The emotion-focused therapy (EPF), as mentioned above, a further development of the Roger´s nondirective psychotherapy and Gestalt therapy, aims to change emotions through emotions. Analogous to a focused transfer concept (e.g., in psychoanalytic focal therapy or crisis interventions), EPF therapists try to activate the unbearable emotions associated with traumatic experiences directly in the therapeutic relationship and to associate them with alternative, corrective emotions. Explicit emotional reactions in therapy are associated with the implicit, the original traumatic experience. According to Lane, both CBT and EPF are suitable for treating patients with symptomatic syndromes, such as depression, who are not situation-specific but have temporary disorders in explicit emotional behavior.

In contrast, there is a differential indication for psychoanalytic psychotherapies in patients with character pathologies that are not situation-specific and temporary, in other words, patients with chronic diseases, because psychoanalytic treatments offer the advantage that they examine early, unconscious pathological object relation experiences, which have entered, e.g., into the procedural memory, directly in the transference relationship.

"Time and cost considerations aside, the technique of meeting three, four or five times per week for several years creates a special opportunity to activate old memories and observe their influence on present-day construal and emotional experiences with an emotional intensity and vividness that is difficult or impossible with other methods (Freud 1914/1958). As such, this approach has the potential to offer something not available with other modalities that can have pervasive effects on a person's functioning in a wide variety of social, occupational, and avocational settings. New learning can involve improvement in function above and beyond symptom reduction, such as better self-esteem, greater ability to tolerate and manage stress, improved flexibility in social relations, a greater capacity for intimacy and the

construction of a coherent life narrative that exceed what would be expected based on symptomatic improvement alone (Shedler, 2010).” (Lane et al., 2015, p. 16)

In the MODE study mentioned above, we take up this hypothesis of Lane et al. and test it empirically (see Peterson et al., 2019).

5.4 Concluding Remarks

This paper sketches a psychoanalytical understanding of depression unconsciously determined by the individual life and trauma histories of the patients and by specific social and cultural factors. Due to the specific history of psychoanalysis as a science of the unconscious, a differentiated knowledge has been collected in over 100 years. The examination of other psychotherapeutic methods and interdisciplinary knowledge has always influenced psychoanalysis in its concepts and treatment techniques. However, despite of all the similarities and the “common factors in healing” (Peterson, 2019), a plea for a differential indication was formulated in this chapter. Like many clinical experiences but also the results of large psychotherapy outcome studies (e.g., the LAC study) show, today’s patients are not looking for a “unified psychotherapy” prescribed for all individuals of a certain diagnostic group but want to be able to choose between different offers, since they probably have an intuitive feeling for which psychotherapeutic interventions are most likely to enable them to deal productively with their psychological suffering. In this respect, patients do not follow a “uniformity myth.” Instead, they want, e.g., to choose between behavioral therapy methods that are primarily aimed at reducing psychopathological symptoms as quickly and efficiently as possible (cf. Habermas, 1971), while psychodynamically oriented methods focus to varying degrees on understanding unconscious fantasies and conflicts that underlie the symptoms as a result of life-history experiences and trauma. In addition to the reduction of symptoms, their goals include sustaining structural changes, i.e., transformations of the inner world of objects and associated longings and conflicts, which have a lasting effect on the ability “to work, to love and to enjoy life” (Freud).

Not only in terms of research and treatment for the mentally ill but also in terms of the training of psychotherapists and medical doctors in psychotherapies, the demand for “standardized,” exclusively evidence-based therapies for certain patient groups based on “uniform science” means a loss of professional competence in my opinion (see, e.g., epistemological papers in Leuzinger Bohleber et al., 2003b; Leuzinger-Bohleber, 2015). For example, in more than 100 years of clinical and empirical research in psychoanalysis, a broad knowledge of the unconscious determinants of mental suffering and its treatment has been gathered, among other things, through the use of transference and countertransference in the therapeutic relationship, which has led to the fact that we have far more differentiated treatment techniques and a diversiveness of psychoanalytically based offers for patients than at Freud’s time. The spectrum ranges from crisis interventions and different forms of

short-term therapies to different forms of long-term therapy in different settings (for individual patients, groups, families, etc.).

The same applies to behavioral therapy with its theoretical justifications and its scientific research paradigm. Therefore, it means a loss of professionalism if a so-called unified psychotherapy is demanded prematurely – due to a shortened and often idealizing reception of RCT studies – which seemingly integrates the results of different school traditions but in reality levels out the specific practical and research experiences of the different therapeutic approaches and their epistemological, methodological, and historical backgrounds in a problematic way. In this respect, in my opinion, evidence-based modules for the treatment of specific disorders, which are independent of procedures and generally binding, risk a loss of psychotherapeutic professionalism, because they deny the importance of the interventions as a scientific frame of reference for psychotherapists in determining the clinical procedure appropriate for the respective patient.

The next generation of psychotherapists will face an even more differentiated, complex world, with patients with new, complex disorders that cannot be understood "schematically" but require an innovative, creative, scientifically based and professional approach. As the sociologists of science around the group of Peter Weingart (Bielefeld) generally postulate, the time of the "universal researcher" (Leonardo da Vinci) is long gone: We live in a globalized, pluralistic knowledge society characterized by media and economic constraints, characterized by highly specialized expert knowledge in various scientific disciplines (Weingart et al., 2007). This also applies to the field of psychotherapy! Therefore, future psychotherapists deserve to be prepared as well as possible for this complex professional situation in their university education, which gives them their approbation, by necessarily receiving a well-founded historical, sociological, and scientific-theoretical orientation in the field of psychotherapy. This includes, for example, imparting knowledge about the history of the various psychotherapy methods, their epistemological and methodological preferences, and objectives (specific tasks, as described in the "Manual" of the MODE study (see Peterson et al., 2019), and the broad spectrum of related research that goes far beyond the field of RCT studies (cf., e.g., Open-Door Review, Leuzinger-Bohleber et al., 2015/2019).

Such attitudes and educational aims increase the professionalism of coping with diversities in our globalized, multicultural world instead of a reductionistic homogenization in the sense of a "myth of uniformity." Societal tendencies in the direction of homogenization lead to the fear of losing a fruitful culture of conflict between different therapy schools, which – according to the ancient historian Christian Meier and many others – guarantees innovative developments.

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Chapter 6
Theory and Interventions in Cognitive Behavioral Therapy for Depression

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6.1 Introduction

Depressive disorders are those that present greater prevalence and considerably harmful effects in the life of persons, as well as implying high treatment costs (American Psychological Association, 2019). Depression is currently one of the mental disorders with the highest world incidence; its prevalence is calculated as more than 300 million globally; in the extreme case, it can even lead to the suicide of affected persons (World Health Organization, 2018a). Based on the results obtained in the most recent study of the Global Illness Load in 2017, the index of years lost through disability indicated that it was the third most frequent cause of disability in the world (James et al., 2018). This study also showed that during the last three decades, depression has progressively increased its index of years of life adjusted for disability (number of years lost to illness, incapacity, or premature death); for men, this index has risen from the 30th to the 23rd place, while for women it went from 17th to 11th in the list of most frequent noncommunicative diseases (Kyu et al., 2018).

The effects also include a wide diversity of aspects, such as the decrease in or loss of work productivity, increase in mortality rate (due to the increase in risk of suicide), and decrease in functional behavior and interpersonal functioning (American Psychological Association, 2019). Given its high prevalence, comorbidity with other disorders, and its adverse effects on functionality and quality of life of affected persons, depression is one of the disorders that have received most attention by the "mental health" disciplines; its causes and the models of intervention

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_6

suggested by these efforts have been widely addressed both theoretically and by scientific research (Hollon & Beck, 2013).

The literature in the area indicates the vulnerability and diathesis that include biological, psychological, and learning factors that interact to produce the development of emotional disorders, such as depression and anxiety (Shadrina et al., 2018; Dunn et al., 2015; Bruijniks et al., 2019; Hong & Cheung, 2014). In spite of years of research and reports on this topic, it is not known how these factors are related and what their effects are on the development, maintenance, and treatment of these disorders (Payne et al., 2014; Barlow et al., 2017). The landscape is more promising in the clinical area, where the cognitive behavior therapy (CBT) has been described as a psychotherapy based on well-established evidence that currently has the greatest growth (Prochaska & Norcross, 2018), with proven efficiency and lasting effects (American Psychological Association, 2019; Cuijpers et al., 2019a; Hollon & Beck, 2013; Tolin, 2010). There are still unsolved questions about the mechanisms that explain the change in CBT (Kazdin, 2014; Cuijpers et al., 2017), which is a crucial process, especially for intervention in depression, given the heterogeneous conditions, frequent chronicity, and moderate indexes of response to treatment (David et al., 2018a).

This chapter will review a general description of depression and its diagnostic characterization and analyze the etiopathogenesis of this disorder, from experimental models to clinical cognitive-behavior theories which give rise to the interventions that currently have wide empirical support. Finally, we will discuss the empirical status of CBT and review new developments in the study of the mechanisms and moderators of change.

6.2 Depression: A pleomorphic and Complex Diagnosis

The different forms of depression are all characterized by a persistent decrease in mood, with various signs and symptoms, such as sensation of emptiness and/or irritability, somatic changes, alteration of vital rhythms, and cognitive changes, which affect significantly the functional capacity of the persons who have it (American Psychological Association, 2019). From the categorical perspective of the fifth edition of the *Diagnostic and statistical manual of mental disorders* (American Psychiatric Association, 2013), different forms of manifestation are described within the framework of the mood disorders, which are differentiated by their duration, moment of presentation, and etiology. They include the following: major depressive disorder, persistent depressive disorder (i.e., dysthymia), premenstrual dysphoric disorder, disruptive mood dysregulation disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder (when the symptoms don't agree completely with any of the other categories), and unspecified depressive disorder. On the other hand, from a dimensional view, there are some common characteristics in the diversity of depressive disorders, including the following: decline in mood,

tiredness and decrease in the energy and activity of the individual, anhedonia, trouble concentrating, decrease in self-confidence, and perturbation of sleep and appetite (World Health Organization, 2018b).

Additional characteristics typical of depression include self-centered attention, perceived uncontrollability and unpredictability, worry and rumination, behavior inhibition and experiential avoidance, intolerance to negative emotions, negative cognitive content, and maladaptive coping strategies (Payne et al., 2014). It has been observed that depressive patients also present a number of cognitive biases with respect to emotionally salient elements (e.g., vital stressing events), persistent attention focus on perceived threats, feelings of deficiency or uselessness, as well as deficits in cognitive flexibility, such as problem solving, motivation, and responses to feedback in their performance (Lapiz-Bluhm et al., 2008). These are related to the cognitive explanations of the etiology of depression, which are based on the hypothesis that depression is maintained by means of negative biases in information processing and dysfunctional beliefs, affecting the behavior and functioning of the person (David, Cristea, & Beck, 2018a). In contrast to the cognitive hypothesis of depression, other proposals from basic research on cognition suggest that depressive individuals may have more precise and realistic inferences, while non-depressive individuals may exhibit biases for positively valued stimuli (i.e., depressive realism; Moore et al., 2016). However, research on this hypothesis using clinically depressed samples has shown contradictory results (Venkatesh et al., 2018).

The so-called complexity factors have been established, which associate depression with biological (e.g., acute illness, sleep disorders, somatization), psychological (e.g., anxiety disorders, traumas, post-traumatic stress disorders), and social (e.g., interpersonal, family or social problems) factors, which, although they do not form part of the depressive condition as such, may concur and interact with depression, complicating its effects (Barton et al., 2017). There are attempts to identify those common cognitive and behavioral processes in the range of depressive conditions, in order to understand their development and maintenance and finally develop treatments which can be applied effectively and efficiently (Andersen et al., 2016).

6.3 Etiopathogenesis of Depression

The variety of depressive conditions that have been described have been widely studied in the search for explanations that allow better understanding of the diverse components and their interactions at the base of these conditions. Experimental behavior analysis has made an important contribution using basic research on animal and human models (e.g., learned helplessness; Overmier & Seligman, 1967; Seligman, 1975; Seligman & Maier, 1967) and the cognitive sciences (e.g., cognitive vulnerability; Beck, 1967; Beck, 2008; Beck et al., 1963; Clak & Beck, 1999) on the conceptualization of the depressive experience and the characterization of cognitive and behavioral deficits which are presented. Important among the deficits present in patients diagnosed with depression compared to healthy patients are a

deficit in executive functioning (Beevers, 2005; Snyder, 2013), overgeneral autobiographical memory (Köhler et al., 2015; Sumner et al., 2010), greater frequency of negative ruminant thoughts (Nolen-Hoeksema, 2000), showing memory biases toward negative information (Elliott et al., 2011; Ellis, 1992), and deficit in processing rewards (Whitton et al., 2015; Vrieze et al., 2013). These characteristics were reviewed exhaustively by Bruijniks et al. (2019). Next, we will review the main contributions of both the experimental models and the theoretical-clinical models to account for the development and maintenance of depression.

6.3.1 Experimental Models

Experimental studies provide an important comprehensive framework for many psychological phenomena; using controlled conditions, they allow us to make causal inferences about behavior. Animal models are an effective tool for understanding normal and abnormal human behavior, offering practical advantages such as control of the genetic history and the environment. The similarity of some processes in humans and other animals allows useful analogies to achieve better understanding of the etiology, treatment, and relapses in a wide range of psychopathologies. Laborda et al. (2012) suggest that the most important motive for using nonhuman models in the study of human psychopathology is the fact that the most effective psychotherapeutic treatments currently available are derived from basic principles discovered in animal laboratories, which supports the relevance of translating laboratory research findings to clinical settings.

Studies with animal models have allowed a significant advance in the development of better antidepressant drugs, especially in terms of secondary effects and security. Given that depression is a highly heterogeneous disorder and usually presents comorbidity, it is complex to make analogies from basic research in trials that evaluate a specific characteristic of animal behavior and the behavior of a depressed individual, who is usually evaluated by self-reporting measures (Dzirasa & Covington III, 2012; Robinson, 2018). However, it is important to consider that the scientific study of a phenomenon often requires decomposing it and then integrating the findings in a coherent model that will be submitted to empirical contrasting. The aim of experimental models of illness is precisely to be able to condense the most outstanding aspects of a disorder in a way that allows testing a hypothesis (Nestler & Hyman, 2010).

These models may be evaluated based on four main criteria (Boddez et al., 2013): (1) the similarity in symptomatology between the laboratory model and the condition which is modeled (face validity), (2) the potential of the laboratory test for clinically effective treatments for the condition being modeled (diagnostic validity), (3) the sensitivity of the laboratory test to clinically effective treatments for the condition being modeled (predictive validity), and (4) the dependence of the underlying process to the laboratory test and the condition being modeled (construct validity).

One of the animal models most studied and validated is that of learned helplessness (LH: Overmier & Seligman, 1967; Seligman, 1975; Seligman & Maier, 1967), which introduced the concepts of unpredictability as probable causes of anguish and psychopathology, improving our understanding of many disorders (Mineka & Kihlstrom, 1978, cited in Laborda et al., 2012). This model has been confirmed in a large number of species, including rodents, carnivores, primates, and humans; it has shown notable parallels with depression related to its causes, symptoms, prevention, and treatment (Overmier, 1986).

In the first experiments, a group of dogs submitted to uncontrollable electric discharges had difficulties in learning an escape-avoidance task in a later phase, compared to the subjects of the control group who were exposed to the same amount and intensity of discharges, but controllable, that is, they could escape (Overmier & Seligman, 1967; Seligman & Maier, 1967). This interference of the uncontrollability of learning persists for at least a week (Seligman & Groves, 1970). A number of later studies led to suggesting the hypothesis that repeated experience with adverse situations perceived as unpredictable and uncontrollable leads to a sensation of uncontrollability of the results, anxiety, and hopelessness (Wang et al., 2017). Faced with this, organisms learn that there is no relation between their behavior and the consequences, and thus it is useless to act or try to change the circumstances, even in new situations in which this behavior might have positive consequences (for reviews, see Seligman, 1975; Maier & Watkins, 2005). The learned helplessness hypothesis suggests that the experience with uncontrollability leads to three main deficits: (1) motivational deficit, reduction of motivation; (2) learning deficit, difficulty in identifying the association between actions and results; and (3) emotional deficit, depression and apathy (Abramson et al., 1978; Maier, 1984). Some experiments show that avoidance training is prejudiced, even when the uncontrollable condition involves an appetitive stimulus (Goodkin, 1976; Wight & Katzev, 1977). Learned helplessness in humans leads to attributing negative events to internal, permanent, and global causes, that is, to a pessimist attribution style; as a consequence, persons avoid participating in activities that activate this attribution style, which generally leads to a separation of significant activities, increasing the probability of producing depression (Abramson et al., 1978; Seligman, 1972). In one human study, the participants had to estimate their possibility of success in a fortuitous ability or task; depressed subjects distorted the results perceptively, classifying them as independent of the response, from which it is deduced that under certain conditions they could show deficits in learning the consequences of the responses. These deficits may reflect learned helplessness and are specific to depression (Miller et al., 1975). Klein et al. (1976) gave depressed university students solvable, unsolvable, and no discrimination problems. Then they were evaluated with a series of anagram drawings. The depressed groups obtained worse results than the nondepressed groups, and the unsolvable groups had worse results than the solution and control groups. When the depressed subjects attributed their failure more to the difficulty of the problems than to their own incompetence, their results improved notably. In a first attempt to approach these deficits, a study of 84 persons found that psychological flexibility moderated the relation between learned helplessness and the deficits in

depression. Greater psychological flexibility appears to protect against the symptomatology of depression (Trindade et al., 2020).

Other animal models of depression have been useful to test and predict the efficacy of antidepressant drugs (Porsolt et al., 1977b), since they simulate depressive behavior in humans (Robinson, 2018). The forced swim test (FST; rat) and tail suppression test (TST; mice) are among the most used. Typically, in FST (Porsolt et al., 1977a), a rat placed in water tries to escape. If it has developed more depressive behavior than a control rat, it is expected that the rat will make fewer attempts to escape and will float until it is rescued. The TST (Steru et al., 1985), as in the forced swim test, is designed to measure the response of the animal to stress, trying to emulate learned helplessness. In this test, a mouse is hung from a bar for 6 min. During this period, the immobile time is measured, which is usually greater in depressive rodents. According to Robinson (2018), FST and TST have some apparent validity, given that the animals exhibit behavioral despair in response to an unavoidable stressor; however, it is not clear how this emulates a specific characteristic of depression. Apparently, these are more measures of stress confronting (Commons et al., 2017).

Among other tests of the effect of antidepressant drugs, we find the following: the open field test (Denenberg, 1969), used to measure anxiety and locomotor activity that may be affected by depression; the anhedonia test (Klein, 1974), which is evaluated by saccharose preference (organisms in a depressed state drink less saccharose dissolved in water than nondepressed counterparts); the elevated plus maze test (Pellow et al., 1985), which evaluates anxiety (non-anxious rodents have a greater number of entrances and spend less time in the open arms, while anxious rodents spend more time in the closed arms; and the chronic intermittent stress test (Katz et al., 1981; Willner, 1991), which is utilized to observe in a natural environment, like the open field test, the process of induction, and gradual development of the depressive state in response to fear. The organisms are exposed unpredictably to several stressors, such as nocturnal illumination, periods of water or food deprivation, inclination of the box and isolation (Duman, 2010), and observing a decrease in the sensitivity to the reward (e.g., decrease of the preference for sweet tastes); however, there is also a decrease in grooming behavior (Taksande et al., 2013), altered sleep patterns (Grønli et al., 2004), and sexual and aggressive behavior of males (Willner, 2005).

Together with the evidence reported by the studies of basic research in animals, clinical evidence has also shown to be useful in illuminating the etiopathogenesis of depressive behavior.

6.3.2 Clinical Models

As mentioned above, the efficacy of CBT has great empirical support (Butler et al., 2006); some theories are strongly sustained by the results of basic research, while others are based on rigorous and systematic clinical observation. Each of these

theories has a particular emphasis – behavioral (Ferster, 1965, 1973; Lazarus, 1968, 1972; Lejuez et al., 2001a; Lejuez et al., 2001b; Jacobson et al., 2001; Martell et al., 2001) or cognitive (Beck, 1967; Beck & Haigh, 2014; Ellis, 1974, 1987); in recent decades, these have been enriched by the inclusion of the emotional, contextual, and/or relational dimensions (Zettle, 2005; Hayes, 2004; Hayes et al., 2004), finally to account for the complexity of the phenomenon of depression. An integral vision of the interaction among components would allow providing the best treatment for each patient (Tolin, 2010).

We can identify three periods in the development of the explanatory theories of depression (Hayes, 2004): behavioral conceptualization until the beginning of the 1970s (first generation), the cognitive break from the end of the 1960s to the present (second generation), and the behavioral reformulation from the beginning of the 1990s to the present (third generation). We will now describe the nuclear characteristics of each of these periods.

6.3.2.1 Behavioral Conceptualizations

*Reinforcement deficit (*Ferster*,* 1965*,* 1973*)*: persons usually learn naturally the consequences of their behavior. We call the desirable consequences reinforcers; they have the function of increasing the probability of the behavior (Skinner, 1938). The first development of a theory of depression, based on the principles of operational conditioning, was developed by Ferster (1965, 1973), who proposed that depression is a behavioral deficit provoked by a decrease or absence of reinforcers or discriminative stimuli (e.g., loss of a loved one), which may potentially have reinforced non-depressive behavior (Ferster, 1973, 1974). A wider vision of this theory suggests that depressive persons are only in a depressive context if they lack a sufficient behavioral repertoire to adapt to the new circumstances, impeding obtaining new sources of reinforcement and extinguishing already known behavior; presenting a low mood, anhedonia, and social isolation and decreasing the activities previously developed; and simultaneously presenting an increase in avoidance behavior (Lazarus, 1968, 1972). Another relevant aspect that would contribute to the establishment and/or maintenance of depression is social abilities, which are understood as behaviors that are positively reinforced by others, which allow access to new sources of reinforcement; thus, depression would depend both on the potential reinforcers (determined by the biological constitution of the organism), the history of reinforcement (number of potentially reinforcing events available), and the ability of the person to obtain and/or provoke reinforcing events (Lewinsohn, 1974). Based on these proposals, in the 1970s Lewinson and colleagues consolidated a number of previous studies sustained by the theories described above in a comprehensive treatment manual (Lewinsohn et al., 1976). This intervention is focused on the patient learning to monitor both daily activities and mood, in order to learn to develop and implement a plan that allows increasing the number of pleasurable activities and incrementing the number of positive interactions with their environment (Kanter et al., 2010).

Self-regulation (Kanfer, 1970, 1971): According to this model, self-regulation is the process by which the individual alters the possibility of a response in the absence of external stimuli that support it. This process consists of three stages; self-monitoring, observation of one's own behavior, its background, and consequences; self-evaluation, comparing the estimated performance (derived from self-monitoring) to a subjective internal standard that judges if the criterion is or is not realizable with this performance; and self-reinforcement, the function of self-administrating rewards or punishments, which serves to maintain consistency when an external reinforce is delayed (Kanfer, 1970, 1971). Rehm (1977) adapted this model and developed a model of self-control for depression, which proposes that depressive symptoms are the consequence of one or more deficits in self-control behavior and in which the depressive episode corresponds to the combined function of the degree of stress felt and the self-control abilities available to confront this stress (Rehm, 1981). Thus, the treatment package for depression consists of the sequential application of the self-regulation processes, intervening in the deficits that occur in each phase, which include the following: selective monitoring of negative events and the consequences of behavior, both immediate and delayed; inflexible criteria and imprecise attributions of responsibility; and insufficient self-rewards or excessive self-punishment (Fuchs & Rehm, 1977). This model includes a number of specific interventions, including group discussions, reinforcement, behavioral tasks, modeling, and self-monitoring (Dobson & Dozois, 2010).

6.3.2.2 Cognitive Conceptualizations

The *cognitive theory of depression* of Aaron Beck (1967, 1969) is based on the concept that depression is sustained by distorted processing of information and dysfunctional beliefs (Beck, 2002). It has been a long time since the first formulations of the model; currently, Beck's theory is called the Generic Cognitive Model and has incorporated advances in cognitive neuroscience and genetics. This model suggests that early exposure to adverse experiences generates a cognitive predisposition in subjects, with dysfunctional schemes of information processing (Beck & Haigh, 2014). It proposes that individuals have various cognitive schemes that guide our attention, perception, and interpretation of events in the environment toward the information that is inherent in our schemes. These schemes are latent and remain inactive until particular stress systems activate them, resulting in a continuous negative interpretation of one's self, the world, and the future (Beck, 2002). Thus, the risk that individuals will develop depression depends if they have negative schemes about themselves, the world, and the future. These thought processes frequently include cognitive distortions that are failures in information processing (e.g., arbitrary conclusions, selective abstraction, overgeneralizing, etc.; Beck, 2008; DeRubeis et al., 2010). Based on the above, in the psychotherapeutic context, cognitive therapy (CT) seeks to teach patients to perform systematic processes of evaluation of their beliefs as well as to become aware of the predisposition for determined forms of information processing (Beck, 1979). This process is implemented through

processes of empirical distrust, in which the patients must treat their beliefs as hypotheses, thus needing to accumulate additional information and perform behavioral experiments to test the precision of their beliefs and interpretations (Hollon & Beck, 2013). Common interventions of CT include daily records of dysfunctional thoughts, Socratic questioning, guided discovery, scheduling activities, etc. (DeRubeis et al., 2010).

Relational emotive theory of Albert Ellis (Ellis, 1974): according to this theoretical model, the essence of human emotional perturbation arises from absolutist dogmatic "musts'" and "must nots" that people think about their failures, rejections, how they are treated by others, and about their frustrations and losses (Ellis, 1991). Thus, psychological problems such as depression are due to a series of illogical thoughts called irrational beliefs, which lead to a tendency to perform devout and absolutist evaluations of the perceived events in their life, and are considered irrational because they usually impede and obstruct persons in their attempts to achieve their objectives and purposes (Ellis & Dryden, 2007). The rational emotive theory proposes that this tendency to irrational thinking has a biological basis, although it also recognizes that environmental variables contribute to the psychological perturbation, fomenting this tendency (i.e., biological demand) toward irrational ways of thinking (Ellis, 1976, 1994). Translating this theory into a therapeutic model, Ellis (1962, 1985) proposed the ABC model, which is a framework of evaluation to conceptualize the problems of clients; it includes the following elements or dimensions: (A) activating event, (B) person's beliefs about that event, and (C) emotional and behavioral responses (i.e., consequences) to holding that particular belief. With this global reference frame, the objectives of relational emotive behavior therapy (REBT) are to aid the client to depose the central irrational beliefs, since otherwise it is probable that these will be maintained and expressed in new ways, as well as encouraging the client to have strong and persistent desires and preferences and to avoid feelings of disinterest, retreat, or lack of involvement (Ellis, 1996). In synthesis, the main goal is to help clients to follow their goals and purposes by accepting themselves completely and tolerating uncomfortable and inalterable life conditions (Ellis & Dryden, 2007). To achieve this objective, therapists implement cognitive (e.g., detection, debate, discrimination), behavioral (e.g., homework, exposition, skill training), and emotional (e.g., humor, unconditional acceptance, self-disclosure, shame-attacking) strategies, all utilized pragmatically to help clients achieve their objectives (Ellis, 1996).

6.3.2.3 Contextual Conceptualizations

The so-called contextual or third-generation therapies (mainly the acceptance and commitment therapy (ACT) and functional analytic psychotherapy FAP; Hayes et al., 2012b; Kohlenberg & Tsai, 1991; Pérez, 2006) have generated new interest in the basic psychological processes and the role of language and cognition in behavioral therapy. These have a common philosophical framework (Radical Behaviorism). Skinner (1966, 1984) differentiated between contingency-shaped behavior and

rule-governed behavior or instructional control. The former is mediated by direct contact with the world, which means that we modify or maintain our behavior due to direct contact with environmental contingencies. In the latter case, behavior is learned or altered by the verbal descriptions of the contingencies of the world (Place, 1988; Skinner, 1966). This allows people to guide their behavior not only by the consequences felt directly (the experience lived) but also by the verbal consequences constructed that may alter the reinforcing or aversive functions of other stimuli (Barnes-Holmes et al., 2004; Hayes et al., 2001; Páez et al., 2006; Whelan & Barnes-Holmes, 2004; Schlinger, 1993). We generate verbal rules that guide our behavior and often make us insensitive to the things that happen in the world. We also learn relations among events arbitrarily and indirectly (Hayes et al., 2001).

Clinically, a patient may have a verbal rule such as "To get out of bed I have to feel good"; in this case, the verbal rule will have direct effects on the behavior of staying in bed, and it is probable that the patient will ignore the possibility that *I can get up if I feel bad*. ACT maintains that the fundamental problem of depression is *experiential avoidance*, avoidance behavior whose objective is to stay away from private experiences, such as images, feelings, thoughts, etc., that cause unhappiness (Kanter et al., 2006). Here, the problem is not the presence of adverse private events, such as the memory of a loved one who is no longer here, images of important events that will not be repeated, etc., but rather the inflexibility with which the subjects cannot experience those events and tend to avoid them to feel better momentarily (Kanter et al., 2006). This pattern of avoidance may be governed by inflexible verbal rules such as "I can't feel bad, I have to forget the painful things" or "It is better not to think about the past." This avoidance process is reinforced negatively in the short term (not thinking about something painful allows momentary relief) but may generate long-term problems, since inflexible avoidance patterns will exclude subjects from various situations in their lives (Hayes et al., 1996). The goals of the therapeutic model may be summarized using its acronym, accept, choose, and take action, in which therapists try to help their clients to accept their difficulties and problems and move in the direction of their values (which is impeded by experiential avoidance and cognitive fusion) by means of several interventions, such as the use of therapeutic metaphors and paradoxes, experiential exercises, and assigning tasks (Hayes, Strosahl, & Wilson, 2012b).

Behavioral activation (BA, Jacobson et al., 2001), in contrast to cognitive interventions, considers that the way persons feel changes when they change the things they do, an idea that boosted the development of a behavioral therapy defined in its own right and not just as a component of cognitive interventions (Martell et al., 2010). From these, two proposals arose in parallel, behavioral activation (Jacobson et al., 2001; Martell et al., 2001) and brief behavioral activation treatment for depression (BATD, Lejuez, Hopko, & Hopko, 2001a; Lejuez, Hopko, LePage, et al., 2001b). The historical basis of both proposals was the hypotheses of Ferster (1965, 1973), Lewinsohn (1974) and Rehm (1977). BA seeks to encourage activity programming to identify environmental deficits in positive reinforcement, and promote the development of social abilities to obtain and maintain the reinforcement (Martell et al., 2010), in an analytical model that allows understanding of the behavior itself

(Haynes & O'Brien, 1990; Kaholokula et al., 2013), in order to involve it in activities that offer better sources of reinforcement. As well as programming activities, the therapeutic context of BA includes behavioral techniques of intervention to maximize the attendance at sessions and procedures focused on covert verbal behavior (e.g., assessment of goals and values, procedures targeting avoidance, procedures targeting verbal behavior, relaxation training, contingency management; Kanter et al., 2010). The objective of BATD is to increase "non-depressive" behavior, based on the principles of the matching law (Herrnstein, 1961), according to which depressive behavior should decrease when it loses the reinforcers that maintain it or when an alternative behavior is reinforced with greater frequency and quality. With this basis, the therapeutic model of 10 BATD sessions includes interventions designed to monitor daily activities, identify values, making a hierarchy of activities according to their difficulty, planning and execution of activities, and increasing access to social support (Maero et al., 2016).

6.4 Cognitive Behavioral Therapy and Depression

One of the distinctive aspects of cognitive behavior therapy (CBT) is the use of scientific evidence as a guide for the development of effective interventions (Nezu et al., 2013). This is particularly relevant given the current context of psychotherapy, where the treatment of a given condition can choose from a wide variety of interventions, some of which have proven to be successful, while others have not passed through the scrutiny of rigorous investigation (David et al., 2018c). From the perspective of the scientific community and evidence-based psychotherapeutic practice, intervention techniques should not be assumed to be effective just because they are derived from a particular theory (Prochaska & Norcross, 2018). On the contrary, interventions based on evidence should demonstrate effectiveness in the reduction of the symptoms for which the treatments were designed, show long-lasting and/or generalized effects in diverse situations, and reduce the probability of relapse (Nezu et al., 2013).

Based on the above, CBT is considered to be an evidence-based therapy, given the empirical effort by which the interventions are tested and validated with the same rigor as the experiments used to investigate any scientific question (Prochaska & Norcross, 2018). CBT has its theoretical roots in the principles of learning (Nezu et al., 2015), which have evolved to include emerging scientific knowledge (derived from research and clinical practice) based on contemporary learning theory, experimental analysis of behavior, neurocognitive and psychophysiological research, and theoretical models of emotion and information processing (Nezu et al., 2013).

Thus, in general terms, CBT refers to a family of interventions with empirical support that incorporate both cognitive and behavioral strategies (Feldman, 2007); in other words, CBT is used as a reference for a large number of interventions, techniques, and clinical styles, which share the use of scientific research methods and the theoretical roots from which they derive (Nezu et al., 2015). Both behavioral and

cognitive interventions are based on the supposition that previous learning is currently involving undesirable consequences for the patient or for others; they try to modify it using therapy with interventions that reduce stress or undesirable behavior or by means of promoting new learning experiences which are more desirable (Brewin, 1996). Thus, the different models and types of intervention grouped under the CBT may be distinguished by the roles that they confer to cognitive change in the explanatory models of different disorders and thus the use and application of cognitive and behavioral strategies in accordance with these models (Hollon & Beck, 2013).

Beyond their differences, the models understand psychological problems based on learning mechanisms, where behaviors are a function of the environmental and internal conditions, and change is produced by learning new experiences and their generalization to different situations (Hazlett-Stevens & Craske, 2008). CBT also has an idiographic approach, in which the therapist should consider the singular factors that sustain the problem (i.e., dysfunctional system), generating a hypothesis with respect to the way these factors interact (i.e., functional analysis; Nezu et al., 2004; Nezu et al., 2013; Nezu et al., 2015; Beck, 1970). Other characteristic aspects of the CBT include the following: interventions designed both to take advantage of the abilities, capabilities, and daily context of the patient (Prochaska & Norcross, 2018) and to develop new abilities; an active and collaborative therapeutic alliance with goals established together by the therapist and patient at the beginning of the treatment that form the focus of the treatment (Sudak, 2012).

In synthesis, cognitive behavioral therapists do not limit themselves simply to applying a set of tools; they guide their clinical practice based on the specific conditions of each patient grounded on a philosophical position consistent with a scientific attitude (Hazlett-Stevens & Craske, 2008).

6.4.1 Empirical Status of CBT

CBT has been established as the gold standard for the field of psychotherapy (David et al., 2018b; Cuijpers et al., 2019a, b) and, in particular, for depression (Cuijpers, 2017; Cuijpers, Karyotaki, et al., 2019b). David, Lynn and Montgomery (2018c) classified the psychotherapies with empirical support. Two main criteria were used by the authors: evidence of the effectiveness/efficiency of the therapeutic package and empirical support for the theory underlying the package. CBT had the highest level of empirical support, with strong evidence of its effectiveness and a well-studied theoretical base. Division 12 of the American Psychology Association (APA), dedicated to investigating treatments with empirical support (APA, 2006), judged both behavioral activation and cognitive therapy in the highest level of evidence. CBT is also the most-researched psychotherapy for depression (Cuijpers et al., 2013). The effects of CBT for depression in adults have compared to control groups, placebos, waiting lists, pharmacotherapy, and other psychological therapies (Cuijpers, 2017). A meta-analysis of 115 randomized controlled trials reported the

mean effect size (ES) of CBT compared to the control group was Hedges $g = 0.71$ (Cuijpers et al., 2013), which indicates that those patients intervened with the respective treatments improved 0.71 standard deviations with respect to the control group. Cuijpers et al. (2013) concluded that the combination of CBT and pharmacotherapy was superior to the latter alone for the treatment of depression and that CBT is generally effective at decreasing symptoms of depression in adults. These results indicate that CBT is effective to treat depressive symptoms.

And for individual administration, CBT has other modalities such as group application, which is an effective and economic way to administer the therapy (Whitfield, 2010). This form of application has several advantages, such as the use of the group space to generate behavioral experiments, sharing experiences with a common base, learning from others, and functioning as co-therapists (Whitfield, 2010). There is literature that considers group CBT as effective in decreasing depressive symptomatology (McDermut et al., 2006); however, it is still necessary to answer essential questions, such as the advantages and disadvantages of group CBT compared to individual therapy (Tucker & Oei, 2007).

Another increasingly popular way of administration to provide interventions in mental health is virtual intervention (Williams & Andrews, 2013; Andrews & Williams, 2015). Another application of CBT for depression is Internet-delivered cognitive behavior therapy (iCBT), which has been associated with large and moderate effects in persons who have depressive symptoms, according to the five meta-analyses of randomized controlled trials (Andersson & Cuijpers, 2009). It has been claimed that iCBT generates effect size equivalent to limited time face-to-face interventions (Andrews & Williams, 2015; Andersson et al., 2015). For the reasons given above, some authors see the future of this kind of application as promising in primary health systems (Andersson et al., 2015). Mobile applications have been developed to provide support in this kind of therapy. Huguet et al. (2016) made a systematic revision of these applications, reporting at least 117 applications for mobile devices. In spite of the large number of applications, only 12 were found to be based on components of CBT or BA. CBT in different administration modalities has shown effectiveness to treat depressive symptoms; group intervention and the Internet have shown results similar to classical face-to-face administration (Cuijpers, Noma, et al., 2019a).

6.5 Mechanisms and Moderators of Therapy Change

We know that CBT is effective for depression (Cuijpers et al., 2013; David, Cristea, & Hofmann, 2018b); however, the mechanisms by which it generates changes in depression and other disorders are the subject of controversy (Kazdin, 2007). To answer the question of what makes psychotherapy work, the mechanisms of change due to psychotherapy have been studied; these are "active ingredients" or processes that explain the improvement in symptoms that a given intervention generates (Johansson & Høglend, 2007), that is, which explain why a therapy is effective

(Kazdin, 2007). In spite of the positive effects of CBT in depressive symptomatology, it was estimated that 47% of the patients diagnosed with major depression and treated with CBT did not respond to the treatment (Cuijpers et al., 2014). Thus, understanding the mechanisms of change is relevant to optimize and personalize therapeutic interventions (Hollon et al., 2002; Kazdin, 2007; Kazdin, 2009).

To study these mechanisms, researchers have chosen to evaluate the role of the mediators and moderators in psychotherapy. Mediators are intermediate variables that give an account of the relation between a given intervention and its results; a mediator may be a guide that allows understanding certain change mechanisms but not necessarily the mechanism (Kazdin, 2007); its objective is to explain how or why the change is produced (Johansson & Høglend, 2007). Moderators are variables that inform us for whom or in what conditions the change will exist (Johansson & Høglend, 2007). Once there is evidence about a relation between a therapeutic intervention and a decrease in symptoms, it is necessary to study the role that third variables (mediators and moderators) play in this relation (Ato & Vallejo, 2011).

A number of mechanisms have been postulated for cognitive-behavioral interventions that would be operating in therapeutic change. Garratt et al. (2007) published a literature review of 31 empirical articles that examined the effectiveness of some type of cognitive therapy and the reduction of symptoms of depression. The studies included ambulatory and hospitalized patients, members of communities, etc., with a total of 1841 participants. The authors concluded that in large measure, the cognitive change preceded and sometimes predicted the reduction in depressive symptoms. They discussed whether the cognitive change would be an element of the cognitive therapy itself or could be present in other types of psychotherapeutic models.

Nearly a decade later, Lemmens et al. (2016) reviewed 35 empirical articles on potential mechanisms of change in 12 types of therapeutic interventions – not only cognitive – on depressive symptoms; 74% of the articles used randomized controlled trials as the experimental design. One requisite for inclusion in the review was that the researchers used statistical tests of mediation to analyze their results. The authors mention that the results were mixed due to the heterogeneity of the methods used; however, the variables automatic negative thoughts, dysfunctional attitudes, attribution styles, and other cognitive constructs (rumination, mindfulness ability, and level of worry) were associated with therapeutic change in most of the studies examined. Both Lemmens et al. (2016) and Garratt et al. (2007) stated that the research is heterogeneous and often unsatisfactory in methodological terms; thus, the results obtained are not conclusive.

These studies support the hypothesis of cognitive change as the mechanism of change for CBT, which agrees with the active ingredients hypothesized by Beck and his associates (Beck et al., 1979). Beck et al. (1979) suggested that intervention is effective, since it is directed to modify the cognitive structures or central schemes. The cognitive change may be understood as the modification of the structure or the content of the cognitions: thoughts, ideas, images, etc. (Bruijniks et al., 2018). In its different modalities, the CBT focuses to a greater or lesser degree on modifying the structure or content of the cognitions of the client. The main intervention that allows

cognitive change is known as *cognitive restructuring*. In spite of the wide use of this concept, the restructuring does not have a unique definition; it is generally understood as a technique whose objective is to be able to identify and modify undesirable cognitions by different means (Clark, 2013; Froján-Parga & Calero-Elvira, 2011) such as direct instruction, self-discovery, Socratic dialog, behavioral experiments, etc.

The third-generation or contextual therapies propose to understand cognitions as behavior, more specifically as verbal behavior (Skinner, 1984). Thus, cognitive change may be seen as a modification in the verbal repertoire of the patients that can generate a change in other behavior, following a behavior-behavior relation. Cognitive restructuring may thus be considered as a shape of verbal behavior (Froján-Parga & Calero-Elvira, 2011).

Contextual therapies have thus sustained that it would not be necessary to modify the content of the cognition for these to stop affecting mood (Hayes, Strosahl, & Wilson, 2012b). For example, CBT proposes interventions in the line of "deliteralizing" language, that is, allowing the subject to separate the union between the significance and the significant in order to be able to feel that their thoughts are what they are, thoughts and not external reality (Masuda et al., 2010). CBT proposes a therapeutic process called cognitive *defusion*, which centers on modifying the function that cognitions have in the verbal context of the patient rather than their content (Hayes et al., 2001). In other words, a patient may continue to think that "something bad will happen" (the content of the cognition is maintained); however, this verbal behavior – after a process of cognitive defusion – may be believed less intensely, generating lower levels of discomfort (Hayes, Strosahl, & Wilson, 2012b). Thus, the function of this cognition would be modified from an aversive to a neutral function.

In the identification of mechanisms of change, evidence has been found that the reduction in depressive symptoms may be related to a different mechanism than cognitive change, such as the increase in reinforcing activities for the patients, better known as the activation hypothesis. According to this hypothesis, the effects of classical CBT (Beck, for example) are generated by the activation of the patients, mobilized by becoming active and making contact with the available sources of reinforcement (Jacobson et al., 2001). Jacobson et al. (1996) performed a historical study of the analysis of components, where they compared two central components of the classical CBT of Beck et al. (1979) – behavioral activation and cognitive therapy. They worked with 152 adult patients diagnosed with major depression and a 6-month follow-up. The first group received only the behavioral activation component (BA, $n = 57$). The second group received the component related to cognitive therapy, specifically identification and modification of automatic thoughts (CT, $n = 44$), while the third group received the two components together (BA and CT, $n = 50$), that is, the complete package of the original treatment (Beck et al., 1979). The results indicated that the patients of the three groups increased the frequency and enjoyment of pleasurable events and decreased negative thoughts (Jacobson et al., 1996). There was no evidence that the CT component was more effective than the other two groups. The BA component explained the variance in depressive symptoms just as well as the CT component. In spite of the enthusiasm that this

finding generated, there has been contradictory evidence. Richards et al. (2016) performed a study with 440 patients whose objective was to investigate the efficacy of BA in primary attention for severe depression. The results did not show evidence that BA was more effective than CT for the studied pathology.

Recently, Lorenzo-Luaces and Dobson (2019) analyzed the hypothesis that BA is more effective than CT for depression. They did not find evidence for the superiority of BA over CT for severe depression during treatment or in the long run. In spite of this, the authors indicated the methodological problems of the study and the cautions to be considered in interpreting the results. The original study of Jacobson et al. (1996) and its successors (Dimidjian et al., 2006) opened the debate on the critical components of the CBT. Currently, BA is presented as an independent treatment scheme that has strong literature in its favor (Chan et al., 2017; Kuroki & Ishibashi, 2015), both for its effectiveness in depressive symptoms and its utility, since it does not require patients or therapists to learn complex abilities (Kuroki & Ishibashi, 2015).

There is still debate in the therapeutic community on the active ingredient of the CBT; is it the cognitions that generate depressive behaviors or the behaviors which finally generate the cognitions? There is evidence in favor of both sides, and there is probably not a linear relation between the type of intervention and the therapeutic change; thus, it is necessary to examine the role of third variables which affect the change. Both moderators and mediators should be studied with methodological and theoretical rigor in order to understand how the change functions and what are the elements related to it.

6.6 Discussion

We are confronted with a complex panorama that reflects the complexity of depressive disorders; these were reviewed mostly in their descriptive aspect. Many behavior analysts have refused to work from this dimension and have opted for analyzing cases clinically from a functional perspective (Kanter et al., 2006). This implies greater complexity, which involves the distinction between the function of behavior and its topography. In simple terms, each person experiments depressive symptoms or behavior that are similar in form (topography) but are related or fulfill very different functions (Catania & Harnad, 1988). This vision implies a complex understanding of depression, which integrates behavioral (motor), cognitive (thoughts, ideas, representations, images, etc.), emotional (mood, vitality, etc.), and contextually linked elements. This is relevant, since each picture is manifested with its own singularities and reflects a particular history of learning of each subject. In spite of the singularities, the empirical evidence sheds light on the role that learning plays in the acquisition of depressive behavior (Harvey et al., 2004; Bruijniks et al., 2019) and how those behaviors learned previously may be modified in therapeutic environments (Bruijniks et al., 2018; Kohlenberg & Tsai, 1991).

Thus, the question of the etiopathogenesis of depression should return to the learning processes that allow the acquisition and maintenance of our behavior, both manifest (e.g., stay at home) and private or internal (e.g., our thoughts), to understand the difference between manifest and private behavior (see Skinner, 1966). The role of the history of learning, especially that developed early, has influenced most of the etiopathogenic models reviewed (Seligman, 1975; Porsolt, Bertin, & Jalfre, 1977a; Steru et al., 1985; Katz et al., 1981; Willner, 1991; Duman, 2010). The importance of history in understanding vulnerabilities is also recognized by the generic cognitive model (Beck & Haigh, 2014), putting emphasis on adverse early experiences that individuals have faced, which would be the basis for the development of dysfunctional schemes of information processing. New developments coming from behavioral contextual science explain how subjects may generate associations among events arbitrarily, without the need to have direct contact with them (Barnes-Holmes et al., 2004; Hayes et al., 2012a). The learning capacity of people expands considerably when verbal elements are introduced, in a way this represents the *dark side of language* (McAuliffe et al., 2014). As an example, if there are three related contexts (e.g., cinema, house, and park) and our partner breaks with us in one of them (e.g., house) and thus this context acquires an aversive function for us, it is probable that the other two contexts will also acquire the same properties. Thus, language has the capacity to transfer functions and generate emotional pain responses in situations that have had relation (but not direct contact) with depressive history in the past. This has been widely developed in the relational frame theory (Hayes et al., 2001; Barnes-Holmes et al., 2004). This is relevant, since it allows us to see that learning not only implies direct contact with the world but also continues operating through language, generating derived relations.

Patients with depressive behavior present (in greater or lesser degree) negative thoughts about themselves, others, and the future. Those thoughts finally influence (and are influenced by) other response systems such as the emotional and behavioral, producing positive feedback. It appears that all the effort of cognitive processes (attention, memory, perception, etc.) is directed to evaluate negatively memories and events in life. All this generates a decrease in activities as a product of persistent avoidance of situations that trigger the cognitions and events mentioned above. By maintaining the distancing of situations and memories, the subject with depressive behavior decreases the probability of reinforcing, making the depressive behaviors chronic. The animal models examined allow us to understand the role that uncontrollability and unpredictability play in these circumstances as well as the importance of stressing factors in the environment of development.

In the same ways we acquire certain behaviors, we may acquire other contrary behavior to generate variability. The CBT tries to be a controlled environment, whose purpose is to begin certain learning processes to generate new behavioral repertoires in patients and thus break the positive feedback cycle of depressive behavior. In spite of the supported effectiveness of CBT for depression (Cuijpers, 2017), we still do not know the *active ingredients* that make this change possible. Understanding these ingredients is essential to optimize and personalize therapeutic interventions (Hollon et al., 2002; Kazdin, 2007; Kazdin, 2009). Two principal

hypotheses have been advanced to explain them, activation and cognitive change (Jacobson et al., 1996; Lemmens et al., 2016). Both hypotheses imply an increase in the repertoire of behaviors of the patient, either modifying the structure of the thoughts or increasing the approximation of behaviors toward certain reinforcers. Thus, a relation is formed between the phenomena of learning (acquisition and extinction) with clinical psychology which must be taken into account to enhance the interventions.

As therapists, we often try to help the patient "eliminate" certain types of behavior; however, it must be asked if this is possible. The literature on basic learning processes informs us that the processes of extinction of some behaviors do not erase or eliminate but only decrease their probability of appearance (Bouton, 2011). In some way, we never "forget" or "erase" anything; thus, a return to an extinguished response is probable under various circumstances, which has been observed in the phenomena of response recovery such as reacquisition, renovation, or spontaneous recovery (Bouton, 2004). Thus, the same principles should operate in the therapeutic context. The literature indicates that trying to make a patient "forget" or try to suppress a given memory may be useless and even counterproductive, generating a paradoxical increase in the frequency, intrusion, and distress associated with the memory that we have tried to suppress (Purdon & Clark, 2000; Páez et al., 2008). Thus, using strategies of thought control may be the wrong way.

If we cannot forget, the alternative that remains is to generate new repertoires, adding content to what now exists. The goal would thus be to make behavior more flexible, keeping in mind that there are times when patients will continue to think poorly of themselves in some circumstances but in others will manage to think well of themselves if this behavior has been made more flexible. (McAuliffe et al., 2014; Hayes, Strosahl, & Wilson, 2012b). Some depressive problems will occur when the behaviors are inflexible (only one course of action is available), and patients can only think "I'm the worst in the world." The histories of individual learning may demonstrate the way in which inflexible behaviors were acquired; the clinical question must approach the ways to generate other learning histories.

6.7 Conclusions

Depression is one of the most relevant mental health problems in the world, due to its high prevalence and social, economic, and personal costs. To understand its development and maintenance, animal research models have been generated that simulate the conditions by which humans acquire depressive behaviors. The theories that support the interventions of the CBT have accounted for a number of elements of the basis of the development and maintenance of the problem. This therapy has been established as the gold standard for its treatment, showing good results of its effectiveness compared to other modalities (i.e., waiting list, placebo, other psychological therapies, pharmacotherapy). In spite of the above, the question of what makes the interventions work has not been yet answered, but two main hypotheses

have been proposed, cognitive change and activation. At any rate, the relation of the history of learning of organisms and depressive behavior has been well established, as well as how CBT can generate alternative learning histories to make depressive behavior more flexible.

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Chapter 7
Genetic and Epigenetic Determinants of Depression: From Basic Research to Translational Medicine

Luis A. Salazar and Tomás Zambrano

7.1 Genetics of Major Depressive Disorder

Major depression is a very complex disorder, resulting from the heterogeneous contribution of genetic and environmental (GxE) interactions. The role of genetics in the development of depressive disorders has been a research subject for more than 40 years (Beckman et al., 1978), and compelling evidence provided by family studies not only shows that the risk to develop depression in first-degree offspring of depressive patients can increase up to threefold but that depression heritability is probably in the range of 31%–42% (Sullivan et al., 2000), an outcome fueling intensive research to identify key genes predisposing to MDD development using methodologies, such as candidate gene studies; however, until recently, results have met with very limited success due to a lack of common genetic variants consistently associated with MDD (Major Depressive Disorder Working Group of the Psychiatric et al., 2013) and also because of poor replication of candidate genes in larger genome-wide association studies (GWASs) (Bosker et al., 2011). For instance, a large meta-analysis performed by Lee et al. (Lee et al., 2012) and encompassing 4346 cases and 4430 controls reported that a set of glutamatergic synaptic genes were significantly associated with MDD. This system mediates stress response through regulating the hypothalamic-pituitary-adrenal (HPA) axis, playing a direct role in the pathophysiology of depression. Nonetheless, the study was unable to

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_7

determine how the genes identified conferred risk to develop MDD. Another large GWAS, assessing 5763 cases, 6901 controls, and more than 1 M single-nucleotide polymorphisms (SNPs), failed to identify any variant contributing to MDD etiology at a genome-wide significance level (Wray et al., 2012).

Despite years of negative GWAS findings that compromised a better understanding of the genetic architecture of MDD, over the last 5 years, several studies have successfully pinpointed different MDD-associated loci beyond genome-wide significance levels. In 2015, the CONVERGE consortium (consortium, 2015) studied 5303 Chinese women with recurrent MDD and 5337 controls and reported two loci on chromosome 10 associated with MDD risk: one near sirtuin 1 (*SIRT1*) and the other within an intron of the phospholysine phosphohistidine inorganic pyrophosphate phosphatase (*LHPP*); these findings were subsequently replicated in an independent cohort. Importantly, the authors state that recruitment of cases who were probably more homogeneous and more severely impaired allowed the association and replication of these two loci with MDD. Shortly thereafter, Okbay and colleagues (Okbay et al., 2016) identified two variants associated with depressive symptoms. These variants were located in the intronic regions of the kinase suppressor of RAS (*KSR2*) and within the Deleted in Colorectal Carcinoma (*DCC*) gene. Moreover, the authors confirmed their associations with depressive symptoms by direct replication of the variants in an independent depression cohort. During the same year, Hyde et al. reported 17 SNPs in 15 loci associated with depression in a cohort of European descent (Hyde et al., 2016). Interestingly, this study found small associations in the *SIRT1* and *LHPP* regions, previously identified in the CONVERGE study (consortium, 2015); however, they did not achieve genome-wide significance, probably because of the differences in gender and ancestry between both cohorts. In 2017, a new susceptibility locus for depression with genome-wide significance was reported by Direk et al. (2017). This locus mapped to an intronic region located in chromosome 3 within the fragile histidine triad (*FHIT*) gene, which codes for a tumor suppressor protein involved in different types of cancer (Waters et al., 2014). It must be noted that the study of Direk and colleagues (Direk et al., 2017) evaluated a depression continuum, meaning that the study did not rely on stringent criteria including homogeneously severe depressed individuals, such as the method of the CONVERGE consortium study (consortium, 2015), but rather it evaluated a depression continuum by combining cases from clinical populations diagnosed with MDD and participants from the general population evaluated for depressive symptoms. Although incorporating a more heterogeneous depression phenotype, this approach also allowed the authors to assess a significantly larger sample size, overcoming the disadvantages of the heterogeneous sample and allowing the successful identification of a novel locus associated with depression.

Most recently, there has been a series of unparalleled advances coming from large GWAS investigations. In 2018, Howard et al. (2018) studied the effect of more than 7 M variants on three depression phenotypes using 322,580 UK Biobank participants, recognizing 17 independent genome-wide significant variants across all three depression phenotypes. While the findings were replicated in an independent

sample, enrichment analysis for the gene sets showed that these variants were related to excitatory synapse, mechanosensory behavior, post synapse, neuron spine, and dendrite functions. During the same year, Wray and colleagues (Wray et al., 2018) conducted a GWAS in 135,458 cases and 344,901 controls and identified 44 independent and significant loci associated with clinical features of major depression. Moreover, they observed that lower educational attainment and higher body mass were putatively causal and that MDD and schizophrenia partly shared biological pathways causal for both disorders, which is consistent with a previous study disclosing common pathways shared between these disorders (Network & Pathway Analysis Subgroup of Psychiatric Genomics, 2015). In 2019, Howard et al. (2019) reported a remarkable meta-analysis testing the effect of more than 8 M genetic variants on a sample of 246,363 cases and 561,190 controls from the three largest GWAS studies to date (Howard et al., 2018; Hyde et al., 2016; Wray et al., 2018), identifying 102 independent variants associated with depression. A following replication study using an independent sample of 414,055 cases and 892,299 controls maintained the significance for 87 of the 102 variants after multiple correction, and further enrichment analyses provided evidence regarding the importance of the prefrontal brain regions for the gene sets significantly associated with depression. Moreover, another GWAS allowed the identification of eight additional and novel depression loci associated with multiple psychiatric phenotypes (Amare et al., 2019).

7.2 Epigenetics of Major Depressive Disorder

The term epigenetics is used to specify stable and heritable modifications in gene expression that are not owed to changes in the DNA sequence. Hence, the epigenome controls differential gene expression, providing each cell type with an unambiguous identity. A clear example and exceptional study model to dissect epigenetic influences are the cases of monozygotic twins (MZT), which share a common genotype but show important phenotypic differences during their lifetime (Fraga et al., 2005). Overall, the mechanisms of epigenetic regulation are generally grouped into three categories: DNA methylation, histone modifications, and small noncoding RNAs (Skvortsova et al., 2018).

7.2.1 DNA Methylation

DNA methylation is a highly conserved modification and represents the most studied epigenetic alteration. In this mechanism, a methyl (CH_3) group is enzymatically added by DNA methyltransferases (DNMTs) from S-adenosyl methionine to the fifth carbon of a cytosine to form 5-methylcytosine (5mC). DNA methylation is not evenly distributed around the human genome. This molecular event occurs at sites

known as CpG islands, which are short (1 kb) regions filled with cytosine-phosphate-guanine (CpG) dinucleotides distributed in more than half of the genome of vertebrates (Jones, 2012) but with a marked preference for the promoter regions, which contain about 70% of CpG islands in human genes. The remaining sequences of the genome are CpG depleted. Methylation induces conformational changes to the chromatin, making DNA inaccessible for transcription factors needed to stimulate DNA transcription; therefore, methylation is associated with transcriptional repression, or "gene silencing," a mark that is epigenetically inherited during cell division (Jones & Liang, 2009).

One of the first large molecular studies shedding light into differential MDD-associated DNA methylation was reported by Sabunciyan and colleagues in 2012, comparing 39 postmortem frontal cortex MDD samples to 26 control brains. Even though the experimental design only covered a fraction of the genome-wide CpG sites and associations were of small magnitude, the findings showed that differentially methylated regions were in or close to genes enriched for roles in neuronal growth and development (Sabunciyan et al., 2012). As previously said, MZT studies provide an exceptional model to investigate the contribution of epigenetics to MDD risk. In line with that, Byrne and colleagues (Byrne et al., 2013) advanced the field in 2013 by completing a twin study that covered a much larger number of CpG sites throughout the genome. Even though the sample size did not allow the identification of methylation differences attributable to MDD, the findings showed a highly significant increase in methylation in MDD-affected twins than their non-affected co-twins. A year later, Davies et al. (2014) studied 50 MZT pairs discordant for depression and found that the Zinc Finger and BTB Domain Containing 20 (*ZBTB20*) – which belongs to a family of transcription factors and acts as a transcriptional repressor – is significantly hypermethylated in MDD individuals. More importantly, this finding was replicated in an independent cohort of 356 unrelated case-control individuals. The authors also observed that twins with MDD showed increased global variation in methylation when compared with their unaffected co-twins (Davies et al., 2014). Later that year, Dempster et al. (2014) evaluated DNA methylation patterns at a genome-wide scale in adolescent MZT discordant for self-reported depression using buccal cell DNA, reporting as their main finding a highly significant differentially methylated probe (DMP) located on chromosome 10q36.3 in Serine/Threonine Kinase 32C (*STK32C*), which codes for a protein member of the serine/threonine protein kinase family of unknown function but with a plausible functional role in the brain due to its high expression levels in this tissue (Yanai et al., 2005). Besides additional validation of depression-associated hypermethylation at this DMP by bisulfite pyrosequencing, the authors also showed that the same CpG site is significantly hypermethylated in samples from MDD patients versus control subjects with no psychiatric diagnosis. In 2015, Cordova-Palomera et al. (2015) extended previous results by assessing the specific genomic loci that could trigger the observed DNA methylation differences in the peripheral blood of 17 MZT pairs. By using DMPs and variably methylated probes (VMPs), the authors reported an interesting association between hypomethylation of a DMP located in the WD Repeat-Containing Protein 26 (*WDR26)* and a lifetime diagnosis of

depression, which could be considered as a biomarker of environmental effects implicated in depression. Additional data show that genetic variation in the form of SNPs within this DMP has a plausible role in depression causality and predisposition (Major Depressive Disorder Working Group of the Psychiatric et al., 2013; Wray et al., 2012). On the other hand, VMPs were located in regions implicated in processes enriched for glucocorticoid signaling, such as Calcium Voltage-Gated Channel Subunit Alpha1 C (*CACNA1C*), Insulin-like growth factor 2 (*IGF2*), and the p38 MAP kinase (*MAPK11*). During the same year, Numata and colleagues (Numata et al., 2015) reported the identification of DNA methylation markers, differentiating MDD patients from nonpsychiatric controls by profiling peripheral leukocytes in a discovery sample consisting of 20 medication-free patients with MDD and 19 controls. They reported 363 CpG sites with a pattern of DNA hypomethylation. Further validation was performed, obtaining 100% accuracy in an independent replication cohort of 12 medication-free patients with MDD and 12 controls.

7.2.2 Histone Modifications

DNA in the cell nucleus is wrapped around histone octamers to form nucleosomes, the basic units of chromatin. The histone octamer contains two copies each of H2A, H2B, H3, and H4. Structural studies have shown that the highly basic histone amino (N)-terminal tails protrude from their own nucleosome unit, making contact with adjacent nucleosomes (Luger et al., 1997). Histone tails are prone to suffer post-transcriptional modifications, including but not limited to acetylation, phosphorylation, methylation, ubiquitination, ADP-ribosylation, and SUMOylation (Bannister & Kouzarides, 2011). These modifications affect the interaction of the DNA-histone duplex, regulating gene expression by rearrangement of the chromatin in a process called chromatin remodeling, a mechanism widely implicated in several psychiatric conditions and crucial to understand long-lasting changes in gene expression (Tsankova et al., 2007).

One of the most studied histone modifications are acetylation and deacetylation, both dynamic processes influencing transcriptional activity; while acetylation is performed by histone acetyltransferases (HATs) in lysine residues on histone tails and correlates with transcriptional activation, deacetylation is induced by histone deacetylases (DACs) and is considered a mechanism of transcriptional repression (Katan-Khaykovich & Struhl, 2002). The role of these mechanisms in depression has been a matter of study for several years. Currently, three distinct classes of HDACs (I, II, III) have been described based on their homology to the yeast genes *rpd3*, *hda1*, and *sir2*, respectively (Kurdistani & Grunstein, 2003), and various reports using animal models show that administration of different HDAC inhibitors (HDACi), or in combination with antidepressants, improve the response to antidepressant treatment (Schroeder et al., 2007; Tsankova et al., 2006; Uchida et al., 2011; Weaver et al., 2004). In 2009, a critical study performed by Covington 3rd et al. (2009) showed that mice with chronic social defeat stress had transient

variations in the levels of acetylated histone H3 in the nucleus accumbens (NAc), which is the center of reward and learning. The authors reported a transient decrease, followed by a persistent increase in H3 acetylation, which was associated with lower levels of histone deacetylase 2 (HDAC2) in the NAc, observing similar results in the NAc of depressed humans evaluated postmortem. They also showed that after a direct infusion of MS-275 – a selective inhibitor of class I HDACs – the effects of chronic defeat stress on the patterns of gene expression in the NAc were reversed in a similar way to the effects of the common antidepressant drug fluoxetine, suggesting that histone acetylation has an adaptive role in both stress and depression; an observation demonstrated later when animals overexpressing dominant-negative HDAC2 in the NAc exhibited "antidepressant" behavior versus control animals, while animals overexpressing a version of a robust chromatin-associated HDAC2 displayed a more depression-like phenotype (Uchida et al., 2011). In contrast, Renthal et al. (2007) showed that HDAC5, a class II HDAC, exerted resilience-like effects in the NAc, disclosing a protective effect of this molecules. Mice vulnerable to chronic social defeat stress showed decreased HDAC5 expression, while imipramine – a chronic antidepressant treatment – displayed the opposing effect. Furthermore, mice lacking HDAC5 presented higher depressive-like behaviors following chronic social defeat stress versus the control group. Therefore, these studies are suggestive of two different gene populations in the NAc involved in the response to stress and depression: gene targets of HDAC2 may be pro-resilient and mediate antidepressant responses, while gene targets of HDAC5 may play the opposite role (Sun et al., 2013).

7.2.3 Small Noncoding RNAs

Noncoding RNAs (ncRNAs) are a set of short untranslated transcripts that play an important regulatory role. Several classes of ncRNAs have been reported to date: small interfering RNAs (siRNAs), microRNAs (miRNAs), PIWI-interacting RNAs (piRNAs), endogenous small interfering RNAs (endo-siRNAs or esiRNAs), promoter-associated RNAs (pRNAs), small nucleolar RNAs (snoRNAs), and sno-derived RNAs; however, miRNAs are by far the most studied and well-characterized ncRNA, and therefore, the discussion will be centered around these particular molecules.

miRNAs are endogenous RNAs of 21–25 nucleotides in length that negatively regulate gene expression by targeting and interfering with mRNA translation via mRNA cleavage or translational repression through complementary base pairing (Bartel, 2004), thus blocking protein synthesis. A single miRNA can target multiple mRNAs, and one particular mRNA can be silenced by several miRNAs; therefore, these molecules represent an extensive regulatory mechanism controlling more than 30% of the human genome (Lewis et al., 2005). Consequently, miRNAs have been implicated in a wide variety of processes, such as cellular division, apoptosis, metabolism, intracellular signaling, immune response, and cellular movement (Ng

et al., 2012; Png et al., 2011; Rayner et al., 2011; Taganov et al., 2006; Zhang et al., 2012), among others.

Due to their ubiquitous presence in almost every biological pathway known – which includes neuropsychiatric paths common for MDD development – several miRNAs have been implicated in MDD susceptibility. As we previously mentioned, the HPA axis is a well-established mechanism implicated in depression. Normally, the axis regulates glucocorticoid production – e.g., cortisol – through positive and negative feedback loops involving the hypothalamus, pituitary, and adrenal glands. The release of corticotropin-releasing factor from the paraventricular nucleus (PVN) of the hypothalamus releases the adrenocorticotropic hormone from the pituitary, stimulating cortisol production from the adrenal glands. Then, cortisol binds to mineralocorticoid receptors (MR), largely expressed in the hippocampus region of the brain, and with lower affinity to glucocorticoid receptors (GR) (Keller et al., 2017), both of which mediate the feedback action at the level of the pituitary. In depressed individuals, this loop has been found consistently overactive (Wasserman et al., 2010), most probably due to a deregulation in the MR/GR ratio (Young et al., 2003), which may be partly explained by modulatory miRNAs. In 2008, Uchida et al. (Uchida et al., 2008) found a lower expression of GR protein but not its mRNA in the PVN of Fischer 344 (F344) rats – a stress-hyperresponsive strain widely used in the study of the HPA axis function – when compared to Sprague-Dawley control rats while also observing increased miR-18a expression in the PVN of the F344 animals. Moreover, using an in vitro model of neuronal cells, the authors additionally showed that miRNA-18a effectively inhibited the translation of GR mRNA. In addition, another study tested a panel of five miRNAs (miRNA-124a, miRNA-328, miRNA-524, miRNA-22, and miRNA-18) and confirmed that miRNA-18 and miRNA-124a were able to decrease GR protein levels, following a luciferase reporter assay experiment (Vreugdenhil et al., 2009). Besides providing evidence of a specific set of miRNAs controlling GR protein expression, these studies also indicate that miRNAs are effectively implicated in the pathophysiology of MDD.

One of the most important molecules involved in depression corresponds to a member of the neurotrophin family of growth factors named brain-derived neurotrophic factor (BDNF), a protein found in the brain and spinal cord that promotes neuron survival by contributing with their growth, maturation (differentiation), and maintenance. Studies show that serum BDNF levels remain low in untreated depressed individuals (Karege et al., 2002; Molendijk et al., 2011). Consistent with this, Li and colleagues (Li et al., 2013) reported low serum BDNF levels in depressed patients, and, through a bioinformatics approach, they identified an interaction between the BDNF mRNA and miRNA-182. Subsequent studies showed an inverse correlation between BDNF levels and miRNA-182 in human neuroblastoma SH-SY5Y cells, and additional experiments revealed that serum levels of depressed individuals had increased levels of miRNA-182 than healthy controls, thus reinforcing the role that miRNAs play in MDD pathogenesis. A more extensive evaluation of depression-related miRNAs was approached by Smalheiser et al. (2012), assessing 367 miRNAs in the prefrontal cortex (Brodmann area 9) of antidepressant-free depressed suicide (n = 18) versus nonpsychiatric controls (n = 17). Besides

disclosing 21 repressed miRNAs, a highly significant finding shown is that depressed suicide subjects had a global mean abundance of miRNA 17% lower (on average) than controls and that miRNA expression in the cases was significantly less variable than their counterpart, which is consistent with hypo-activation of the frontal cortex in depressed individuals (Flor-Henry et al., 2004; Werner et al., 2009).

7.3 Concluding Remarks: The Role of Translational Medicine

MDD is a highly heterogeneous disorder. It is generally accepted that the more information we obtain from biomedical investigations, the better we can understand the underlying basis of this remarkably complex condition. Certainly, advances in the field of MDD hold the potential to accomplish the translation from biomedical research into clinical practice; however, this may not always be the case. For instance, a very recent systematic review and meta-analysis – a highly valuable asset for evidence-based decision-making in medical practice – was aiming to disclose prospective biomarkers derived from diverse and leading theories on a variety of mechanisms implicated in MDD, such as neuroimaging, gastrointestinal factors, immunology, neurotrophic factors, neurotransmitters, hormones, and oxidative stress alterations (Kennis et al., 2020). The authors performed an initial assessment on the basis of 67,464 articles that showed, to some extent, positive findings. After applying stringent PRISMA guidelines criteria, the final number of reports included was reduced to 75 studies, and the results only revealed that increased cortisol had a minor predictive effect on onset/relapse and recurrence of MDD, but this effect was dependent of the disease state (Kennis et al., 2020). This lack of reliable evidence, complicating the turnaround of basic research findings into valuable and usable information for clinicians, gives a measure of the extremely complex architecture of MDD and points toward an even more integrative approach, where the "omics" sciences are expected to play a central role, such as the good examples from the recent success found in GWASs performed over the last 5 years, not to mention the auspicious epigenetic field. Without a doubt, one of the most interesting and promising research avenues is the one devoted to identify biological markers for MDD, and intense efforts and resources are being poured into this line of investigation, but significant challenges remain to be answered. For instance, if plausible MDD epigenetic markers are to be considered, they must rely on an accessible and noninvasive sample type – such as buccal cells – due to obvious difficulties when studying the brain. Importantly, reports have shown good correlation between brain tissue and blood samples (Davies et al., 2012), and to date, an ever-increasing amount of research show that miRNAs are the predilect molecules to be considered as general and potential circulating biomarkers for several illnesses (Wang et al., 2016) and specifically for major depression (Gururajan et al., 2016) due to their exceptional extracellular stability (Gilad et al., 2008; Mitchell et al., 2008).

Nonetheless, trivial but important difficulties lie ahead, such as the collection tubes employed for blood withdrawal, as studies show that the EDTA anticoagulant, commonly found as an additive in blood sampling tubes, can affect the detection of circulating miRNAs (Leidinger et al., 2015), this detrimental effect being proportional to the time course of sample processing. Moreover, serum samples have been shown to contain a higher number of miRNAs than their corresponding plasma counterparts, even when analyzing the same individual, an outcome extremely dependent on the measurement platforms employed (Wang et al., 2012). More recently, some interesting research noteworthy of attention demonstrated important diurnal variations in miRNA levels (Heegaard et al., 2016; Hicks et al., 2018; Rekker et al., 2015), imposing poorly explored questions that still defy the arrival of potential MDD markers onto patient care.

Acknowledgments This work was funded by the ANID Millennium Science Initiative – Millennium Institute for Research on Depression and Personality (Grant No. IS130005).

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Chapter 8
Neurobiology of Depression

Hernán Silva

8.1 Introduction

Major depressive disorder (MDD) is one of the most common and debilitating mental disorders; however, its etiology remains unclear. The monoaminergic depression hypothesis was formulated more than 50 years ago and argues that depression is associated with an absolute or relative monoamine deficiency at functionally important receptor sites in the brain. Antidepressants work by correcting these deficiencies. For many years, this has been the leading hypothesis and has formed the basis for the synthesis of the most commonly used antidepressants.

Knowledge about the pathophysiology of depression has substantially evolved in recent years, and the most current hypotheses involve gene-environment interactions, endocrine and inmunologic systems and neurogenesis as mechanisms which provide unitary explanations for the pathophysiology of depression. In this chapter, the most important hypotheses about the biological basis of depression are reviewed.

8.2 The Monoamine Hypothesis

The monoamine hypothesis posits that depression is caused by the alteration of monoamine levels, including serotonin (5HT), norepinephrine (NE), and dopamine (DA). A preliminary finding was that monoamine depletion by the antihypertensive drug reserpine caused depression in patients not previously affected by the disease.

The serotoninergic hypothesis is based on research showing that serotonin metabolites are reduced in patients with major depression. In contrast, antidepressants such as tricyclics (TCAs), selective serotonin reuptake inhibitors (SSRIs), and

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_8

serotonin-norepinephrine reuptake inhibitors (SNRIs) increase serotonin levels in the brain. Chronic antidepressant treatment has been shown to downregulate inhibitory presynaptic 5-HT1A somatodendritic autoreceptors. These presynaptic autoreceptors inhibit 5-HT release, and their downregulation increases 5-HT release, which has been associated with antidepressant response. The depletion of tryptophan, an essential amino acid needed for 5-HT synthesis, has been shown to induce depressive symptoms in patients who were successfully treated for depression with an antidepressant but had no effect on untreated depressed patients.

Subsequent research has shown reduced concentrations of monoamine metabolites in the cerebrospinal fluid (CSF) of depressed patients, leading to the hypothesis that a deficiency of not only 5-HT but also NA and dopamine (DA), or of all three molecules together, may occur in monoaminergic synapses. The role of monoamines in depression has been further examined with the use of NA and 5-HT depletion paradigms in normal and drug-remitted individuals with depression (Miller HL, 1996). The results of this study demonstrated that, although the depletion of NA and 5-HT did not lead to depressive symptoms in normal individuals, patients who experienced remission after treatments were vulnerable to relapse on depletion of these monoamines. Monoamine depletion was correlated with depressed mood both in patients with a family history of MDD and in drug-free patients in remission (Ruhé HG, 2007). All these data indicate that NA and 5-HT are somehow involved in the maintenance of the antidepressant response but cannot alone explain either the pathophysiology of depression or the mechanism of action of antidepressants. This conclusion is also supported by the time required for the therapeutical action of antidepressant treatments to be evoked (several weeks), even though levels of monoamines are increased rapidly (within minutes) by these treatments.

The role of NE in depression is also evidenced by the fact that medications that inhibit NE reuptake, such as TCAs, SNRIs, and norepinephrine-dopamine reuptake inhibitors (NDRIs), and those that increase NE secretion, such as mirtazapine, are effective antidepressants (Leonhard BE, 2001). Chronic stress is associated with depression and alters the noradrenergic system, leading to an increase in the activity of tyrosine hydroxylase, the enzyme involved in NE synthesis, in the locus coeruleus. The increased secretion of corticotropin-releasing factor (CRF) from the hypothalamus triggers the release of ACTH from the pituitary gland, which subsequently stimulates the adrenal gland to release NE and cortisol. Then, increased levels of cortisol and NE increase sympathetic drive and the release of cytokines, which have been shown to have reciprocal effects on the HPA axis as well as neurotoxic effects.

The dopaminergic system is also involved in the neurobiology of depression. There are evidences that dopaminergic transmission in the mesolimbic pathway is altered in depressive patients. The mesolimbic pathway mediates the reward pathway, while motivation and some neurovegetative symptoms of depression, including anhedonia and reduced motivation, are related to a malfunctioning of the reward system. Antidepressant agents that increase dopamine levels in the brain, such as bupropion, provide indirect evidence for the role of dopamine in mood regulation (Dean & Keshavan, 2017).

Glutamate and GABA have also been found to be involved in the pathophysiology of MDD. As a major excitatory neurotransmitter, glutamate plays a critical role in neuroplasticity and in learning and memory processes. The vast majority of neurons and synapses in brain areas and circuits mediating complex cognitive-emotional behaviors use glutamate as a neurotransmitter, and long-term changes in these areas and circuits represent the biological underpinnings of mood disorders (Sanacora G et al., 2012, Amidfar M et al., 2019).

The fact that ketamine, an NMDA receptor antagonist, acts as a potent and fast-acting antidepressant has led to great interest in the glutamatergic system as a possible target for antidepressant treatment. Ketamine leads to a rapid antidepressant effect, occurring in hours, rather than weeks, as is the case with traditional antidepressants (Machado-Vieira et al., 2010). However, the neurobiological mechanisms of this process have not been fully identified. At subanesthetic doses, ketamine acts as an NMDA receptor antagonist that blocks the NMDA receptors found on inhibitory GABAergic interneurons, which stimulates the release of glutamate. Subsequently, glutamate selectively binds to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Increased stimulation of AMPA receptors leads to several second messenger cascades, including eEF-2 k inhibition, GSK-3 inhibition, and mTOR activation, all of which results in increased neuroplasticity (Dean & Keshavan, 2017). In contrast to this disinhibition hypothesis, the direct hypothesis proposes that ketamine targets NMDA receptors on excitatory pyramidal neurons (Duman R et al., 2019). Ketamine has also been shown to increase the release of BDNF in hippocampal pyramidal neurons, which increases neuroplasticity as well (Iadarola et al., 2015). These findings suggest that glutamate may be involved in mood regulation, possibly through the maintenance of neuroplasticity. Furthermore, future research on unresolved questions about the mechanisms of action of NMDA receptor antagonists will help to develop new rapid-acting antidepressants with fewer side effects and better efficacy than traditional antidepressants (Amidfar M et al., 2019).

8.3 The Diathesis-Stress Model

The link between stressful life events and the origin and development of depression has been widely investigated, providing an increasing body of evidence in support of this association. Stressful life events can precipitate depressive episodes in vulnerable individuals. Most researchers report severely threatening life events before the onset of depression. Notable life events that precede depression can include the death of a spouse, divorce and marital separation, loss of job or redundancy and retirement, unwanted pregnancy, social isolation, rape, childhood abuse, fighting and war, and major accidents (Jesulola E et al., 2018). Likewise, childhood stress in the form of abuse or neglect increases the risk of depression later in life.

There is great individual variation in vulnerability to depression in the general population. This variation is usually understood within a diathesis/stress model that

considers issues of vulnerability (diathesis) and precipitation (stress) separately. In individuals with increased vulnerability, the level of stress needed to precipitate an episode of depression is lower. The occurrence of an episode of depression itself increases the diathesis for future episodes (Wilner P et al., 2013).

The predisposition (or diathesis) to become depressed may arise in a variety of ways and at different stages of the life cycle. These include a genetic predisposition, early life experiences such as inadequate emotional contact with parents, and childhood abuse. Prenatal environmental stressors, such as placental insufficiency, food shortage, or nicotine exposure due to smoking of the pregnant mother, may predispose the child to depression in later life. Interactions between multiple risk genes and early environmental factors seem to explain a large part of individual variability; likewise, much of the diathesis for depression is laid down in early childhood. Much of the influence of both genetics and early traumatic events on chronic depressive symptomatology is mediated through the personality factor of neuroticism, which is associated with a negative information-processing bias.

The main physiological response to stress is an activation of neuroendocrine systems, most notably, the hypothalamus-pituitary-adrenal (HPA) axis. The corticotropin-releasing factor (CRF) is released from the paraventricular nucleus of the hypothalamus to stimulate the pituitary gland to produce adrenocorticotropic hormone (ACTH), which in turn stimulates the release of cortisol from the adrenal cortex into the bloodstream. This exerts negative feedback effects on the pituitary and hypothalamus that limit the degree of activation of the HPA axis. Depression could be explained as a possible outcome of dysregulation of the stress response system. Stress induces structural and functional changes in the brain. Following exposure to various stressors, structural changes in the prefrontal cortex, amygdala, hippocampus, and nucleus accumbens have been shown to contribute to the development of depression (Duman RS, 2009).

The close association between exposure to stress and depressive disorders development is also dependent on the epigenetic mechanism. Environmental risk factors will lead to epigenetic modification in depression risk genes (BDNF, SERT, GR, and FKBP5) through DNA methylation and miRNA regulation, resulting in long-lasting and even heritable effects on risk gene expression. Such epigenetic mechanisms can cause structural and functional brain alterations, ultimately increasing vulnerability to depressive disorders. Meanwhile, epigenetic regulation will interact with subjects' genetic background to affect the predictive role of stressful life events in vulnerability to depressive disorders. Therefore, as a mediator of environmental risk factors, stress will function together with genetic risk factors and epigenetic modification to generate impacts on brain structure and function, as well as physiology and psychology, to predispose subjects to depressive disorders (Ding & Dai, 2019).

The sex difference observed in depression may be related to the hyperactivity of CRH neurons and, thus, of the HPA axis. Since MDD is twice as prevalent in women of reproductive age as in men, the organizing and/or activating effects of sex hormones directly or indirectly in the HPA axis have been proposed as risk factors for depression. The possible importance of fluctuating levels of sex hormones as a risk

factor for depression is underlined by the higher prevalence of premenstrual depression, antepartum or postpartum depression, and depression during the transition to menopause (Bao & Swaab, 2018).

8.4 The Inflammatory Model of Depression

Increased levels of inflammatory markers, such as interleukin (IL), IL-1b, IL-2, IL-6, tumor necrosis factor TNF-a, C-reactive protein (CRP), and PGE2, have been found in patients with depression. A number of clinical conditions which create significant neuroinflammation in the brain (e.g., systemic lupus erythematosus, traumatic brain injury, and multiple sclerosis) are associated with high prevalence rates for major depression. Depressed patients have an increased rate of autoimmune disorders; also, there are higher rates of depression among patients with inflammatory diseases. Another indication that inflammation may play a key role in depression is the high rate of comorbidity of major depressive disorder with chronic inflammatory illnesses, including cardiovascular disease, diabetes, and cancer. Long-term inflammatory processes are key drivers of pathogenesis in these systemic diseases (Wohleb ES, 2016).

The administration of cytokines [e.g., interferon-alpha (IFN-α)] and cytokine inducers (lipopolysaccharide and typhoid vaccination) have led to behavioral changes similar to those seen in depressed patients. Several cellular and humoral neuroimmune pathways are involved in the development of depressive-like behaviors and may be related to "sickness behavior," which has overlapping symptoms with depression. Inflammation induces behavioral sequelae characterized by lethargy, anorexia, pain hypersensitivity, and reduced social interaction, collectively termed sickness behavior. Similar symptoms are observed in major depressive disorder (MDD), thus prompting the hypothesis that immune or inflammation-related mechanisms are involved in the pathophysiology of mental health disorders.

Depressive symptoms may be produced via peripheral inflammatory cytokines crossing the blood-brain barrier to induce neuroinflammation. However, identifying markers of inflammation that have an entirely cerebral origin is indicative of a more central role for neuroinflammation in depression pathophysiology (Jesulola E et al., 2018).

The molecular mechanisms through which cytokines may impact behavior are manifold: cytokines may influence both the metabolism of NA, 5-HT, and DA and neuroendocrine functions, leading to flattening of the cortisol curve and increased evening cortisol concentrations, suggesting the existence of a link between inflammation and the HPA axis. Increases in the levels of markers of peripheral inflammation (such as cytokines and C-reactive protein (CRP)) in patients with major depression are associated with significant reductions in connectivity between the ventromedial PFC and the ventral striatum, which in turn are correlated with increased anhedonia, a core symptom of depression.

As psychological stress has been shown to increase the production of cytokines, such as IL-1b, IL-6, and TNF-a, there exists a positive feedback between depression and inflammation, with the latter causing depression and psychological stress, which in turn is pro-inflammatory (Steptoe et al., 2007). Anti-inflammatory agents have been used successfully as adjuncts to antidepressants.

Chronic immune dysregulation or inflammation is an important pathological feature of recurrent major depressive disorder, and excessive release of pro-inflammatory cytokines inhibits the negative feedback of the HPA axis, increases the permeability of the blood-brain barrier, reduces serotonin synthesis, disturbs the glutamatergic system, and can even result in depression relapse (Liang S et al., 2018; Liu et al., 2019).

It is important to note that other studies have suggested that immune dysregulation may be observed only in certain subtypes of major depression. For example, patients with melancholic depression display elevated HPA axis function, whereas patients with atypical depression show higher levels of circulating pro-inflammatory markers (Lamers F et al., 2013). It has been postulated that these pathophysiological differences may contribute to the neurovegetative or cognitive symptoms that characterize each subtype of major depression (Gold PW, 2015). Understanding not just the clinical presentation but also the underlying mechanisms of both subtypes of MDD would make it possible to provide patients with tailor-made therapy regimens matching their unique biological characteristics (Woelfer M. et al., 2019).

8.5 Reduced Neurogenesis and Neuroplasticity

Thanks to its remarkable plasticity, the brain can rapidly create and eliminate synapses as well as alter functional circuits in adaptation and learning. Neurogenesis in adult individuals involves the generation of entirely new neurons and neuronal connections in the dentate gyrus of the hippocampus and the sub-ventricular area of the lateral ventricles. Experimental studies show that exposure to stress may cause alterations in processes or number of neurons, atrophy of hippocampal CA3 pyramidal neurons, and decrease of cell proliferation in the dentate gyrus (Ferrari F, Villa RF, 2017). Also, neuroimaging studies in depressed patients have demonstrated selective structural changes across various limbic and non-limbic regions: in the prefrontal and cingulate cortex, both metabolism and volume are reduced, while hippocampal atrophy occurs with further syndrome progression (Gould E. et al., 2000).

Neurotrophins have multiple roles in the developing nervous system and also in the adult brain: they influence synaptic plasticity, the morphology of dendritic spines, and the proliferation, differentiation, and survival of neurons. Both the adult and the developing and maturing brain are influenced by factors, such as brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), and neurotrophin-3. The expression of these factors is strongly regulated by stimuli, such as stress and psychotropic drugs.

BDNF is one of the most extensively studied molecular factors of neuroplasticity. BDNF is a neurotrophin that promotes the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses. The finding that serum levels of BDNF are reduced in patients diagnosed with MDD (Monteleone et al., 2008) suggests that BDNF may play a role in the pathophysiology of depression. During intense stress episodes, BDNF expression is downregulated in dentate gyrus neurons and CA3 and CA1 pyramidal cell layers. This downregulation process leads to the atrophy of CA3 neurons and, consequently, reduces neurogenesis in the granular cells of the hippocampus. Conversely, sub-chronic treatment with clinically effective antidepressants increases BDNF expression in the hippocampus and frontal cortex, with behavioral studies revealing that BDNF upregulation is an essential factor for the therapeutic action of antidepressants and, thus, successful therapy (Villas Boas GR et al., 2019). Thus, MDD may be associated with structural plasticity impairment and cellular resilience, which can be normalized with antidepressant pharmacological therapies.

It has been suggested that the expression of BDNF is directly correlated with stress, neurogenesis, and hippocampal atrophy during depressive episodes. Moreover, it is important to note that CREB upregulates the BDNF gene and that antidepressant treatments currently used in clinical practice, which increase norepinephrine and/or 5-HT concentrations in the synaptic cleft, stimulate CREB expression; thus, BDNF can be said to be closely connected to the monoaminergic hypothesis of depression (Villas Boas GR et al., 2019).

8.6 Biological Basis of Depression: An Integrated View

From the perspective described here, a combination of factors (genetic, environmental, immunologic, neurogenic, biogenic amine deficiency related, and endocrine) has been found to be involved in the pathogenesis of depression, with abundant evidence indicating that all of them play a significant role in its development. All of the proposed biological pathophysiological mechanisms of depression, including inflammation, an increased stress response, and reduced neuroplasticity, are reciprocally connected with each other and neurochemical pathways, including monoamines, glutamate, and BDNF.

From a genetic point of view, the heritability of depression does not follow a classical Mendelian pattern, meaning that inheriting a single gene locus does not explain all the increased intrafamilial risk for developing depression. Similarly, the association between immunologic factors and depression does not fully explain why depression develops; neither does the presence of environmental stressors nor the hyperactivity of the HPA axis alone explains the pathogenesis of depression. The conclusion is that depression is a complex disorder caused by an interplay of genetic, environmental, immunologic, and endocrine factors (Jesulola E. et al., 2018).

According to the diathesis-stress model, the HPA axis provides a central link between the various contributing factors underlying the development of depression.

In summary, environmental stressors acting through immunologic response and heritable genetic factors initiate structural and functional changes across many brain regions, resulting in neurogenesis and neurotransmission dysfunctions which manifest themselves as the combination of symptoms that constitute depression.

Heritable genetic factors that generate vulnerability have a reciprocal interaction with environmental stressors. In vulnerable subjects, environmental stressors activate the HPA axis and increase CRF secretion, leading to the hypercortisolemia seen in depression. In turn, hypercortisolemia (from HPA axis hyperactivity) causes structural and functional changes in brain regions, especially in the prefrontal cortex, hippocampus, and amygdala, areas which are believed to be involved in the development of psychological, cognitive, physical, and emotional symptoms of depression. Likewise, high glucocorticoid concentrations negatively influence the rate of proliferation of neural progenitor cells in the hippocampus, thus inhibiting neurogenesis. Other structural and functional changes attributed to hypercortisolemia include alterations in the connectivity between certain brain regions (e.g., prefrontal cortex and amygdala), increased dendritic branching resulting in volume increases in areas such as the amygdala, and cell apoptosis resulting in decreased prefrontal cortex and hippocampal volume. These changes present as the emotional and behavioral symptomatology of depression, including apathy, mood disturbance, cognitive dysfunction, withdrawal, and anhedonia (Kanter JW et al., 2008).

Genetic factors acting through the HPA axis promote excessive secretion of CRH and cortisol, the effects of which are structural and functional changes in brain regions which then contribute to depression. Environmental factors acting indirectly through genetic factors may cause the HPA axis hyperactivity seen in depression.

Cytokines are also involved in the HPA axis central model. Increased pro-inflammatory cytokines directly produce depressive symptomatology by reducing 5HT production and interfering with brain neuroplasticity and monoamine activity. Pro-inflammatory cytokines increase glucocorticoid receptor resistance, inhibiting CRF downregulation and enabling the consequent hypersecretion of cortisol. Thus, immunologic factors modulate depression indirectly through the HPA axis (R. Dantzer et al., 2007). However, it is also plausible that psychological or environmental stressors act through the HPA axis principally by increasing hypothalamic CRF production; this secondarily increases the production of pro-inflammatory cytokines, the actions of which directly or indirectly result in depression (Raison CI et al., 2006).

The relationship between stress, the HPA axis, pro-inflammatory cytokines, and BDNF is illustrated in Fig. 8.1.

In summary, environmental stressors and heritable genetic factors acting through immunologic and endocrine responses initiate structural and functional changes in many brain regions, resulting in neurogenesis and neurotransmission dysfunctions, which then manifest themselves as a constellation of symptoms which typify depression.

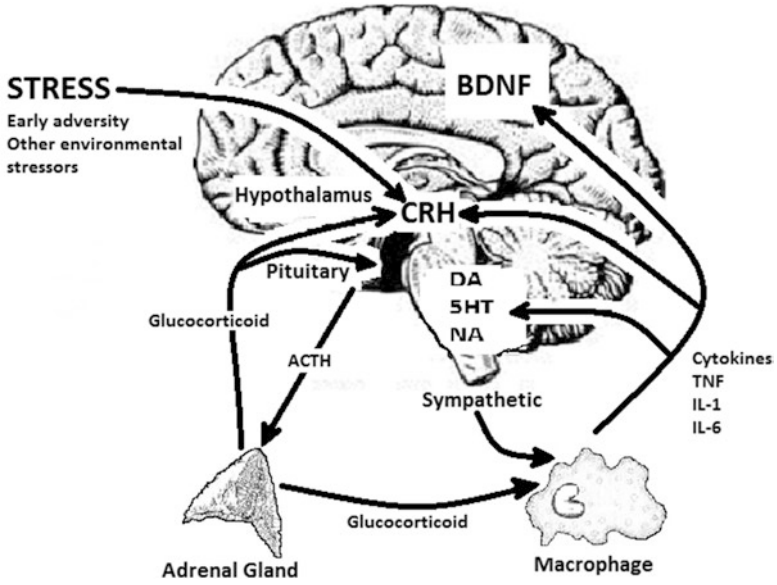

Fig. 8.1 Stress–immune interactions and depression
Stressors activate central nervous system stress circuitry, resulting in the release of glucocorticoids and corticotropin-releasing hormones (CRH) and pro-inflammatory cytokines (TNF, IL-1, IL-6). Pro-inflammatory cytokines, in turn, can access the brain, induce inflammatory signaling pathways, and ultimately contribute to altered monoamine metabolism, increased excitotoxicity, and decreased production of relevant trophic factors such as BDNF. The disruption of serotonin (5-HT), norepinephrine (NE), and dopamine (DA) transmission impairs the regulatory feedback loops that "turn off" the stress response

8.7 The Heterogeneity of Major Depression

One of the main difficulties of research on the neurobiological basis of depression is the heterogeneity of the cases included in the diagnostic category of major depression. Depressive disorders exhibit different phenotypes and comorbidities, with variations in the number, severity, and persistence of their symptoms. Even though the DSM-5 and the ICD-11 represent a step forward from their predecessors, they both remain subjective categorical classification systems that are fundamentally descriptive in nature, being primarily based on self-reported symptoms, clinical signs with observer bias, and few confirmatory tests.

From the point of view of etiopathogenesis, one possibility is that depression is a syndrome that has common pathophysiological mechanisms that constitute a unified matrix. Another possibility is that there are several different subsyndromes of depression. In this conception, each subsyndrome may consist in a grouping of pathophysiological mechanisms that form discrete sets with little or no overlap. Finally, each pathophysiological mechanism may represent a discrete disorder. Thus, the pathophysiology of depression may represent one disorder composed of

an interactive matrix of mechanisms, a few disorders representing separate groups of pathophysiological mechanisms, or numerous discrete biological mechanisms (Dean J., Keshavan M., 2017).

One way to progress in this field is to adhere to the Research Domain Criteria (RDoC) with the ultimate goal of grouping patients according to the underlying pathophysiology of their disorder, subsequently mapping out the relationship between pathophysiology and its phenotypic expression (Casey BJ et al., 2013). The current RDoC paradigm approaches psychiatric illnesses by identifying domains that run across different diagnoses and then singling out the various factors involved in each level of detail, from genes and molecules to neural circuits and behaviors.

As an alternative way of making progress in this area, the need to clarify specific molecular mechanisms has been raised. Among the strictly biological pathophysiological factors in depression, the common end pathway appears to be reduced neurogenesis, leading to functional hypoconnectivity in higher cortical regions and hyperconnectivity in limbic areas; yet, the precise way in which these biological factors lead to reduced neurogenesis or the way in which reduced neurogenesis leads to depression remains unclear. Targeting this common pathway with the goal of understanding how a hyperactive HPA axis, inflammation, and alterations in neurotransmitters cause reduced neurogenesis would be of paramount importance, as intervention at this level may hold great promise for good clinical outcomes (Dean & Keshavan, 2017).

Accumulated knowledge acquired over the past few decades is expected to be translated into new therapies and ultimately into better patient outcomes. Meanwhile, the use of precision medicine in psychiatry has been suggested as a promising strategy that could improve patient treatment outcomes (Bousman CA et al., 2017; Pitsillou E et al., 2020). Currently, treatments and antidepressants are primarily chosen using a "trial and error" approach. By taking into consideration genetic heterogeneity and the contribution of environmental factors, it may be possible to develop treatments that are more individualized, effective, and better tolerated.

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Chapter 9
A *Dimensional* and *Dynamic* Approach to the Neurobiology of Mood Disorders: On Intermediate Phenotypes and Their Interaction with Early Stress

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9.1 Introduction

Depression is a highly heterogeneous clinical syndrome (Leuchter et al., 2014), given not only the variety of mental symptoms included in the nosological entity but also the various clinical trajectories that the same diagnostic category encompasses. Patients with depression characterized by anergia and psychomotor slowdown are likely to present with neurobiological alterations different from those displayed by patients with the same diagnosis but whose symptoms are marked by anxiety, psychomotor restlessness, and insomnia. In a similar vein, it is plausible to suggest that neurobiological alterations may differ among depressed patients with different illness courses. The age of presentation of the first depressive episode, or the presence of a recurring mood pattern, might be associated with psychopathological phenomena of various types, which would add complexity to the challenge of describing a neurobiology of mood disorders.

Despite the wide variability among depression phenotypes, patients receive the same categorical diagnosis and, consequently, similar therapeutic recommendations. In this context, practitioners overlook variables beyond the behavioral level, such as genetic variants, the functioning of neural networks, or other physiological measures. This way of generating therapeutic recommendations may have led to the current situation, when only one-third of the patients with a major depressive disorder achieve a satisfactory recovery after the first treatment with antidepressants (Krishnan, 2010). Clinical practice recommendations have left out a dimensional approach that can contribute to the study of the multiple phenotypes of depression and their association with biological markers as indicators of clinical response. The establishment of clinical subgroups with less intragroup variability in terms of variables of a different level (environmental, behavioral, neural, cellular, molecular)

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_9

could pave the way for better predictions regarding the degree of effectiveness of therapeutic interventions (Tanti & Belzung, 2010).

Interestingly, studies in animal models that have yielded knowledge about the neurobiological basis of depression have focused on experimental paradigms of "stress exposure," either acute or chronic (Nestler, 2010). Research in animals with "depression" is limited not only by the use of variables that provide no access to the subjective dimension of depressive diseases but also by the examination of symptoms (or behavioral alterations) that are too unspecific for delivering a categorical depression diagnosis. This situation makes it necessary to advance toward a dimensional approach to the study of the neurobiology of depression by encouraging the examination of more specific behavioral alterations, thus making it possible to describe the neural circuits affected (Cuthbert, 2015) and establish connections with other levels of description. In addition, it is necessary to consider exploring the variable "exposure to stress," due to exposure to either early events (childhood trauma) or recent events, as a fundamental factor in the study of the neurobiology of the multiple types of depression.

In brief, this chapter proposes that the study of the neurobiology of depression requires a *dimensional* approach due to the high variability of phenotypes within this diagnostic category. The text highlights the identification of intermediate phenotypes as a strategy for conducting an inter-level analysis of the pathophysiological mechanisms involved in mood disorders. In addition, the chapter will focus on describing studies that incorporate the variable "stress response" to add consistency to the contributions of basic neuroscience to research on the neurobiology of clinical syndromes, such as depression. It should be noted that most of the said knowledge has been produced through research that has used experimental paradigms of stress response to model the neurobiology of animals with "depression." Given this context, the chapter will describe some of the studies that have incorporated this variable through the design of gene-environment interaction models in the field of mood disorders, specifically those that, adopting a dimensional perspective, have focused their main outcomes on intermediate steps (intermediate phenotypes). This perspective makes it possible to advance toward an understanding of the neurobiology of mood disorders as a *dynamic* phenomenon in constant interaction with environmental variables.

First, the chapter includes a short section on conceptual aspects; then, it provides reflections on clinically relevant examples of major depressive disorder and bipolar disorder.

9.2 Intermediate Phenotypes as a Strategy for Describing the Neurobiology of Mood Disorders

Intermediate phenotypes are quantifiable physiological traits or processes that are interposed between gene and clinical phenotype, but they do not necessarily fulfill all the criteria that define endophenotypes (Leuchter et al., 2014). The study of

intermediate phenotypes is a strategy for describing the intervening steps involved in psychiatric disorders, stressing inter-level analysis with a spectrum-wide perspective that includes genetic and cellular levels, neural circuits, and behavioral domains. Each of these intermediate phenotypes can be characterized through a particular set of experimental measures, such as genomics, proteomics, neurophysiological measures, neuroimaging, and symptom measures (Leuchter et al., 2014), which make it possible to generate a more biologically plausible description that is closer to the etiological process.

Meyer-Lindenberg provides an interesting analogy in this regard. He proposes that the study of *intermediate phenotypes* in psychiatric disorders is akin to moving from the study of cardiac insufficiency or stroke (complex diseases) to the study of *ventricular hypertrophy* or the *metabolism of cholesterol* (Meyer-Lindenberg and Weinberger, 2006). This strategy was consolidated by the National Institute of Mental Health through the Research Domain Criteria (RDoC) initiative, which has led to systematic efforts to identify *intermediate phenotypes*, leading to more homogeneous intermediate diagnoses, and thus achieve better treatment response levels (Insel, 2014).

One of the aims of seeking *intermediate phenotypes* is to identify groups of patients with a common neurobiological substrate that can be targeted with more specific interventions. In this case, research will focus on identifying biomarkers that make it possible to predict treatment response. The set of intermediate steps believed to have a common neurobiological substrate – which would enable practitioners to predict treatment response –constitutes the set of *static intermediate phenotypes*. Such intermediate phenotypes are very hard to identify in psychiatric disorders, probably due to the great complexity and dynamism of the pathophysiological mechanisms involved. Neural networks are constantly responding to environmental demands through complex neuroplasticity mechanisms, which makes it difficult to identify pretreatment (static) markers that can be used to predict the behavior of multiple, permanently interacting variables.

Given these difficulties, researchers developed the concept of *dynamic intermediate phenotypes*, which involve the identification of state-dependent biomarkers. In this case, the act of predicting treatment response considers the phenomena taking place in intermediate steps as a result of exposure to a given treatment or intervention. Therefore, this is a dynamic measure that makes it possible to describe the initial steps taking place in the domain studied (e.g., expression of a protein or functioning of a neural circuit) as a consequence of the treatment (EI-Hage et al., 2013), which enables to advance a prediction of the main outcome (e.g., antidepressant response). Obviously, this indicator must be able to yield a prediction of the main outcome within a time frame that ensures that it will remain clinically useful. In this regard, and considering the psychiatric treatments available for dealing with mood disorders, measurements of dynamic intermediate phenotypes yielding a prediction before 10 days can be useful, given the 4- to 6-week limits for evaluating therapeutic antidepressant response and the 12- to 14-week limits for remission indicators (Leuchter et al., 2014).

Lastly, any intermediate phenotypes identified should be distant from the ends of the spectrum (genome and diagnostic category). It would be unlikely for intermediate phenotypes too close to the genome to predict responses, given the great complexity and variability of the interactions within the pathophysiological cascade, leading to the expression of the diagnostic category. In this case, we might be measuring risk rather than predicting potential benefits. In contrast, intermediate phenotypes too close to the clinical syndrome may be tautologically expressing changes that reflect the treatment response of only some symptoms of the diagnostic category, without necessarily fulfilling their role of predicting greater therapeutic effectiveness.

As pointed out in the introduction, the description of intermediate phenotypes related to the neurobiology of mood disorders should not leave out the *"stress response"* variable. This may be especially important given the need to discuss theoretical developments that, with a marked biomedical bias, view the description of the physiopathology of mood disorders as the study of a hypothetical *"internal dysfunction"* that characterizes the diagnostic category. The trajectory of this perspective may have been influenced by the historical development of the psychopathological tradition.

Nineteenth-century descriptive psychopathology was based on semiology, a discipline that developed a notion of disease by attempting to link a set of signs and symptoms (phenomenal signifiers) with organic lesions responsible for their appearance (meanings) (Berrios, 2001). In contemporary psychiatry, this approach appears to remain in vogue, mainly in the clinical treatment of patients with psychiatric disorders, such as bipolar disorder or major depressive disorder. In clinical practice, it is not uncommon for such diseases to be regarded as the expression of "organic dysfunctions" that still require a better description. Regrettably, this biomedical understanding of the "meanings" of mood disorders often manifests itself in clinical actions.

The following section provides a reflection on the process whereby mental symptoms develop, based on an analysis of the role of early stress in the clinical course of mood disorders. Its core hypothesis encourages us to understand the neurobiology and psychopathology of mood disorders as a dynamic phenomenon that depends on interactions with environmental variables. This interaction is believed to shape the set of "phenomenal signifiers" (signs and symptoms) observed, in contrast with the notion that a symptom is an expression that emerges purely out of an *"internal"* and *"static"* dysfunction *"inherent"* to the diagnostic category.

9.3 Gene-Environment Interaction Models and Intermediate Phenotypes in Depression

The body of evidence regarding the absence of associations between genetic variants and diagnostic categories, even in studies that examine the full genome (GWAS) (Cichon et al., 2009), has redirected the search for correlations between genetic

variants and intermediate phenotypes. Searching for intermediate phenotypes adds power and validity to the detection of the effect of genes on psychiatric disorders (Rasetti & Weinberger 2011), which has encouraged a dimensional approach to the design of some more recent studies.

From another perspective, genetic research that has incorporated the *early stress* variable through gene-environment interaction models has yielded evidence of associations between some genetic polymorphisms (linked with neurobiological regulation systems triggered by stress, socioemotional regulation, and neural plasticity processes) and the presence of a depressive disorder (Hornung & Heim, 2014). Caspi, in 2003, advanced a pioneering research model that considers genetic and environmental variables to predict depression. This study reported the interaction of genetic variants of the 5-HTTLPR, specifically the s-allele, with early stress events (child abuse) in the prediction of depression (Caspi et al., 2003). Likewise, the dopamine receptor, specifically the rs40184 polymorphism of the dopamine receptor gene, interacted with perceived *maternal rejection (adverse environment)* in the prediction of a depressive disorder (Haeffel, 2008). Examples of similar gene-environment links have been reported in pathophysiological mechanisms that involve the corticotropin-releasing hormone receptor, with an interaction being demonstrated between a background of child abuse and polymorphisms in the CRHR1 gene in the prediction of depression (Bradley et al., 2008). Another link was reported between the glucocorticoid receptor and FKBP5, revealing an interaction between rs136078 of the FKBP5 gene and child abuse in the prediction of major depressive disorder (Appel et al., 2011). Similarly, Aguilera et al. reported an interaction between the polymorphism of the brain-derived neurotrophic factor (BDNF) (rs6265) and reports of childhood sexual abuse in the prediction of depression in adult life (Aguilera et al., 2009). Other studies have yielded similar results for the prediction of a depressive disorder, including genetic variables associated with the oxytocin receptor (Thompson et al., 2011) and the endocannabinoid receptor (Agrawal et al., 2012).

Despite the above, subsequent studies have produced heterogeneous results regarding the involvement of specific genetic variants in the development of a clinical syndrome with high phenotypic variability, such as depression. In this regard, it is less biologically plausible to conclude that a single genetic polymorphism is involved in the development of a highly complex clinical syndrome in an early stress environment, which is equally difficult to conceptualize. In other words, establishing an association between a single gene and the development of a clinical syndrome seems to be too great a leap, which would reflect a lack of interest in understanding the neurobiological mechanisms that may underlie this connection. In this regard, the concept of intermediate phenotypes could make it possible to work toward describing new gene-environment interaction models, whose main outcome is focused on intermediate steps. This type of dimensional approach is aimed at correlating the gene studied with a pathophysiological mechanism that has a more biologically plausible role in the development of a given clinical syndrome.

Some of the few studies that have employed such research designs to devise gene-environment interaction models focused on intermediate phenotypes have

selected intermediate steps with a clear relevance for the development of depressive disorders. In this group of studies, evidence has been found that establishes HPA axis activity as an *intermediate phenotype*. Some researchers have observed an interaction between the 5-HTTLPR genotype and early stress events, reporting that adolescents who carry the s-allele display higher and longer-lasting cortisol levels than carriers of the l-allele (Gotlib et al., 2008). Taking into account the involvement of other allelic variants – such as the rs110402 and rs242924 functional polymorphisms in the CRHR1 gene – in stress regulation mechanisms, Tyrka et al. reported that carriers of the GG allele who had reported childhood abuse displayed high levels of cortisol in the dexamethasone/CRH test (Tyrka et al., 2009), thus providing valuable information for improving our understanding of the potential mechanisms involved in *gene-early stress* interaction for depression.

Similarly, other studies of this type have employed *intermediate phenotypes* by functionally and structurally examining specific brain regions plausibly linked with the pathophysiological cascade of a depressive syndrome. For instance, Frodl et al. found that patients with depression who had experienced emotional negligence in childhood and who carried the s-allele of the 5-HTTLPR had a smaller hippocampus volume (Frodl et al., 2010). Interestingly, this study also demonstrated that patients with a history of early stress, but who carried the l-allele, displayed greater prefrontal cortex development, possibly reflecting a compensatory or protective mechanism in response to early adverse events. Within the same subset of studies focused on the measurement of the volume of specific brain regions (intermediate phenotypes), BDNF met carriers exposed to high levels of early stress were found to have lower hippocampus and amygdala volumes (Gatt et al., 2009).

Among the studies focusing on cognitive functioning as an intermediate phenotype, Thomason et al. found that carriers of the s-allele of the 5-HTTLPR displayed greater attentional bias in emotional processing tests when shown fearful faces compared to carriers of the protective l-allele (Thomason et al., 2010). Within the same intermediate phenotype domain (cognitive functioning), it has been reported that variations in the CRHR1 gene (rs110402) seem to moderate neural response to emotional stimuli, suggesting that this polymorphism is involved in the appearance of a depressive disorder (Hsu et al., 2012).

In conclusion, research focused on intermediate phenotypes is likely to offer an approach that allows a greater understanding of the pathophysiological mechanism involved in mood disorders.

9.4 Cognitive Functioning as an Intermediate Phenotype and the Omission of Early Stress in Patients with Bipolar Disorder

It should be noted that strategies for identifying intermediate phenotypes through the study of interactions with environmental stressors have also been adopted in research on recurrent mood disorders, specifically in patients with bipolar disorder

(BD). For instance, Savitz reported that increased-risk allelic variants linked with BDNF were associated with poorer performance in memory-based cognitive tests in people who had experienced sexual abuse (Savitz et al., 2007). In a similar vein, Aas et al. reported that homozygotic carriers of the s-allele of 5-HTTLPR experiencing high levels of childhood trauma (physical abuse and negligence) showed more cognitive dysfunction across domains compared with all other groups, even after adjusting for age, sex, and parents' educational level (Aas et al., 2012). Also regarding the BDNF gene, the same author reported that carriers of the methionine (met) allele exposed to high levels of childhood abuse demonstrated significantly poorer cognitive functioning compared to homozygotic valine (val/val) carriers (Aas et al., 2013).

In this context, conducting research that considers childhood abuse in patients with bipolar disorder is relevant, given the evidence for its higher frequency (Garno et al., 2005) and its association with a poorer clinical course (Agnew, 2016). The impact of a poorer clinical trajectory is likely to be mediated by the association between early stress and intermediate phenotypes, such as cognitive functioning. A study conducted by our group proposed a gene-environment interaction model to evaluate the association between childhood abuse and performance in a social cognition test (intermediate phenotype), measuring the possible modulation effected by the BDNF rs6265 genetic polymorphism in euthymic patients with bipolar disorder type I. The study was carried out in the Mood Disorders Unit of the Hospital Psiquiátrico del Salvador of Valparaíso, Chile. A cross-sectional analytic design of an observational nature was employed with n = 117, calculated according to minimum allele frequency (MAF). Euthymia was checked using the Hamilton Rating Scale for Depression and the Young Mania Rating Scale; childhood abuse was measured with the Childhood Trauma Questionnaire (Spanish version); and the intermediate phenotype was conceptualized as social cognition functioning, measured through an emotional processing test (TASIT). We found a high rate of childhood abuse (64%). This element was found to be linked to early illness onset (odds ratio = 3.3 p.02) and at least one suicide attempt (OR = 3.5 p.00). Patients exposed to emotional abuse were able to recognize fear situations more accurately when they carried the C allele (C/C r = 0.4 p.02; C/T r = 0.7 p.01). In the cases of sexual abuse, participants with the same allele variant were able to recognize anger more accurately (C/T r = 0.6 p.04). Finally, we concluded that *BDNF rs6265* modulates the impact of early stress on social cognition functioning in patients with bipolar disorder. Given the high frequency of child abuse and its impact on clinical trajectory, we consider that it is necessary to emphasize the clinical evaluation of early trauma in patients with bipolar disorder (Ríos, 2019). In this regard, it should be noted that research has left out the analysis of early stress as a relevant variable when examining the characteristics of cognitive dysfunction in bipolar disorder. Several publications on cognitive functioning in bipolar disorder, including systematic reviews and meta-analyses, have concluded that average performances appear to be altered in patients with BD, which has shifted the debate toward the identification of a characteristic dysfunction in these patients (Bora & Pantelis, 2016; Samame, 2013). This seems like a rushed conclusion, given that these studies have not included the *early stress* variable in their analyses. The omission of variables that make it possible to

describe the phenomena that occur before the *"onset"* of the disease reflects the biomedical approach adopted in the psychopathological description of a psychiatric disorder with a well-known genetic component, such as BD. It would seem that researchers have assumed that this psychopathological phenomenon is associated with *an internal dysfunction* typical of the disorder that may be present from its onset or appear over the course of its clinical evolution. This biomedical bias can be observed not only in research but also in clinical practice, as evidence exists that clinicians devote insufficient energy to detecting early stress, mainly childhood abuse, in patients with psychiatric diseases characterized by psychotic symptoms (Read et al., 2016).

A number of hypotheses have been proposed about the possible mechanisms, whereby childhood trauma interacts with cognitive dysfunction. First, it has been hypothesized that cognitive deficits resulting from an environment devoid of basic care are linked to inadequate nutrition, a lack of cognitive stimulation in childhood, and negligence in physical and psychological care, all of which are common features of families where abuse occurs (Hackman & Farrah., 2009). Other authors have suggested that abusive parents may have a lower intelligence quotient (IQ), which could be genetically inherited, or that lower-IQ children could be at a higher risk for abuse (Perez & Spatz., 1994). However, both theories have been challenged using data from studies that have controlled for variables such as educational level and measurements of premorbid IQ (Aas et al., 2011a, b). From another perspective, the potential impact of childhood trauma on the functioning of the hypothalamic-pituitary-adrenal axis (HPA) could be a relevant variable for cognitive performance. Childhood trauma has been linked to persistent sensitivity and hyperactivity of the HPA axis (Heim et al., 2000), a situation that has been proven in a clinical sample of patients with first-episode psychosis, who also display a performance reduction in all cognitive domains compared with controls (Aas et al., 2011a, b). Altered cortisol response upon waking up has been associated with more verbal memory and processing speed deficits, two points that appear to support the role of the HPA axis in cognitive functioning modulation in patients with psychotic episodes (Aas et al., 2011a, b). Nevertheless, some evidence exists which provides contradictory data regarding cortisol levels and stress response tests in patients with first-episode psychosis and a background of childhood trauma (Mondelli et al., 2010). These results indicate that other variables may be involved in the complex relationship between childhood trauma, HPA axis activation, and cognitive functioning. Interestingly, a systematic review and meta-analysis of the functioning of the HPA axis in BD was published in 2016, which ruled out the possibility that functional alterations might be a typical characteristic of this disorder. This study yielded no data in support of the view that these alterations constitute an endophenotype of the disorder; rather, they appear to be related to early exposure to environmental variables such as childhood abuse (Belvederi et al., 2016). Lastly, it is relevant to note that a history of childhood abuse can have a stronger effect on people with a psychiatric pathology compared to controls, a situation that may be related to a higher level of exposure to abuse-derived stress and more neurobiological vulnerability to stress, which may be related to genetic aspects (Modelli et al., 2008).

As pointed out at the start of this chapter, research on cognitive dysfunction in BD has overlooked relevant evidence about the role of early stress in the psychopathology of this disease. Even though some studies have considered this variable, the main clinical practice guidelines, systematic reviews, and meta-analyses have left it out as a relevant factor that may shape the psychopathological phenomena of cognition (intermediate phenotypes) in patients with BD.

9.5 Conclusions

The gene-environment interaction models that have selected intermediate phenotypes as their main outcome provide a valuable design that enables us to generate evidence for developing a clearer understanding of the complexities of the study of the neurobiology of depression. Research of this type takes into account the problem of the high phenotypic variability of the diagnostic category, focusing on intermediate dimensions that are closer to the neurobiological mechanism involved. In addition, it includes environmental variables, chiefly measurements of early stress, as a way of highlighting the dynamism of the neurobiological mechanisms involved in the development of mood disorders. From this perspective, disorders are not "internal, static dysfunctions inherent to the disease"; rather, it is assumed that pathophysiological mechanisms remain in a state of constant dynamism, permanently interacting with genetic and environmental variables.

The identification of neurobiologically distinguishable depression subtypes resulting from exposure to early stress should be emphasized in the analysis of responses to treatment (Heim et al., 2008); in this regard, Nemeroff et al. found differential therapeutic responses to psychotherapy and pharmacotherapy, depending on the presence or absence of childhood abuse in patients with major depressive disorder (Nemeroff et al., 2003). Similarly, clinical approaches to bipolar disorder should take into account childhood abuse as a relevant variable associated with the prognosis of the clinical course of the disease. The high frequency of childhood abuse in BD challenges us to consider more specific psychotherapeutic interventions for this group of patients, as psychosocial strategies other than the well-known psychoeducation workshops are needed to address the numerous clinical reports of early trauma events.

We propose that mental symptoms must be understood as *dynamic processes*, inasmuch as they are emergent and self-organizing processes based on recurrent interactions between dynamically coupled elements (Varela, 1995). From this perspective, it is necessary to adopt an "embodied" notion of psychopathology, according to which the material basis of the system determines the possible dynamic patterns. That is, the nervous system as a whole and its connections with the rest of the body (e.g., muscles, viscera, sensory organs) constitute the structure that will enable psychopathology to express itself while at the same time limiting it. The intermediate phenotypes examined here, specifically those focused on cognitive functioning dimensions, should be regarded as part of a *dynamic system* with

emergent and *sub-emergent* properties. In a dynamic system, a property is emergent if the elements that comprise the system lack that property but the system as a whole possesses it (Rodríguez, 2008). That is, the property (in this case, cognitive functioning) emerges from the interaction between the elements in the system (sets of neurons) and not from the isolated activity of these elements. *Sub-emergent properties* (Thompson & Varela, 2001) are those whereby a system already equipped with emergent properties uses said properties to control or modulate the local properties of the constituent elements of the system (Rodríguez, 2008). It is the latter process that enables us to understand the phenomena of consciousness, and therefore of experience, as causality variables. In other words, the psychopathological phenomenon of cognition does not only result from emergent properties derived from the interaction of multiple individual elements (neuron groups and electrochemical processes) that configure a global process (cognitive functioning); rather, said cognitive process (understood as a global process) should also be able to control or modulate individual elements in the opposite (*sub-emergent*) direction. Some interesting evidence has been published about phenomena related to sub-emergent properties, which has revealed that the maintenance of a mental state, in this case, time devoted to meditation (global process), intensely and permanently modifies neural activity, according to the measurement of neural synchrony indexes (particular element) (Lutz et al., 2004). In conclusion, cognitive functioning (intermediate phenotype) should be understood as an essentially dynamic process, far from the classical notion of psychopathological phenomena as the expression of an *internal and static neurobiological dysfunction inherent to the disease*.

The above arguments prompt a critical approach to classical psychopathology and its descriptions of nosological entities, such as bipolar disorder or some types of depression. Research on the neurobiology of mood disorders often suggests an *internal and cryptogenic* origin, which is believed to express itself after a temporal milestone that leads to the supposed "onset" of the disease. Authors talk of a "process" that interrupts the patient's life cycle, presuming that it is the expression of a previously constituted neurobiological dysfunction. These classical notions are likely to be present in the clinical imaginary of psychiatrists who treat patients with mood disorders without taking into account psychosocial variables as an essential part of the disease. This approach has predominated in clinical practice and research with patients with mood disorders and may be related to practitioners' failure to look for early trauma events as a relevant variable during the diagnostic and therapeutic process.

Child abuse is a dramatic experience whose impact can be felt at multiple levels. From a dynamic perspective, this *global* experience can modify particular elements, leading to morphological alterations in the central nervous system (Aas et al., 2013), inflammatory alterations (Danese & Baldwin, 2017), changes in neurogenesis processes (Kauer-Sant'Anna et al., 2007), and epigenetic modifications (Klengel et al., 2013), to mention but a few. The impact of early stress, specifically child abuse, on cognitive functioning (intermediate phenotype) has been examined in several studies. Most of them have found a negative effect on the functioning of several cognitive domains, many of which are connected to the operation of brain regions

characterized by a higher density of corticosteroid receptors, such as the hippocampus and the prefrontal cortex. This characteristic grant biological plausibility to the association between early trauma and cognitive dysfunction, since early stress results in a sustained increase in cortisol, which alters neural plasticity processes, especially in brain regions with more receptors (Teicher et al., 2003).

A look at the available evidence makes it difficult to understand why intermediate phenotypes have been studied without taking early traumatic events into account. Given this omission, this chapter is a way of critically addressing the biomedical bias in research and in clinical practice aimed at patients with mood disorders. Developing an understanding of the neurobiology of mood disorders as a dynamic and dimensional process, in permanent interaction with generic and environmental factors, emerges as a desirable goal both for developing new theories about the pathophysiological processes that underlie mood disorders and for designing new treatments.

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Chapter 10
Psychophysiology and Psychoneuroendocrinology of Stress and Reward in Depression

Jaime R. Silva, Franco Medina, and Manuel S. Ortiz

10.1 Introduction

Affective neuroscience has helped to deepen the understanding of emotions and to dispel myths and false beliefs about the affective life of human beings that have permeated the sciences about the human psyche (Davidson, 2003). Research informed by this perspective has allowed a more detailed description of the emotional functioning of individuals, but especially the ways in which this process can go awry.

Major depressive disorder is one of the pathological conditions marked mainly by an alteration of the patient's emotional life. Although there are several symptoms associated with MDD, emotional ones are their nuclear characteristic.

Emotions play a critical role in the survival of the individual and his/her adaptation to the environment in which he/she finds himself. The emergence of emotion in an individual most often depends on perceiving that something affects our well-being, for better or for worse (Ekman, 2018).

Well-defined neural circuits are responsible in the perception and response to both threats and rewards. These are called the stress and reward system. Models about the etiology and pathophysiology of MDD refer to how a certain configuration of the stress system and the reward system are potentially disadvantageous in the face of stressful events (Pizzagalli, 2014). This approach is referred to as a

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*,
Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_10

diathesis-stress model: particular characteristics make individuals more likely to develop particular responses in the face of stressful events (Monroe & Simons, 1991).

Both the stress system and the reward system are constrained by the architectural organization and functional dynamics of the brain. Both brain organization and its functional dynamics have influenced the development of models on motivation and regulation of behavior, affect, and cognition.

The following chapter will describe general principles of brain functioning. We will then review the scientific evidence on the functioning of the stress and reward systems and how it differs in patients with MDD. This will be followed by a review of evidence on how these characteristics are configured during development.

10.2 The Functional Hierarchy of the Nervous System

The functioning of the brain shows us that, in general terms, there is an order that follows a rule of complexity: as the processes move away from the brain stem and toward the cortical areas, the complexity of the functions to which it is associated increases (Perry, 1999).

This heuristic principle is portrayed by the triune brain model (Maclean, 1990). Paul MacLean developed a model that summarizes, in general terms, the macro-organization of the brain architecture. This author defines three levels that are superimposed (as layers) and that are related to particular functional domains.

The first layer consists of the brain stem and the cerebellum, which specialize in automatic functions (such as involuntary breathing, heartbeat, etc.) and regulatory functions (such as blood pressure regulation) with an emphasis on survival.

The second layer consists of the septum, amygdala, hypothalamus, hippocampal complex, and cingulate cortex. Classically, this area is called the limbic system. The specialization functions of these areas are closely related to emotions and motivation. Specifically, it is associated with the emotions and motivations that are associated with parenting, reproductive behavior, and eating.

The third layer is composed by the cerebral cortex and gives room to complex cognitive processes that are classically associated to higher primates. These complex cognitive processes refer to abstraction, language, etc.

There are several criticisms of this model. Among them, author Robert Sapolsky (2017) lists the following criticisms:

A. The evidence shows that there is considerable overlap between the different layers.
B. There are interactions from layer 1 to layer 3 without being mediated by the second layer.
C. Many authors consider that the automatic aspects of emotions and thoughts cannot be separated.
D. There is evidence that changes occur in the first layer, despite it being evolutionarily conserved.

Nevertheless, it is a good starting point for understanding the brain architecture in general terms.

These different brain layers maintain reciprocal and hierarchical relationships with each other. This is what has been called circular causation or two-way causation in the brain functioning (Northoff et al., 2011). The authors postulate a model of nested hierarchies of the brain/mind. In contrast to Maclean' triune brain model, the different functional levels are contained within each other and relate to specific brain circuits. The activations of basal areas regulate the functioning of the upper areas (bottom-up regulation), just as the upper areas regulate the functioning of the basal areas (top-down regulation).

This principle and evidence permeate psychological models of emotion regulation. In general, particular models have the following structure: first, an activation phase and, then, a regulation phase (Koole, 2009). During the activating phases, there are variables linked to bottom-up temperamental aspects that regulate a level of activation in response to stimuli. During the recovery phases, there are variables linked to top-down aspects that optimize the activation level according to an ideal level.

Although these processes are highly related, there is a distinction in relation to the underlying motivations of the bottom-up process. This distinction between the underlying motivations is due to another organizing principle of brain architecture: the brain's dissociation of motivational systems into the brain hemispheres.

10.3 The Lateralization of the Motivational Systems in the Brain

Lateralization refers to how a particular function or structure is divided from the hemispheres, generating a degree of specialization in each of them (Rogers, 2015). This lateralization of the nervous system is present in both invertebrates and vertebrates (Frasnelli, 2013). There is evidence that shows us that the evolution of lateralization of the nervous systems, at the population level, is facilitated by the exposure to social environments (Niven & Frasnelli, 2018). This evidence tells us how fundamental this organizing principle is.

This lateralization of functions in the nervous system is born from an original specialization associated to processing our evolutionary environment. Actual computational simulation models of evolutionary pressures have shown that, in our evolutionary conditions, approach and avoidance behaviors for external positive and negative affective stimulus are an emergent specialization that an organism develops autonomously (den Dulk et al., 2003).

This specialization of approach and avoidance behaviors is maintained in human beings. Much of the evidence points to emotion and motivation being lateralized in the brain hemispheres. Specifically, positive affect and approaching behaviors are lateralized in the left hemisphere, while negative affect and avoidance behaviors are

lateralized in the right hemisphere. This was proposed as the valence hypothesis (Davidson, 1985). Later evidence showed that this hypothesis is consistent with the lateralization of motivation but not that clearly with the lateralization of emotions (Harmon-Jones et al., 2010). This is because emotions of negative valence can lead to either avoidance (e.g., fear) or approach motivations (e.g., anger).

Evidence on the segregation of motivational systems has allowed researchers to develop a number of hypotheses that relate to the functioning of the prefrontal cortex as a top-down regulator of basal tendencies. Specifically, the asymmetry of brain potentials in resting states is associated with an affective style that functions as a trait (Wheeler et al., 1993). Right frontal asymmetry is associated with a facilitation of appetitive behaviors and positive affective experiences. In its counterpart, the left frontal asymmetry is associated with a facilitation of avoidance behaviors and negative affective experiences.

This structure of hierarchical related components that are symmetrically specialized can be observed in relevant psychological functioning models. An important model crucial for understanding psychopathology is the tripartite model of self-regulation (Nigg, 2017). We see reflected both the lateralization of motivational processes (approach and avoidance in bottom-up regulation) and hierarchical feedback processes between levels (Bottom-up and top-down regulation).

10.4 Self-Regulation of Emotion and Its Relation with Psychopathology

Considering all of the above, a current model that allows us to understand the way these processes interact to result in the regulation of behavior, affect, and cognition is the updated tripartite model of self-regulation (Nigg, 2017). Two bottom-up components are described here as regulatory mechanisms: the bottom-up tendency to avoidance and the bottom-up tendency to approach. These two tendencies interact, regulating each other. For example, toward 8 months of age, there is an innate avoidance tendency toward strangers and a tendency to approach our caregiver figures.

Another element of the model considers the interaction between bottom-up and top-down processes in relation to a filter or update threshold. This filter generates a parameter from which the bottom-up processes, reaching an indicated level, impact the top-down control processes.

This model is fundamental to understanding the development of depression: the decrease in bottom-up approach motivation without an effective top-down control. This is reflected in the functioning of processes that are relevant for both kind of motivations. On the one side this is evidenced by the avoidance of stressful situations and on the other side by the approach to rewarding situations.

10.5 Sensitivity to Stress and Differential Susceptibility to Reward

The foundation of this chapter lies in the definition of the systems of stress and reward and the evidence associated with their variation in such magnitude that they form a diathesis in the development of depression.

Both the stress system and the reward system have been developed throughout evolution to respond to the pressures present in the evolutionary environment. Both systems are refined throughout development to suit the context in which organisms live.

10.5.1 Stress

It is common, when reading a study on stress, not to find a clear definition. There seems to be a tacit principle of keeping certain general definitions as the ones that founded the study of stress phenomena. The scientific literature on stress varies in the depth of understanding of the phenomenon, and this is often reflected in an overemphasis on concepts that make accurate communication difficult (MacDougall-Shackleton et al., 2019). Nevertheless, the concept of stress has evolved as a consequence of the results of the investigations that have developed the different programs of research around stress (Goldstein & Kopin, 2007).

The general definition of stress was coined by Hans Selye as "the nonspecific response of the body to any demand made upon it" (Selye, 1976). This foundational definition drove research in a wide range of areas, which began to refine this definition in accordance with his results.

One important area of discussion concerns the "non-specificity" of the body's response. Several papers in this area have shown that the response of an organism varies according to the type of stress it faces. That is, the body's response to a physical threat may have a different pattern of response than the response to social threats.

It has also been discussed that this phenomenon is highly personalized. What is considered a stressful demand for one person may not be so for another. This is what Lazarus tries to capture through his transactional model of stress: a demand is stressful when we appraise the resources it requires to be adequately addressed, but the appraise of the resources themselves to address it is insufficient (Lazarus, 2012).

Other authors have focused their energies on the search for the fundamental elements (i.e., characteristics common to different types of demands) that make an external demand threatening. Two fundamental characteristics have been described here: the uncontrollability of the demand and the threat to the social image. These two elements make a demand a robust stressor (Dickerson & Kemeny, 2004).

For human beings, the demands that arise from interpersonal relationships are especially relevant. In the literature on stressful life events, it has been shown that in the face of different life situations that can affect people by generating stress, it is

the situations made by people that generate the greatest impact on their health. This is coupled with the idea that interpersonal stressors are the most robust in generating a stress response, which emphasizes the importance of personal relationships as a source of protection but also of threat in people's lives. Now, in temporal terms, we can distinguish steps that result in the stress response: the processing of demands, the triggered neuroendocrine response, and the coping response.

When a subject is confronted with stressful stimuli, different sources are processed through different pathways to the activation of endocrine responses. On the one hand, physical demands (e.g., pain) activate basal areas of the brain, which generate signals directed at triggering the endocrine response. On the other hand, psychosocial demands (e.g., negative social evaluation) are processed in the prefrontal cortex, sending signals that seek to generate the same endocrine response. Although there are different ways to generate the stress response, the endocrine response is in charge of the same circuits: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis. Both circuits generate a series of concerted movements that allow the release of hormones that change the state of the body in order to respond to environmental or internal threats. These endocrine changes have a strong impact on the neural functioning of the individual and are biased toward particular responses.

These responses range from primary startle responses to complex behavioral programs requiring high energy levels. Next, we will review the processing of stressful stimuli and the neuroendocrine response to these situations with correspondent evidence of their dysfunction in subjects with MDD.

10.5.1.1 Psychophysiology of Stress

Commonly, one of the techniques used to understand the psychophysiology of stress is functional magnetic resonance imaging (fMRI). This allows investigators to understand the neural areas associated to the processing of threatening stimuli and regulatory processes that follow. The tasks used for this purpose were the presentation of images, sounds, or videos and some kind of annoying or painful stimulation. The problem is that these types of tasks were not always able to activate the HPA axis. The tasks that functioned as robust stressors were those that required social judgment situations, such as the Trier Social Stress Test or aspects of the Maastricht Acute Stress Test.

These types of protocols are robust for eliciting the stress response but difficult to implement in fMRI settings. Through methodological innovations, a series of protocols were developed to transfer this type of experimental manipulations in the fMRI (Noack et al., 2019).

The stress response to stimuli depends on the detection and interpretation of a threat, either real or potential. That is what is known as a stressor. Stressors come in two types of stimuli that can trigger a stress response: physical stressors and psychosocial stressors.

Physical stressors are usually those that are experienced as threatening to an individual's well-being, such as pain. They are processed through the brain stem and the amygdala (Dayas et al., 2001) to activate the HPA axis. It has also been shown that there is a decrease in neural activity in the left dlPFC during the processing of physical stressors (Schaal et al., 2019).

Psychosocial stressors are those that threaten social self, such as social judgments and the performance of complex mental operations. Psychosocial stressors activate the HPA axis through the frontal cortex (orbital, medial, and ventrolateral portions), the hippocampus, and the anterior cingulate cortex. The role of the amygdala has been demonstrated in the anticipatory processing of psychological stressors (van Marle et al., 2009).

10.5.1.2 Psychoneuroendocrinology of Stress

The other fundamental component of stress is the ordered cascade of bodily changes that result in a state of readiness to respond to the demands required by the stressor. These changes are general throughout the body through the effect of corticosteroids on both the brain and the rest of the body. In general terms, they allow for greater energy expenditure and therefore have greater resources to deal with stressors in an optimal way.

The specific effects on the brain occur mainly on the functioning of the PFC. For anyone, the effect of cortisol on their functioning is reflected in the executive functions that are localized in the PFC. These functions allow us to organize and act consistently and in anticipation of future events. Stress responses can inhibit our ability to think long term, focusing on the most relevant and urgent aspects of a threat.

Stress responses measured at the endocrine level present a similar pattern of response in the population with variability, given by the sex and age of the individual most importantly (Kudielka et al., 2009). However, different psychopathological pictures show alterations in this response pattern, being depression one of the most known.

In depressive subjects the alterations of the cortisol pattern in front of psychosocial stressors can be described as a blunted cortisol response, a high basal cortisol level, and a slow recovery period (Burke et al., 2005). However, current evidence indicates that the different subtypes of depression have great variability in the way in which the HPA axis disturbance is presented (Stetler & Miller, 2011).

10.5.2 Reward, Reward Sensitivity, and Reward Processing

When people are confronted with stimuli, sensory signals are processed in order to assign properties to these stimuli. When we speak of a reward, we refer to a positive value assignment on the stimulus. Rewards have certain particular properties that allow a more complex resolution of our environment.

A first characteristic to consider of a reward is the subjective value assigned. The assigned value refers to the magnitude associated with a reward. Thus, we can differentiate between low-reward stimuli and high-reward stimuli.

This process is subjective, so we assign different values to different rewards. This process allows us to compare them. One explanation for this phenomenon is the common value hypothesis (Landreth & Bickle, 2008). This hypothesis states that regardless of the type of reward, we use a dimension of magnitude common to all of them and this allows us to generate comparisons. While there is evidence to support this hypothesis (Levy & Glimcher, 2012), current perspectives strain this explanation. Specifically, it has been discussed that those stimuli that have been especially important for our survival from evolutionary pressures have facilitated pathways of valuation over other stimuli of the same valuation magnitude (Pearson et al., 2014), especially in contexts of increasing ecological complexity.

Another characteristic of a reward is the effort required to obtain it. This refers to an analysis that compares the costs and benefits of obtaining a reward. This is a fundamental element in the development of a motivational state of approach. When we approach the objects that surround us, we can ascribe a positive or negative value to that object in terms of our adaptation to the environment. This object and his/her positive valuation can be described as a reward.

Once we evaluate an object as rewarding, the processing of this stimulus is continued in order to make decisions about our behavior, its planning and execution.

Reward processing and sensitivity is the core of the approach-motivation system. It is a multiple component and stage process that allows for valuating and seeking fitness-increasing stimulus. It can be parse over three major components (Berridge & Robinson, 2003): the motivation to obtain a reward ("wanting" component), the learning of cues related to reward ("learning" component), and the emotion or affect related to the reward attainment ("liking" component).

A modal model of reward processing can be described over four phases. In the first step, the subject makes a prediction about the impact that the hedonic stimulus may have on him/herself. In the second step, the integration of information results in a decision related to approach and obtains the stimulus. In the third step, the subject acts and maintains his/her behavior to obtain the stimulus. In the fourth step, once the stimulus is obtained, the subject experiences the hedonic impact that is related to the stimulus.

There has been several investigations that relate anhedonia in depression with a dysfunction in the reward system. We will review the most important evidence related to electrical activity and hormonal correlates that inform us to specific phases and their associated symptomatology given this disruption.

10.5.2.1 Psychophysiology of Reward Processing

As noted above, reward processing is a multicomponent process that is temporarily deployed. Given the temporary nature of reward processing, the technique of event-related potentials is commonly used. This technique has the comparative advantage

of obtaining a greater temporal resolution of mental processes and therefore is a useful tool for distinguishing the different phases of reward processing.

To achieve this, the computerized tasks make use of three events; the anticipatory cue and the motor preparation time correspond to the anticipatory processing, and the reward after the desired response corresponds to the consumptive processing. For each of these events, brain potentials have been associated that change during rewarding conditions. Importantly, these brain potentials allow us to know how reward processing varies in relation to MDD patients.

While current evidence on these neural components associated with reward uses monetary stimuli, the importance of using various types of reward (e.g., food, social, etc.) has been highlighted (Oumeziane et al., 2017, 2019). In particular, blunted responses to social rewards during adolescence have been identified as especially relevant in the pathogenesis of depression (Olino et al., 2015). This will be further elaborated and discussed in the section on developmental pathways of differential sensitivity to reward.

When subjects are exposed to a cue that indicate them whether or not they are likely to get a reward, a positive potential is generated 300 ~ 500 milliseconds after the onset at the center-parietal area. This neural component is called cue-P3 or cue-locked P3. This component has been associated with attention allocation to motivationally salient cues (Zhang et al., 2017), and its activation covaries with measurements of BOLD signal from the ventral striatum (Pfabigan et al., 2014). Consequently, the amplitude of this potential is greater when the cue indicates that the subject can obtain a reward in comparison with non-reward cue (Zhou et al., 2019).

Anhedonia has been related with this component. Specifically, consummatory anhedonia has been related to a minor cue-P3 amplitude (Chen at al., 2018; Zhou et al., 2019). This evidence is counterintuitive. One can expect that anticipatory anhedonia self-report relates to cue-p3 amplitude. This contrary evidence could be interpreted that, when subjects think about consummatory hedonic experiences, they describe an expectation of the experience but not the experience itself.

In adolescent patients with MDD, Landes et al. (2018) found that they had a delayed cue-P3 compared to a healthy control group. This indicates that the anticipation occurred later, which can have an impact on the posterior phases of processing the reward.

More recently, modulation of the N200 component has been associated with exposure to reward-related cues. This component occurs earlier than the one described above and is composed of a negative deflection generated around 200 ~ 400 milliseconds after the onset in the fronto-central area. This component is called cue-N2 or cue-locked N2. Unlike cue-P3, the amplitude of the cue-N2 component is lower when the cue indicates that the subject can get a reward as compared to non-reward cues (Pornpattananangkul & Nusslock, 2015).

In ERP paradigms, when subjects are confronted to a feedback reward, a neural indicator of the individual differences in their sensitivity is the reward positivity (RewP; Proudfit, 2015). RewP is a neural marker that occurs between 250 and 350 ms that reflects the difference between reward and non-reward responses in

P300 amplitudes after feedback. This can be understood as the hedonic experience associated to a reward consumption. The RewP component has shown confiability in test-retest stability and validity in relation with similar measurements associated to reward sensitivity in different levels of analysis.

There is robust meta-analytic evidence that shown that MDD patients have blunted RewP responses to feedback (Keren et al., 2018) and that depressive symptoms negatively relate to RewP amplitudes (Moran et al., 2017). This evidence is an expression of a deficit in the approach-related system and can be interpreted as the expression of consummatory anhedonia in the clinical expression of this characteristic.

10.5.2.2 Psychoneuroendocrinology of Reward

Unlike the limited functions associated with the neural activations that characterize the processing of reward, the psychoneuroendocrine changes associated with reward have a generalized action on the whole organism.

We can consider three major interactions between endocrine processes with reward. First are the hormonal changes associated with a break in homeostasis (e.g., hunger, thirst, etc.). These changes prepare the body for the implementation of strategies to restore homeostasis (search for food, water, etc.). Second, there are the hormonal changes associated with the hedonistic impact of a reward (e.g., increased testosterone from the consumption of a rewarding object). Third, endocrine tone can affect the processing of the reward through long-term potentiation or inhibition of areas related to this process.

Cortisol has been shown to decrease the brain activity associated with reward. Specifically, cortisol decreases the activity of the striatum and basolateral amygdala (Montoya et al., 2014).

Another fundamental aspect of hormonal variation concerns the impact of testosterone on reward processing. The impact of testosterone is inverse to that of cortisol: both behaviors and affects associated with the search for reward are enhanced (Welker et al., 2015).

10.6 Depression in the Context of Developmental Psychopathology

Principles of Developmental Psychopathology

As a scientific discipline, there are several principles that guide and give sense to research of the development of psychopathology. These principles reformulate the comprehension of psychopathology and allow researchers more flexibility regarding the consideration of the variables that are studied in this discipline.

Developmental Pathways

Developmental psychopathology researchers refer to the concept of path to illustrate the idea that, during a journey through time, there are several factors that probably change the route we take. These paths are probabilistic, since during the journey a series of interactions occur between factors at different levels of analysis that make a state the most probable at a particular time of development. In terms of psychopathology, the expression of a clinical picture is a probabilistic state of the organism from a series of interactions between previous factors that resulted in that moment of development.

Moreover, the expression of this clinical picture is associated with a possible response of the organism to a context that requires an adaptation strategy. The maladaptation of the organism to that context comes from a maladaptive trajectory, which makes that maladaptive response the most probable or the only possible one. In contrast, an adaptive developmental trajectory makes a state of the organism where it is more likely to respond effectively to the demands of the context.

In depression, the (probabilistic) maladaptive outcome comes from a trajectory that affect sensitivity to reward and stress throughout development. These characteristics of the organism make the expression of depression the most likely response to a context with particular demands. On the other hand, due to the probabilistic nature of these trajectories, it is possible to find different trajectories that lead to the same result and different results from the same trajectories.

Equifinality and Multifinality

These concepts refer to the probabilistic nature of both the trajectory and the outcome. All psychopathologies present equifinality. This means that the expression of a clinical picture may be due to different trajectories leading to the same result. On the other hand, the characteristics and factors that impact development may lead to diverse expressions of pathologies (i.e., multifinality, Cicchetti & Rogosch, 1996). This has been described for the case of stress sensitivity. There are several psychopathologies that are characterized by deregulation of the HPA axis. Likewise, early experiences that impact on the dysregulation of the HPA axis are a risk factor for various clinical syndromes. A better description and knowledge of the interaction of the different variables that impact a developmental trajectory increases its predictability and narrows the range of possible outcomes.

10.6.1 Developmental Pathways of Stress Sensitivity

One of the most important aspects of developing a stress system has to do with the length of exposure to stressful events. While exposure to stressors initially generates an overreactivity of the stress system, chronic exposure generates the opposite effect. This has been proposed as the wear and tear effect of physiological systems. The following are the fundamental areas that affect the development of the stress system:

Temperament

The first fundamental aspect that impacts on the trajectories of stress sensitivity development has to do with temperamental aspects. Temperament consists of early basic dispositions that are at the base of the expression of activity, affectivity, attention, and self-regulation (Goldsmith et al., 1987; Shiner et al., 2012). Temperament is a relatively stable construct that develops throughout an individual's life. In its conformation it depends on genetic bases and fetal programming that clearly mark a temperamental style toward the pole of exuberance or inhibition.

From this categorical distinction, the evidence indicates that infants with inhibited temperament have higher basal cortisol levels than exuberants and more pronounced curves in response to stressors (Watamura et al., 2003). In this sense, the basic regulatory strategies of inhibited infants do not allow attenuation of the stress response to threats and, therefore, require sources of other regulation to deal with these stressful events.

Attachment

A second source of variability above the baseline of individual functioning has to do with the development of early attachments that are responsive and effective in protecting the infant from perceived threats.

At the end of the infant's first year, the pattern of interaction between the infant and caregiver is consolidated into the organization of attachment behaviors. Attachment behaviors are those that, in the face of perceived threats, are directed toward seeking out the caregiver and achieving protection. The most general distinction in the organization of attachment behaviors is between secure and insecure attachment. These different qualities of attachment provide a frame of reference for the future behavior of the child in the face of threats and function as a model for the development of new attachments (Ainsworth et al., 2015).

The quality of the bond has an effect on buffering the activity of the stress system. This is observed in the response of infants to common stressors at their developmental stage. One of the most important stressors in early childhood is separation from the caregiver. This event triggers the stress response accompanied by attachment behaviors. Inhibited or fearful Infants who are securely attached to their primary caregivers show less pronounced cortisol curves in response to separation to their caregivers and lower basal cortisol levels overall.

However, some infants have varying levels of disorganization of their behavior in response to stressful situations. In these cases, the children do not present a clear strategy to face threats, performing contradictory or bizarre behaviors. Disorganized attachment behaviors have been observed more commonly (but not exclusively) in the cases of highly aberrant care. This characteristic is less common than infants with organized attachment, but its effects on the development of the HPA system are more severe. Infants who show disorganization during separation with their caregivers have flattened cortisol curves (Bernard & Dozier, 2010). Such effects are also present in those who have not received sustained care at this stage of life, thus revealing a sensitive period that determines the functioning of the stress response system (McLaughlin et al., 2015).

Early-Life Stress

Studies on the developmental pathways of stress sensitivity have focused their efforts on understanding how the neural areas involved in the stress response vary in their functional and architectural aspect as a result of childhood events. The events that are the focus of research are those that cause early-life stress (ELS). Events that generate ELS are categorized as those of abuse (physical, emotional, sexual), neglect, and exposure to violence. The changes they provoke at the level of the nervous system result in a higher likelihood of developing depressive and anxiety disorders in adulthood when exposed to stressors. This increase in the likelihood of developing depression during adulthood is over four times more likely than a person without ESL (Chapman et al., 2004).

There is evidence indicating that experiencing adverse events at some point during childhood can affect the pattern of attachment (Waters et al., 2000), moving from a secure to an insecure attachment. This means that the interpersonal strategy in times of stress is modified, thereby diminishing its regulatory effectiveness.

Adolescence

Current evidence shows that adolescence is a period marked by changes in the functioning of the HPA axis. These changes are mainly a consequence of the maturation of the cortical and limbic areas associated with the stress response (Eiland & Romeo, 2013). These areas are especially affected by the occurrence of stressful events during adolescence. Although this means a greater risk of developing anxious and depressive symptoms, other authors have proposed a possible window of plasticity to promote an adaptive development of the stress response. This is what has been proposed as the hypothesis of pubertal recalibration.

The evidence in favor of this hypothesis has shown intraindividual changes in the functioning of the HPA axis in institutionalized adolescents (DePasquale et al., 2019; Gunnar et al., 2019). Specifically, individuals who were affected by early institutionalization show hyporesponsiveness of the HPA axis to common stressors. Targeted intervention during the peripubertal stage has succeeded in normalizing the reactivity of these adolescents toward more typical response curves.

10.6.2 Developmental Pathways of Reward Sensitivity

The study of reward sensitivity trajectories is more recent compared to the study of stress sensitivity trajectories. The neural areas associated with the processing and experience of rewards vary in a normative way throughout development. This variation in the activity of the neural areas follows a inverted U-shaped pattern from childhood to adulthood. A decrease in reward-associated neural activity is associated with an increased likelihood of developing depression throughout this trajectory, but more particularly during its peak in mid-adolescence (Luking et al., 2016).

On the other hand, intraindividual differences along these normative changes depend on experience and configure during adulthood a differential functioning

expressed in sensitivity to reward. Blunt responses to reward have been observed in 9-year-old children, indicating that differences occur due to early developmental factors. For example, material deprivation has been shown to correlate with behavioral and neural differences in reward processing (Dennison et al., 2019).

Parental Antecedents of Depression

Studies have linked reward response and maternal mental health to the development of depressive symptoms. Children with blunted or normal responses to reward are at increased risk of developing depressive symptoms in adolescence, whereas children with an increased response to reward are not at risk (Kujawa et al., 2019). Mothers with a lifetime history of depression have children with reduce response to rewards, but this effects is not present in mother with both depression and anxiety (Kujawa et al., 2014)

This risk of developing more depressive symptoms may be due to temperamental characteristics that are expressed through inherited temperamental traits or early interaction patterns (Kujawa et al., 2015) that lead to a relational style that impacts the processing of reward. A combination of both elements is also possible, although studies that consider both are rare. The evidence on both aspects will be reviewed below.

Temperament

In relation to temperament, the impact of behavioral inhibition on neural indicators of reward has been measured longitudinally in late childhood (Lahat et al., 2018) and early (Bar-haim et al., 2009) and late adolescence (Helfinstein et al., 2011). In the study considering late childhood (Lahat et al., 2018), behavioral inhibition measured at 2 years of age was related to caudal activation. Based on the authors' discussion, they suggest that it may be related to either a hypersensitivity to reward or an excessive motivation to avoid making mistakes.

The following two studies on this topic are part of the same longitudinal study sample. The behavioral inhibition profile was measured at 4 months of age, and those who presented this profile were selected. Then, they were evaluated at 14, 24, and 48 months of age on behavioral inhibition and shyness measurements. Thus, two groups were selected: those who presented a stable strategy of behavioral inhibition throughout all the measurements and another group that did not present such stability. These were compared during their adolescence (early and late) in the neural response to decision tests with rewards.

Adolescence

In their early adolescence, the neural areas of interest that showed differences between the two groups were the left core accumbens when their decisions were contingent on reward. Here, the adolescents who showed stability in the inhibitory trait were more sensitive to rewards. These same adolescents were evaluated in the later stages of feedback on reward. Here, differences in the ventromedial prefrontal cortex and the caudate nucleus were evident according to the type of feedback. Adolescents who presented stability in the inhibitory trait presented a greater

response to negative feedback, while adolescents who did not present stability in the inhibitory trait presented a greater response of these areas to positive feedback.

10.7 Conclusion

Depression is a common problem with a heterogeneous clinical presentation. It is common because it has a high incidence in the population, and it is heterogeneous because its clinical manifestation is varied. These varied manifestations are due to the fact that its underlying causes are also varied.

In this chapter we address a model of etiopathogenesis that relates to the configuration of the stress and reward system in the presentation of anhedonic depression. In patients who present this type of clinical manifestation, there is a malfunctioning of the brain circuits associated with the reward, so that the hedonic impact of the rewarding stimuli is blunted. This type of response underlies the manifestation of anhedonia in these patients, which generates the difficulties inherent in this condition. Mainly the lack of motivation about the search of rewarding activities can lead to an overexposure to daily stress, leaving aside the pursuit of activities that can serve as a buffer. This is combined with a disadaptive development of the stress system, which presents two types of alterations: blunted responses or overreactive responses.

The genesis of this malfunctioning is found in a series of individual factors and sustained exposure to interpersonal stressful events that shape these systems throughout development. This takes shape throughout early childhood and adolescence, giving way to anhedonic symptomatology during late adolescence. As has been shown, people who experience their first episode of depression normally have an effect at the end of adolescence, which presents relapses during the rest of their lives.

In terms of clinical practice, it is important to accurately differentiate the subtype of depressive disorder. Specifically, the development of reliable measures that account for the anhedonic subtype is necessary in order to adjust clinical practice to this particular configuration.

On the other hand, the expression of depression in adulthood requires that interventions emphasize top-down modulation of reactivity to interpersonal events. Top-down modulation strategies are specifically along the lines of reappraisal strategies (McRae et al., 2012). These make use of the prefrontal areas to decrease the amygdalar activity associated with emotional reactivity (Goldin et al., 2008).

The development of robust indicators of the performance of reward and stress systems that are practical in their clinical implementation requires further research. This can be useful not only in the development of intervention plans but also in their preventive effects throughout development. Preventive intervention can help achieve developmental trajectories that lead to more plastic and adaptive interpersonal strategies in adults.

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Chapter 11
Depression and (Expert) Culture: Psychiatric, Regulatory and Moral Frameworks Underpinning the Absence of Depression in Occupational Health in Chile

Sofía Bowen

11.1 Introduction

The relationship between depression and culture has been a very productive subject of study for anthropologists and cultural psychiatrists. Scholars have long argued that the lived experiences of depression and other illnesses vary across times and places and are inextricable from particular social and historical processes. Amongst the most important works in this tradition is Arthur Kleinman's (1986) seminal research about depression and neurasthenia in Modern China. Kleinman was one of the first authors to challenge biological reductionism and universalism in psychiatry and give greater emphasis to the role of culture in shaping the symptom expression of patients and the diagnostic rationales of clinicians. Much of this type of research, especially that which is situated within cultural psychiatry, focuses on cross-cultural comparative studies amongst culturally diverse populations and their mental health needs (see Kirmayer & Minas, 2000). The notion of culture is, in this early line of thought, often used to highlight different characteristics of social and ethnic groups, including their shared values and beliefs as they relate to mental health and disease.

Approaches to culture and its relationship to health have changed considerably since the 1990s (Good, 1994; Kirmayer, 2006). As scholars turned to study Western medical knowledge and practices as cultural and social products, they started to explore not only how depression and other forms of mental suffering are shaped by culture but also how 'psychiatry itself is the product of a specific cultural history' (Kirmayer & Minas, 2000: 438). Anthropological work within this line of thought has focused on local experiences of psychiatry in diverse cultural and historical contexts (e.g. Béhague, 2009, 2019; Behrouzan, 2016; Ecks, 2013; Kitanaka, 2012, 2014, 2016; Kleinman, 1986; Martin, 2007; Raikhel, 2016; Young, 1997; Zhang,

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*,
Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_11

2020). These studies have demonstrated how psychiatric knowledge, categories and practices are embedded in local, social, political and cultural worlds.[1]

Building on this literature, this chapter offers an ethnographic example from my year-long fieldwork on workers' mental health and occupational psychiatry in Santiago of Chile (2018–2019). Depression appears to be an uncommon diagnosis for workers at local workers' insurance hospitals – known as *mutualidades*' hospitals, currently the main specialised healthcare service available to workers in the country. Why does a globally widespread psychiatric concept such as depression, which has been identified in academic research and public debate across the globe as a salient term for work-related problems, have little presence in occupational health and psychiatric practice in Chile? Using Lakoff's concept of 'ecologies of expertise' (Lakoff, 2005:17), I look at how experts' culture, practices and discourses are embedded in Chile's social milieu and local regulations (see also Béhague, 2009, 2019; Behrouzan, 2016; Ecks, 2013; Hacking, 1998; Kitanaka, 2012, 2014, 2016; Molé, 2012; Raikhel, 2016; Zhang, 2020). Instead of examining biomedical or clinical forces, I focus on the entanglement of social and cultural factors, such as occupational psychiatry's epistemic, moral and regulatory frameworks underpinning experts' choice in avoiding depression.

Scholars of occupational psychiatry in Chile do acknowledge that depression is a plausible occupational illness. However, this is generally only the case when it is considered a 'reactive disorder' (González, 2018). Views on what constitutes an 'occupational mental disorder' are informed by regulations (Law 16.744) that define occupational diseases as *directly caused* by workplace risks. As will be further explained in this chapter, what prevents local doctors from diagnosing depression in the workplace is the belief that depression is an expression of workers' 'inner weaknesses' that are beyond the workplace's accountability (except when clearly demonstrated). Most general practitioners and psychiatrists in occupational healthcare diagnose 'adjustment disorder' instead, which, although similar in symptomatology to depression, is believed to be more in tune with medicolegal views on occupational disorders (milder and entirely caused by environmental factors).

My analysis suggests that the absence of depression reflects 'competing politics of causality' of disease (Kitanaka, 2016:56), in which local moral evaluations of work and workers come to the fore. In my view, these 'competing politics of causality of disease' are embodied by the medical processes and practices of evaluation that attribute accountability for a disease to either the individual or the environment – two opposing possibilities. Such medical evaluation processes also entail

[1] For an in-depth theoretical account of the co-productive relationship between society, culture and scientific categories, see Jasanoff (2004). For a social analysis of medical and psychiatric categories, see Hacking (2000), Rosenberg (2006) and Rose (2019). Particularly relevant for this chapter is Hacking's (2000) observation regarding how medical categories are continuously changing in an imbricated relationship with society and culture by means of a 'looping effect'. Looping effects occur when a form of knowledge is appropriated and changed by subjects, which in turn provokes a change in the terms whereby subjects think and act amongst themselves and in the world around them.

moral judgements (Rose, 1999). As Didier Fassin (2012) has argued, 'medicine is not solely a technical activity based on biological and biochemical knowledge; it also implies a moral intervention grounded on values and expressing sensibilities, with claims of altruism by professionals and expectations about the role the sick should play in the management of their illness' (Fassin, 2012:12). Chilean psychiatric practice is no exception, as it has historically been involved in the moral evaluation of workers as lacking self-control – interpreted as partially representative of the working-class' cultural character (Maino, 2019). As will be further developed, such believe combined with a psychiatric emphasis on individual responsibility (Rose, 1999) are crucial elements explaining the dismissal of depression as a workplace problem.

The material I present here is based on 12 months of ethnographic research on work-related mental health and psychiatry in Santiago, Chile, from May 2018 until May 2019.[2] During my fieldwork, I undertook more than 40 semi-structured interviews with experts including psychiatrists, public officials, psychologists and general practitioners in the occupational health world. I also attended public occupational health events and conducted participant observation sessions in the waiting rooms of two different workers' insurance hospitals.[3] I conducted ethnographic fieldwork with 15 workers on work-related psychiatric sick leave, from the moment they were first medically evaluated until their return to work. In this chapter, I primarily focus on 20 interviews with psychiatrists and general practitioners working at different workers' insurance hospitals, describing how they explain the absence of depression in Chilean occupational health.[4,5]

In what follows, I begin by reviewing anthropological literature on the concept of 'ecologies of expertise' (Lakoff, 2005) and how it can help explain the absence of the psychiatric category of depression. Secondly, I briefly describe the history and current regulation of occupational psychiatry in Chile, as well as local medico-legal views about disease causality. Thirdly, I describe my interlocutors' main positions on why depression is dismissed in occupational psychiatry, showing that negotiations over accountability are vital, as are moral judgements about workers and the workplace. Finally, I end by discussing how the absence of depression in Chile's occupational healthcare system ensues from the juxtaposing of several factors beyond the medical domain: local regulatory and legal demands, specific and historical psychiatric epistemologies, theories of causality of disease and moral views about the worker and the workplace.

[2] The findings presented in this chapter are part of my ANID-funded PhD research project on work-related psychiatric claims and occupational psychiatry in Chile.

[3] I obtained ethical clearance from the Ethics Committee of King's College London and the Ethical and Scientific Committees of the participating workers' hospitals.

[4] All participation in this research project is anonymous.

[5] It is important to note that the material presented in this chapter does not represent the totality of the opinions and views in the occupational psychiatric community in Chile. The chapter looks at the dominant views with respect to a specific topic connected to depression and accountability.

11.2 Depression and Psychiatric 'Ecologies of Expertise'

The anthropologist Andrew Lakoff (2005), following the work of the philosopher Ian Hacking (1998) on 'ecological niches' of mental illnesses, studied psychiatric and psychoanalytic culture and practice in Argentina. He proposed the term 'ecologies of expertise' to refer to the situated expert practices that are embedded in a social milieu and governed by shared principles of regulation (Lakoff, 2005:17). Depression and other contemporary psychiatric categories, Lakoff argues, are entrenched in a complex set of relationships involving not just the clinic but also the insurance, legal and governmental regulations, classification protocols and reimbursement bureaucracies. These relationships play a key role in the way depression is conceptualised and treated (Lakoff, 2005). In his ethnographic book *Pharmaceutical Reason*, Lakoff compares the case of depression in Argentina with the situation in Europe and North America to highlight the different expert practices that prevail across diverse settings, along with the political and administrative contexts that 'structure the adoption of new knowledge and techniques' (Lakoff, 2005:14). He observes that, in Argentina, there has been a rapid growth of antidepressant sales without an increase in the diagnosis of depression as a discrete clinical entity. This stands in contrast with northern countries, where diagnosis and pharmaceuticals have been rising hand in hand. According to Lakoff (2005), this difference can be explained by paying attention to regulatory demands and psychiatric epistemologies – in northern countries, where biomedical psychiatry is dominant, regulations establish that prescription drugs must correspond to specific illnesses (such as anti-depressants and depression). In Argentina, because psychodynamic approaches are more prevalent, there is a general absence of the notion of depression as a biological condition in the brain and as a target of anti-depressant actions. There is no regulatory scheme demanding drug-diagnosis specificity; rather, pharmaceutical intervention is often viewed as a way to treat socially induced stress rather than biological faults.

Cultural psychiatrists have described depression as a 'robust Western ethno psychological construct' (Jadhav, 1996:278) that gradually displaced melancholia (Jackson, 1986; Jadhav & Littlewood, 1994). Historians and sociologists of biomedicine argue that, currently, depression has come to be understood globally in terms of biological individual vulnerability (e.g. Ehrenberg, 2009, 2016; Rose & Abi-Rached, 2013; Rosenberg, 2006). Such an approach, it is argued, is closely attached to dominant values in contemporary and neoliberal societies of self-control and autonomy – especially in the European and North American context (Ehrenberg, 2016; Rose, 1999). In her ethnographic work with psychiatric students in the United States, the anthropologist Tanya Luhrmann (2000) shows how such values of self-management and self-control are part of psychiatric training: medical students learn to expect patients to behave as self-caring consumers even when they understand depression (or any other form of mental distress) as a non-intentional neurological injury. These psychiatric notions of depression, however, should not be viewed as totalising. Following Duncan's suggestion, 'psy disciplines' and concepts 'are

negotiated on the ground by actors in particular sociocultural contexts with unique histories, possibilities and professional orientations' (Duncan, 2017:38).

The anthropologist Junko Kitanaka (2012, 2014, 2016), for example, has shown how there can be different conceptualisations of depression associated with stress and social ills. Her ethnographic work illustrates how in Japan, since the 1990s, depression has come to be understood as a national disease of labour that is rooted in both biology and society. She describes how such a view is the result of a complex historical interplay between particular psychiatric professional orientations, cultural values, litigation battles and changes in work health regulations. The author argues that the emergence of depression as a salient concept in Japan is partly due to the engagement of psychiatrists in the social movement against overwork – a movement that has won cases in courts against large corporations. Japanese psychiatrists have argued that workers' depression is the result not merely of workers' biological traits but also of a stress-laden work environment. The most vulnerable to becoming depressed, they think, are not the faulty workers but the model ones – those who have a strong work ethic and are susceptible to overwork and suicide. Legal and policy debates have contributed to conceptualising mental illness as a product of the interaction between individual and society by creating controversial tools to prevent and measure stress levels in the workplace.

The case of Chile, as it has been suggested by historian Claudio Maino (2019), differs from both the American/European and Japanese situations. In his research about the social history of depression in Chile, Maino (2019) argues that local Chilean psychiatry has never been too attached to the European notions of melancholia or overwork. Rather, during the twentieth century, there was a strong fixation on workers' alcoholism and feelings of guilt. The author observes that, since the 1990s, psychiatric discourse in Chile has replaced the figure of the alcoholic worker with that of the depressed one while maintaining ideas about the individual as having little self-control and motivation – which leads them to failure and indebtedness. Chilean psychiatric debates over the origins of the alcoholic tendency and lack of self-control have fluctuated between psychological, biological and culturalist explanations, including suggestions of a flawed national psychological character of the working class. However, as Maino (2019) suggests, a more socially oriented approach has also been present in local debates, with psychiatrists and other experts calling into question recent socioeconomic changes and stressful working environments affecting people's mental health (e.g. Almonte et al., 2016; Echeverría, 2007; Aceituno et al., 2012). Although this social perspective in psychiatry is not unusual in Latin American contexts (see Béhague, 2009; Brotherton, 2020; Fonseca, 2020; Han, 2012; Lakoff, 2005), in Chilean occupational psychiatry, it is not a mainstream view (see Miranda, 2012).

The different psychiatric epistemological notions of depression mentioned above are inevitably entangled with moral judgements about work and responsibility for health (Fassin & Retchman, 2009; Kitanaka, 2012; Rose, 1999). Psychiatry, as social research has demonstrated, plays a particularly important role in defining and certifying the boundaries between socially acceptable and unacceptable behaviours in society and the workplace (Rosenberg, 2006). The sociologist Nikolas Rose

(1999) argues, for example, that psychiatric and psychological practice and techniques play an important part in workplace management by developing workers' moral notions of self-awareness and self-evaluation. Following Dodier (1994), psychiatrists in occupational health have to assume an ethical position regarding workers' claims: they need to assess their place in an apparatus of social justice and make a final decision regarding accountability. Such medical assessments are inevitably fraught with moral ambiguities and questions regarding whether accountability is found in the individual or the pathogenic environment (Kitanaka, 2014). Similarly, moral judgements about workers' traits and working environments are part of occupational psychiatry's 'ecology of expertise' in Chile. Together with regulatory and epistemic demands, these moral views play a key role in experts' evaluations of accountability of disease and their avoidance in diagnosing workers with depression.

11.3 The Absence of Depression in Occupational Psychiatric Practice in Chile

Depression is a high-profile global issue in contemporary societies and a major topic of public debate. Since the early 2000s, the World Health Organisation has classified depression as a major contributor to the global burden of disease, leading to high costs due to loss of productivity (WHO, 2002, 2019). Furthermore, alongside anxiety, depression has been associated with negative working environments (e.g. Schmidt et al., 2014; WHO, 2019). In some countries, depression and suicide are understood to be a result of work stress and, therefore, a 'problem of labour' (see Kitanaka, 2016, for the case of Japan). In Chile, in particular, depression has been a pressing issue since the 1990s prompting discussions on mental health awareness, public policy and access to medical treatments (e.g. Krause, 2019; Minoletti & Zaccaria, 2005; Markkula et al., 2017a; MINSAL, 2013, 2017; Vicente et al., 2006; WHO, 2017). In terms of public policy, depression is ubiquitous in all the most relevant national healthcare policies (MINSAL, 2013, 2017; Araya et al., 2009, Minoletti et al., 2012). Further, it is currently the reference concept amongst medical professionals in the mental health programme at the primary healthcare level – depression is the most common diagnosis alongside anxiety (Minoletti et al., 2018).

Despite the ubiquity of depression in public policy as well as in global and local mental health debates and studies,[6] there is one area in Chile from which it is largely missing: the workplace. In 2019, the most common psychiatric diagnosis at workers' insurance hospitals was not depression but the diagnosis of 'adjustment disorder' – which accounted for 52.1% of all diagnoses of occupational diseases at these

[6] See Clara Han's (2012) for an ethnographic account of the notion of depression as a reference category amongst laypeople in the neighbourhood of La Pincoya in Santiago of Chile.

centres (SUSESO, 2020).[7] There is no official data about the rates of depression-related diagnoses at workers' insurance companies, except for a brief mention in the report for the year 2017, which classes 3% of all occupational disorders as 'mixed anxiety and depressive disorder' (SUSESO, 2018). According to data obtained through interviews with public officials from the Superintendency of Social Security (SUSESO), in 2018, less than 1% of all occupational diseases at workers' hospitals were specifically diagnosed as 'depressive episodes'. This low percentage coincides with a study by Markkula et al. (2017b) about psychiatric sick leave from 2012 to 2016 at the workers' insurance known as ACHS (Asociación Chilena de Seguridad). The authors found fewer than 150 cases of depressive disorders out of a total of 1,709,366.

The apparent absence of depression in the workplace occurs while psychiatric problems display an exponential rise in Chile. Currently, an unprecedentedly large number of workers are going to the occupational healthcare and insurance system claiming that their mental distress is work-caused. Authors have estimated a 1000% increase in the last 15 years (Almonte et al., 2016). The fact that depression is not being diagnosed much in this context is odd, especially when it is considered a possible 'occupational disorder' by the local authority and psychiatric community (SUSESO, 2019b – Circular N3448). Further, depression remains absent at workers' hospitals even when academic research in Chile has flagged the presence of depressive-like symptomatology in the workplace. These authors argue that symptoms are associated with exposure to work-related psychosocial risks[8] (see Ansoleaga et al., 2014; Ansoleaga & Miranda, 2014; Díaz, 2009; Garrido et al., 2013; González-Medina et al., 2020; Jiménez & Dahuabe, 2019). Recently, academics have given special attention to the relationship between depression and overall psychological distress with workplace violence and unfair treatment (Ansoleaga et al., 2016; Ansoleaga et al., 2019; Candia, 2019; Palma-Contreras & Ansoleaga, 2020).

The Chilean occupational 'ecology of expertise', however, prevents experts from diagnosing depression, especially if the claims are associated with workplace violence and unfair treatment. A case study by Trucco and Rebolledo (2011) in a workers' insurance hospital shows that cases classified as occupational mental disorders are more often associated with overwork than with problematic interpersonal relationships. Some of my interlocutors would argue this is because overwork is simpler to measure numerically and encapsulate in simple actions (e.g. overtime). Problems of violence and harassment, they would add, are difficult to prove as they are too 'subjective'. However, as I will show next, beyond surface problems of measurement, what underlies is the belief that depression does not comply with regulations and the dominant view of what an occupational mental disorder is. This is because of the presence of 'subjective issues', especially in the case of interpersonal

[7] In 2018, adjustment disorder accounted for 49% of all occupational disorders (SUSESO, 2019a).

[8] In 2020, local academic research focused on workers' depressive-like symptoms and their relationship with COVID-19-related changes in the workplace (e.g. Traub & Sapag, 2020; Urzúa et al., 2020).

problems, which reflect workers' 'inner traits' or 'weaknesses' as the 'real' cause of disease.

11.4 Occupational Psychiatry, Workers' Insurances and Medicolegal Views on Occupational Disorders in Chile

Occupational psychiatry in Chile has a short history: it has not yet been recognised as a sub-discipline of occupational medicine and is largely missing as a subject of study in medical schools. According to local scholars, occupational medicine in Chile emerged in the early twentieth century in connection with physical injury and silicosis (Almonte et al., 2016; Ortúzar, 2015; Vergara, 2005). Mental health practice developed later as complementary medical support for workers with physical injuries and, only occasionally, to treat mental illnesses associated with what is currently known as 'psychosocial risks' in the workplace (Almonte et al., 2016). Notably, with the current rise of psychiatric sick leave in Chile and the world, the latter area of expertise has become more active, especially at workers' insurance hospitals.

The workers' insurance hospitals are owned and run by employer-paid private and public non-profit organisations (locally known as *mutualidades*) that act as workers' insurers and medical service providers for work accidents and 'occupational diseases'. The *mutualidades* are regulated by an old law (N° 16.744) for social security and work-related healthcare from 1968, which stipulates that employers are obliged to provide medical insurance for all their employees through a workers' insurance scheme (there are only four in the country, of which one is public and three private). In turn, workers' insurance provides prevention plans and good medical care for workers who suffer an injury or disease that can be classified as job caused. Each workers' insurance company works in parallel and completely separate from the national healthcare system, with all their medical specialities being related to different branches of occupational medicine. This separation from the national healthcare system occurred back in 1968, amidst a big debate over workers' social security and welfare. Supporters of the 1968 law argued that, unlike the state and its alleged lack of infrastructure, the existing private employers' associations (*mutualidades*) were showing fairly good results in caring for their workers' health (Consejo Nacional de Seguridad, 2004; Miranda, 2012). It was then decided to make these organisations, instead of the state, the legal agencies in charge of providing social health insurance for workers in Chile. The law also established that the Superintendency of Social Security (SUSESO) would oversee and regulate them.

According to interviews with public officials at SUSESO, the social profile of workers that claim for occupational mental disorders are low- to moderate-income employees working in the retail and public and private service sector (viz. health and education). Such profile is very different to the low-waged manual worker that

has historically claimed insurance at workers' hospitals. Traditionally, workers' insurance claims and resources have been associated with work accidents and physical injury – mostly in the industry, agriculture, mining and construction sectors (Miranda, 2012; Oyanedel et al., 2014). Local scholars and some of my informants believe that the appearance of the service-related workforce[9] at workers' insurance hospitals responds to the recent growth of the country's service economy (Almonte et al., 2016; Miranda, 2012). They highlight that this workforce's psychiatric claims might be reflecting the low levels of job quality in Chile (see OECD, 2017; Sehnbruch, 2006).[10] Others mention that recent public visibility of mental illnesses and workplace issues have probably contributed to the increase of psychiatric claims.

The growth in the number of people seeking access to healthcare and compensation at workers' hospitals has provoked profound changes within local occupational health institutions. Recently, workers' insurance companies have been forced to expand their mental health staff and renovate the tools for measuring 'objectively' the 'direct cause' between work and disease. In an effort to standardise evaluation processes, in 2015 the SUSESO launched a new protocol for the evaluation of occupational diseases with a series of medical and quasi-legal procedures that workers' insurance companies need to follow to assess the cause of the disease and accountability. Firstly, the worker is medically evaluated and provisionally diagnosed by a general practitioner – often with adjustment disorder (SUSESO, 2019a, 2020). A psychological evaluation is also required to study personality traits. Secondly, there is a review of psychosocial risks in the workplace through interviews with workplace 'witnesses'. Finally, a medical committee composed of psychiatrists and other medical professionals at each insurance company analyses the cases and makes a final decision. Currently, only 20% approximately of all psychiatric claims arriving at workers' hospitals are qualified as 'occupational disorders' (SUSESO, 2019a, 2020).[11]

[9] Local sociologist Alejandro Marambio (2018) proposed the category of 'post-industrial working class' to describe the retail and service workers in Chile – namely salespersons, clerks, cashiers and transportation workers. Although this concept characterises many workers claiming for occupational mental disorders, it does not include a portion that, according to interviews with SUSESO's public officials, is also part of this group. These are workers with a more stable situation and with a slightly higher income – such as qualified technicians and administrative staff in the public and private service sector.

[10] The growth of the service sector developed hand in hand with a neoliberal economic policy, which, amongst other things, provoked the disarticulation of social laws and fostered a precarious job market (Fraile, 2009; Garretón, 2000). Currently, Chile shows low job quality levels (including the service sector), characterised by long working hours, job instability, low wages and high levels of subcontracting.

[11] If the disease is not found to be job-caused (a 'common disease'), then the worker is referred to the national healthcare system – which is much more limited in terms of resources (see Errázuriz et al., 2015). Within the non-occupational healthcare system, the worker's diagnosis of adjustment disorder is often disregarded and changed. On the contrary, if a claim is classified as occupational, the worker's insurer pays the sick leave and provides the worker with psychiatric (and in some cases psychological) treatment free of charge. In both cases, the worker's insurance company informs the workplace about the worker's disease and its cause. If it is considered to be an 'occu-

Although doctors in the first medical appointment may see symptomatic similarities with depression or other psychiatric diagnoses, they prefer diagnosing adjustment disorder because it provides an epistemic possibility: complying with the local medicolegal framework on occupational diseases as 'directly caused' by workplace risk factors. At an academic event organised by the Chilean Society of Occupational Medicine (SOCHMET) on what they termed 'Occupational Mental Disorders', psychiatrists from several workers' insurance hospitals, public hospitals and state agencies discussed their views on the rise of adjustment disorder diagnoses in the occupational world. A psychiatrist revealed that, during medical training processes on mental health in workers' hospitals, adjustment disorder took a leading role amongst the experts and was chosen to be the main diagnosis for 'occupational mental disorders'. The doctor explained that they preferred this concept above others (like depression) because it complies with regulations and local ideas over occupational injury/disease as it explicitly establishes a causal link between environmental factors and the disease. 'Adjustment disorder was the concept within the ICD-10 [nosology] that covered this idea in the purest way',[12] he added.

Hence, in the context of Chilean occupational psychiatry, regulatory frameworks strongly influence the local epistemic view about what occupational mental disorders should be. Most of the practitioners with whom I talked believe that mental illnesses are multifactorial and that it is very difficult – if not impossible – to brand a single issue as directly causing mental distress. However, they say, to evaluate, diagnose and treat workers at workers' insurance hospitals, it is essential to find a causal link between their distress and a (single) stressor in the workplace. During an interview, a psychiatrist, Dr A., told me that his hospital had established that work factors must be sufficient and necessary for the disease to happen independently of other factors. These other factors include any environmental issues happening outside the workplace (like family issues) and 'personal vulnerabilities' – which can include biological and personality traits. Such reasoning follows SUSESO's recent regulation and definition of professional mental disorders, according to which 'exposure to professional settings' must be assessed as a sufficient cause for the disease, 'regardless of personality, biographic, or family factors of the worker' (SUSESO, 2019b).

pational disease', the insurance company asks the workplace to remedy the risk factors identified while raising their insurance premium.

[12] Diagnosing adjustment disorder also serves a more strategic aim as it allows experts to provide workers with sick leave and treatment while the evaluation of their claim unfolds.

11.5 Depression as Having an Internal Origin: Questions of Accountability

In one interview, Dr B. and I were looking at the ICD-10 diagnostic manual, reading about depressive episodes, and he told me: 'it does not say anything about the environment'. In the same vein, another doctor told me: 'if you go to a psychiatry book it says that depression is about an alteration in the genes, early experiences (…) there is nothing really about the environment, nothing'. The belief that depression is not related to environmental factors was held by most of the practitioners with whom I talked at workers' hospitals. In contraposition with occupational mental disorders, depression is understood as having an 'internal origin' rather than being a reaction to circumstances in life (and work). This internal origin of depression is of two different types: biological and/or psychological. Dr C. told me that the biological origin could be explained in neurological, chemical or genetic terms. This can be clinically observed by asking the person for previous depressive episodes in their lives and if they have relatives with a history of depression. Psychological tendencies towards depressive moods are also considered 'internal causes', as they are believed to result from chemical imbalances in the brain and/or early childhood experiences. Concerning the latter, Dr A. emphatically stated: 'most of the literature says your mental health is determined during the first 18 years of life'. Therefore, as personality traits are understood as fixed during childhood, they are considered to be something inherent to and independent from adult-life environmental factors. In contrast, psychiatrists at workers' hospitals argue that adjustment disorders can be more easily understood as occupational disorders, as they do not originate from the biological or psychological characteristics of each individual but from external and specific factors independent from workers.

The notion of depression as having an internal origin can be linked with an old psychiatric model that separated 'endogenic' and 'exogenic' types of depression (e.g. Gallagher & Thompson, 1983; Lewinsohn et al., 1977). The concept of 'endogenic' would sometimes appear in the discourses of psychiatrists, although they would clarify that these categories are no longer encouraged in the psychiatric community. However, as Dr A. suggests, they appear to continue to be relevant in this medicolegal context, as they meet the demand of defining accountability for mental illness. Dr A. argues:

> It was said that endogenic pathologies were produced inside the individual, that is, the individual was somehow flawed, and that exogenic [diseases] were due to the individual's exposure. This concept of the 1980s was eliminated, and it was eliminated based on the idea that everything was mixed, therefore it was impossible to separate them. But what they did before was to separate: if depression was exogenic then [the person] would need psychoanalysis. If the depression was endogenic then it needed to be given pharmaceuticals. (…) In the end, it was decided to make some sort of truce (…) but to me, that is not correct. [The endogenic and exogenic distinction] seems like a serious issue to me, but nobody wants to keep thinking about this. (…) so OK, the endogenic and exogenic concepts were abandoned, right? But when I first came to work here there was a law from 1968 (…) And the law literally says, I can show you, that a work accident is something which happens in the

> workplace or in connection with a person's job… that is, [a person with an occupational disease] is considered exposed to risk factors that are inherent to the patient's job. That is a direct, causal relationship. Then, what [the law] is asking for is that you [as a doctor] say or declare what has caused the patient's symptoms.

For Dr A., only very few people develop a mental illness due to situations that exclusively happened in their adulthood and their workplaces: what happens in the majority of cases is that work issues can help to develop a disease that was already there in the person's biology or personality. However, according to a strict application of the legal notion of 'direct cause', later triggers cannot be defined as the origin of the disease.

In the above excerpt, Dr A. illustrates the extent to which conceptual concerns and legal and social demands influence the work of psychiatrists at workers' insurance hospitals. The notion of an internal origin of depression or endogenic depression is prevalent today amongst medical experts not just because of current dominant psychiatric theories of causation (biological and/or psychological), but also because it serves a socio-political purpose: defining and clarifying the criteria for the legal demand to find a direct cause of the disease. Many times, I heard the practitioners say: 'in the end, this is an insurance [company]'. By this, they meant that the purpose of defining the direct cause is not of vital importance for doctors but for those who pay for and receive compensation and medical treatment.

In brief, as Dr C. argues: 'depression can be occupational, but a very deep analysis is required to determine this. It must be demonstrated that if the occupational factor had not existed, then the person would have not developed depression. Everything else in their environment, personal traits and genetics must be discarded'. In the words of Dr B., there is one main question in every classification process: 'Does the person's symptomatology depend on their work (that might be inadequate) or does it depend on the person not being able to "adapt" to a new situation at work due to a trait in his/her personality/biology?'.

As depression is understood to be mostly internally caused, workers with clear symptomatology of depression are thus often regarded by experts as having personality traits or faults that make her/him less able to cope with workplace problems. 'I think it is probably something inside him', a general practitioner said when I asked him about a hypothetical case of a worker who had previously been diagnosed with major depressive disorder. I explained to the doctor that the worker would have had serious problems in the workplace (overwork and interpersonal conflicts) and presented with symptoms of depression and suicidal thoughts. The doctor replied: 'there can be problems in the workplace, but there must be something *in* him to provoke *this* response'. Arguably, the underlying moral belief here is that the ideal worker, the worker with no internal faults, cannot be 'depressed'. Depression represents a symbol of personal weakness in the worker, a matter of their own individual responsibility; it is something that exceeds the accountability of the workplace except when the contrary is clearly demonstrated.

11.6 Depression as Too Severe to Be an Occupational Disease: Moral Evaluations of the Worker and the Workplace

According to psychiatric manuals, depressive episodes and adjustment disorder can have very similar symptomatology, such as low mood and eating and sleep disruption (Bachem & Casey, 2018). In fact, according to the ICD-10 manual, adjustment disorders include 'depressed mood, anxiety or worry (or a mixture of these)'. For local psychiatrists, however, the difference between adjustment disorders and depression is that the first is less severe and persistent than 'internally caused' depression. This belief persists even though medical researchers around the world have argued that adjustment disorders are strongly associated with high suicide rates (see Bachem & Casey, 2018; Casey & Bailey, 2011).

The distinction, according to Dr C., is partly based on the *intensity* of the symptoms – the consensus amongst practitioners at workers' hospitals is that 'occupational mental disorders' should be mild and short-lived. In this regard, Dr C. argues that when a patient is not improving over a long period and shows signs of anhedonia, the diagnosis is probably depression and not adjustment disorder. The persistence of severe symptoms, even when the patient is on sick leave, is a sign for general practitioners and psychiatrists that 'the origin is really not in the workplace but there is another origin [internal]'. Workers' suicidal actions or thoughts are the extreme examples of severe symptoms that are understood as signalling an internal origin of the disease.

This focus on the intensity of symptoms allows practitioners to classify 'difficult' cases; for example, when a risk has been clearly identified in the workplace but there are doubts about the causal link between the risk and the worker's severe reaction. In such cases, the intensity (severity) of the symptoms, even when there are no clear signs of biological faults, indicates psychiatrists that the origin of the disease is internal. This reasoning concerning symptoms can also help to differentiate between what they call 'triggers' and 'causes' of disease. This distinction often appeared when discussing hypothetical cases of workers with depressive symptoms in a proven bad working environment. If the clinical and psychological evaluation suggests that there are genetic or psychological traits that indicate an internal origin for depression, then the stressor is considered a trigger and not a cause.

One worker I met in the waiting room of one of the workers' hospitals came to his first medical appointment with several documents showing how overwork and exposure to threatening situations at work should be held accountable for his suffering. He was feeling 'depressed' and had recently tried to commit suicide in his workplace. He came out of the doctors' appointment thinking he had convinced the doctor to take him on as a patient and support his case as job-caused – the worker even mentioned he was advised to take legal action. A month later, he told me the

workers' hospital medical committee had rejected his case. I later mentioned this case to one psychiatrist (without disclosing the patient's details), and his response was that even if there are 'triggers' in the workplace, the suicide attempt shows that work is not the direct cause of the worker's distress. Quoting the relevant regulations, he said that workers' exposure to workplace risks is not sufficient to provoke a suicide attempt. Simply put, the occupational psychiatrists' evaluation of an occupational disease considers not only its cause but also the workers' response to the stressors. There are expected responses to stressors that serve as a measure for assessing accountability. Dr D. explains: 'if because of overwork you start having visual hallucinations or persecutory delirium, it cannot be a direct consequence of work because it requires a personal vulnerability. If we have ten people, we expose them to overwork, and they get ill, some of them will be understandably sick and others will have activated diseases of a common [internal] origin.'

Underlying this reasoning, I argue, are not just legal and medical theories of disease causation but also moral and social expectations of workers' behaviours and workplaces. One important aspect discussed in the academic event on 'Occupational Mental Disorders' organised by SOCHMET was the perception that society is more open to understanding that the workplace can provoke mental distress and disease. However, the overall view is that common workplace problems are not severe enough to provoke serious damage. The reason depression and suicide are dismissed as occupational problems is that they are considered to be disproportionate responses. Thus, the workplace is seen as somewhat innocuous and isolated from other related social factors affecting workers' well-being.

Experts' scrutiny and expectations about workers' responses reflect a historical disciplinary fixation with 'worker's character' as allegedly unable to self-control, an idea often associated with the figure of the alcoholic worker (Maino, 2019). For example, Dr D. mentioned that an unexpected response to overwork would be to start drinking alcohol because that would indicate that the worker's 'way of addressing problems has failed'. A more 'adaptive' approach, Dr D. argues, would be 'to recognise that one is feeling bad and establish what to do. The most reasonable decision would be to refuse or reduce [overwork]. And if one cannot do that, the normal reaction would be to lose sleep, lose appetite, start feeling discouraged, with low energy (…) and make sure that this situation doesn't go on for too long, because if I say that this has been happening for five years, then there is an element of mine that is interfering in my capacity to recognise the risks (…) I should have the capacity to self-manage and say 'no, this is not doing me good' and do something about it'.

Representations of the worker's character as prone to depression and alcoholism due to their lack of self-management, and the workplace as more or less innocuous, are probably entangled with current trends in global psychiatry that highlight self-control and biological origins of disease (Rose, 1999). But at the same time, they resonate with representations of the working class and the workplace that go beyond the clinic and psychiatric practice. As several local social studies have shown, views of the working class as lacking self-control are inherent to Chile's culture and marked issues with inequality and classism (e.g. Araujo & Martuccelli, 2012; Bowen, 2015; PNUD, 2017; Romero, 1997). This suggests how in

workers' hospitals not only individuals' health and working conditions are negotiated but also broader social and political forms of representation. . As the anthropologist Lochlann Jain (2006:62) has shown in her book on injury in the United States, safety laws and structures force parties 'to articulate positions and assumptions about objects and people', which may incorporate underpinning systems of class and political power.

11.7 Discussion

Following Hacking's (1998) notion of 'ecological niches', occupational mental illnesses are not just social nor medical or legal; they are the result of the concatenation of an extraordinarily large number of diverse elements, including moral views about society, the workers and work. Depression is not entirely absent in the occupational world in Chile; but for the experts, it is a difficult category to work with. Depression could be thought about, as psychiatrists in Japan do, as useful for thinking on labour issues (Kitanaka, 2012). However, in contrast with the Japanese case where depression is seen as a 'problem of labour', in Chile depression is largely understood as a reflection of workers' inner weaknesses.

Current global trends in psychiatry and organisational health emphasise the moral worthiness or unworthiness of patients/workers, which largely depends on individual responsibility (see Cooper & Dewe, 2008; Maija & Katri, 2018; Väänänen et al., 2012). In occupational psychiatry, global ideas on self-management and self-control get entangled with local moral evaluations about the working class. Unlike Japan, where workers are traditionally regarded as hard-working and diligent (Kitanaka, 2012), in Chile, they are often viewed as inefficient and lacking self-control (Araujo & Martuccelli, 2012; Maino, 2019). These moral evaluations combined with the epistemic notion of depression as internally caused provoke workers' depressive-like symptoms to be easily regarded as the result of their 'inner (moral) faults'. In the eyes of the workers' insurances, the severely ill and depressed workers are understood as inherently unable to adapt correctly to workplace issues. Such a view about workers, in a context where regulations force a competitive system of accountability of disease, limits possibilities for a more nuanced perspective that sees individual and work-related factors as interdependent.

For occupational psychiatrists, adjustment disorders are symptomatically similar to depression but, importantly, cannot be associated with inner weaknesses. The diagnosis of adjustment disorders functions as an epistemic option consistent with the local medicolegal definition of occupational diseases. More accurately, occupational psychiatrists think adjustment disorder unfolds like a work accident; the disease is directly caused by a single and measurable risk factor that is considered sufficient to cause damage. This prevents considering the complex interplay of social, structural and workplace risks factors involved in workers' suffering (e.g. job insecurity, low wages, etc.). Furthermore, the workplace is regarded as somewhat innocuous, unable to cause the worker severe and long-lasting

psychological distress. Workers' suffering, especially that which is labelled depressive, ends up being dismissed and unrecognised by the workers' insurances. This keeps occupational psychiatric practice from forming a part of global debates around depression and the workplace while also limiting psychiatrists' ability to imagine ways of preventing work-related mental distress beyond the individual and medical scope.

These ethnographic findings show how psychiatric practices, beliefs and categorisations are entangled with particular social, historical, political and cultural contexts, making it possible to better understand why medical categories seem to appear (and disappear) at different times and places. The chapter illustrates how culture does not just shape experiences that can be termed 'depressive' by medical professionals; first and foremost, it shapes expert practices and understandings relating to the category itself. Therefore, to better understand the relationship between depression and culture, it is necessary to include a cultural analysis of psychiatric categorisations and practices. Such a view prevents falling into over-deterministic and one-way theories of sociocultural (or even psychological and/or biological) causation (Béhague, 2019). In this regard, Kirmayer and Minas (2000:440) note that beyond the culture of the 'patient', what also defines cultural differences in psychiatry and mental health are the 'personal and professional background of the clinician, and the social context of practice'. As I have shown, local 'ecologies of expertise' of psychiatric practice in Chile juxtapose various levels of complexity. Medical concepts, knowledge and practice, and particularly the category of depression, are in constant interplay with the social world beyond the clinic.

Acknowledgements I would like to thank all the interlocutors of my PhD project for their very important contribution to this research project. I also thank Dr Dominique Béhague, Dr Rasmus Birk, Professor Lochlann Jain and Dr Carlo Caduff for their valuable feedback on previous versions of this chapter. Finally, I am grateful to Dr Juan Pablo Jiménez and the Millennium Institute for Depression and Personality Research (MIDAP-Universidad Católica de Chile) for their support to this research project, and to the colleagues at the Platform for Social Research on Mental Health in Latin America (PLASMA) for their useful comments on my work. Funding for carrying out the research for this chapter was received from PhD Studentship 'Becas Chile' awarded by the Chilean National Agency for Research and Development (ANID) and a small grant awarded by the Department of Global Health and Social Medicine, King's College London.

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Chapter 12
Poverty, Social Inequity, and Depression

Alvaro Vergés

12.1 Poverty and Depression

Since the advent of the social determinants of health framework, which provided a foundation for the study of how the social condition in which individuals live have a structural influence on their overall health (Commission on Social Determinants of Health, 2008; Wilkinson & Marmot, 2003), epidemiologic research on mental health have accumulated evidence on the strong association between the social determinants and psychopathology (Compton & Shim, 2015). Moreover, it has become evident that some of the same pathways from structural factors to individual distress that increase the probability of physical illness also have an impact on mental disorders (e.g., Evans et al., 2003; Jones, 2017; Paul & Moser, 2009).

In particular, the vulnerability associated with material and social conditions of poverty can have a substantial impact on mental health (McLeod & Shanahan, 1993). Moreover, as stated by the World Health Organization (1995), extreme poverty is "the world's most ruthless killer and the greatest cause of suffering on earth" (p. 1), pointing to the pervasive impact of poverty on both physical and psychological health. Although the world has witnessed substantial progress in the reduction of poverty during the last decades, extreme poverty is still a reality for millions of individuals worldwide (World Bank, 2018). Moreover, increased levels of income inequality and other forms of social inequity are a matter of concern even among developed countries. As the most recent estimations suggest a global trend of increasing inequality (although a small reduction has been reported since the 1990s; World Bank, 2016), and an economic recession seems likely to occur in the proximal future (Rogoff, 2020), it is of utmost importance to take a look at the evidence on the association of both poverty and inequality with depression, given that

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_12

depression is one of the most prevalent mental disorders and the largest contributor to non-fatal health loss (World Health Organization, 2017).

12.1.1 Epidemiologic Findings

One rich source of information regarding the association of socioeconomic status (SES) and depression comes from large epidemiologic studies that have included standardized measures of depression together with self-reported education, income, and other indicators of SES (see Cerigo & Quesnel-Vallée, 2017, for a review). In the United States, the Epidemiologic Catchment Area study, which assessed DSM-III disorders (American Psychiatric Association, 1980), found that whereas depression was associated with dependency on public financial aid and unemployment, other indicators such as income and education showed no association (Weissman et al., 1991). Similarly, results from the National Comorbidity Survey, a nationally representative survey that assessed DSM-III-R disorders (American Psychiatric Association, 1987), showed that income was negatively related to the presence of both lifetime and past-year affective disorders, whereas education was only associated with past-year affective disorders (Kessler et al., 1994). Further, the National Comorbidity Survey Replication, which incorporated assessments of disorders as defined in DSM-IV (American Psychiatric Association, 1994), also found an association of family income with past-year and past-year severe, but not with lifetime major depression, whereas education was associated with lifetime and past-year, but not with past-year severe major depression (Kessler et al., 2003).

Another epidemiologic study, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), is a nationally representative survey that assessed DSM-IV disorders in over 43,000 adults, showing an association of lifetime major depression with personal income, but not with education (Hasin et al., 2005). In contrast with previous epidemiologic studies, the NESARC considered a longitudinal design, so that participants were assessed again 3 years later, allowing for an examination of SES with rates of incidence (i.e., new cases within a given period) and persistence (i.e., maintenance of a diagnosis over a specified period) of depression. Again, results showed an association of family income, but not education, with the first incidence of major depression (Grant et al., 2009). However, none of the SES indicators reported (i.e., individual income, education, and employment status) predicted persistence of chronic major depression (Garcia-Toro et al., 2013).

The most recent large epidemiologic study is a new version of NESARC, conducted in 2012–2013, evaluating DSM-5 disorders (American Psychiatric Association, 2013), and is called NESARC-III although it is not a new wave of the previous NESARC data collection. Findings of NESARC-III indicate an association of both past-year and lifetime major depression with family income, though educational level only showed an association with past-year depression (Hasin et al., 2018).

In sum, epidemiologic studies have found relatively consistent evidence for an overall association between SES and depression. However, findings become less consistent when specific SES indicators and depression outcomes are considered. For instance, the association seems to be more robust for income than for education. Similarly, the general association involving the prevalence of depression may be due to the effect of SES on incidence rather than persistence of depressive disorder. However, it should be noted that this last inference is in contrast with the findings of a very influential meta-analysis that reported odds ratios for the comparison of the lowest SES group versus the highest with regard to prevalence, incidence, and persistence of depression (Lorant et al., 2003). Results were in line with the aforementioned epidemiologic studies in showing a significant effect for prevalence (OR = 1.81 [95% CI = 1.57–2.10]) and incidence (OR = 1.24 [95% CI = 1.04–1.48]) of depression. Nevertheless, they also estimated a considerable effect for persistence (OR = 2.06 [95% CI = 1.39–3.05]), thus diverging from the epidemiologic findings.

12.1.2 Causation and Mechanisms

Although the overall association between SES and depression is well established, this does not imply a particular direction of causality. Indeed, it is possible that lower SES increases the probability of depression due to higher exposure to adversity and stresses (i.e., social causation), but it is also possible that depression has an influence on SES by preventing individuals from moving out of or precipitating them into low SES (i.e., selection or drift) (Dohrenwend et al., 1992; Muntaner et al., 2004). Moreover, it should be noted that both directions of causality can take place over time within the same population.

As shown in the previous section, epidemiologic evidence supports the notion of social causation, as baseline SES predicted first incidence of depression (Grant et al., 2009). In this study, the selection process was discarded by studying first incidence, thus limiting the possibility that depression caused SES only to participants who failed to recall having experienced depressive symptoms in the past (i.e., false negatives). Other attempts to disentangle social causation from selection processes in longitudinal studies have found more evidence for the former (e.g., Johnson et al., 1999; Lorant et al., 2007; but see Goodman et al., 2011).

Another way of analyzing changes in income and their association with depression is by taking advantage of population changes, such as those that take place when economic recessions occur. Frasquilho et al. (2016) conducted a systematic review of the literature on economic recessions and mental health outcomes (including common mental disorders, such as depression) and concluded that there is substantial evidence across countries for a link between recessions and common mental disorders, as well as suicidal behaviors. More recently, Forbes and Krueger (2019) analyzed longitudinal data collected before and after the Great Recession that occurred between 2007 and 2009 in the United States. They found a significant

association of financial, job-related, and housing impacts of the recession with symptoms of major depression, adjusting for baseline levels of depressive symptoms. Interestingly, this association was not moderated by sociodemographic variables, suggesting that the economic impact of recession may have an effect even among privileged groups.

However, longitudinal designs are not the only (nor, necessarily, the best) way to clarify the nature of the association between SES and depression. More sophisticated methods developed for causal inference have been introduced in this literature in recent years, taking advantage of genetic designs and instrumental variables (IV). For instance, Mezuk et al. (2013) used a genetically informed design to determine the direction of causality between SES and depression, finding that twins from low SES households (evaluated in terms of education and occupation of the main support in childhood) had higher rates of depression in adulthood, even after accounting for genetic factors. Similarly, Crespo et al. (2014) used schooling reforms in several European countries, which extended the age of compulsory schooling, as IV for the effect of education on depression, finding a large protective effect of educational attainment (but see Dahmann & Schnitzlein, 2019, for a negative finding involving overall mental health, using a similar approach). In contrast, Viinikainen et al. (2018) used Mendelian randomization, involving a genetic risk score as an IV for years of education, and found that a causal effect of education on depression was not supported by the data. Clearly, more studies using causally oriented designs are needed to determine whether the SES-depression link is causal or not.

Several mechanisms have been proposed to account for the association of low SES and depression. There is evidence that adverse experiences linked with poverty, especially during childhood (see Cabieses et al., 2016), have a biological impact that might predispose to the onset of depression. In particular, recent evidence points to the influence of poverty on epigenetic modifications that lead to increased threat-related amygdala reactivity (Swartz et al., 2017), reduced connectivity of the hippocampus and the amygdala with other brain regions (Barch et al., 2016), reduced activity in the ventrolateral and dorsolateral prefrontal cortex as well as failure to suppress amygdala activation during the effortful regulation of negative emotion (Kim et al., 2013), and higher levels of systemic inflammation (Muscatell et al., 2020). These biological mechanisms can be characterized by a common association with chronic stress, which in turn correlates with psychological processes such as diminished coping and self-regulation skills (Evans & Kim, 2013), and executive function abilities (Blair & Raver, 2016). Indeed, chronic stress can lead to a process of allostatic load (i.e., accumulated long-term changes in the regulatory system from its homeostatic level) that, eventually, can reach the level of psychopathology (Doan & Evans, 2018). However, it should be noted that the number of findings pointing to psycho-biological impairments derived from poverty should not be translated into a default "deficit model," given that poor individuals can also develop strengths that allow them to cope with the challenges of poverty (Frankenhuis & Nettle, 2020).

12.2 Social Inequity and Depression

In contrast with concepts such as poverty or socioeconomic status, which are attributes of an individual (even if determined in terms of comparison with the other individuals in a community or society), the notion of inequality constitutes an attribute that characterizes a population. Although different dimensions (including categorical inequalities, such gender or ethnicity) and different measures of inequality are studied in the literature, the most common dimension that is investigated in the research reviewed in this section is income inequality, and the most common measure of it is the Gini coefficient. To understand the calculation of the Gini coefficient, it is useful to introduce the Lorenz curve (see Fig. 12.1). The Lorenz curve, developed by Max Lorenz in 1905, is a cumulative distribution of income percentiles (or any other quantile), such that for any percentage of people in the bottom of the income distribution (*x*-axis), the cumulative respective percentage of income (*y*-axis) is shown. This generates an ascending curve that goes below the 45-degree line, representing perfect income equality. The Gini coefficient, developed by Corrado Gini in 1912, is simply the ratio of the areas A and (A + B) in Fig. 12.1, so that a Gini coefficient of zero implies that everyone has the same income (perfect

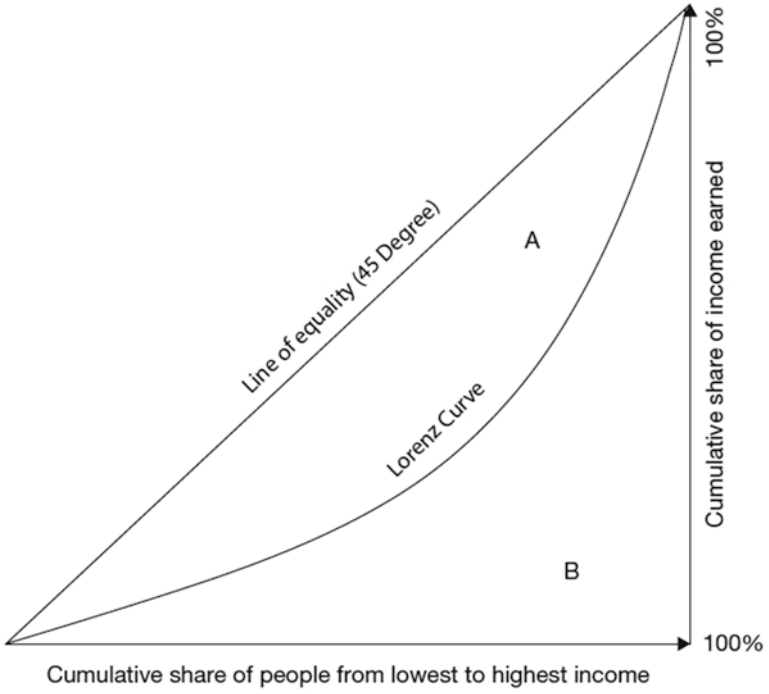

Fig. 12.1 The Lorenz curve. (Reproduced with permission of the Licensor through PLSclear, from Galbraith, 2016)

equality), whereas a coefficient of one (or 100%) implies that only one person has all the income and everyone else has none (perfect inequality).

Whereas the term inequality refers to general differences among individuals and groups, the notion of inequity denotes a sense of injustice in the distribution of resources and is more commonly used in the health literature to refer to differences in health that could plausibly be avoided by reasonable means (Arcaya et al., 2015).

Two recent meta-analyses have estimated the pooled association between income inequality and depression (Patel et al., 2018; Ribeiro et al., 2017). Ribeiro et al. examined this link in the context of a comprehensive study of the association between income inequality and mental health. With regard to depression, they found 6 studies that met inclusion criteria, providing 17 independent effect sizes. The pooled Cohen's d effect size was estimated as 0.12 (95% CI 0.05–0.20). However, they reported some evidence of publication bias according to the Egger's test.

In the same way, Patel et al. (2018) included 12 studies in their meta-analysis (corresponding to 12 effect sizes) and estimated a pooled risk ratio of 1.19 (95% CI 1.07–1.31), indicating again a greater risk of depression in populations with higher income inequality. However, no measure of publication bias was reported. Notably, although both studies found a small effect size, an effect at the population level translates into a large number of individuals potentially affected.

Though establishing a causal link between income inequality and depression is even more difficult than determining a causal role for poverty, a review by Pickett and Wilkinson (2015) showed that there is good accumulated evidence of causality for income inequality and overall health. There is good reason to think that a similar conclusion will be reached regarding depression when more specific evidence is available. In fact, income inequality has been shown to predict the incidence of depression among women (but not men) without a history of depression at baseline (Pabayo et al., 2014). However, one recent study using a twin design to control for genetic and shared environmental factors showed no significant association between neighborhood income inequality and depression (Cohen-Cline et al., 2018). This could be due to the fact that the most relevant unit of analysis for the association of income inequality and depression is the city or state, rather than the neighborhood, but this possibility should be explored in future research.

In terms of potential mechanisms by which income inequality can lead to an increase in the prevalence of depression, Patel et al. (2018) conducted a scoping review of the literature, identifying hypothesized mechanisms at the individual, neighborhood, and regional or national levels. Briefly, at the individual level, the main mechanism is psychological stress (e.g., Vilhjalmsdottir et al., 2016), which can be considered as a converging mediator for a number of pathways. At the neighborhood level, two potential mechanisms are social comparison (i.e., comparing oneself to those in a better position may lead to status anxiety; Buttrick & Oishi, 2017; Cheung & Lucas, 2016) and social capital (i.e., income inequality has a negative impact on dimensions of social capital such as social trust; Kawachi et al., 1997). Finally, at the regional or national level, income inequality leads to material deprivations (due to lack of access and deficits in public investment) that cause both physical and psychological health problems (Lynch et al., 2000). However, this last

mechanism might be difficult to disentangle from the effects of poverty, as seen in the first section of the current chapter.

12.3 Intersectionality, Syndemics, and Discrimination

Although the current chapter focuses on poverty and social inequity, it is indispensable to briefly address other social factors and medical conditions that might concurrently contribute to the onset and course of depression. In this regard, the notion of intersectionality, first introduced by Crenshaw (1989) to understand how multiple social and political identities (e.g., gender, race, class) combine to create unique modes of discrimination, is particularly helpful to develop a more comprehensive perspective on the effects of poverty and inequity in interaction with other social factors. In recent years, the concept of intersectionality has been introduced in the mental health inequality literature to illuminate how the presence of simultaneous social disadvantages might have interactive – rather than additive – effects (for a review, see Trygg et al., 2019). For instance, an interaction of SES with gender has been reported (e.g., Assari, 2017; Ross & Mirowsky, 2006; Van de Velde et al., 2010), such that women tend to show a stronger effect of SES than men. Adding more complexity, Wamala et al. (2009) reported higher odds of psychological distress among women from an ethnic minority in a low-income household, and Assari (2017) found an effect of household income among White women, but not White men or African American women (though a marginally significant effect was reported among African American men in the opposite direction). These findings suggest that the effect economic disadvantage is particularly pronounced among certain subgroups of the population.

A complementary concept, derived from the literature in medical anthropology, is that of syndemics (Singer, 2009). Syndemics, understood as "the aggregation of two or more diseases or other health conditions in a population in which there is some level of deleterious biological or behaviour interface that exacerbates the negative health effects of any or all of the diseases involved" (Singer et al., 2017, p. 941), encompasses the study of interactions between diseases and their simultaneous interaction with social and economic factors, which configure a particular way of presentation and course of the disease in a given population. Notably, depression has been identified as an aspect of several syndemics affecting disadvantaged populations. For example, depression has been found to cluster together with diabetes in contexts of poverty (Mendenhall et al., 2017). In fact, the presence of a medical condition greatly increases the risk for depression, and in contexts of disadvantage, this co-occurrence of disorders substantially complicates both the medical and psychiatric treatment (e.g., Benton et al., 2007; Krishnan et al., 2002).

Several mechanisms have been proposed in the literature for the synergistic effects of SES and other social factors and health conditions on depression, including material and psychosocial variables (e.g., Belle & Doucet, 2003; Green et al., 2014; Gustafsson et al., 2016). One psychosocial mechanism that has recently

gained attention in light of the intersectionality and syndemics perspectives is perceived discrimination (e.g., Fuller-Rowell et al., 2018). In a very influential meta-analysis, Pascoe and Smart Richman (2009) (see also Schmitt et al., 2014) found that perceived discrimination correlated negatively with mental health ($r = -0.16$, 95% CI = −0.20 to −0.12, after adjustment for bias). An analysis including only studies examining depressive symptoms yielded a similar result.

As individuals with minority status are more likely to experience discrimination (e.g., Benner et al., 2018; Lee et al., 2019; Schmitt et al., 2014), researchers have investigated the role of discrimination in the association between social disadvantage and depression (Belle & Doucet, 2003). In a recent review of the mental health outcomes of having multiple sources of discrimination, Vargas et al. (2020) found that experiencing multiple forms of discrimination was associated with higher rates of depression. However, some studies have reported higher levels of discrimination and, in turn, more risk for depression among persons from minority groups with higher SES. For example, Cheng et al. (2015) reported that, although parent education is generally protective against depression, this effect is overshadowed by the increased levels of discrimination experienced by Black individuals from more educated families. Further, Loret de Mola et al. (2016) found that individuals with higher SES and higher African ancestry were more likely to be discriminated by skin color and therefore had higher risk for depression. The complexity of these associations calls for further research with other populations in order to examine the generalizability of previous findings.

12.4 Longitudinal Data from Indigenous and Non-indigenous Individuals in Chile

To explore some of these issues in the context of an underdeveloped country, data from a large, longitudinal study conducted in Chile was used to compare the association of SES, perceived discrimination, and depression between indigenous and non-indigenous individuals. Moreover, these data allow for investigation of depression persistence, an important outcome that has been relatively unexplored in the literature on SES and discrimination.

12.4.1 Methods

Participants Data for this chapter was drawn from the Longitudinal Study on Intercultural Relations (ELRI; Centro de Estudios Interculturales e Indígenas [CIIR], 2017), a representative study of 8 out of the 16 regions that constitute Chile's first-level administrative division. The target population was individuals 18 years

and older, with a random selection of indigenous and non-indigenous participants sampled from the same urban block or rural entity.

An initial wave of face-to-face interviews was conducted during 2016 and includes 3617 respondents, including 424 Northern Andean participants, 593 non-indigenous participants from the Northern Andes, 1308 Mapuche participants from central and southern regions, and 1292 non-Mapuche participants from central and southern regions. A follow-up second wave of face-to-face interviews was performed during 2018 and contains 2879 of the same respondents, including 351 Northern Andean participants, 445 non-indigenous participants from the Northern Andes, 1064 Mapuche participants from central and southern regions, and 1019 non-Mapuche participants from central and southern regions (CIIR, 2019).

Measures Participants completed the Chilean version of the Patients Health Questionnaire-9 (PHQ-9; Baader et al., 2012) at both waves. The PHQ-9 is comprised of nine items evaluating the presence of depressive symptoms in the last 2 weeks. Item response options are as follows: 0 = never, 1 = some days, 2 = more than half the days, and 3 = almost every day. Scores are summed, so the possible range goes from 0 to 27. A cutoff score of 10 indicates the presence of significant depressive symptomatology. The Chilean version of the PHQ-9 has shown a sensitivity of 92% and specificity of 89% (Baader et al., 2012).

Socioeconomic status (SES) was defined according to a classification that has been widely used and validated in Chile (Asociación Investigadores de Mercado, 2000). This classification, based on variables including family income and educational level, divides the population into five socioeconomic groups (ABC1, C2, C3, D, and E). Due to sparseness of data when testing interactions among indigenous and non-indigenous participants, the five groups where collapsed into middle higher (ABC1, C2, and C3) and middle lower (D and E).

Perceived day-to-day discrimination was measured through 6 items (e.g., "Have you been treated with less respect than others") adapted from Krieger et al. (2005), with a 5-category response format (from 1 = never, to 5 = always). Given that half of the participants answered "never" to all items, day-to-day discrimination was coded as present if any of the items was endorsed in a category different from "never." In addition, change in day-to-day discrimination across waves was coded as 0 = stable absent (i.e., no reported discrimination at both waves), 1 = decrease (i.e., present at wave 1 and absent at wave 2), 2 = increase (i.e., absent at wave 1 and present at wave 2), and 3 = stable present (i.e., present at both waves).

Analytic Plan To evaluate cross-sectional associations among SES, discrimination, and depressive symptomatology, logistic regressions were conducted with depression symptomatology at wave 1 as dependent variable, SES, perceived day-to-day discrimination, and SES by discrimination interaction as predictors, and age, gender, and marital status as co-variates. These logistic regressions were conducted separately among indigenous and non-indigenous participants. Similarly, to examine predictors of persistence in depressive symptomatology, logistic regressions were conducted among participants who were above the threshold for significant

depressive symptomatology at wave 1. The same predictors and co-variates were included, with the only difference that day-to-day discrimination was coded to capture change between wave 1 and wave 2. The ELRI utilized a complex survey sampling design. SUDAAN was used to adjust for sampling weights in the calculation of standard errors of parameter estimates (statistical package version 11; Research Triangle Institute, 2012).

12.4.2 Results

Table 12.1 presents descriptive statistics for indigenous and non-indigenous participants. As expected, given that indigenous and non-indigenous individuals were matched across demographic variables by design, no significant differences were observed between both groups in age and gender, as well as marriage status, in the total sample. However, indigenous participants showed a higher percentage of middle lower SES and were more likely to report day-to-day discrimination. Although the prevalence of depression symptomatology was almost the same in both groups at wave 1, an increase in prevalence was observed at wave 2, particularly in non-indigenous participants, leading to a significant difference between groups at follow-up (Wald $F(1,577) = 10.72$, $p = 0.001$).

Table 12.1 Characteristics of indigenous and non-indigenous participants in the total sample and among those with depression symptomatology at wave 1

	Total sample			W1 with DS		
Variable	Indigenous	Non-indigenous	Wald *F*	Indigenous	Non-indigenous	Wald *F*
N	1.732	1.885		231	252	
Mean age	42.62 (0.44)	42.95 (0.50)	0.24	42.90 (1.38)	44.06 (1.32)	0.36
% female	55.88 (1.36)	54.41 (1.46)	0.55	61.78 (3.91)	61.15 (4.01)	0.01
% SES middle lower	65.16 (1.28)	56.13 (1.55)	23.23*	69.16 (3.72)	60.43 (3.94)	2.50
% married	44.12 (1.36)	52.84 (1.47)	0.23	43.33 (3.76)	47.60 (3.96)	0.66
% day-to-day discrimination	57.56 (1.37)	48.96 (1.58)	21.74*	75.01 (3.10)	74.58 (3.21)	0.01
% with DS 2016	13.31 (1.00)	13.10 (0.93)	0.03	–	–	
% with DS 2018	14.01 (1.07)	19.43 (1.28)	10.72*	28.86 (3.41)	40.69 (4.39)	4.65*

Note. Values in parenthesis are standard errors. Married includes participants living as if married
DS depression symptomatology, *SES* socioeconomic status
* = $p < 0.05$

With regard to the subgroup of participants to be included in analyses of persistence (i.e., those with depression symptomatology at wave 1), they were characterized by a larger percentage of females, individuals of middle lower SES, married (and living as if married) participants, and persons who report day-to-day discrimination, when compared with the total sample. However, for all these variables, no significant differences were observed between indigenous and non-indigenous participants. In contrast, a significant difference was observed between groups in wave 2 depression symptomatology (Wald $F(1,577) = 4.65$, $p = 0.031$), which implies that the difference between groups in the total sample is at least partially due to different persistence rates in symptoms of depression.

Results of logistic regressions predicting wave 1 depression symptomatology are presented in Table 12.2. As can be seen, although the lower percentage of depression symptomatology is similarly captured in both groups, this reaches significance only among indigenous participants. Also, no age effects were found in any of the groups, suggesting that depressive symptomatology is relatively stable across adulthood in this sample. Marital status is only significant in the indigenous group, pointing to the protective effect that a supportive partner can have for the indigenous population. More importantly, a significant interaction between SES and day-to-day discrimination was found in the indigenous group (OR = 0.39 [95% CI = 0.19–0.82]), such that the experience of discrimination increases the probability of suffering depressive symptoms among poorer (Wald $F(1,577) = 26.04$, $p < 0.001$) but not richer (Wald $F(1,577) = 0.72$, $p = 0.396$) individuals. In contrast, the main effect of day-to-day discrimination (OR = 3.85 [95% CI = 2.54–5.83]) is not qualified by an interaction with SES among non-indigenous individuals, so that perceived discrimination increases the probability of suffering depressive symptoms in both poorer (Wald $F(1,577) = 40.89$, $p < 0.001$) and richer (Wald $F(1,577) = 16.71$, $p < 0.001$) individuals.

Results of logistic regressions predicting persistent depression symptomatology are presented in Table 12.3. No significant effects were found for gender, age, and

Table 12.2 Summary of logistic regressions predicting depression symptomatology at wave 1 in indigenous and non-indigenous participants

	Indigenous		Non-indigenous	
Variable	OR	95% CI	OR	95% CI
Gender (Female ref)	0.69	0.48–0.99	0.70	0.49–1.00
Age (18–34 ref)				
35–49	0.78	0.50–1.21	0.84	0.52–1.36
50–64	0.85	0.57–1.27	0.91	0.58–1.44
65+	1.18	0.76–1.84	1.42	0.86–2.34
SES (middle low ref)	1.61	0.85–3.05	0.80	0.42–1.51
Marital status (married ref)	1.65	1.18–2.30	1.27	0.89–1.82
Day-to-day discrimination (no ref)	3.27	2.07–5.17	3.85	2.54–5.83
SES*day-to-day discrimination	0.39	0.19–0.82	0.98	0.45–2.12

Note. Married includes participants living as if married
OR odds ratio, *CI* confidence interval, *ref*. reference group, *SES* socioeconomic status

Table 12.3 Summary of logistic regressions predicting depression symptomatology persistence in indigenous and non-indigenous participants

	Indigenous		Non-indigenous	
Variable	OR	95% CI	OR	95% CI
Gender (Female ref)	0.66	0.30–1.44	0.51	0.23–1.12
Age (18–34 ref)				
35–49	0.77	0.31–1.90	0.79	0.29–2.15
50–64	0.62	0.22–1.76	0.82	0.30–2.26
65+	0.61	0.19–1.94	0.85	0.29–2.49
SES (middle low ref)	0.28	0.04–2.00	0.04	0.00–0.41
Marital status (married ref)	0.49	0.23–1.05	1.73	0.81–3.67
Change in day-to-day discrimination (stable no ref)				
Decrease	0.34	0.08–1.42	0.54	0.14–2.04
Increase	1.86	0.40–8.63	1.23	0.32–4.73
Stable presence	0.87	0.28–2.68	1.55	0.52–4.66
SES*change in day-to-day discrimination				
Middle high-decrease	12.11	0.80–183.40	14.98	0.87–258.03
Middle high-increase	1.79	0.06–53.47	50.33	2.62–968.35
Middle high-stable presence	7.66	0.92–63.61	29.91	2.11–423.24

Note. Married includes participants living as if married
OR odds ratio, *CI* confidence interval, *ref*. reference group, *SES* socioeconomic status

marital status. Again, a significant interaction was found involving SES and change in day-to-day discrimination, but this time the interaction was significant only among non-indigenous participants (OR[middle high-increase] = 50.33 [95% CI = 2.62–968.35], OR[middle high-stable presence] = 29.91 [95% CI = 2.11–423.24]), such that changes in the experience of discrimination increase the probability of persistence in depressive symptoms among richer (Wald $F(3,577) = 5.01$, $p = 0.002$) but not poorer (Wald $F(3,577) = 0.98$, $p = 0.404$) individuals. In contrast, neither the interaction nor the main effects of SES and change in day-to-day discrimination predict persistent depressive symptomatology in the indigenous group.

Robustness of Findings As different indicators of SES have been developed, each one having distinct strengths and weaknesses (Howe et al., 2012), analyses involving SES should be replicated using different indicators in order to assess their robustness. Two specific indicators of SES (as opposed to a composite index as the one used in previous analyses) that are commonly used in the literature are education and family income. Briefly, analyses replacing SES with education yielded no significant interactions in any of the groups, although a non-significant trend was found for negative changes in the experience of discrimination increasing the probability of persistence in depressive symptoms among individuals with higher education (Wald $F(3,577) = 2.44$, $p = 0.063$) but not lower education (Wald $F(3,577) = 1.37$, $p = 0.252$) in the non-indigenous group. On the other hand, analyses replacing SES with family income yielded a significant interaction among non-indigenous

participants (OR = 5.13 [95% CI = 1.57–16.72]), such that the experience of discrimination increases the probability of suffering concurrent depressive symptoms among richer (Wald $F(1,577) = 24.33$, $p < 0.001$) but less so among poorer (Wald $F(1,577) = 15.73$, $p < 0.001$) individuals. Analyses with family income predicting persistence in depressive symptoms yielded unestimable odds ratios due to cell sparseness. Taken together, although the pattern of the non-significant interaction involving education was the same as the one found when using SES, these analyses using specific indicators of SES point to a lack of robustness in the findings, which implies that results for SES should be taken with caution and interpreted in light of the complexities of comparing different SES indicators (Howe et al., 2012).

12.4.3 Discussion

The current findings do not replicate previous reports of higher rates of depression among ethnic minorities with higher SES who have experienced discrimination (Cheng et al., 2015; Loret de Mola et al., 2016). On the contrary, indigenous persons with higher SES seem to be protected against the influence of discrimination on depression, which was found among poorer indigenous and all non-indigenous participants. Moreover, indigenous individuals exhibited lower rates of depression persistence, possibly due to lower sensitivity to discrimination. Although these findings were not robust to different measures of SES, they point to the need for studies investigating potential sources of strength (see Frankenhuis & Nettle, 2020) in the indigenous population, particularly given that they are exposed to higher levels of poverty and discrimination in Chile. Furthermore, they point to the importance of longitudinal studies to go beyond overall rates of depression by investigating outcomes related to its course, such as persistence.

12.5 Implications for Interventions

In this last section, some implications of the association of poverty, inequities, discrimination, and depression for public health and clinical interventions are briefly considered. Social policies addressing structural inequities by promoting increases in minimum wage, greater union coverage, progressive taxes, social insurance, and investment in disadvantage communities have been shown to successfully reduce income inequality and its consequences (Galbraith, 2016; Lynch et al., 2000). With regard to prevention, it is essential to embed prevention efforts in existing structures and ongoing activities occurring in the community such as education and pregnancy and child care, as well as to promote social norms in which mental health is positively regarded and prioritized (Ormel et al., 2019). Structurally embedded prevention programs have a better chance at dealing with structural determinants of mental health, such as poverty and inequities. In terms of treatment, one interesting

initiative to highlight the importance of poverty and social inequity for mental health care is the proposal to promote (and even enforce) the recording of psychosocial adversities such as poverty in clinical charts (Allsopp & Kinderman, 2017). Also, several interventions have been found to be effective in the treatment of depression in low SES populations, but this effect can be maximized by including culturally specific training for providers and booster sessions (Rojas-García et al., 2015). Moreover, the occurrence of depression as part of a syndemic cluster requires the design of a syndemic care model in which mental health care is integrated with primary care (Anwar et al., 2018) and several tasks are transferred to less-skilled health workers or members of the community (i.e., task-shifting; Fulton et al., 2011), so that syndemic care providers have the time and resources to address multiple disorders and social vulnerabilities in a holistic manner.

In addition, both structural and individual strategies to address discrimination have been proposed (Lewis et al., 2015; Williams et al., 2019). Although most of the research on interventions for discrimination is focused on gender and racial discrimination, it is reasonable to expect that some of these strategies can be effectively translated to socioeconomic discrimination. In particular, institutional interventions such as mandatory programs to deal with discrimination within organizations (Kalev et al., 2006); community interventions combining public and private partners in multisector, place-based initiatives (Bailey et al., 2017); and racism countermarketing (Kwate, 2014) have shown promising results. Similarly, individually focused interventions such as values affirmation exercises and forgiveness interventions might be helpful to cope with experiences of discrimination (Lewis et al., 2015).

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Part III
Evolution and Development as an Integrating Framework

Chapter 13
An Integrative Developmental Psychopathology Approach to Depression

Patrick Luyten and Peter Fonagy

13.1 Introduction

Depression is one of the most common and most prevalent mental health problems and ranks among the leading causes of disability, morbidity, and mortality (Collins et al., 2011). Depression is best conceptualized as dimensional, ranging from subclinical to mild to severe and persisting mood problems. The distinction between normal variations in mood and depression as a clinical condition that warrants treatment is therefore to some extent arbitrary and influenced by sociohistorical factors (Jackson, 1986). Yet, even subclinical mood problems are responsible for considerable suffering, and the highly recurrent nature of depression in a sizeable proportion of individuals is associated with large personal and socioeconomic costs.

A wide variety of effective pharmacological and psychosocial interventions for depression have been developed and empirically evaluated. A recent review included more than 500 clinical trials examining the effects of antidepressants and more than 600 trials investigating the effects of psychotherapy for depression, with little evidence for superiority of any bona fide treatment for depression (Cuijpers et al., 2020b). A recent meta-analysis including 385 comparisons of 15 different types of psychotherapy reached a similar conclusion, reporting little or no differences in the effects of these treatments (Cuijpers et al., 2020a).

Depression is a relatively common and highly prevalent condition. Studies suggest that 3–8% of children and adolescents meet criteria for clinical depression

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_13

(Birmaher et al., 1996; Costello et al., 2006). Lifetime estimates of prevalence range between 15% and 20% (Birmaher et al., 1996; Demyttenaere et al., 2004). In childhood, depression is equally prevalent in boys and girls, but from age 14, women are twice as likely as men to be diagnosed with depression (see Angold et al., 2002; Birmaher et al., 2007). Hence, a developmental view is necessary but surprisingly lacking in many extant theories of depression. Moreover, there is still a lack of integration between biological and psychosocial approaches to depression.

This chapter presents an integrative developmental psychopathology approach to depression building on other integrative efforts (Auerbach et al., 2014; Davey et al., 2008; Gilbert, 2006; Luyten & Fonagy, 2018; Pizzagalli, 2014). It focuses on the developmental emergence of depression. Three biobehavioral systems that are centrally involved in depression throughout the life span are discussed: the *stress*, *reward*, and *mentalizing* systems (Luyten & Fonagy, 2018). We integrate findings concerning disruptions in these three systems in depression within a broad developmental psychopathology perspective, focusing on disruptions in both the content of cognitive-affective schemas or internal working models of self and others, on the one hand, and mentalizing or metacognitive capacities, on the other hand (Luyten et al., 2013).

In brief, the need to adapt to ever-changing environments, and the growing complexity of human communication, exchange, and collaboration, fostered the development and coordinated action of (a) the stress/threat system, involved in responses to threat and distress; (b) the reward system, which produces feelings of reward particularly related to experiences involving attachment relationships (e.g., infant–caregiver, caregiver–infant, pair-bonding, and other attachment relationships and experiences of agency and autonomy); and (c) the mentalizing or social cognition system, as the capacity to understand oneself and others in terms of intentional mental states (e.g., feelings, desires, wishes, attitudes, and values) is essential for humans to be able to establish fundamentally positive relationships with others that also reinforce their feelings of agency and autonomy (Luyten, 2017; Luyten & Fonagy, 2018).

From this perspective, depression is not in itself maladaptive or pathological. Depressive states of mind can be seen as attempts to minimize or end distress associated with separation and loss (Davey et al., 2008; Gilbert, 2006; Panksepp & Watt, 2011). However, excessive and/or age-inappropriate stress, particularly in combination with biological vulnerability, may lead to a vicious cycle characterized by impairments both in reward sensitivity, which results in attachment and agency/autonomy becoming less rewarding, and in the capacity for mentalizing or social cognition (Fig. 13.1), hindering the effective negotiation of normative developmental tasks and further increasing the risk for depression and associated conditions.

Hence, from a developmental perspective, the risk for depression typically increases during developmental transitions (e.g., from childhood to adolescence, from adolescence to early adulthood, and from adulthood to old age), when the individual faces challenges that rely on the stress, reward, and mentalizing systems. For example, adolescence involves the establishment of new and more complex relationships, as well as a sense of agency and autonomy: both of these tasks rely

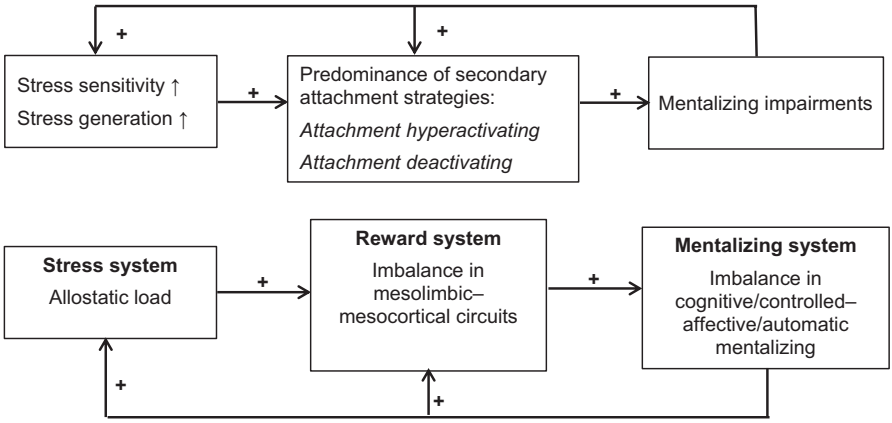

Fig. 13.1 The role of the stress, reward, and mentalizing systems in depression. (Adapted from Luyten and Fonagy 2018)

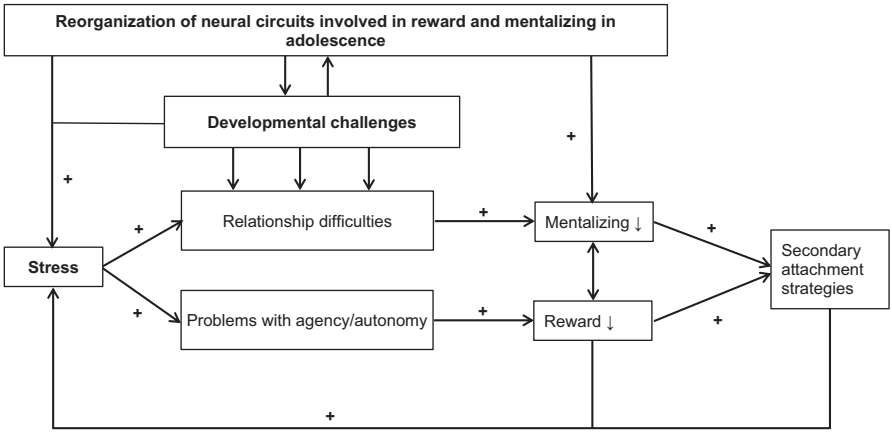

Fig. 13.2 Developmental challenges in adolescence and vulnerability for depression. (Adapted from Luyten and Fonagy 2018)

heavily on the three biobehavioral systems, which may explain the increased prevalence of depression during adolescence (Fig. 13.2), particularly in those that are at greater risk because of biological and/or environmental factors. With the onset of old age, issues of autonomy and relatedness are challenged once again, as the aging individual is increasingly confronted with the loss of physical and mental capacities and loved ones (Van Assche et al., 2013). In what follows, we discuss research findings concerning the role of these three biobehavioral systems in depression.

13.2 The Stress System

The role of stress in explaining vulnerability to depression is fairly well established. First, there is good evidence to suggest that early adversity plays a key role in vulnerability to depression (Auerbach et al., 2014; McCrory et al., 2012; O'Brien & Sher, 2013). Estimates of the population attributable fractions – that is, the proportion of psychiatric disorders and suicide that could be explained by early adversity – range from 20% (Afifi et al., 2008) to 80% (Dube et al., 2001), with the vast bulk of the explained variance being related to depression, in particular chronic depression (Negele et al., 2015). For many individuals with chronic depression, trauma is deeply ingrained in their experience of themselves and others, and experiences of (perceived) rejection, criticism, or abandonment are re-traumatizing (Luyten et al., 2020; Luyten & Fonagy, 2014). The effects of early adversity on the onset of depression remain stable across the life span, even when controlling for the onset of previous episodes, suggesting that there are strong "programming" effects of the stress response, which are reviewed in more detail below (McLaughlin et al., 2010). These findings may also explain why chronic depression is so difficult to treat (Rost et al., 2019). Not surprisingly, longer-term treatments have been shown to be more effective for individuals with chronic depression (Leichsenring et al., 2016; Rost et al., 2019).

Second, there is also good evidence for the role of later-life stress in depression. Both major and minor life stressors, as well as chronic stress, have been causally related to the onset of depression, either alone or in interaction with personality features (e.g., neuroticism and self-critical perfectionism) and genetic factors (Kendler et al., 2004; Kendler & Gardner, 2014; Luyten et al., 2006). Mechanisms underlying the relationship between early and later-life stress involve both increased stress sensitivity and the active generation of stress (Auerbach et al., 2014; Blatt, 2004; Hammen, 2005; Kendler et al., 2004; Luyten et al., 2006; Shahar, 2006). Indeed, individuals who are vulnerable to depression unwittingly and unconsciously tend to generate their own stressful environment, typically involving self-fulfilling prophecies (Luyten & Fonagy, 2018); for instance, highly dependent individuals who constantly fear rejection and abandonment tend to become emotionally demanding and clinging in interpersonal relationships, leading to the others in their relationships becoming frustrated and angry, thus increasing the risk that they will be abandoned and rejected by those others. Similarly, highly perfectionistic individuals, who typically fear criticism and failure, tend to become competitive and demanding in their relationships, leading to criticism from others, which confirms their underlying conviction that they are unlovable.

Research suggests that these interpersonal dynamics play a greater role in the transition to adulthood than in other developmental phases (Auerbach et al., 2014). Indeed, in adolescence, peers play an increasingly important role at the same time as issues of autonomy and achievement take center stage (see Fig. 13.2); this may in part explain the increase in prevalence of depression during adolescence, particularly in girls (Auerbach et al., 2014). Within Western societies at least, women tend

to place greater emphasis on relatedness and attachment (for a review, see Blatt, 2008), which may make them more vulnerable to internalizing disorders, including depression (Kendler & Gardner, 2014).

From a neurobiological perspective, the stress system is one of the most extensively studied and best-circumscribed systems. It involves the amygdala, the hippocampus, and the anterior cingulate cortex, orbitofrontal cortex, and medial prefrontal cortex (MPFC) (McEwen, 2007; Pervanidou & Chrousos, 2012). These neural structures underpin the human capacity for *allostasis*, the capacity to continuously adapt to changing circumstances (McEwen, 2007), and serve the fight/flight/freeze response when the individual is faced with acute stress (Gunnar & Quevedo, 2007; McEwen, 2007; Pervanidou & Chrousos, 2012). This response involves the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system, the metabolic system, the gut, the kidneys, and the immune system. Each of these systems has relatively distinct biomediators (e.g., cortisol, sympathetic and parasympathetic transmitters, metabolic hormones, and cytokines). The effects of stress on these systems explain why stress-related disorders such as depression are highly comorbid with somatic disorders (e.g., cardiac disorders, diabetes) and functional somatic disorders (e.g., chronic pain and fatigue) (Afari et al., 2014; Anda et al., 2006).

Meta-analyses have suggested that depression is typically associated with HPA axis hyperactivity in adolescents (Lopez-Duran et al., 2009) and in adults (Zorn et al., 2017). However, findings in this area have not always been consistent, and short-term hyperactivity of the HPA axis seems to be largely due to chronic stress/early adversity. In the longer term, a switch from HPA hyperactivity to hypoactivity seems to be typical because of the wear and tear on physiological systems (Miller et al., 2007). In addition, HPA axis hypoactivity may delineate atypical depression and/or be more typical of depression in women (Zorn et al., 2017); this observation may also explain the high comorbidity and overlap between depression and functional somatic syndromes (Luyten et al., 2019).

Animal studies have yielded some of the strongest findings on programming of the stress system associated with (early) stress. Early development in particular seems to be characterized by high sensitivity to programming effects, which may last until early adulthood in humans (Heim & Binder, 2012; Lupien et al., 2009). Of particular importance are findings that neural structures involved in the stress system undergo structural changes and functional reorganization in adolescence, at a time when the stress system is particularly challenged by increasing demands for autonomy and relatedness. Indeed, adolescence has been shown to be characterized by a marked increase in HPA axis reactivity to stress (Casey et al., 2008), particularly in response to social rejection (Masten et al., 2009; Sebastian et al., 2010; Sebastian et al., 2011). Sleeping problems and problems related to disturbances of the circadian rhythm (Tsuno et al., 2005) also seem to be related to increased stress sensitivity associated with depression.

Genetic factors are also important when considering the role of stress in depression, particularly as heritability estimates of depression are estimated to be around 30–40% in adults (Middeldorp et al., 2010; Sullivan et al., 2000). Studies in this

context have focused on gene–environment correlations and interactions in depression, although there is still mixed evidence at best from studies in humans given the many methodological problems of studies in this area (Auerbach et al., 2014; Bleys et al., 2018; Dick et al., 2015), and the fact that the vast majority of studies in this domain have been conducted in samples of people of Western descent (Krause et al., 2016; Leighton et al., 2017). Similarly, while findings of research on epigenetic effects (i.e., the effects of environmental factors on gene expression) in animals have been quite consistent, more research concerning their potential role in depression in humans is needed (Cecil et al., 2020).

13.3 The Reward System

Phenomenologically, depression can to a large extent be described as a reward depletion disorder: the depressed person feels that everything is hopeless and meaningless and that nothing brings joy, pleasure, or satisfaction. Various theories suggest that two key areas of reward are central in depression: *social/attachment relationships* and *agency/autonomy* (see Fig. 13.2) (Beck, 2009; Blatt, 2008; Dawood et al., 2018; Gilbert, 2006; McFarquhar et al., 2018; Ryan et al., 2016).

Most research in this area has focused on issues of reward associated with attachment relationships (Feldman, 2017; Insel & Young, 2001; Panksepp & Watt, 2011; Rutherford et al., 2011; Swain et al., 2007), although there has been increasing interest in the role of impairments in agency/autonomy in relation to the reward system, particularly from the perspective of self-determination theory (Murayama et al., 2010; Ryan et al., 2016; Vandenkerckhove et al., 2020).

From a neurobiological perspective, the reward system involves mesolimbic and mesocortical pathways. Mesolimbic pathways include the ventral tegmental area, with projections to the ventral striatal regions (and the nucleus accumbens in particular), the hippocampus, and the amygdala. Mesocortical pathways involve projections to the prefrontal cortex and the anterior cingulate cortex (Pizzagalli, 2014; Russo & Nestler, 2013; Spear, 2000). Dopamine, oxytocin, opioids, and cannabinoids are the key biological mediators of the reward system, reflecting the fact that there is a close relationship between depression and substance use disorders, as both disorders involve the same biological mediators (Hsu et al., 2015; Panksepp & Watt, 2011; Spear, 2000). From this perspective, substance abuse can be seen as an attempt to deal with feelings of depression and despair.

The reward system plays a central role in the development of the stress system and its regulation throughout the life span (Feldman, 2017; Hostinar et al., 2014; Strathearn, 2011; Swain et al., 2014). Secure attachment experiences serve to buffer the effects of stress. In early development, secure attachment has been shown to be key in fostering adaptive hypoactivity of the HPA axis (Gunnar & Quevedo, 2007). Insecure attachment experiences, by contrast, lead to impairments in the reward system and, as a result, dysfunction of the HPA axis (Auerbach et al., 2014; Pizzagalli, 2014; Strathearn, 2011).

These effects have been particularly demonstrated by research on the hormones oxytocin and vasopressin. Oxytocin fosters affiliative behavior in individuals who are faced with distress, albeit only in relation to in-group members and for those who are securely attached. In such circumstances, opportunities for the distressed individual to effectively co-regulate stress with others are optimized. These effects have their roots in early development and thus tend to generalize to other attachment relationships. Mothers with high serum levels of oxytocin, for example, tend to make more affectionate contact with their infants and are more likely to follow their infant's gaze with an affectionate touch (Apter-Levi et al., 2014; Kim et al., 2014). Oxytocin has also been shown to have direct anxiolytic and anti-stress effects via downregulation of the HPA system (Feldman et al., 2014). Importantly, oxytocin also fosters mentalizing and trust in others, which leads to the effective downregulation of stress (Bartz et al., 2011; Neumann, 2008).

However, the downregulatory effects of oxytocin are limited to close relationships, (i.e., parent–infant and partner relationships) and in-group members. By contrast, the experimental administration of oxytocin has been shown to lead to decreases in trust and cooperation in relation to out-group members (Bartz et al., 2011). In addition, individuals with an insecure attachment history not only have lower basal levels of oxytocin but also show increased distrust of others and an increased cortisol response to stress following oxytocin administration (Bartz et al., 2011). The effects of oxytocin thus seem to be fundamentally mediated by the context and factors related to the individual.

Consistent with these findings from biological studies, behavioral studies have consistently reported robust associations between vulnerability for depression and impairments in reward associated with both relatedness and autonomy. Most research in this area has focused on impairments in agency/autonomy expressed as, for instance, high levels of self-criticism or self-critical perfectionism – a pernicious combination of high personal standards and high levels of self-criticism. As a result, self-critical individuals have great difficulty experiencing a sense of joy or accomplishment, as they always fall short of the standards they set for themselves. Features of self-critical perfectionism have been empirically associated with increased vulnerability for depression. Self-critical/perfectionistic individuals have also shown a poor response to treatment across a number of therapeutic modalities, although they may respond better to longer-term treatments (Blatt et al., 2010; Rost et al., 2019; Shahar, 2015).

Various theoretical approaches have focused on the association between vulnerability for depression and impairments in reward associated with affiliation, as expressed in high levels of dependency (Blatt, 2008), sociotropy (Beck, 2009), and insecure attachment (Agerup et al., 2015; Grunebaum et al., 2010; Lee & Hankin, 2009). For instance, a meta-analysis of 55 samples ($N = 4386$) in which attachment was measured with the Adult Attachment Interview (George et al., 1985) reported that insecure individuals had higher levels of depression compared with secure-autonomous individuals ($d = 0.21$, 95% CI [0.08, 0.33]) (Dagan et al., 2018). This effect was particularly pronounced in insecure-preoccupied individuals ($d = 0.48$, 95% CI [0.30, 0.65]), whereas it was small for insecure-dismissing individuals

($d = 0.09$, 95% CI [–0.03, 0.22]). The difference between insecure-preoccupied and insecure-dismissing individuals should be interpreted with caution, as dismissive attachment has been associated with the denial and underreporting of distress (Mikulincer & Shaver, 2007). Adults with unresolved attachment showed higher levels of depression than those with organized attachment ($d = 0.29$, 95% CI [0.13, 0.44]). Similarly, a comprehensive meta-analysis in children and adolescents, including 643 effect sizes based on 123 independent samples, found an overall effect of $r = .31$ between insecure attachment to primary caregivers and depression (Spruit et al., 2020). Importantly, there is good evidence from prospective multi-wave studies showing that attachment anxiety and avoidance are both associated with increases in depressive symptoms over time (Khan et al., 2019), suggesting a causal role for attachment experiences in vulnerability for depression. Moreover, longitudinal studies have shown that insecure working models of self and others mediate the relationship between early adversity and later vulnerability for depression through their negative effects on affect regulation, stress responsivity, and impairments in social problem-solving skills (Bifulco et al., 2006; Brown et al., 2019; Styron & Janoff-Bulman, 1997; Widom et al., 2018).

There is some evidence that dismissive attachment is associated with greater vulnerability for a hostile/aggressive subtype of depression (MacGregor et al., 2014), while attachment disorganization, characterized by the use of both attachment hyperactivating and deactivating strategies, may be typical of individuals with marked borderline-level functioning, expressed in more severe depression and marked feelings of emptiness, anger, shame, and identity diffusion (Lecompte et al., 2014; Luyten & Fonagy, 2014).

From an evolutionary perspective, insecure attachment strategies appear to reflect different strategies to deal with the (perceived) unavailability, unresponsivity, or intrusiveness of attachment figures (Ein-Dor et al., 2010). Hence, these responses are, at least in the short term, adaptive. However, in the long term, they typically seem to lead to considerable intrapersonal and interpersonal costs. This functional–adaptive perspective on depression contrasts markedly with a disease model that considers depression as a static end-state.

How can the relationship between reward and depression be understood at a more subjective, phenomenological level, including its many embodied manifestations? This leads us back to the groundbreaking work of pioneering researchers on the association between depression and loss, namely, René Spitz (1945), John Bowlby (1973), Harry Harlow (1958), Joseph Sandler and Walter Joffe (1965), and Anna Freud (1963). They were among the first to systematically describe the often detrimental consequences of early loss of an attachment figure, and their descriptions were to become the foundation for current understanding of the relationship between mourning and depression.

Loss of a loved object by separation or death – and, by extension, the loss of any ideal or wished-for state – leads to massive activation of the attachment system (Mikulincer & Shaver, 2007). However, with the loss of the object (or wished-for state), a source of reward has disappeared from the individual's life. The object exists only at the representational level and is particularly difficult for those with

mentalizing impairments to hold on to, as they typically experience difficulties representing mental states (a more detailed discussion of the role of mentalizing impairments in depression is provided in the next section). However, as depressed mood impairs mentalizing, a vicious cycle is set in motion, and the individual increasingly finds him/herself in a state of despair and loneliness, which is accompanied by psychological and embodied manifestations of that despair and loneliness. Typical human responses to loss, as first described by Spitz and Bowlby, entail protest (e.g., anger, aggression) and/or denial of the loss, followed by resignation, which is typically only partial. A painful psychobiological, embodied response is involved in the loss of an attachment figure, marked by acute distress lasting from minutes to hours (evident as, e.g., crying, agitation, or sighing). As well as this acute distress, more chronic features, typically lasting for a period of weeks to months (e.g., social withdrawal, cognitive problems, eating problems, sleep disturbances), are characteristic of loss (Hofer, 1984).

Particularly during the acute distress associated with loss, the individual is constantly reminded of their lost loved one, who provided an important regulatory function – that is, as an important source of reward. Now the lost object exists only at the representational level and is thus physically missed, but at the same time, the individual is constantly reminded of the lost object by environmental cues. The ensuing activation of the attachment system may be so strong that it leads to delusional experiences (e.g., denial that the lost person has gone, the conviction that they will return, or feeling the presence of the lost person). This is probably one of the main reasons why depressed states typically tend to last for weeks to months, as the relinquishing of the lost object is usually a slow and gradual process, which takes longer with loved attachment figures who were more important to the individual. As Freud noted in his seminal paper *Mourning and Melancholia* (Freud, 1915), memories of the lost person/object are activated during the mourning process one by one, as if the individual needs to revisit all the memories associated with the lost object before he/she can move on. Hence, depressed states of mind and the tendency to cling on to the lost object, which is impossible to replace, are understandable responses to loss. As Freud commented to one of his friends who lost his son to an illness: "We know that the acute sorrow we feel after such a loss will run its course, but also that we will remain inconsolable, and will never find a substitute. No matter what may come to take its place, even should it fill that place completely, it yet remains something else. And that is how it should be. It is the only way of perpetuating a love that we do not want to abandon" (Freud, 1961). As is now well known, the above-described basic psychobiological response to loss may be complicated by various defense mechanisms, such as anger (i.e., protest, in an attempt to relieve the pain associated with loss), survivor guilt (particularly when the attachment relationship with the lost object was characterized by high levels of ambivalence), and/or shame.

This model of loss of an attachment figure can be generalized to the loss of a wished-for state more generally. Just as a lost person may provide an important regulatory function for the individual, so can a wished-for state, and the loss of this wished-for state can lead to a similarly painful psychobiological response marked by increased distress and reward deficiency. Consider, for example, the depressed

adolescent sitting on the school bus on his way home, contemplating a life very different from his current one; or the nurse who has just heard that she has been fired, dreading telling her husband, fearing losing her friends at work, and worrying about whether she will find a new job any time soon.

Again, adolescence may be a pivotal stage in the emergence of vulnerability to depression. The reorganization of the reward system in adolescence, combined with changing sociocultural expectations, makes it even more difficult for adolescents to deal with experiences of (perceived) loss. Adolescents are faced with challenges both in peer and romantic relationships (as is also expressed in increased rejection sensitivity during this stage of life) and in terms of increasing demands for achievement (as is reflected in increased sensitivity to failure). Perhaps not surprisingly, therefore, adolescence is characterized by a "reward deficiency syndrome" (Spear, 2007). Compensatory behaviors such as risk-taking, self-harm, or substance abuse may be used to ward off feelings of depression, explaining in part the high comorbidity with externalizing disorders observed in adolescents with depression (Davey et al., 2008; Spear, 2000). Reward deficiency in adolescence may also explain the high levels of novelty- and sensation-seeking behavior typical of this developmental phase; these behaviors serve to foster autonomy and enable the formation of romantic relationships. Yet, as adolescents increasingly have the ability to realize that things that they perceive as rewarding (e.g., love, status) are temporally distant and can be truly achieved only in the distant future, they may experience alternating feelings of excitement and depression (Davey et al., 2008).

13.4 The Mentalizing System

Mentalizing is a largely species-specific human capacity that enables complex forms of communication and collaboration. It also greatly facilitates self-awareness and self-consciousness, including the capacity to envision oneself in the future. Yet, this capacity for increased self-awareness and self-consciousness also has a flipside (Luyten et al., 2012). Self-awareness and self-consciousness also enable self-conscious emotions such as shame and guilt. While these emotions serve important adaptive interpersonal functions, when they are too intense or chronic, they lead to depression. Furthermore, self-consciousness also implies the awareness that one may not be able to achieve one's goals and desires (related to either autonomy or relatedness or both), leading to feelings of despair and depression (Luyten et al., 2012). We have already discussed how this latter process may be even more important in certain developmental stages and transitions (such as adolescence, mid-life, and old age). The fact that neural circuits involved in mentalizing undergo major structural and functional changes in both adolescence and old age may help to explain the increased risk for depression associated with these developmental stages (Cusi et al., 2012; Drevets et al., 2008; Kerestes et al., 2014). Moreover, age-specific changes typically further challenge mentalizing capacities. For example, in adolescence, the emergence of sexuality and new forms of aggression typically challenge

mentalizing capacities even further. Adolescents are often unable to make sense of these changes, leading either to excessive mentalizing (so-called pretend mode functioning or hypermentalizing) or to the avoidance of mentalizing (hypomentalizing, typically expressed in psychic equivalence mode functioning: "I feel worthless, so I am worthless, and everything is worthless"). In the teleological mode of functioning, adolescents often try to deal with such unmentalized experiences by trying to evacuate them through acting out (e.g., self-harm, substance abuse, reckless behavior). Likewise, in old age, the loss of physical capacities and loved ones may lead to extreme feelings of despair in psychic equivalence mode ("everything is lost") or extensive rumination about lost opportunities in the past in pretend mode functioning ("if only I had made other choices in life").

Studies suggest that depression in individuals who predominantly use attachment hyperactivating strategies in response to stress results in part from a failure to reappraise and regulate negative affect, suggestive of problems with controlled mentalizing, leading to a predominance of automatic, affect-driven mentalizing. Attachment deactivating strategies, by contrast, appear to result in an excessive downregulation of reward circuitry in combination with hyperactivation in the MPFC and ventral anterior cingulate cortex, suggesting a pattern of cognitive overcontrol and overregulation (Luyten & Fonagy, 2015; Vrticka & Vuilleumier, 2012).

Mentalizing impairments in depression have been extensively documented, ranging from impaired facial emotion recognition and theory of mind to more complex mentalizing capacities involved in human interactions (Billeke et al., 2013; Bistricky et al., 2011; Kerestes et al., 2014; Weightman et al., 2014). Moreover, these impairments have been shown to be related to the severity and duration of depressive episodes, to prospectively predict relapse in major depression, and to persist in euthymic patients, suggesting that such impairments often remain present as latent vulnerability (Bistricky et al., 2011; Schreiter et al., 2013; Weightman et al., 2014).

13.5 Conclusions

This chapter outlines a developmental psychopathology approach to depression across the life span. Basically, we suggest that depression results from a disruption – due to biological or environmental factors, or a combination of both – of the balanced functioning of three key biobehavioral systems involved in stress and arousal regulation, reward, and social cognition or mentalizing. As each developmental transition in life typically entails a biological reorganization of these three biobehavioral systems, and new environmental demands challenge the balanced functioning of these systems, life transitions and other events that challenge the functioning of the three systems (e.g., loss of a loved one, unemployment, migration) are likely to increase the risk for depression.

From the perspective of prevention and intervention strategies, a transdiagnostic and transtheoretical approach is needed. The biobehavioral systems involved in

depression are also involved in many if not all other psychological disorders (e.g., anxiety disorder, posttraumatic stress disorder, anorexia, antisocial personality disorder, and borderline personality disorder) and are a central focus of many pharmacotherapeutic and psychosocial treatments. This view is also consistent with the developmental psychopathology principles of *equifinality* and *multifinality* (Cicchetti & Rogosch, 1996) – that is, that different etiological factors (e.g., childhood trauma) are involved in developmental pathways toward depression (equifinality) and etiological factors that are implicated in depression may also be involved in the etiology of other psychological disorders (multifinality).

The efficacy of treatments may be improved by a greater and more consistent focus on each of the biobehavioral systems involved in depression. For instance, several antidepressant medications primarily target the stress system, while psychological treatments often primarily focus on the social cognition/mentalizing system. Moreover, a stronger focus on the developmental roots of dysregulations among the biobehavioral systems in depression may similarly increase the effectiveness of treatments for depression. There is increasing consensus that most psychological disorders, including depression, have their roots in development and that this reflects a broader underlying general vulnerability for psychopathology (Caspi et al., 2014). Research on this general psychopathology factor, or "p" factor, suggests that treatments (with the exception of those for the mildest psychological problems) should thus focus on this broader underlying vulnerability.

Consistent with the assumptions expressed in this chapter, we suggest that both biological and environmental factors may constrain individuals' capacity to adapt to their ever-changing environment, leading to disruptions in the balance between the stress, reward, and mentalizing systems. This view may also explain why distorted mood and symptoms of depression are implicated in most psychological conditions. We hope that this chapter will contribute not only to a greater developmental focus in research on depression but also to the development and empirical evaluation of broad transdiagnostic and transtheoretical psychosocial interventions that focus on the underlying biobehavioral systems implicated in depression and associated conditions.

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Chapter 14
Depression and Personality Dysfunction: Moving from Descriptive Comorbidity to the Identification of Common Intermediate Phenotypes

Alex Behn and Mariane Krause

14.1 Introduction

Globally, the lifetime prevalence of major depressive disorder (MDD) is 10–15% of the population (Lépine & Briley, 2011), constituting the third cause of morbidity and accounting for 4.3% of the global burden of illness. Especially when depression is long-lasting and of moderate or severe intensity, this illness may become a serious health condition in which the person suffers greatly and functions poorly at work, at school, and in the family. At its worst, depression can lead to suicide. Over 800,000 commit suicide every year, and it is the second leading cause of death in 15- to 29-year-olds. Treating depression should be a priority worldwide due to the high subjective, social, and economic burden of the illness. However, treatment effectiveness can be greatly improved. A study by Craighead and Dunlop (2014) found that even though two thirds of patients enrolled in randomized clinical trials (RCTs) for depression show a positive response, only 30–40% present remission of symptoms. An additional factor adding to the social and subjective burden of depression has to do with the recurrent nature of the illness (DeRubeis et al., 2008). Between 50% and 60% of patients experimenting a first major depressive episode will experience a second episode, and of these patients, 70% will experience a third one and 90% a fourth episode (Hart et al., 2001). This means that many depressed patients spend up to 21% of their lives clinically depressed (Vos et al., 2004), which increases the risk for suicidality, comorbidity, and chronic physical illness and impairs physical and psychosocial functioning (Hardeveld et al., 2013).

Substantial contents of this chapter were taken from Behn et al. (2018).

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_14

14.2 Phenotypic Variability in Depression: Theoretical Heterogeneity

There is sufficient evidence in the field of psychology and psychiatry to support the clinical and scientific contention that depression is a rather heterogeneous clinical entity (Maj, 2012; Zimmerman et al., 2015). Furthermore, it has been argued vehemently that the somewhat disappointing scientific and clinical results may be related to substantive heterogeneity of the syndrome as well as to artificial heterogeneity related to diagnostic rules. In part, diagnostic heterogeneity across mental health conditions, including depression, is a structural result of the polythetic diagnostic system of DSM: a given clinical diagnosis can be arrived at by using different combinations of symptoms. As a result, there are 227 different symptom combinations that follow diagnostic rules for depression (Olbert et al., 2014; Zimmerman et al., 2015). Resulting combinations are varied and can be quite different and even contradictory at the phenotypic level. For example, a patient presenting with depressed mood, weight loss, insomnia, and psychomotor agitation can be diagnosed with major depressive disorder (MDD) as well as a patient suffering from anhedonia, weight gain, hypersomnia, and psychomotor retardation. Within the polythetic structure of DSM and ICD, this proliferation of seemingly opposite presentations can be accounted for by the existence of compound symptoms (including dimensional opposites, e.g., "sleep disturbances") in addition to single symptoms (e.g., anhedonia) (Zimmerman et al., 2006). However, it can be argued that this heterogeneity is artificial, merely a result of theoretical symptom combinations due to the polythetic structure of DSM, and does not necessarily capture substantial heterogeneity in the clinical syndrome of depression as it occurs in nature, that is, at patient level. Thus, above and beyond the issue of theoretical heterogeneity, empirical heterogeneity needs to be examined as a way to map clinically relevant types of depression naturally presenting in individuals.

14.3 Phenotypic Variability in Depression: Instrumental Heterogeneity

An additional source of heterogeneity that is also not substantive is related to instrumental heterogeneity. Whatever method is used to analyze patient-level data, symptoms need to be collected using specific instrumentation. These instruments can be interview schedules, used by clinicians, or self-report questionnaires. There are many instruments that are typically used to measure depressive symptoms in individuals, both in clinical and research setting. The underlying assumption is that all these instruments map on the same set of symptoms that constitute a prototype for depression. However, many of the widely used screeners for depression are rather idiosyncratic, that is, there is scarce content overlap between items. According to Fried (2017), taken together, the most common measures used for research in

depression map on 52 distinct symptoms, and some of them are compound symptoms that can be disaggregated in such a way that even more symptoms are available. Many of these symptoms are idiosyncratic, that is, they are present in only one or two measures. According to Fried (2017), only 12% of all symptoms were present in the seven most used depression schedules or questionnaires. Thus, the extent to which heterogeneity can be examined in depression appears to be largely contingent on the number of items included in a given instrument. For example, if one is to use the Patient Health Questionnaire (PHQ-9) to measure depression in a patient, less information is available (fewer items, fewer symptoms) compared to using the Beck Depression Inventory (more items, more symptoms). Whether a given questionnaire includes coverage of too few symptoms or too many symptoms depends on the specific use. Typically, practical needs (e.g. fast screening versus detailed case formulation) need to be weighted to decide on how to best strike a balance between fidelity (i.e. how much information is captured by an instrument) and compression (i.e. fewest number of items used to capture this information).

14.4 Phenotypic Variability in Depression: Empirical Heterogeneity

In contrast to theoretical and instrumental heterogeneity which stems from polythetic diagnostic criteria, empirical heterogeneity requires collecting patient-level data, typically using symptoms described in diagnostic systems and with specific instruments. This means that empirical heterogeneity is still fundamentally constrained for the most part by instrumentation and diagnostic systems. With this idea in mind, Fried and Nesse (2015) found 1030 unique symptom patterns emerging from a sample of 3703 outpatients diagnosed with depression from the STAR*D trial. An overwhelming majority of these profiles (84%) were present in only a handful of individuals, and half of the profiles were exclusively exhibited by one individual. Looking at empirical heterogeneity, other authors have tried to examine the latent structure of depressive symptoms in clinical samples using advanced statistical techniques, most notably latent class or latent profile analysis and taxometric analysis (Baptista et al., 2019; Wardenaar et al., 2017). This research has led to a plethora of studies and scientific articles that can be used to map symptomatic profiles occurring in real patients. However, it is still difficult to aggregate results from this literature, in part because of the great number of parameters that can be adjusted in this statistical models and that can result in different latent class descriptions (van Loo et al., 2018). Thus, if one takes into account the diagnostic rules advanced by the DSM as well as the latent structure literature, profile variability is ubiquitous and at times idiosyncratic, so that more stable patterns of heterogeneity are difficult to map. It is quite likely that heterogeneity cannot be sufficiently parsed out at the phenotypic level.

14.5 Intermediate Phenotypes as a Way to Parse Out Symptomatic Heterogeneity of Depression

Heterogeneity stemming from all these theoretical, instrumental, and empirical sources is problematic, basically because of the different sources of artificial heterogeneity. This has resulted in many authors advocating for substantial research in the area of differential etiopathogenic pathways towards depression. The principle behind this literature is that if variability cannot accurately or confidently be found at the level of the phenotype, there may be more stability to be found at the etiopathogenic level. The Research Domain Criteria (RDoC) strategy proposed by the National Institute of Mental Health (NIMH) represents perhaps the strongest push in this direction (Cuthbert & Insel, 2013). If stability is to be found in heterogeneity, this will not be accomplished at the phenotypic level but, rather, at the level of genetic vulnerability or at the level of intermediate phenotypes or endophenotypes which connect genetic components to symptom heterogeneity. This focus may be better suited to arrive at substantive models that can aspire to organize phenotypic variability as a secondary phenomenon. Interesting work has been carried out examining the endophenotype by phenotype interaction, including the review by Hasler et al. (2004). Heterogeneity in depression can thus be located not solely at the phenotype level but rather at the interaction between observable depressive symptoms and intermediate phenotypes, including negative mood bias, deficits in reward function, and increased stress sensitivity, among others. Observable symptoms are also not a unique manifestation of a specific vulnerability expressed by an intermediate phenotype. Different intermediate phenotypes can lead to similar symptoms in the same way that different conditions can lead a patient to develop a fever. Just like a fever, depressive symptoms are not univocally related to intermediate phenotypes. In terms of treatment development, this leads to personalized treatment models that target underlining disease mechanisms (intermediate phenotypes). Similarly, authors have looked at the genes by phenotype interaction searching for stability in the seemingly endless proliferation of distinct symptomatic profiles in depression (e.g., see Milaneschi et al., 2016 and Thorp et al., 2019). The great empirical heterogeneity of depressive presentations can be thus reconducted towards a distinct set of intermediate psychological and biological domains that bridge the relationship between genomic complexity and disease heterogeneity in depression (Insel & Cuthbert, 2009).

14.6 Domains of Personality Functioning Are Intermediate Phenotypes for Depression

The arguments presented above can be organized around two basic ideas. First, depression is a notoriously heterogeneous syndrome. Multiple attempts to organize things at the phenomenological level have largely failed (from Jaspers to the DSM,

perhaps), to the extent that even though DSM-5 remains to be a categorical diagnostic tool for the most part, in the introduction of DSM-5, it can be read that "the once plausible goal of identifying homogeneous populations for treatment and research resulted in narrow diagnostic categories that did not capture clinical reality, symptom heterogeneity within disorders, and significant sharing of symptoms across multiple disorders" (APA, 2013, p. 12). Second, different (or the same) depressive symptoms can be explained by vulnerabilities in one or in several intermediate phenotypes; there are no established univocal pathways between symptoms and underlying causes. Thus, the question of the etiology of depression needs to be replaced by the etiologies of depression, in the plural. The concept of intermediate phenotypes is useful in this context.

At the level of intermediate phenotypes, one can locate psychological functions that can be broadly organized within the construct of the personality. The contention that heterogeneity in depressive symptoms can be partially explained by the operation of intermediate phenotypes related to personality functioning is consistent with a common clinical finding: many patients with depression also present with personality dysfunction, and in turn, many patients with personality dysfunction present with depression. The comorbidity of mood disorders including major depressive disorder (MDD), bipolar disorder (BP), and dysthymia (DY) with personality pathology is quite common in clinical settings. In a meta-analysis (Friborg et al., 2014), it was estimated that approximately 45% of patients with major depressive disorder also had a personality disorder and approximately 60% of patients with a diagnosis of personality disorder also have a concurrent diagnosis of a depressive disorder. One likely explanation for the frequency of this concurrent presentation is that there is partial overlap in intermediate phenotypes for both classes of disorders. Depression and personality researchers have not always shared this view, which has led to decades of diagnostic debates ever since systematic empirical research on personality pathology emerged in the 1980s, about three decades later than systematic empirical research on depression. Landmark studies that have characterized the occasional polarization of this debate include, from the mood disorders specialist perspective, Akiskal and McKinney Jr.'s (1973) widely cited study published in *Science*, arguing that depression is a single and stable clinical entity with rather strong diagnostic borders with other clinical entities. On the personality disorders specialist side, Gunderson and Phillips (1991) have argued that the most prototypical personality disorder, namely, borderline personality disorder (BPD; regarding the status of BPD as a prototypical personality disorder presentation, Wright & Zimmermann, 2015, offer a comprehensive review), exhibits weak and non-specific relationships to depression.

Significant research has also showed that first-line psychotherapeutic and pharmacological interventions to alleviate depressive mood have a diminished effect in patients with BPD and that depressive symptoms can remit with successful treatment of BPD (Gunderson et al., 2004), indicating that mood instability in the setting of personality pathology may exhibit a different pathogenesis than common depression (Stoffers et al., 2010). This debate is still quite active, and, according to recent

accounts, "(…) the problem of the boundaries of mood and personality disorder is central to the identity of psychiatry and to its future" (Paris, 2015, p. 7).

Both clinically and scientifically, it is extremely important to further understand the interaction between depression and personality functioning. Personality can be defined as the integrated operation of multiple psychological systems, cognitive and self-functioning (including identity), affect modulation and regulation, behavioral control, and interpersonal functioning. These domains of functioning are consistent with the diagnostic criteria for personality disorders of DSM-IV through DSM-5's Alternative Model as well as with the new diagnostic scheme proposed by the ICD-11. According to Hasler et al.' (2004) review on endophenotypes of depression, negative mood bias, impaired learning and memory, impaired reward function, increased stress sensitivity, and executive functioning deficits are all stable endophenotypes for major depressive disorder (MDD). Three of these endophenotypes are also shared with BPD. Thus, personality dysfunction (i.e., impaired operation of psychological systems empirically related to depression) can contribute to the parsing out of symptomatic heterogeneity in depression. For enhanced precision of the argument, we would say that personality functioning can be understood more broadly as an intermediate phenotype, because it refers to psychological mechanisms related to phenotypic complexity (i.e., heterogeneity of depression), sometimes in the absence of clear or reasonable heritability, which is important for the consideration of endophenotypes (Goldman & Ducci, 2007; Gottesman & Gould, 2003; Lenzenweger, 2013). Intermediate phenotypes are a crucial component if one sets out to understand the complex and well-debated relationship between depression and personality dysfunction because, as Choi-Kain and Gunderson state in the conclusion of an excellent book on the subject of mood disorders and BPD (2015), both disorders are "superficially divergent [but] fundamentally overlapping" (p. 257). This formulation expresses precisely the idea that phenotypic variability can be reconducted to common disease mechanisms, that is, to common or at least overlapping intermediate phenotypes.

14.7 When Depression Is Complicated by Dysfunction in Intermediate Phenotypes Representing Personality Vulnerabilities

The issue of shared or overlapping intermediate phenotypes between personality dysfunction (particularly the case of BPD) and depression has been often framed in terms of a *common-cause* model (Klein et al., 2011). This model predicts that depression and personality disorders can be distinct entities, with seemingly robust diagnostic borders at the phenotypic level, but they likely share common etiopathogenetic mechanisms that mediate between genomic and symptomatic complexity. This view presupposes no causal influences between both entities in this specific model. In other words, patients frequently present with depression and personality

dysfunction, because both problems have the same or similar causal influences, but a patient's depression is not caused by his or her personality problems. A recent review by Goodman et al. (2015) has argued that MDD and BPD are likely two distinct disorders, sharing common disease mechanisms that account for affective dysregulation, regardless of specific phenotypes. Depressive disorders and personality disorders – in particular BPD, which likely constitutes a prototypical presentation in the realm of personality dysfunction – mainly overlap in the functional domain of affect regulation, that is, they share affective symptomatology. Clinically, BPD patients very often present with a major depressive episode (Newton-Howes et al., 2014). This co-occurrence has also been explained in terms of a diathesis of affective regulation, by an etiological influence related to the personality trait of negative affectivity or neuroticism (Reichborn-Kjennerud et al., 2010; Wright et al., 2012). Negative affectivity expresses a heritable trait characterized by exacerbated negative emotions, sensitivity, and reactivity to stress (Widiger, 2009), that is, it constitutes an endophenotype. In a meta-analysis, the negative affective trait managed to explain almost 30% of the variability in BPD symptoms and 22% of the variability in symptoms of a major depressive episode, suggesting an underlying etiological dimension to both disorders (Kotov et al., 2010; Samuel & Widiger, 2008).

It is likely that the recurrence and treatment challenges related to depression are connected with underlying personality vulnerabilities that complicate the clinical management of patients (see Newton-Howes et al., 2014). These personality vulnerabilities may constitute a personality disorder, but additional clinical presentations where depression is nested within sub-threshold personality vulnerabilities are also likely part of this scenario. In fact, depressive disorders and personality disorders commonly present together. The ubiquity of this comorbidity has important consequences for patient prognosis and typically results in an augmentation of the burden of disease for patients with a depressive disorder (Soeteman, Verheul, & Busschbach, 2008) and consequently an increase in number of life years lost due to disability (Wittchen et al., 2011). Thus, the nature of personality pathology, or even subthreshold personality vulnerabilities, needs to be examined to understand its contribution to the complication, recurrence, and treatment resistance of complex depression. Patients with comorbid depressive disorder and personality disorders have typically poorer adherence to treatments (Pompili et al., 2009), and their presentation usually configures a more clinically complex level of psychopathology (Friborg et al., 2014). In addition, patients with this dual presentation have almost double the risk to be non-responders after antidepressant psychotherapy compared to those patients with a single diagnosis of depression (Newton-Howes et al., 2014). Moreover, the psychosocial and occupational impairment is higher for patients with comorbid depression and personality pathology (Markowitz et al., 2006), and they appear to be at a higher risk to develop additional formerly designated Axis I psychopathology, especially anxiety (Stein et al., 1993).

In a systematic review and meta-analysis, Köhling, Erenthal, Levy, Schauenberg, and Dinger (2015) concluded that depression in borderline personality disorder (BPD) is characterized by elevations in anger/hostility and self-criticism (as expected in introjective experiences of depression; Blatt & Zuroff, 1992); and for

those patients with comorbid depression and BPD, depressive symptomatology is typically more severe when compared to depressed controls (Kohling et al., 2013). Even though a shared intermediate phenotype for depression and BPD includes affect dysregulation, in MDD, affect variability shows a different pattern than in BPD, and in the later, it appears to be restricted to affective reaction to interpersonal rejection (Goodman et al., 2010). A recent study using frequent ecological momentary assessment showed that MDD with BPD patients did not present with higher affective instability, compared to MDD patients (Köhling et al., 2015). The fact that MDD and BPD phenotypes of affect dysregulation are not easily distinguished provides compelling evidence for shared or largely overlapping intermediate phenotypes.

14.8 Longitudinal Course in Depression and in Personality Dysfunction

Initial accounts indicated that while in depression mood disturbances were episodic, more sustained, and less reactive to environmental stressors, mood dysregulation in BPD exhibited more intense fluctuations and high reactivity to environmental and, in particular, interpersonal stressors (Gunderson, 2007) and specifically sensitivity to interpersonal rejection (Staebler et al., 2011). However, data from longitudinal studies has revealed that the difference between episodic and stable mood symptoms in MDD and intense fluctuations in BPD is not necessarily warranted. Depression often exhibits a recurrent course with inter-episodic maintenance of residual symptoms (Frodl et al., 2008) or even a chronic course from the beginning (Klein, 2010). Notably, early-onset forms of chronic depression typically go along with severe impairment of interpersonal functioning, similar to those found in personality disorders (Klein, 2010), and have been conceptualized as a personality disorder in previous times (Herpertz et al., 1998). BPD patients, on the other hand, typically stop presenting diagnostic threshold symptomatology as time passes (Paris & Zweig-Frank, 2001; Zanarini et al., 2005). In longitudinal studies, remission of BPD in one wave is highly predictive of sustained remission in subsequent waves to a greater degree than remission of depression, which has been shown to have a rather recurrent course.

Taking this evidence into account, strong phenotypic differences between MDD and BPD are not quite as clear as initially had been thought. In fact, phenotypic stability of disorders is largely discussed in current research, particularly in light of recent large-scale studies that have argued for the presence of one common factor underlying pathways to severity across formerly called Axis I mental disorders (Caspi et al., 2014), as well as across personality disorders (Sharp et al., 2015). Regarding the later, the most recent version of the International Classification of Diseases (ICD-11) eliminates the specific classes of personality disorders (e.g., narcissistic, histrionic, and schizoid) and presents dimensional criteria for one single

personality disorder, based on domains of functioning and a five-factor model of personality traits, while retaining BPD as qualifier of severity (Herpertz et al., 2017). This diagnostic modification in the realm of personality disorders was already available in part in the hybrid alternative model presented in DSM-5 (Widiger, 2011), which also relies on domains of functioning (which result in dimensional assessment of personality pathology) and on personality traits (which can lead to a categorical diagnosis based on specific trait configurations). Both modifications are substantial and contribute to solve the problem of frequent comorbidity among different personality disorders (Clark, 2005), underlining the idea of a single personality dysfunction component which can present phenotypic variability as a function of profiles of maladaptive personality traits.

14.9 The Issue of Differential Response in MDD and BPD to Antidepressant Pharmacological Interventions

As indicated before, concurrent presentation of MDD and personality dysfunction is common, and this is consistent with the idea of a *common-cause* or shared intermediate phenotypes. However, the issue of differential response to antidepressant medication in MDD with or MDD without concurrent personality pathology needs to be considered. If both disorders share the same intermediate phenotypes, then both disorders should exhibit similar patterns of response in depressive symptomatology when antidepressants are administered following clinical protocols, as long, of course, as medication effectively targets these underlying functions. This is, however, not the case. There may be different explanations for this. One explanation is that MDD and BPD (we are focusing on BPD because it concentrates most of the scientific evidence in personality dysfunction research and because it can be considered a prototype or a common factor across different personality disorders) share some intermediate phenotypes, but not others, and alas, common antidepressant medication may provide superior coverage of those intermediate phenotypes that do not significantly overlap with BPD. Another explanation is that MDD and BPD do share the same or most intermediate phenotypes but concurrent presentation of MDD and BPD represents a more extensive deficit of these functions, which may explain diminished effectivity of medication.

14.10 Is There a Specific Phenotype of Depression in Borderline Dysfunction?

The idea of two distinct yet commonly co-occurring disorders is largely sustained by the evidence pointing towards common disease mechanisms (i.e., a shared diathesis in affect regulation). From this perspective, of course MDD and BPD will

often present together. However, authors have also advanced the idea of specific forms of depression that are secondary to personality dysfunction. This causal influence of personality over depression can be understood from the perspective of a *predisposition model* (Klein et al., 2011), which predicts that specific depressive phenotypes stem from specific personality vulnerabilities.

Most prominently, Sydney Blatt proposed in 1974 that depression may be a by-product of deficits in the structure of object relations, further advancing the idea of two distinct forms of depression, namely, anaclitic and introjective (Blatt, 1974). In his effort to understand the heterogeneity of depressive presentations, Blatt argued that anaclitic depression was characterized by a disruption of interpersonal relatedness (typically fears of abandonment), whereas introjective depression was characterized by deficits in self-integrity and in self-esteem (typically extreme self-criticism; Blatt & Zuroff, 1992). This initial distinction was further developed into a comprehensive theoretical model connecting personality predispositions with stressful life events. The latter is quite interesting, given the pertinence of the early life maltreatment literature to understand depression, personality pathology, and the interaction between the two (Heim & Binder, 2012; Pagano et al., 2004). Recently, Silva et al. (2017) have provided experimental evidence indicating that biological stress reactivity of individuals is modulated by their positioning within an anaclitic or introjective polarity of experience, with introjective individuals exhibiting more objective biological stress reactivity compared to anaclitic individuals, but anaclitic showing higher scores in self-report instruments. Thus, personality predispositions in the anaclitic versus introjective continuum provide a specific vulnerability for the development of depression, particularly when an individual is confronted with stressors.

Within the predisposition model, depression in the setting of BPD has been often investigated as a specific depressive phenotype alongside the literature on phenotypic heterogeneity of depression. This phenotype of borderline depression would be characterized mainly by accelerated patterns of emotional variability (Mneimne et al., 2018; Trull et al., 2008), emerging and hardly identifiable with retrospective self-reports, since these frequently over-represent extreme or concurrent affective states at the time of answering the questionnaire, not knowing the moment-to-moment variability in mood (Fredrickson, 2000; Hufford et al., 2001). In addition, patients with borderline depression would exhibit greater impulsivity, aggressiveness/hostility, and interpersonal hypersensitivity (Fertuck et al., 2013; Rogers et al., 1995). They are also patients who would present a greater risk of developing self-injurious and/or suicidal behaviors (Lieb et al., 2004). In summary, this particular phenotype would be characterized, therefore, by emergent and rapid psychic variability and by deficits in intermediate phenotypes underlying BPD, including affective dysregulation, impulsivity and behavioral dysregulation, and interpersonal hyper-responsiveness (Gunderson & Lyons-Ruth, 2008). This evidence may contribute to differential diagnosis between concurrent MDD and BPD, on the one hand, and borderline depression, on the other.

The predisposition model predicts that depression is tributary to, not concurrent with, the personality dysfunction. A careful evaluation of the level of the personality

dysfunction within a continuum of severity is called for and prescribed by current diagnostic guidelines, including the ICD-11 and the DSM-5 alternative model. The level of personality function can be most aptly evaluated within the spectrum of self-other representations (Leising & Zimmermann, 2011). The operationalized psychodynamic diagnosis (OPD) system offers a useful theoretical and empirical framework for research and for clinical use (OPD Task Force, 2008). The OPD is a psychodynamically informed multiaxial system, initially developed over 25 years ago with the goal of providing a reliable diagnostic and research tool that would allow a more comprehensive evaluation of patient's functioning, beyond symptomatic presentations typically covered by standard diagnostic manuals. A comprehensive review of the OPD system can be found elsewhere (e.g., in Cierpka et al., 2007). We will focus our discussion on Axis IV, which covers the concept of *structure* and that is useful to evaluate levels of personality functioning. Specifically, OPD operationalizes structure in terms of self-other functioning, including perception and cognition of the self and others, regulation of self and others, regulation of internal versus external representations of others, and the level of attachment to internal and external representations of the self and others (Zimmermann et al., 2012). What is essential to our current discussion is that the level of personality functioning appears to be sensitive in distinguishing between borderline depression and MDD comorbid with BPD, because it exhibits high correlations with clinically rated personality disorders, but not with Axis I diagnoses. This may indicate that the OPD system may go beyond the fact that MDD and BPD have likely common causes and provide subtle coverage of the predispositional component in borderline depression (Zimmermann et al., 2012).

14.11 Discussion

Significant advances in research on the etiology of depression are urgently needed. Treatment effectiveness is still not where it should be, and many patients do not experience full remission, or even remission that may translate in noticeable improvement of life quality. Complicating the advancement of robust etiological models is the fact that depression is a notoriously heterogeneous clinical syndrome, and this heterogeneity can be established at the theoretical, instrumental, and empirical level. Treatment development and delivery needs to be personalized and for this to be achieved, phenotypic heterogeneity must be parsed out at the level where it matters. This level can be aptly represented by the concept of intermediate phenotype. Intermediate phenotypes are underlying functional domains that may lead to different observable symptoms. Symptom heterogeneity is vast, but vulnerability in relevant functional domains that express at the phenotypic level can perhaps be reduced to only a few candidates.

Functional domains related to personality are good candidates to explain some of the heterogeneity of the depression. In other words, the question about the etiologies of depression is intimately related to the question of personality function,

understood as a set of interrelated functional domains that can be conceptualized as intermediate phenotypes. Research in this area has been growing and presents a promising direction to improve models of disease mechanisms and, more importantly, to develop differential treatment components for patients that differ not at the level of phenotype but, rather, at the level of affected intermediate phenotypes. Future instrument development should also be calibrated to measure deficits in these dimensions. Thus, measuring personality functioning may be a promising route to design and deliver personalized mental health treatment.

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Chapter 15
Gender and Depression: Women, Transgender, and Gender Nonconforming Depression

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15.1 Women and Depression

15.1.1 Life Cycle Prevalence

The World Health Organization (Ferrari et al., 2013a, b) has estimated that nearly 300 million people worldwide currently experience depression. Women have a lifetime risk of major depression double that of men, an observation that has been replicated worldwide (Gater et al., 1998) with approximately 20% of women being likely to experience depression at some point in their lives (Kuehner, 2003). According to estimates from depression prevalence studies, boys and girls do not show large differences in depression prevalence (Kessler et al., 2001). Before puberty, prevalence of depression is commonly low, with boys being more likely to meet criteria for major depressive disorder (Douglas & Scott, 2014; Wang et al., 2013). Gender differences in depression prevalence (higher in females than males) first begin to emerge between the ages of 12 and 15 (Sundström Poromaa et al., 2017). However, this gender difference widens the most between ages 15 and 18 (Breslau et al., 2017; Hankin et al., 1998; Hankin et al., 2015), declining and remaining stable in adulthood (Sundström Poromaa et al., 2017). Non-psychotic depression is a common health problem among women during their childbearing years, with an atypical prevalence of around 14% (O'Hara & Swain, 1996), though in some contexts it appears to be considerably higher (Cooper & Murray, 1998). Maternal depression commonly occurs in the context of social and family risk factors, such as low socioeconomic status, unemployment, lack of parental support, and other family stressors. Research on the mental health of men has rarely

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_15

considered the effects of fatherhood. However, the couple goes through a number of potentially stressful events during the reproductive period, and both mothers and fathers are at risk of developing peripartum depression. The prevalence of paternal perinatal depression is approximately 10% (Goldstein et al., 2020). Hence, contrary to popular belief, the prevalence of depression in men and women does not converge after menopause, but rather higher rates of female depression continue into old age (Fang et al., 2019; Wang et al., 2010). In contrast, the results of longitudinal studies show no conclusive differences between genders in terms of remission, recurrence, or chronic course of depression and risk factors for recurrence (van Loo et al., 2018). However, there are two gender-related moderating factors of the course of depression. First, the incidence of completed suicide is higher in men than in women, although the sex ratio varies greatly across regions and countries. Nevertheless, this observation cannot account for gender difference in depression, because suicide itself continues to be an infrequent event. Second, the over mortality observed in depressed individuals compared with the general population is clearly higher among depressed men than among depressed women. This observation can be attributed to the greater number of suicide deaths, somatic comorbidity, and substance use in men. Prescription of medication for depression is another gendered phenomenon: women are prescribed medication more often than men.

15.1.2 Symptomatic Profile

Women with depression have more atypical symptoms than men, mainly increased appetite and hypersomnia. They are more likely to report somatic symptoms such as low energy, fatigue, and pain. In women, comorbidity with other internalizing disorders is more frequent, while in men, comorbidity with externalizing and substance use disorders predominates (Cavanagh et al., 2017).

15.1.2.1 Subtypes of Depression

Some authors have asserted that the gender difference in depression is due to the greater proportion of women with non-psychotic depressions of medium severity who report having no depressed relatives, also called somatic depression (Silverstein et al., 2017). However, in the melancholic or psychotic subtype of depression, no gender differences have been identified in the age of onset of first episodes or the incidence rates of depression (Bogren et al., 2018). It has been observed that different symptoms are associated with greater functional disability in depression among men and women. In men, dysfunctionality tends to be associated with anxiety and sleep disturbances, while in women it is generally associated with the severity of depressive symptoms (Carmona et al., 2018).

There now is consensus that the gender difference in depression has a multifactorial etiology (Salk et al., 2017). Theories of developmental psychopathology argue

that there are multiple pathways to gender difference in depression involving combinations and interactions of risk factors that span multiple levels of analysis. More specifically, these pathways to gender difference in depression occur in a developmental context. Theories highlight how specific vulnerability factors are triggered at critical periods of development in adolescence and/or interact with adolescent stressors to produce the gender difference in depression. Thus, a developmental approach is key to understanding the patterns of this gender difference.

Generally, explanations of the gender difference in depression are based on psychopathological models of stress diathesis. This model proposes that individuals have characteristic ways of coping with stressors in their lives. Some individuals, due to a "vulnerability" in their constitution whose origin may be behavioral/temperamental (e.g., negative cognitive styles), physiological or endophenotypic (e.g., highly physiologically reactive), or genetic (e.g., short 5-HTTLPR alleles), are disproportionately likely to be adversely affected by an environmental stressor. The interaction between these diatheses and stressors leads to depression. It should be noted that this model predicts a gender difference in depression when either the diathesis or the stressors, or both, are more prevalent in women than in men.

15.1.3 Possible Explanations for the Gender Gap in Depression

15.1.3.1 Artifact Hypotheses

Artifact hypotheses postulate methodological errors in data collection (Gaviria Arbeláez, 2009). From this perspective, depression is equally common in both genders: differences are not real because women over-report, while men under-report somatic and psychic complaints to their physicians. Measurement procedures do not differentiate symptoms by gender (Araya et al., 2013), although some indicate that standardized tests should have different cutoff points. Possible artifacts include as follows: women are more willing than men to admit, even to themselves, that they feel depressed; women are more willing than men to report depressed feelings when asked; and women are more willing than men to seek help when they feel depressed. However, researchers who have considered these possibilities have uniformly concluded that none of them contribute to the gender difference in depression (Girgus & Yang, 2015). Still, the evidence for this view is limited. Prevalence estimates are generally derived from representative general population studies and should therefore not be biased by gender differences (Kuehner, 2017) in treatment seeking, the tendency of physicians to diagnose, or increased symptomatic complaints of women. Furthermore, there are no grounds to posit a gender-specific recall of mental disorders, including depression, in the general population, or their detection in treatment settings.

15.1.3.2 Individual Vulnerability or Diathesis

Biological Factors

Hormonal Factors

Estrogens and progesterone have been shown have an impact on the neurotransmitter, neuroendocrine, and circadian systems, which have been found to be linked to mood disorders. Sex hormones modulate various neurotransmitter systems in the brain, including serotonergic, dopaminergic, and GABAergic systems, and affect sensitivity to environmental influences over the life span. Changes in hormone levels at puberty, the luteal phase of the menstrual cycle, the postpartum period, and perimenopause are associated with depressive symptoms in vulnerable women (Gaviria Arbeláez, 2009). The luteal phase of the menstrual cycle, a period of estrogen and progesterone suppression, is frequently associated with dysphoric mood changes, as well as with the worsening of a major depressive episode. Approximately 5% of women meet criteria for a severe form of premenstrual syndrome known as premenstrual dysphoric disorder. The similarity of this disorder to major depression may indicate an increased vulnerability to hormonally based depression in some women. The postpartum period is also a common trigger for depressive symptoms. More than 80% of women experience minor mood changes during this period, known as maternity blues or postpartum dysphoria. Postpartum depression occurs in 10 to 15% of postpartum women, with those who experience postpartum depression being at risk for future episodes. The risk of a subsequent postpartum episode exceeds 50%. Minor depressive symptoms are common in the perimenopausal stage, especially in women with severe vasomotor symptoms (Deecher et al., 2008).

Research has found that ovarian hormone fluctuations modulate women's susceptibility to stress, brain structure and function, and inflammatory activity and reactivity. These effects are highly context-dependent, varying as a function of several factors including sex, age, reproductive state, endogenous versus exogenous hormones, and hormone administration mode and dose (Slavich & Sacher, 2019).

Sex hormones as hormonal mediators of the immune system:

Estrogen Estrone (E1), 17beta-estradiol (E2), estriol (E3), and estetrol (E4) are the four major types of endogenous estrogens. Estrogen production occurs primarily in the ovaries and in the placenta during pregnancy, while small amounts are produced in the liver, pancreas, brain, and adrenal glands, as well as in the skin, bone, and adipose tissue. E2 is considered the most prevalent and potent form of circulating estrogen (Slavich & Sacher, 2019). To assess the effects of E2 on the immune system, it is necessary to consider not only E2 concentration but also density, distribution, and type of estrogen receptor. E2 affects both cell-mediated and humoral immune responses, with the effect of estrogens on the immune system apparently depending on E2 concentrations. For example, in low concentrations, E2 stimulates the production of pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α; in high concentrations, E2 blocks the production of these cytokines and other interleukins that have anti-inflammatory effects.

Progesterone Progesterone (P4) is synthesized by the corpus luteum in the ovaries during the second half of the menstrual cycle and by the placenta during pregnancy. P4 signaling is mainly mediated via progesterone receptors but can also occur via glucocorticoid and mineralocorticoid receptors. P4 mostly promotes an anti-inflammatory state by decreasing IL-1β and TNF.

Androgens The most important androgens are testosterone (T); dihydrotestosterone (DHT), which is a metabolite of testosterone; and dehydroepiandrosterone (DHEA), which is the primary precursor of both testosterone and estrogens. Testosterone can decrease NK cell activity and attenuate TNF, although androgens have mainly immunosuppressive and anti-inflammatory effects.

In brief, immune cells have sex hormone receptors and therefore respond directly to changes in sex hormone levels (Slavich & Sacher, 2019). Sex hormones usually do not act in isolation but in synergy; therefore, their effects on immune system activity are complex and not simple to characterize. In general, however, progesterone and testosterone have been described primarily as anti-inflammatory. In the case of estrogens, a U-curve pattern seems to better explain their effect on the immune system, with a pro-inflammatory function generally occurring at low concentrations and an anti-inflammatory state being promoted at high concentrations. These dynamics are directly related to depression risk, as individual oscillations in a woman's mean ovarian hormone levels greatly affect her vulnerability to mental disorders over time (Labaka et al., 2018).

Life stress is strongly associated with depression risk, especially for women undergoing periods of changes in ovarian hormones. Studies have shown that greater social support during stress predicts less depression in women, though the reduction is weaker for men. Thus, exposure to stress and especially to social stressors seems to be more strongly related to depression in women than in men. In this regard, it has been postulated that these effects of life stress on mood are modulated by fluctuations in ovarian hormones. However, the effects of estradiol appear to be highly context-dependent, as indicated by studies reporting increased negative mood in the face of psychosocial stress after menopause. Several theories of hormonal sensitivity to stress and depression have been proposed to elucidate the mechanisms that may underlie these effects. The mechanisms identified include the estrogen-sensitive upregulation of monoaminergic metabolization, the capacity of estradiol to regulate gene transcription (Eid et al., 2019), dynamic fluctuations in hippocampal estrogen receptor expression, and the linking of estrogen-responsive epigenetic mechanisms to serotonergic signaling changes (LeGates et al., 2019).

On the other hand, by contrast with boys, early maturation in girls is associated with more severe and longer-lasting psychopathology, and with depressive disorders in particular (Kuehner, 2017). Contextual adversities, such as a poor parent-child relationship and childhood sexual abuse, predict early maturation in girls, but not in boys; therefore, female pubertal transition seems to be more responsive to adverse environments than the male transition. Studies have found that sex hormone levels alone account for minor variations in depressive symptoms during adolescence (Girgus & Yang, 2015). However, sex hormones are more likely to have an indirect effect. For instance, girls' negative self-evaluation in response to

hormone-induced bodily changes and the early onset of puberty may be associated with the earlier onset of intimate relationships and sexual activity, both of which may elevate the risk of stress and depression as a result of the interaction between a person's pubertal state and their environmental adversities (Balzer et al., 2015). Furthermore, studies have shown that the gender difference in depression ceases to be significant when adolescent body image and self-esteem are statistically controlled for in regression analyses. In summary, these data argue for a context-dependent role of sex hormones in shaping susceptibility to depression; highlight social stress as a potent risk factor for depression, particularly for women with greater sensitivity to hormonal fluctuation; and provide evidence for sex-specific interconnections between life stress exposure, inflammation, and depression.

It has been proposed that fluctuations in reproductive hormones and their metabolites lead to impaired GABAergic regulation of the hypothalamic-pituitary-adrenal (HPA) axis in women. Commonly, men show stronger physiological responses to a wider variety of psychosocial stressors compared to women, including greater HPA axis activation, higher diastolic blood pressure, more negative and aggressive emotional responses, and more intense conditioned fear reactions. Sex differences in HPA axis activation begin in adolescence and are small or absent before puberty and after menopause. Among women, physiological responses to stress vary as a function of cycle phase, contraceptive use, pregnancy, and menopausal status. Stress responses also changes as a function of the nature of the stressor, with men showing stronger responses to achievement challenges and women showing stronger responses to rejection and social conflict. Estrogens show attenuating effects on sympathoadrenal responsiveness and may exert activating or attenuating effects on HPA axis responses. Differences in arginine vasopressin, oxytocin, and corticosteroid-binding globulin concentrations have also been linked to sex differences in HPA axis activation.

From an evolutionary perspective, the attenuated response of women to stress has been hypothesized to be a way to protect the fetus from the adverse effects of maternal stress. However, an attenuated HPA axis response to stress may predispose individuals to an increased risk of depression. Results from some experiments demonstrate that cortisol is able to buffer subjective stress and negative affect, thus contributing to the normalization of emotional circuitry after exposure to stressors. Hypoactivation of the HPA axis is observed in several stress-related disorders and in premenstrual dysphoric disorder, in which hypoactivation of the HPA axis is associated with increased premenstrual symptoms. Studies of HPA axis dysregulation in depression have found both hypercortisolism and hypocortisolism and inconsistencies in gender differences associated with depressive disorder.

Another vulnerability factor is related to the function of the hypothalamic-pituitary-thyroid axis, as about 25% of depressed subjects show an abnormal increase in plasma thyroid-stimulating hormone levels after intravenous injection of thyrotropin-releasing factor (TRH) (Gaviria Arbeláez, 2009). Thyroiditis and other autoimmune abnormalities, which are much more prevalent in women than in men, have been linked to depression.

Genetic Factors

The heritability of major depressive disorder is estimated at 30–40%. Family and twin studies have investigated genetic factors as an explanation for higher rates of depression in women. Although genetic transmission plays an important role in the etiology of depression, researchers have found similar heritability in men and women. The search for specific susceptibility genes on the X chromosome has so far been unsuccessful. Gene-environment interaction studies (GxE) investigate whether individual biological/genetic susceptibility towards stressful life events is moderated by genetic factors. Genes might play a role in explaining the gender gap, since some GxE studies have reported that the interactions between some genes (5HTTLPR, FKBP5, CRHR1) and environmental stressors are stronger in men or in women.

Temperament, Personality, and Coping Styles.

Vulnerability or diathesis due to differences in temperament, personality, and coping styles can be summarized as follows:

Effortful Control

Gender differences in effortful control are consistent in early childhood. For instance, girls manage to regulate attention and inhibit impulses better than boys, in line with boys' higher incidence of external problems. Boys also score higher than girls on the urgency test, related to the Big Five personality trait extraversion, indicating that boys are slightly more active and impulsive and derive more pleasure from high-intensity stimuli. Prospective studies have shown mixed evidence that low extraversion predicts depression, probably due to the broadness of the construct; however, a lack of positive affect, a subfactor of extraversion, has been associated with an increased risk of depression. Evidence for a mediating effect of extraversion on the gender gap in depression is lacking.

Neuroticism

Negative affectivity, related to neuroticism, does not differ between boys and girls in early childhood. Girls' neuroticism scores increase substantially during adolescence, with their higher scores remaining higher than boys' over the life span. Neuroticism is a robust risk factor not only for major depression but also for the broader dimensions of internalizing and externalizing symptoms. There is mixed evidence that the relevance of neuroticism as a risk factor for depression is greater for females than for males (Kendler & Gardner, 2014). The magnitude of the gender gap in personality traits such as neuroticism shows cross-cultural variation, pointing to culture-related gender stereotypes in their configuration. Contrary to expectations, the largest gender gap in neuroticism was found in developed countries. One explanation for this finding is the attribution of masculine and feminine behaviors to roles rather than traits in traditional cultures and to intrinsic trait characteristics in more egalitarian societies.

Empathy and Prosociality

There is a considerable body of data indicating that females are more interpersonally oriented than males (Girgus & Yang, 2015). Traits indicative of interpersonal orientation, such as empathy, prosociality, agreeableness, and warmth, are more frequently observed in girls from childhood onward. Although empathy is generally linked to positive mental health outcomes, several models have proposed trajectories from empathy to internalizing problems in women, beginning in adolescence (Tone & Tully, 2014). This view is compatible with women's greater susceptibility to interpersonal stress than men, although studies testing the causal effects of empathy on gender differences in depression are lacking. In a longitudinal study examining the relationships between sociotropy (dependence on others and a high need for approval and affirmation), negative inferences, and depressive symptoms, both sociotropy and negative inferences partially mediated gender differences in depression (Calvete, 2011).

Body Shame and Dissatisfaction

Body shame and dissatisfaction have been identified as taking part in the development of gender differences in depression in adolescents (Hyde et al., 2008). Gender differences in body shame and dissatisfaction precede those in depression and mediate the association between gender and the increase in depression in adolescents (Hankin & Abramson, 1999). More specifically, girls identify more strongly with a feminine stereotype of needing to appear thin and consequently become more dissatisfied with their body shape and physical appearance, which in turn is associated with increased depression.

Ruminative Response Style

It has been proposed that the ruminative response style – the tendency to passively and repeatedly analyze one's distress, problems, and worries, without engaging in problem-solving or distraction – could explain a substantial part of the gender gap in depression. Rumination predicts depressive symptoms over time and the occurrence of depressive episodes while also interacting with stress to predict depressive symptoms. It is linked to neuroticism but shows incremental effects in predicting depressive symptoms. Research has found evidence for the transdiagnostic qualities of rumination in predicting various types of psychopathology, mainly internalizing but also externalizing, and their co-occurrence (Kuehner, 2017). There is not much data on rumination in childhood, but numerous studies have found that adolescent girls score higher than boys on rumination.

Rumination partly explains the gender difference in adolescent and adult depression. In addition, co-rumination, the tendency to discuss problems in dyadic relationships at length, is more common among adolescent girls than boys. Overall, the effects of rumination on the development of internalizing symptoms are similar across genders, but co-rumination in response to stress appears to be particularly more detrimental for adolescent girls than for boys (Girgus & Yang, 2015).

Preexisting Anxiety

The comorbidity of depressive and anxiety disorders is higher in women than in men. According to Breslau (Breslau et al., 2017), the higher prevalence of depression in women is explained by the preexistence of anxiety disorders, which are about twice as frequent in women as in men and originate in childhood in most cases. Prior anxiety increases the risk of depression similarly in men and women, but the higher prevalence of anxiety disorders in women than in men may contribute to the difference in depression. In women, it is common for the preexistence of anxiety disorders to form a pattern of internalizing symptoms, whereas men are more likely to experience disorders such as alcoholism, antisocial personality, and substance abuse, which are of an externalizing nature. In this regard, Parker (Parker & Hadzi-Pavlovic, 2004) demonstrated some specificity in linking the onset of depression temporally in early adolescence with generalized anxiety disorder and panic disorder.

Stress Generation

In addition to gender differences in the experience of stress, there may also be gender differences in stress-generating behaviors. Stress generation proposes that depressed individuals contribute to the creation or continuation of a stressful environment that may then interact on an ongoing basis with existing diatheses to maintain depressive symptoms or lead to recurrent depressive episodes. Relatively little research has been done on the question of whether gender differences exist in the process of stress generation and thus in its contribution to depression's gender difference.

Attributional/Negative Inferences for Negative Events

Individuals have characteristic ways of describing the causes of negative and uncontrollable events that occur in their lives (Girgus & Yang, 2015). Those who attribute negative events to causes that are internal, global, and stable are more likely to become depressed than those who attribute negative events to causes that are external, specific, and unstable. It is unclear what role negative inferences might play in explaining the gender difference in depression (Hankin & Abramson, 1999).

In the face of these cognitive gender differences, it is worth asking: *How do these differences arise?* It is quite clear that there are gender differences in rumination and in interpersonal orientation in adolescence. The prevailing theory is that socialization processes shape the interpersonal orientations, coping styles, and attribution styles of girls and boys. Compared to boys, adults encourage girls' play to be more interpersonally focused, collaborative, and harmonious rather than aggressive and competitive, a pattern that persists through adolescence. Parents and educators tend to have different expectations for children of different genders, which may result in females becoming more fearful and preoccupied with the evaluation of others; boys, on the other hand, develop a greater sense of dominance and independence. Such differences lead to differences in self-worth and coping styles, which may generate vulnerability to depression. Adolescence may be a time of gender role intensification, with increased sex role socialization and stereotyping of girls to be more

interpersonally oriented. In addition, girls may be socialized to engage in more passive coping strategies such as rumination, rather than more active coping styles.

Environmental Factors.

Recent or Chronic Stress Exposure

Data from the Netherlands Mental Health Survey and Incidence Study (NEMESIS) (Plaisier et al., 2008) showed that paid work, including full-time employment, was associated with a lower prevalence of depressive and anxiety disorders for both men and women, but in women, the protective role of work was limited to those without children. For both genders, the partner role was protective, whereas the parenting role was not. These and other findings suggest that the beneficial effect of employment on mental health among women is reduced if there is role overload due to role multiplicity. Results from Kendler's twin study (Kendler & Gardner, 2014) showed gender-specific stressors contributing to the development of major depressive disorder. In women, it was most frequently associated with the stress of perceived failure in interpersonal relationships; in men, it was linked with work, financial, and legal problems. Insufficient social support appears to be a stronger predictor of depression among women than among men. Data from NEMESIS-2 (de Graaf et al., 2013) did not identify any gender differences in stress exposure over a 12-month period in individuals with no history of depression or alcohol-related disorders. Cumulative stressors more strongly predicted the first onset of major depressive disorder among men than among women, while separation from a partner during the study was more strongly related to the onset of substance use disorders in men than in women (Slopen et al., 2011). Another nationally representative sample study (González & Vives, 2019) found that doing housework, reporting a serious family problem, and experiencing a high level of financial stress were associated with a higher prevalence of depression in both genders. The authors conclude that the gender gap in depression is associated with social factors such as participation in housework, family problems, and financial stress, all of which are more common in women. Exposure to daily life stress or differential susceptibility does not appear to contribute substantially to gender risk for depressive disorders. In other words, depression is triggered by different stressors in women and men, but both genders appear to be equally sensitive to stressors.

Violence Against Women

Violence against girls and women is a serious worldwide public health and human rights problem. It takes multiple forms, including CSA (child sexual abuse), intimate physical and sexual violence, rape, sex trafficking, and, in some world regions, female genital mutilation, child or forced marriage, or violence in the name of so-called honor. Gender-based violence has serious effects on mental, physical, and reproductive health and a huge economic impact (Kuehner, 2017).

Two models have been described (Dunn et al., 2012), to explain how exposure to interpersonal violence might contribute to gender differences in depression: (1) through women's *differential exposure* to violence and (2) through women's *differential sensitivity* to the effects of exposure to violence (Hankin et al., 1998).

The *differential stress exposure* hypothesis holds that women are more likely to be exposed to stressors, which increases their risk of becoming depressed. This is a "mediating" model which is empirically tested in four steps that determine whether:

1. There are gender differences in depression.
2. There are gender differences in exposure to violence, with women presumably being more exposed.
3. Exposure to violence is associated with depression.
4. The association between gender and depression is weakened after accounting for exposure to violence (the "mediator").

For example, Fergusson (Fergusson et al., 2002) studied a cohort of 1265 youths born in Christchurch, New Zealand, between the ages of 16 and 28. The authors examined whether exposure to sexual abuse before age 16 and sexual assault between the ages of 16 and 28 explained the association between gender and depression. They found that the probability of experiencing depression decreased by 24% (from OR = 2.5 to OR = 1.9) after controlling for exposure to sexual violence. In another study, Kessler (Kessler, 2003) also estimated that the odds of a first onset of depression were reduced by half after accounting for exposure to rape and sexual trauma, suggesting that these exposures partially explain gender differences in depression.

The *differential stress sensitivity* hypothesis asserts that men and women experience the effects of interpersonal violence differently. This hypothesis is the "effect modification or moderation" model, which is backed by the observation that women are more likely to experience depression in response to stressors than men, leading to more depression cases in women. Girls may be more likely to respond to violence in the form of depression than boys for several reasons. For example, girls are probably more likely than boys to ruminate and co-ruminate. This cognitive style may sensitize girls to stress in a way that leads them to experience greater stress reactivity. Girls are also more likely than boys to experience internalizing symptoms, whereas externalizing symptoms are more common in boys. However, research on the differential stress sensitivity hypothesis is inconsistent; while some studies have observed no gender differences in the effects of abuse on depression risk, others have found that women are more vulnerable to the effects of childhood sexual or physical abuse and exposure to violence. Thus, although there is more evidence to support the *differential stress exposure* hypothesis, both models are plausible explanations for gender differences in depression. In fact, these models are not mutually exclusive but may work simultaneously.

Childhood Sexual Abuse

Kendall and colleagues (Kendall-Tackett et al., 1993) reviewed 45 studies and concluded that sexually abused children clearly had more symptoms than non-abused children and that abuse accounted for 15–45% of the symptomatic variation. The authors also linked certain characteristics of sexual abuse to higher degrees of depressive symptomatology. Penetration, duration and frequency of abuse, force, relationship of the abuser with the child, and maternal support affected the degree

of symptomatology. Dunn (Dunn et al., 2012), in the National Comorbidity Survey Replication (NCS-R), found that women were more likely than men to have been exposed to rape, sexual assault, and witnessing violence. Exposure to rape and sexual assault partially mediated the relationship between depression and gender.

In the United States, an estimated 19.3% of women and 1.7% of men have been raped in their lifetime, while 43.9% of women and 23.4% of men have experienced other forms of sexual violence in their lifetime, including being made to penetrate, sexual coercion, unwanted sexual contact, and unwanted non-contact sexual experiences (Breiding et al., 2014). Most respondents report that these forms of violence are frequently experienced at a young age, with the first victimization generally occurring before the age of 25 and a substantial proportion taking place in childhood or adolescence. Consistent with previous studies, the results suggest that women, in particular, are highly impacted throughout their lives. However, the results also indicate that many men experience sexual violence.

In a Canadian study of adolescents (n = 8194 participants, mean age = 15.35) (Hébert et al., 2019), 14.9% of girls and 3.9% of boys reported having experienced child sexual abuse. Childhood sexual abuse was independently associated with increased risk of psychological distress, increased health service utilization, and increased health risk behaviors, after controlling for other forms of childhood maltreatment experienced.

A meta-analysis (Shamblaw et al., 2019) found a robust association between childhood abuse and prenatal depressive symptoms. These results reinforce the well-established association between trauma victimization and later psychopathology, expanding current knowledge to specifically target prenatal depression. These results show the importance for women abuse survivors to receive appropriate support and treatment to decrease their risk of prenatal depression.

Physical and Sexual Partner Violence

Violence against women is an endemic problem throughout the world (Western, 2013). True (True, 2012) notes that it is the gendered social and economic inequalities between women and men that make women most vulnerable to violence and abuse in whatever context. Violence against women is a major problem, affecting women in every socioeconomic group and at every life stage. Nowhere in the world do women share equal social and economic rights with men or the same access as men to productive resources.

The widely recognized definition in the United Nations' Declaration on the Elimination of Violence Against Women states that violence against women is "any act of gender-based violence that results in, or is likely to result in, physical, sexual or psychological harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or private life" (UN Women, 1995, p. D113). Behavior that controls or dominates a family member and causes that person to feel fear for the safety or well-being of their family is also considered to constitute family violence. Economic globalization and development are creating new challenges for women's rights as well as some new opportunities for advancing women's economic independence and gender equality. Yet, when

women have access to productive resources and enjoy social and economic rights, they are less vulnerable to violence across all societies.

Research has consistently documented that violence against women is a gendered occurrence and a gendered crime (Garcia-Moreno & Watts, 2011; WHO, 2005; World Health, 2013) and it is estimated that one in three women throughout the world will experience physical and/or sexual violence at some point in their lives. For instance, in a multi-country study conducted mainly in developing nations, between 15% and 71% of women aged 15–49 years reported physical and/or sexual violence by an intimate partner at some point in their lives (WHO, 2005).

Violence exposure across the life span is a pervasive problem that is unevenly distributed among the genders (Gonzalez & Frey, 2020). Women are at greater risk of being victims of multiple instances of severe coercive, and sexual, and severe physical partner violence than are men. Female violence victims are twice as likely to develop depression and substance-related disorders compared to non-affected women. An important risk factor for being a victim of adult sexual abuse is childhood sexual abuse, with revictimization further increasing the risk of psychopathology in adulthood above that of childhood sexual abuse alone. Women are known to be at a higher risk of violence during and after pregnancy. A systematic review and meta-analysis found a prevalence of past-year domestic violence of 27–30% in women with peripartum depression, while the longitudinal studies included in the literature review revealed that women who experience partner violence or pregnancy during their lifetime are about three times as likely to develop postpartum depression (Howard et al., 2013). Longitudinal data for other mental health outcomes are scarce, but individual cross-sectional studies indicate similar associations of domestic violence with peripartum depression, anxiety, and posttraumatic stress disorder symptom outcomes.

In the United States (Breiding et al., 2014), the lifetime prevalence of rape by an intimate partner for women was estimated at 8.8%, while an estimated 0.5% of men experienced rape by an intimate partner during their lifetimes. An estimated 15.8% of women and 9.5% of men experienced other forms of sexual violence by an intimate partner during their lifetimes. Severe physical violence by an intimate partner (including acts such as being hit with something hard, being kicked or beaten, or being burned on purpose) was experienced by an estimated 22.3% of women and 14.0% of men during their lifetimes. Consistent with previous studies, the overall pattern of results suggests that women, in particular, are heavily impacted over their lifetime. However, data also indicate that many men experience sexual violence, stalking, and, in particular, physical violence by an intimate partner.

Gender plays a role in the occurrence of gender-based violence against women and in the depression suffered by women. Gender refers not merely to the biological differences between men and women but also to the broad differences that exist between men and women in their daily life experiences. Gender has a differential impact on men's and women's access to, ownership of, and influence over power and resources, employment, land property, income, secure accommodation, political representation, and other roles in society. Violence against women is significantly enabled by gender inequality, while gender-based violence is seen as a major

contributing factor to gender inequality. In this context, people who do not consider gender equality to be a key value or goal within their community tend to understand domestic violence as insignificant, uncommon, and perpetrated equally by men and women.

As knowledge of the scope, nature, and impact of violence against women has increased in recent decades, new perspectives have been adopted to understand and contextualize gender-based violence. One of the changes observed in recent decades is that violence against women is now recognized as a violation of women's human rights. And this shift in perspective reframes violence from an insignificant, inconsequential, and hidden event to a visible, highly dangerous, and prevalent global problem for which all individuals and communities are responsible. The human rights framework reminds us that gender-based violence against women is a form of discrimination that prevents women from enjoying rights such as freedom and security while also liberating them from erroneous gender stereotypes, torture or cruel punishment, and inhuman or degrading treatment.

Violence against women has short- and long-term consequences, including the impact on women's mental health. A meta-analysis of 37 studies (Beydoun et al., 2012) found that the risk of major depressive disorder increased by a factor of 2–3 and that the risk of elevated depressive symptoms and postpartum depression increased by a factor of 1.5–2 among women who had experienced intimate partner violence compared to women who had not experienced violence. The authors also estimated that 9–28% of the depression experienced by women was attributable to having experienced domestic violence in their lifetime (adjusted for other contributing factors such as previous depression).

The consequences of depression on women's perceptions of the violence against them, their rights to live free of violence, and their abilities to recover from depression (Calvete et al., 2007) result in maladaptive cognitive schemas associated with reduced use of coping strategies and increased use of disengagement coping. Women often felt powerless in the relationship and in their ability to change their situation, unable to cope with their situation, had little hope that their situation could change, and were unconfident that they could trust people or services for support or assistance (Filson et al., 2010). In addition, women felt that there was something inherently wrong with them because of the violence they had experienced and the difficulties they felt they had in coping with the violence. In turn, these perceptions could lead women into deeper depression by causing them to "disengage" from attempts to seek support to understand the impact of violence on them. The traditional and rigid gender roles often imposed by male perpetrators of violence also diminish women's power and control due to the expectation that women are passive and dependent, responsible for the care of others and for unpaid domestic and agricultural work.

Despite its severity and prevalence, violence against women is preventable (Ellsberg et al., 2015). One of the most important determinants of gender-based violence against women is the unequal distribution of resources and power between women and men (Kearns et al., 2020). Often the result of conventional and rigid attitudes to the position of men and women in society, these seemingly outdated

issues still exist, although they are often not overt or acknowledged. For example, there is still an economic gap between men and women: even in wealthy countries, men are often paid more than women for doing the same work (W.G.E.A. (WGEA), 2019). Women may be at a greater risk of violence when they lack the financial security necessary to support themselves and their children or make decisions about how to live their lives. In addition, women have fewer options for leaving or managing a violent domestic situation if they do not have access to independent financial support. Moreover, beliefs and adherence to rigid and stereotyped gender roles for women and men may be expressed at the individual, societal, cultural, community, and institutional levels and may include the belief that what happens within a family is personal business and a responsibility of that family. Cultural attitudes may hold that violence is a valid means of resolving conflicts and that the use of violence and control against women are acceptable ways to maintain social order. The concept of gender is closely linked to attitudes towards violence against women. However, community attitudes towards gender equality and gender equity are even more influential predictors of attitudes towards gender-based violence against women (Uthman, Lawoko, & Moradi, 2009).

Sociodemographic Factors.

It seems that trying to explain the differences between women and men on the basis of biological, intrapsychic, and interpersonal differences and through the analysis of differences in variables such as personality, coping, or stressful experiences is not enough. At the social level, efforts are made to analyze the cultural, social, economic, and political processes that give rise to different health risks for women and men (Matud et al., 2006).

From a psychosocial perspective, it has been suggested that the greater vulnerability to depression of the female gender derives from conditioning factors generated by their lower social status and power, as well as from the internalization of expectations associated with traditional female roles (discussed above), all of which leads to feelings of helplessness, dependence on others, low aspirations, and low self-esteem (Western, 2013). Although social, legal, and economic discrimination have changed in the last three or four generations, there is no clear evidence that gender differences in depression are disappearing, because, despite the changes, there remain inequalities in salary, power, and autonomy at home and at work, as well as in family and home care responsibilities.

Marital Status

Several studies have analyzed the relationship between marital status and depression, with contradictory results. Although it has been suggested that both marriage and having children represent a greater burden for women than for men, the association of both with women's depression depends on complex interactions, such as the level of income, the type and conditions of the woman's work, the number of children, their health and age, the type of relationship with the husband, and the distribution of domestic burdens between the two spouses. It appears that marital status is especially relevant in men, for whom being married seems to be particularly

beneficial, whereas being widowed has a very negative effect (Gaviria Arbeláez, 2009). Although marriage was previously considered a risk factor for depression in women, it is now considered to be less protective for women than for men. A good marriage, in which there is good partner support during stressful times, may decrease the risk of depression in both genders; however, married women continue to sustain higher rates of depression, and in an unhappy marriage, woman are more likely to become depressed than men.

Educational Level

Educational level also seems to have an influence on depressive symptomatology, which is slightly greater than being female or male, with more symptoms in people less formal education (Gaviria Arbeláez, 2009).

Labor

A similar phenomenon occurs regarding employment, with fewer symptoms and fewer differences in depressive level between professional women and men, while the differences between genders are maximized in the groups with less qualified jobs.

The relevance of the type of employment in depressive symptomatology in women stands out: as the limitations in education and employment that have traditionally been imposed on women disappear, the differences between women and men in depressive symptoms decrease. A rewarding job can help decrease a woman's risk of becoming depressed, but only if she has chosen to work, rather than feeling forced to do so by economic pressures. The impact of this obligation is greater especially when the woman works outside the home and has difficulty delegating childcare to someone she trusts. Another key factor regarding the impact of work performance on the difference in depression between men and women is that men tend to earn more money than women in the same profession (Matud et al., 2006).

Poverty

Women's socioeconomic status has been proposed as a possible factor leading to high rates of depression in women. Similar to victimization, there is abundant evidence suggesting a link between financial hardship and depression in both males and females (Salk et al., 2017). A disproportionate share of the global burden of poverty in the world rests on the shoulders of women, undermining their physical and mental health. 70% of the 1.2 billion people living in poverty are women. Because of the feminization of poverty (Gaviria Arbeláez, 2009) and the link between poverty and depression, gender differences might also be linked to income inequality and a national's overall wealth. Most of these sociodemographic factors are more predictive of depressive symptomatology in both genders than belonging to one gender or the other, a result which has been confirmed by several other authors (Aluoja et al., 2004; Emslie et al., 2002; Hyde et al., 2008; Lafaurie Villamil, 2010; Saarni et al., 2007).

Gender Role

Rydberg, Sterner et al. (2020) found that feminine traits with low social desirability expression (i.e., anxious, disoriented, naïve, overcautious, oversensitive, and self-doubting) were associated with both depression and the burden of depressive symptoms. More specifically, the authors found that femininity was associated with higher levels of depression, irrespective of biological sex. In addition, masculinity and androgyny were associated with lower levels of depression. Some authors have redefined the classic values of "femininity" as a variant of learned helplessness; however, depression is not a typical female personality trait.

From a gender perspective, the roles historically attributed to women contribute to low social recognition and low self-esteem. The stereotype of femininity carries in its essence a complete absence of ambition and self-confidence. All these characteristics of femininity incorporated in the social imaginary have led to the exclusive assignment of caregiving tasks to women. Feminine roles have been related to depression, since the latter has been assigned characteristics of dependence, passivity, and low self-esteem typical of the female gender.

One of the greatest and most recent achievements of women has been to obtain the right to access any type of remunerated work. In this context, employment becomes a scarce commodity that must be shared. On the other hand, the incorporation of women into work outside the home without bringing along profound changes in social organization results in many women becoming overburdened by work and also causes social dysfunctions related to the care of children, the elderly, and the sick.

Traditional society is based on a marked gender dichotomy and the prioritization of one gender over the other, the greater appreciation of the masculine, and the normalization of the feminine, which results in the establishment of relations of domination/submission between the genders and a type of socialization of boys, girls, women, and men that leads them to internalize their place in the role structure (POAL, 1995). Several studies point out how women nowadays are trying to overcome the traditional opposition of the sexes in order to make progress in their new roles. However, the traditional values that assign differential roles, tasks, and characteristics to men and women continue to prevail. According to Montesó-Curto (2015), the characteristics attributed to the different roles are the following:

Male role: It is a role inherent to the concept of transition and change. Boys are educated to leave the place where they spend their childhood and to enter and progress in a different sphere, the public sphere. This fosters the learning of skills such as searching, weighing, deciding, and choosing. On the other hand, it should be noted that men have no choice but to make this transition. It is a prestigious role, since the public domain is a socially well-regarded and economically remunerated sphere. It is a role that induces incorporation into a broad and open environment which affords a diversity of possibilities and promotion opportunities. Adaptation to the role requires certain self-demands and entails potential failure due to the fact that the public domain is very competitive. Success in this role depends not only on the individual but also on diverse external factors, such as the political and economic situation. The ideal role is prestigious, but not very accessible to the majority.

Failure in this role is more visible because it is in the public domain. Sons' education tends to be result-oriented, which is a trap that leads them to attitudes of urgency and competition. All in all, this role is the product of the mandate to be the material provider against the female mandate to be the emotional provider.

Female role: It is a role inherent to the concept of permanence, stability, and non-transition. It is a low-prestige or even discredited role, which means that it lacks social recognition and economic remuneration in the public sphere. It is a role that induces people to remain in a limited environment which is therefore restricted in terms of possibilities and options. Adaptation to the role requires major self-denial because the private domain is a limited sphere. Success in this role depends basically on the individual. The ideal role is limited but accessible to the majority. Failure in this role is less visible because it is a private domain. This role does not foster the need to learn and use skills such as searching, weighing, deciding, and choosing, which are important for moving into the public sphere. However, although women are induced to remain in this role, they have the option to transition to the male one.

Some authors have described that, in early childhood up to the age of 2 or 3 years, boys and girls show an equivalent development in terms of behaviors but that from schooling onwards, boys prioritize achievement and girls relationships. In adolescence, the divergence is more pronounced: boys emphasize logic and girls feelings.

According to others (Montesó-Curto, 2014), the objective of action in women is the creation and protection of affective relationships, the maternal model: connection with the needs of the other, availability, and continuous care. This has led to consequences in women such as the postponement and/or ignorance of their own desires, a type of self-worth that rests exclusively in playing an active role in the creation and maintenance of loving relationships, and the tendency to repress and/or inhibit everything that threatens the maintenance of relationships such as feelings, attitudes, and ideas.

For contemporary women, education for the traditional female role may conflict with their created and idealized expectations. For instance, they may feel guilty for only being housewives or performing domestic tasks such as procreation or raising and educating children, all of which falls within the semantic field of the natural and is therefore not considered work by society. This population has the highest rate of disease, which may be due to the lack of social recognition and the negative social status of this role. On the other hand, women who work outside the home are also more prone to suffer from depression due to the stress of simultaneously performing several roles. Those who perceive an equitable distribution of household tasks with respect to their husbands report feeling good with their partners and perceive a state of general well-being. Excessive demands and a lack of resources in one role or the need to perform several roles simultaneously can be a very important reason for stress and health problems (Gómez, 2004).

The mandate that is deeply rooted in women is that they must always be good. This mandate is externalized in a constant search for approval. For some, it is their own role that predisposes them to depression. It is femininity itself as it is conceived in our culture that leads to a greater risk of depression. "That being for others

introjected for centuries in women, dictated by society and religion, gets in the way of their desires and possibilities for happiness" (Montesó-Curto, 2014 p. 111).

Based on current literature, women who meet the following characteristics should be expected to be more vulnerable to depression: stereotyped femininity with no attributes of masculinity such as ambitions and self-confidence; presence of the most negative attributes of femininity (dependence and submission); and absence of the positive attributes of femininity (sympathy and willingness to soften).

The universal role of women, which is to provide care, is sustained by a moral virtue which goes beyond assuming a simple responsibility; it is no mere obligation routine, since it entails a personal commitment. Therefore, when a woman tries to fulfill her desires or needs, she feels that she is failing to take care of others and therefore stops being a good mother, wife, or daughter, predisposing her to become guilty and depressed. When women cannot be available, affectively empathetic, and supportive, they feel self-persecuted and self-blamed, and this is the ultimate source of chronic stress, and its consequence is depression. On the other hand, and maybe contradictorily, if she continues to fulfill her role as a good caregiver, she will require the approval of others to feel worthy, since the needs and desires of others take precedence over her own.

All these social conditioning factors that influence women's depression affect not only women but also men in the way they perceive reality, how they experience or can experience the disease, and how they externalize their demands to combat the disease, because depression is also a warning symptom, a defense mechanism that indicates that something is happening. And when it is constructed in a feminine way, it often leaves out the other half of the population: the male gender, which often does not even have the opportunity to ask for help, leading to – for instance – suicide or higher mortality due to cardiovascular diseases.

As previously noted, interpersonal relationships are very important for some women's self-esteem. Therefore, when women are in relationships that do not provide them with support or care, they may be at risk of developing depression. This risk is expected to increase when women are in relationships characterized by stereotypically feminine and masculine attributes in which, for example, women are expected to be passive and dependent and men are expected to be dominant and assertive.

Some authors (Ali et al., 2002) introduced the idea of "silencing the self" to explain the development and incidence of depression in women. In order to create and maintain the social relationships that are important to them, many women try to avoid confrontation or interruptions that threaten these relationships. Self-silencing is enforced by social and cultural norms, values, and beliefs that value women's passivity, caring for others, and selflessness. As a result, women refrain from seeking to have their needs met and from holding and representing their own opinions and beliefs. Women are more likely to suffer from depression as the importance of the relationship to them increases. Women whose primary source of sense of self comes from non-relational domains, such as career, exercise, or spirituality, are less likely to "silence" themselves.

The notion of self is central to understanding the development and impact of depression in women. The concept refers to each person's experience as a unique, unitary, autonomous self that is separate from others, perceived with continuity across time and place. The experience of self includes awareness of one's own physicality as well as one's inner character and emotional life. Moreover, one is less likely to have a unified self than to have multiple and shifting selves and identities (or subjectivities) that are adapted to and influenced by the contexts in which one lives (Qin, 2004). Historical, social, political, political, legal, cultural, and economic contexts, which are always evolving, result in differences among women in terms of the selves that they experience and maintain.

However, the impact of differential contexts and power relations also means that women may be inhibited and constrained in developing and changing their senses of self and identity. Lafrance and Stoppard (Lafrance, 2007), for example, found that women with depression tend to describe their self-identities in terms of their gender roles and their efforts to meet social expectations. Thus, the concepts of authentic and false self become relevant in thinking about how depression might develop in women and how women might perceive and understand their experiences and recovery processes.

Winnicott theorized that authentic and false selves develop in childhood and that a false self develops when it is necessary to protect and conceal the true self. This is likely to occur when the spontaneity and creativity of the true self, and thus the infant's inner reality, cannot develop in a safe and predictable way. The false self, which is characterized by compliance with social and environmental demands and expectations, takes over from the true self. As the infant develops, so does the false self along with the relationships based on the false self. The true self, however, can remain, be recognized, and, when safe, be returned to the global self, though over a long period of time and with intensive support and/or therapy. These theories reflect the notion of the role of the "good woman," represented by women who focus on the needs of others.

Although women with depression do not self-identify as cynical performers, understanding the development of depression as a possible result of consistently playing an inauthentic role, or acting as the false self, may give them the opportunity to stop playing their roles, understand how their depression may have developed, and reevaluate their sense of self and identity.

One possible negative consequence of emphasizing the preponderance of women with depression is that depression becomes a female-stereotyped disorder. Such a stereotype can be harmful to both women and men. The stereotype might lead to over-diagnosis of depression in women and, potentially, overmedication. For men, the stereotype may mean that their depression is overlooked. It is important that clinicians do not overlook depression among men, particularly because gender biases in diagnosis have been documented (Hartung & Widiger, 1998). Men may be less likely to develop depression than women; however, this does not mean that depressed men are not distressed and impaired.

15.2 Gender Diversity and Depression

Gender absorbs many meanings that go beyond the categories that usually restrict it; it encompasses, like sexuality, multiple cultural and psychological aspects that make it something that can be both grounded and fluid in individuals (Harris, 2009). Perhaps where we can see the greatest expressive deployment of this multiplicity and fluidity is in the world of transgenderism, which itself represents an immense diversity of communities and individuals engaged in political, institutional, and personal transformations (Harris, 2009). Transgenderism is a cultural construct that suggests that gender is not binary (e.g., male-female) and that both gender identity and gender expression (e.g., male-female) are not intrinsically linked to the sex assigned at birth. However, because the opposite view is pervasive in society, transgender people cannot avoid being perceived as different, so this binary conception reinforces their marginalization and discrimination (Staples et al., 2018).

The term transgender, or more broadly Trans*,[1] is a large umbrella term that includes a diverse group of people who experience an incongruence between their gender identity and the gender assigned by society according to the sex assigned at birth (W Bockting, 2014; Reisner et al., 2016). Within this diversity, we find not only the traditional categories of transgender or transsexual people but also a vast diversity of people who are not considered to fit neatly into our society's binary definitions of gender – the traditional "masculine" or "feminine" categories – and who are referred to within categories such as gender fluid or non-binary (Chodzen et al., 2019).

Transgender and gender nonconforming (TGNC) people are a group that has been marginalized and discriminated against. This discrimination reflects a culture of stigmatization rooted in systemic oppression of gender minorities (Puckett et al., 2020; Restar & Reisner, 2017; White Hughto et al., 2015). This oppression is based on the assumption of CIS normativity, according to which the norm for a gender identity is to reflect the socially expected manner of physical sex assigned at birth, and that both sex and gender correspond to binary categories.

Both theoretical (Hatzenbuehler, 2009; Hendricks & Testa, 2012; Lev, 2004; Ilan H. Meyer, 2003) and empirical literature (Baams et al., 2013; Bockting WO, 2013; Connolly et al., 2016; Puckett et al., 2020) establish an association between discrimination and poor health outcomes for TGNC individuals, including depression and suicidal behavior. International literature reports prevalence of suicide attempts and self-destructive behaviors in the transgender population between 23% and 50% higher than their cisgender peers (Klein & Golub, 2016; Moody & Smith, 2013; Peterson et al., 2017; Tucker, 2019). Moreover, in the latest national LGBTQ youth mental health survey conducted in the United States in 2020, of 13,600 transgender

[1] In this chapter, in addition to the acronym TGNC which refers to "trans and gender nonconforming people," we will use Trans* with an asterisk, which in academic contexts is being used more frequently and which alludes to the openness of the category, to maintaining the uncertainty of what the category may contain (Halberstan, 2017; Hatzenbuehler, 2009).

and non-binary youth who responded, approximately 50% acknowledged that they had ever seriously considered suicide (Klein & Golub, 2016; Moody & Smith, 2013; Paley, 2020; Peterson et al., 2017; Tucker, 2019).

The minority stress model (MEM, (Ilan H. Meyer, 2003) has been one of the most important and useful theories for understanding social processes – such as discrimination – that underlie negative mental health indicators in sexual and gender minority populations. This model identifies four processes that constitute sources of stress for minorities and can be categorized as either distal or proximal. External and more socially structural events such as victimization and discrimination are considered distal stressors; heterosexist attitudes such as the assumption of heterosexuality and/or problematization of sexual diversity are considered intermediate stressors, while internalization of sexual stigma and concealment of gender identity and diverse sexual orientation count as proximal stressors (Herek et al., 2009; I.H Meyer, 2007).

Originally this model was developed specifically with cisgender sexual minorities (i.e., lesbian, gay, and bisexual individuals), but in recent years, it has been empirically applied to the TGNC population (Cristiano Scandurra, Amodeo, Valerio, Bochicchio, & Frost, 2017a, b), showing its potential for understanding the experiences and challenges faced by this population. It has been widely demonstrated that experiencing violence and discrimination at high rates leads TGNC people to direct negative social attitudes towards themselves while exerting resistance to contrast the stigma nested in a society that discriminates on the basis of gender identity (Testa, 2015). As some authors have suggested, stigma affects the mental health of TGNC people at structural, interpersonal, and individual levels. Each of these dimensions has been studied separately, but there has been an increasing number of studies that seek to assess their interactions and intertwining (Reisner et al., 2016; C. Scandurra et al., 2018; White Hughto et al., 2015).

In the individual dimension, one of the most confronted aspects in psychiatry and clinical psychology, the internalization of sexual stigma has been considered as a psychological explanation for negative rates of depression and suicide (W Bockting, 2014). This consists of the internalization of stigma by the individual belonging to a sexual or gender minority as part of their value system, involving adaptation to normative gender expectations and a conformity of self-concept to social stigmatization. In the Trans* population, this internalization of stigma can be manifested "outwardly," also called internalized horizontal transphobia, for example, through negative global attitudes and language towards other LGBT people, which implies alienation from one's own community and group identity; or it can be expressed "inward," called vertical transphobia, producing discomfort with disclosure of sexual orientation to others, self-exclusion and shame about oneself, discomfort with same-sex sexual activity, diminished self-esteem, self-hatred, and self-inflicted violence (Austin & Goodman, 2017; WO Bockting, 2015; Martínez, 2017; Pereira, 2015; Tomicic et al., 2016). In the transgender identity development model, Lev (Lev, 2004) asserts that TGNC individuals may experience shame and self-loathing in their early stage of transgender identity, when they become aware of living an incongruence between gender identity and sex assigned at birth. The persistence of

these feelings after this stage could be read as a sign of internalized transphobia (C. Scandurra et al., 2017a, b). However, even though many Trans* people may access social support and benefit from community connection, many may experience feelings of alienation towards people belonging to the same community due to the accumulation of stressors associated with the social context in which they live. Proximal stressors are dependent on the individual because they are linked to subjective feelings, thoughts, and actions; however, they remain embedded and connected to a broader social context that perpetuates negative views towards TGNC groups (C. Scandurra et al., 2018).

In an interesting recent research conducted in Italy by Scandurra et al. (C. Scandurra et al., 2018), 149 TGNC individuals were assessed for internalized transphobia by establishing horizontal and vertical differentiation in its expression, considering indicators of mental health and discrimination. The results showed that internalized horizontal transphobia – alienation – is associated with both anxiety and depression while internalized vertical transphobia, shame, was only associated with depression. It is possible to infer that anxiaty has more to do with fear of discrimination, i.e., a more explicit social burden, whereas depression would have to do with a sense of hopelessness or loss of self-esteem, which are more covert and suffered alone. Probably the feeling of shame towards one's own TGNC identity and negative self-evaluation is strictly connected with intense feelings of self-worthlessness and unworthiness. These findings are consistent with what we have found in Chile in studies on the suicidal experience of young TGNC, in which hopelessness, with or without the presence of depressive symptomatology, is associated with suicidal ideation and attempts (Martínez, 2017).

Furthermore, in a mediational analysis conducted by Scandurra et al. (C. Scandurra et al., 2018), it was found that both vertical and horizontal internalized transphobia mediated the relationship between discrimination – distal stressor – and depression. Therefore, the effect of structural aspects of social rejection and discrimination would be mediated by individual and interpersonal aspects associated with internalized stigma. Thus, negative expectations about the future, strongly associated with high levels of hopelessness, depression, and anxiety in both TGNC and cisgender individuals (Horwitz et al., 2017), would find fertile ground for triggering suicidal ideation in a rejecting and discriminatory society or culture.

Other recent research with TGNC youth explored the role of body appearance congruence associated with gender identity and its relationship to internalized transphobia and diagnostic indicators of depression and anxiety disorder (Chodzen et al., 2019). Findings suggest that gender identity-associated body appearance and expression and internalized transphobia may significantly predict symptoms of depressive disorder and generalized anxiety disorder. For example, young people who perceived their physical appearance to be highly congruent with their gender identity were less likely to meet diagnostic criteria for depression; however, young people with high internalized transphobic beliefs were more likely to meet diagnostic criteria for both depression and generalized anxiety (Chodzen et al., 2019).

These findings show how seemingly superficial aspects associated with social gender transition, such as dress, hairstyle, or pronoun use, actually go beyond

political and ideological affirmation but relate to deep psychological aspects capable of sustaining one's identity and regulating internalized stigma. This supports previous research suggesting that appropriate social transition may be associated with a decrease in mental health disparities experienced by both Trans* youth and adults (Durwood et al., 2017; Kozee et al., 2012; Olson KR, 2016).

As we have seen, research that has emphasized the interactions between individual and social factors has highlighted the need to look at the multiplicity of biological, interpersonal, social, and contextual factors surrounding risks to TGNC people's mental health (Reisner et al., 2016). To mitigate these risks and build resilience, a comprehensive approach is needed that includes affirmation of diverse genders as a public health framework, quality evidence-based healthcare, and effective partnerships with local trans communities to ensure responsiveness and cultural specificity in planning interventions (Snow et al., 2019).

Access to healthcare, in a broad sense, is very important for trans people, as it is often the pathway to shaping their identity and sense of self. Without medical technologies that facilitate the expression of their identity, the fulfillment of individual and social roles for many trans people is severely compromised. It is critical to recognize the role of interventions and procedures aimed at reducing the distress and suffering that may be associated with a TGNC person's birth sex characteristics and to ensure the availability of safe and appropriate health contexts for an affirmation of bodily and sexual identity as a psychologically necessary issue (Coleman et al., 2012). This healthcare of TGNC persons requires a set of skills, attitudes, and behaviors that goes beyond technical knowledge about specific sexual, reproductive, or endocrine health conditions. Current education and training programs for healthcare workers must integrate cultural competence into the rationale for care specific to this population (Hagen & Galupo, 2014; Kanamori & Cornelius-White, 2017; Martínez, 2017; Tomicic et al., 2020).

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Part IV
Clinical Practice as a Meeting Place for Etiopathogenic Models

Chapter 16
Models in Depression and Clinical Judgment, or How to Use Different Etiopathogenic Models with a Particular Patient

Juan Pablo Jiménez and Alberto Botto

16.1 Introduction

Unlike the rest of medicine, psychiatry has not yet found a single and integrated paradigm. This is due to a fundamental problem, which is the difficulty of bridging the gap between the mind and the brain. While it is true that every mental process correlates with a brain substrate, it is no less true that the mind resists being reduced to mere biological mechanisms. This problem has been formulated in terms of a two-faced conception (Solms & Turnbull, 2002): on the one hand, a materialistic mind/brain *monism* (the mind and brain as one and the same thing) and, on the other, an epistemological *dualism* (the mind as an emergent level of organization with its own laws and processes that cannot be reduced to mere brain mechanisms). The method of study proper to the brain is that of the natural sciences; the mind, on the other hand, is the proper domain of hermeneutics, the social sciences, and the humanities. In our conception, the mind not only does include the phenomena studied by psychology but also extends to macro-social phenomena and cultural evolution. Certainly, there exists a gap between the psychological level itself and the sociocultural level, and the relative epistemological autonomy of both domains must be respected. These dualities run through the whole of psychiatry and are responsible for the many controversies and dilemmas that plague the field (Kecmanovic, 2011). There are, however, interesting and promising efforts to narrow the gap between the mind and brain, integrating subjectivity (first-person perspective) into scientific research (third-person perspective), among which neuro-phenomenology (Varela, 1996) and neuro-psychoanalysis (Solms & Turnbull, 2011) stand out.

Of course, the problem is highly complex: although it is evident that brain alterations can manifest themselves through mental changes, the opposite is also true.

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J. P. Jiménez et al. (eds.), *Etiopathogenic Theories and Models in Depression*, Depression and Personality, https://doi.org/10.1007/978-3-030-77329-8_16

There is evidence, for example, that childhood abuse leads to alterations in brain structure, function, and connectivity (Teicher et al., 2016). Furthermore, process and outcome research in psychotherapy has shown that psychological interventions impact the brain, producing structural changes in its functioning and connectivity (Kandel, 1998; Peres & Nasello, 2008). Thus, there is a two-way causality between the mind and brain: "bottom-up" from the brain to mind and "top-down" from the mind to brain (Jiménez et al., 2018). In the same vein, the interaction between genes and culture has recently been highlighted (Laland et al., 2010).

Even when we approach our patients from a predominantly biomedical standpoint, according to which disorders of the mind are *no more* than diseases of the brain, we are confronted with the reality that all psychopathology, the basis of diagnosis in psychiatry, is expressed from a first-person perspective. That is to say, the motivations and reasons that bring patients to consultation, as well as the symptoms that we mental health professionals diagnose, are always subjective: emotional suffering, discomfort, or moral pain. Patients tell us about experiences that make them suffer, be them states of anxiety and fear, sadness, grief, excessive worry or guilt, various negative emotions, or feelings of being threatened, among other issues. Thus, from a psychopathological point of view, the data obtained by the clinician comes from what patients say (their stories) and the way they behave.

The problem for psychiatrists and mental health professionals arises when they must apply to individual patients – who consult an expert for advice on subjective ailments – knowledge achieved through natural science methods, that is, "objective" knowledge, which does not consider (and, by its very nature, does not need to consider) patients' subjectivity. For Kendler, this is the great challenge of psychiatry in the twenty-first century:

> *Our central goal as a medical discipline is the alleviation of the human suffering that results from dysfunctional alterations in certain domains of first-person, subjective experience, such as mood, perception, and cognition*. Our nosological constructs are largely composed of descriptions of first-person experiences (e.g. sad mood, hallucinations, and irrational fears). The clinical work of psychiatry constantly requires us to assess and interpret the first-person reports of our patients. Many of the target symptoms that we treat can only be evaluated by asking our patients about their subjective experiences. *While we want to take advantage of the many advances in the neurosciences and molecular biology, this cannot be done at the expense of abandoning our grounding in the world of human mental suffering*. (Kendler, 2005, pp. 433f; italics added)

In place of biological reductionism, and following the tradition of other thoughtful commentators – like George Engel (1977) and McHugh and Slavney (1986) – Kendler advocates "*explanatory pluralism* as the approach best suited to understanding the nature of psychiatric illness. *Explanatory pluralism hypothesizes multiple mutually informative perspectives with which to approach natural phenomena. Typically, these perspectives differ in their levels of abstraction, use divergent scientific tools, and provide different and complementary kinds of understanding*. Explanatory pluralism is especially appropriate for psychiatry because psychiatric disorders are typically influenced by causal processes operating at several levels of abstraction" (Kendler, 2005, p. 436; italics added).

In this book, we have unfolded the extent of the diversity of causal models in depression and, by extension, in all of psychiatry. These models range from depression as a disorder caused by dysfunction at the genetic and neurotransmitter level (Chaps. 7, 8, 9 and 10) to depression as a sociocultural construct (Chaps. 4, 11, and 12). And, in between, there lie psychoanalytic and cognitive-behavioral theories of depression (Chaps. 5 and 6). Chapters 13, 14, 15 and this chapter present the *evo-devo* (evolutionary and developmental) and gender perspectives, through which modern psychiatry seeks to integrate the various etiopathogenic domains. In our opinion, the problem is that, in a given patient, all these levels are present and interact simultaneously for the entire duration of the clinical picture (or even before the symptoms appear if we consider depression as a disruption in psychobiological development). Thus, the challenge facing the clinician is to take advantage of these *multiple mutually explanatory perspectives* in the diagnosis and indication of treatment in a particular patient. However, as we saw in Chap. 1, the problem is that the various existing theories and perspectives often do not converse with each other or have few points of contact. Contributing to bridge that gap has been one of the purposes of this book.

We have described depression as a clinically heterogeneous and etiopathogenically complex phenomenon (Chap. 1). In the face of the great diversity of approaches and perspectives in the study of depression – ranging from the level of neurotransmitters and systems neurology to psychology and even culture – we embrace a *pragmatic epistemology* (Brendel, 2003, 2006), one of whose pillars is scientific *pluralism*. This means that we believe it is unrealistic to expect that we will ever develop a single model or paradigm capable of fully encompassing all the aspects of depression reviewed in this book or be able to wholly bridge the science/humanism divide in psychiatry. However, this does not mean that we can abandon our search and adopt an eclectic, "anything goes" approach. Diagnosis and indication must be rigorous – following the state of the art – but they are always *provisional*, until new clinical or scientific information is available. In turn, the diagnostic process must include the *participation* of all stakeholders, first and foremost the patient him/herself. Epistemological pluralism and ethical pragmatism are dialectically related. Both dimensions interact and modify each other permanently in the clinical decision-making process, because it is one thing to explain a phenomenon like depression (looking for the causes and mechanisms that produce it), another to describe it, and yet another to understand and interpret it in a particular case.

Indeed, knowledge about the causal domains of depression continues to increase all the time, even if it may never coalesce into a single, fully unified paradigm. As knowledge advances, we must accept patchy reductions leading to piecemeal integration. This necessarily implies that the clinician not only should be well aware of the state of the art but also must be able to produce in his or her head the best integration of scientific knowledge available to help a particular patient. In technical epistemological terms, the clinician must be able to translate nomothetical knowledge down into ideographic and practical knowledge.

We assume that the clinician's work differs from the scientist's work in that *the clinician has before him or her the ethical task of understanding and helping a*

patient who seeks to relieve his or her suffering. Ideally, a clinician working with patients should be able to use all the knowledge accumulated by the natural sciences, since he or she has an ethical mission to fulfill in his or her capacity not as a scientist but as a health *professional*.

In this chapter, we will first review the issue of clinical guidelines, that is, the way in which evidence-based medicine puts accumulated scientific knowledge at the service of the care of individual patients, with special reference to the reception that these clinical guidelines have had in psychiatrists and their use by general practitioners (GPs) at the primary healthcare level. We will then describe the role of clinical judgment in the diagnostic process of depressive patients. This will lead us to the need to stress the relevance of case formulation as the culmination of the diagnostic process. Case formulation should weigh the relative relevance of the multiple etiopathogenic domains found in a particular patient and setting and thus facilitate the indication of multimodal treatments when necessary. Finally, we propose a staggered diagnostic model that considers what is currently known about the etiopathogenesis of depression.

16.2 Clinical Guidelines and Evidence-Based Medicine

Many public mental health institutions and professional associations of several countries have developed evidence-based guidelines for clinical practice. They should serve as a framework for making clinical decisions and supporting best practices. Clinical practice guidelines are statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options.

By definition, these *guidelines* are *suggestions* or *recommendations of* specific professional behavior, endeavor, or conduct for psychiatrists, psychologists, and other mental health professionals. Guidelines differ from standards in that standards are mandatory and may be accompanied by an enforcement mechanism. Thus, guidelines are aspirational in intent. They are intended to facilitate the continued systematic development of the profession and to help assure a high level of professional practice. Guidelines are not intended to be mandatory or exhaustive and may not be applicable to every professional and clinical situation. They are not definitive and do not take precedence over the judgment of clinicians.

A recent review (Zafra-Tanaka et al., 2019) of clinical practice guidelines (CPGs) for depression published in English and Spanish between January 2014 and May 2018 ($N = 11$) found many differences in the quality of these documents, particularly regarding the incorporation of patients' views, the rigor of the development of the guidelines, and the lack of clarity in the process used to develop recommendations. The authors of this review suggest that stakeholders as well as developers and users of CPGs should take this into account not only when choosing CPGs but also when interpreting and implementing their recommendations.

Recently (2019), the American Psychological Association issued clinical practice guidelines for the treatment of depressive disorders (including major depression, subsyndromal depression, and persistent depressive disorder). The expert panel that developed the guidelines comprised health professionals from the psychology, psychiatry, and primary care fields, as well as community members who reported having depression. The effectiveness of psychological treatments and complementary and alternative medicine treatments was examined. The panel also examined the comparative efficacy of psychological treatments (alone and in combination with pharmacotherapy) and the comparative efficacy of psychological treatments in relation to pharmacotherapy and complementary and alternative treatments.

Clinical practice guidelines provide recommendations for the diagnosis *and* treatment of depression. In this chapter, we will leave out the treatment aspect to focus on the conditions that must be met in order to carry out the *best* diagnostic process. Certainly, a well-conducted diagnostic process should lead to an appropriate therapeutic indication.

16.2.1 General Recommendations for the Diagnosis of Depression

In its *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*, the American Psychiatric Association (2015) provides a decalogue of general management recommendations that should be considered during the diagnostic (and therapeutic) process. The following is an adapted summary of these recommendations:

1 *Establish and maintain a therapeutic alliance*. The clinician should collaborate with the patient in decision-making and take into account his or her preferences and concerns about diagnostic and prognostic matters. Management of the therapeutic alliance should include awareness of transference and countertransference issues, even if these are not directly addressed in treatment. It should not be forgotten that the diagnostic process in psychiatry is of an intersubjective nature, that is, the clinician cannot dispense with the insight of his own emotional reactions in the interaction with the patient. Moreover, the importance of exploring the subjective experience of being depressed together with the patient cannot be overestimated, because patients' perception of their illness and health services greatly influences how they access and interact with the health system.
2 *Complete the psychiatric assessment*. Patients should receive a thorough diagnostic assessment in order to establish the diagnosis of major depressive disorder, identify other psychiatric or general medical conditions that may require attention, and develop a comprehensive plan for treatment. This evaluation generally includes a history of the present illness and current symptoms; a psychiatric history, including identification of past symptoms of mania, hypomania, or

mixed episodes and responses to previous treatments; a general medical history; a personal history, including information about psychological development and responses to life transitions and major life events; a social, occupational, and family history (including mood disorders and suicide); a review of the patient's prescribed and over-the-counter medications; a review of the patient's systems; a mental status examination; a physical examination; and appropriate diagnostic tests as indicated to rule out possible general medical causes of depressive symptoms. Assessment of substance use should evaluate past and current use of illicit drugs and other substances that may trigger or exacerbate depressive symptoms. It is very important to assess the patient's personality, as evidence shows that when depression is embedded in severe personality pathology, psychotherapeutic treatment of personality disorder precedes improvement in depression (Leichsenring et al., 2011; see Chap. 15).

3 *Evaluate the safety of the patient*. A careful and ongoing evaluation of suicide risk is necessary for all patients with major depressive disorder. Such an assessment includes specific inquiry about suicidal thoughts, intent, plans, means, and behaviors; identification of specific psychiatric symptoms (e.g., psychosis, severe anxiety, substance use) or general medical conditions that may increase the likelihood of acting on suicidal ideas; assessment of past and, particularly, recent suicidal behavior; delineation of current stressors and potential protective factors (e.g., positive reasons for living, strong social support); and identification of any family history of suicide or mental illness. In addition to assessing suicide risk per se, it is important to assess the patient's level of self-care, hydration, and nutrition, each of which can be compromised by severe depressive symptoms. As part of the assessment process, impulsivity and potential for risk to others should also be evaluated, including any history of violence or violent or homicidal ideas, plans, or intentions. An evaluation of the impact of depression on the patient's ability to care for dependents is an important component of the safety evaluation. The patient's risk of harm to him- or herself and others should also be monitored as treatment proceeds.

4 *Establish the appropriate setting for treatment*. The clinical act of diagnosis includes creating (together with the patient) the best conditions for the treatment of his or her disorder. The clinician should determine the least restrictive setting for treatment that will be most likely to guarantee the patient's safety while promoting improvement in the patient's condition. The determination of an appropriate setting for treatment should consider the patient's symptom severity, co-occurring psychiatric or general medical conditions, available support system, and level of functioning. The determination of a treatment setting should also take into account the patient's ability to adequately care for him- or herself, provide reliable feedback to the psychiatrist, and cooperate with his or her major depressive disorder treatment. Measures such as hospitalization should be considered for patients who pose a serious threat of harm to themselves or others. Patients who refuse inpatient treatment can be hospitalized involuntarily if their condition meets the local jurisdiction's criteria for this type of admission. Admission to a hospital or, if available, an intensive day program may also be

indicated for severely ill patients who lack adequate social support outside of a hospital setting, have complicating psychiatric or general medical conditions, or have not responded adequately to outpatient treatment. The optimal treatment setting and the patient's likelihood of benefiting from a different level of care should be reevaluated on an ongoing basis throughout the course of treatment.

5 *Evaluate functional impairment and quality of life*. Major depressive disorder can alter functioning in numerous spheres of life including work, school, family, social relationships, leisure activities, or maintenance of health and hygiene. The clinician should evaluate the patient's activity in each of these domains and determine the presence, type, severity, and chronicity of any dysfunction. In developing a treatment plan, interventions should be aimed at maximizing the patient's level of functioning while also helping him or her to set specific goals appropriate to his or her functional impairments and symptom severity.

6 *Coordinate the patient's care with other clinicians*. Many patients with major depressive disorder will be evaluated or treated by other healthcare professionals in addition to the psychiatrist. If more than one clinician is involved in providing care, all of them should have sufficient ongoing contact with the patient and with each other to ensure that care is coordinated, relevant information is available to guide treatment decisions, and treatments are synchronized. In ruling out general medical causes of depressive symptoms, it is important to ensure that a general medical evaluation has been carried out, either by the psychiatrist or another healthcare professional. Extensive or specialized testing for general medical causes of depressive symptoms may be conducted based on individual characteristics of the patient.

7 *Monitor the patient's psychiatric status*. The patient's response to treatment should be carefully monitored. Continued monitoring of co-occurring psychiatric and/or medical conditions is also essential to developing and refining a treatment plan for an individual patient.

8 *Integrate measurements into psychiatric management*. Tailoring the treatment plan to match the needs of an individual patient requires a careful and systematic assessment of the type, frequency, and magnitude of his or her psychiatric symptoms as well as ongoing determination of the therapeutic benefits and side effects of treatment. Such assessments can be facilitated by integrating clinician- and/or patient-administered rating scale measurements into initial and ongoing evaluation.

9 *Enhance treatment adherence*. The psychiatrist should assess and acknowledge potential barriers to treatment adherence (e.g., lack of motivation or excessive pessimism due to depression; side effects of treatment; problems in the therapeutic relationship; logistical, economic, or cultural barriers to treatment) and collaborate with the patient (and, if possible, the family) to minimize the impact of these potential barriers. In addition, the psychiatrist should encourage patients to articulate any fears or concerns about treatment or its side effects. Patients should be given a realistic notion of what can be expected during each treatment phase, including the likely time course of symptom response and the importance of adherence for treatment and prophylaxis success.

10 *Provide education to the patient and the family*. Education about the symptoms and treatment of major depressive disorder should be provided in language that is readily understandable to the patient. With the patient's permission, family members and others involved in the patient's day-to-day life may also benefit from education about the illness, its effects on functioning (including family and other interpersonal relationships), and its treatment. Common misconceptions about antidepressants (e.g., they are addictive) and psychotherapy should be clarified. In addition, education about major depressive disorder should address the need for a full acute course of treatment, the risk of relapse, the early recognition of recurrent symptoms, and the need to seek treatment as early as possible to reduce the risk of complications or a full-blown episode of major depression. Patients should also be told about the need to taper antidepressants, rather than discontinuing them precipitously, to minimize the risk of withdrawal symptoms or symptom recurrence. Patient education also includes general promotion of healthy behaviors such as exercise, good sleep hygiene, good nutrition, and decreased use of tobacco, alcohol, and other potentially deleterious substances. Educational tools such as books, pamphlets, and trusted web sites can augment the face-to-face education provided by the clinician.

16.2.2 Clinical Practice Guidelines and Diagnostic Classification Systems

Clinical practice guidelines for the diagnosis of depression are based on the nosological systems that underlie them. Therefore, an important part of their applicability in actual practice depends on the more general problem of mental health professionals' acceptance of these classification systems. Some years ago, the *WHO Department of Mental Health and Substance Abuse* (Reed et al., 2011) conducted a global survey of 4887 psychiatrists in 44 countries regarding their use of diagnostic classification systems (ICD-10) in clinical practice and the desirable characteristics of a classification of mental disorders. The participants overwhelmingly preferred a simpler system of diagnosis with 100 or fewer categories and *over two-thirds preferred flexible guidance to a strict criteria-based approach*. Opinions were divided about how to incorporate severity and functional status, while most respondents were receptive to a system that incorporates a dimensional component. Significant minorities of psychiatrists in Latin America and Asia reported problems with the cross-cultural applicability of existing classifications, advocating for a national classification of mental disorders to be used in their countries. Overall, ratings of ease of use and goodness of fit for specific ICD-10 categories were fairly high, but several categories were described as having poor utility in clinical practice. However, the diagnostic task is even more problematic, since ethnographic studies have shown that culture does not just shape "depressive" experiences: first and foremost, the

cultural and administrative environments inform expert practices and understandings associated with the very psychiatric concept of depression (see Chap. 11).

16.2.3 Reception of Clinical Guidelines by Mental Health Professionals

Although clinical guidelines have been postulated to improve clinical practice, implementation has been difficult to achieve due to the characteristics of the guidelines themselves, such as clarity, complexity of treatment recommendations, perceived credibility, use of evidence-based medicine, and (pharmaceutical) sponsorship, which have been shown to affect clinicians' acceptance (Saddichha & Chaturvedi, 2014). Just as any mental health program needs to be monitored in its implementation, the question of clinicians' acceptance and adherence to clinical practice guidelines cannot be ignored. The mere fact that there are many different guidelines in various countries throughout the world shows us that there are many opinions about what the best clinical practice should be. In the face of this, it seems reasonable for clinicians to receive guidelines as recommendations rather than as algorithms. Several studies have shown that adherence to guidelines is a real problem. We have seen that more than two-thirds of the psychiatrists interviewed by the WHO in the global survey preferred flexible guidance to a strict criteria-based approach to diagnosis. Studies conducted in Canada (Davis & Taylor-Vaisey, 1997; Hayward, 1997) and France (Samalin et al., 2011) have reported that, to a large extent, psychiatrists have not yet integrated the use of guidelines into their practices. Furthermore, a panel of experts interviewed using the Delphi methodology concluded that implementation efforts focusing on individual physicians with a single strategy are unlikely to be successful. Rather, implementation efforts must use a range of strategies that take into account the multiple characteristics of the guidelines, practice organization, and the external environment (Solberg et al., 2000). A good example of the difficulties in adhering to clinical guidelines is their use by GPs working at the primary care level.

16.2.4 Clinical Practice Guidelines for Depression Treatment at the Primary Care Level

General practitioners (GPs) working at the primary care level are the gatekeepers of the healthcare system. In this context, a WHO study on psychological problems in general healthcare (Ustun & Von Korff, 1995) conducted across 14 countries found that only 54.2% of patients who met the criteria for depression were judged by their treating physician (GP) as having a psychological illness, although rates of accurate diagnosis of depression ranged from 19.3% in Nagasaki (Japan) to 74.0% in

Santiago de Chile (Chile). In this study, over-detection – i.e., the generation of false positives – is less discussed but nevertheless important. To clarify the level of accuracy of the diagnosis of depression at the primary care level, a meta-analysis (Mitchell et al., 2009) that included 50,371 patients pooled across 41 studies was conducted. The study concluded that GPs can rule out depression in most people who are not depressed; however, the modest prevalence of depression in primary care means that misidentifications outnumber missed cases. Research has shown that, despite efforts to train GPs in primary healthcare, difficulties persist in establishing timely diagnosis and appropriate treatment (Levav et al., 2005). In Chile, Alvarado et al. (2005) found similar evidence in their evaluation of a program for the detection, diagnosis, and comprehensive treatment of depression. Vicente et al. (2007) observed that merely cognitive training in depression for GPs had limited impact on clinical practice: there was little change in knowledge and attitudes. They conclude that it is more promising to extend training programs by including specific clinical attitudes and skills. In Chile, we implemented one such training program for GPs to improve the detection and management of depressive disorders at the primary care level (Jiménez et al., 2009). Although no improvements in depression detection rates were found, participants' satisfaction with the training program was high. The main changes that participants perceived in their diagnostic skills were as follows: (a) less mechanical way of using the ICD-10 criteria to diagnose depression; (b) more confidence in the diagnostic process; (c) more observation capacity and more alertness and connection with the patient; (d) more efforts devoted to inquiry and information searches; (e) more diagnosis-oriented empathy with the patient; (f) greater order in the application of mental schemes for diagnosis; (g) greater capacity for emotional self-observation in relation to patients' life histories; and (h) less haste in making the diagnosis, given the knowledge acquired and the possibility that the symptoms do not necessarily indicate depressive disorders (Acuña et al., 2016; Huepe et al., 2015). These findings confirm the gap that exists in primary care between clinical guidelines for the detection and management of depression and their implementation by GPs. Qualitative studies allow a better understanding of the reasons for this gap.

Two systematic reviews of qualitative studies on depression diagnosis and management in primary care shed light on this topic. The first one (Schumann et al., 2012) reviewed 13 qualitative studies interviewing a total of 239 primary care providers who met the inclusion criteria. Three distinct themes with nine subthemes that specify attitudes, diagnostic processes, and barriers while diagnosing depression were identified. The authors concluded that that GPs use approaches to diagnose depression that are usually based on their knowledge of the patient's long-term history, an established patient–doctor relationship, and an algorithm for ruling out other diagnoses. As such, *these strategies markedly differ from the diagnostic criteria for depressive disorders that are used in psychiatrically oriented classification systems*. The second one (McPherson & Armstrong, 2012) reviewed, identified, and extracted findings from 13 qualitative studies that examined how GPs managed depression. A thematic analysis of this systematic review of qualitative research was carried out, which revealed four main themes with various subthemes: "negotiating

the nature of depression," "detect and diagnose," "interventions," and "burden." The authors concluded that *the results of the analysis illuminate the complex dilemma faced by GPs in managing depression, which appears to be characterized by a sense of dissonance between the medicalization of depression and a sense of its social determinants*.

Both systematic reviews reviewed virtually the same qualitative studies and came to similar conclusions, which increases the validity of their findings. The authors of both studies conclude that clinical guidelines are not appropriate for the primary care setting and that GPs use their intuition and relational skills more than clinical guidelines to detect depression. Depression is basically understood as a "normal" response to psychosocial factors. Thus, a discrepancy appears between the psychosocial causation model of depression and the pharmacological model of its treatment.

16.3 Diagnostic Classifications and Etiopathogenic Theories of Depression

The classification schemes in common usage (ICD and DSM) are based on separate (but often overlapping) categories of disorder schemes which are intended to be atheoretical with regard to etiology. The main criticism is that these systems (after adequate training in their application) increase reliability but reduce validity. Atheoretical diagnostic systems arose as a way to bring order into the previous diagnostic chaos in psychiatry, where diagnoses depended on each clinician's favorite etiopathogenetic theory. Amid the "battle of the paradigms" (Kendler, 2005), each psychiatric orientation had its own classification, with major disagreements with other "psychiatries." This is an important difference between psychiatry and the rest of medicine. The discovery of pathophysiological mechanisms that produce medical symptoms remains the basis for progress in medicine. Given the variety of etiopathogenic theories of depression and, in general, of mental disorders, many of which are hardly compatible with each other, mental health professionals face an additional challenge in applying diagnostic systems and, therefore, clinical practice guidelines. As we have emphasized throughout this book, the phenomenology of depression is heterogeneous. However, first-person descriptions of depressed patients often point to unique experiences that differ from the catalogue of symptoms listed in diagnostic manuals such as the DSM. Furthermore, the way the subject feels in the world may be expressed not only in terms of symptoms but also in terms of corporality, spatiality, temporality, and interpersonality, dimensions that are not considered in such manuals (Ratcliffe, 2015).

Although the diagnostic classifications in use are intended to be atheoretical, we think that there is an implicit theory in them: that of the biomedical conception of depression. Virtually all the guidelines in use emphasize the medical treatment (antidepressants), based on the causal theory of intersynaptic neurotransmission,

ignoring the fact that depression is a complex condition, where etiopathogenesis may be associated with both bottom-up and top-down mechanisms. Assuming a complex causation naturally leads to a comprehensive treatment plan that combines a pharmacological approach with psychotherapy and psychosocial measures.

The question that arises is whether, despite efforts to construct an atheoretical psychiatric taxonomy, it is actually possible to dispense with causal theories in the diagnosis of depression. This problem is well illustrated in the endless discussion about the relationship between the diagnosis of depression and bereavement, i.e., in the differential diagnosis between depression and the "normal" response to a significant loss (Horwitz & Wakefield, 2007; Wakefield & Demazeaux, 2016). Mario Maj points out that the DSM-IV-R "is very clear in stating that the diagnosis of major depression should be made whenever the severity, duration, and distress/impairment criteria for that condition are met, even if the depressive state is the understandable response to a psychosocial stressor. The only exception is bereavement: if the depressive state follows the loss of a loved one, the diagnosis of major depression should not be made even if the diagnostic criteria are fulfilled, unless some further elements are present (the symptoms persist for longer than 2 months, or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation). So, *in any case – whether depression is related to bereavement or not – explicit criteria are provided, and no mention is made of the use of clinical judgment*" (Maj, 2013, p. 89; italics added). Thus, according to the DSM-IV-R, it is possible to diagnose depression even in the presence of clinically manifest grief. In this sense, the DSM-IV-R distinguishes between descriptive and etiological diagnoses, which means that a person, no matter what the cause of his or her grief, can meet the criteria for a depression diagnosis.

However, the DSM-5 takes a step back, as a note included in the criteria for "major depressive disorder states that 'responses to a significant loss (e.g. bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include feelings of intense sadness, rumination about the loss, insomnia, poor appetite and weight loss, which may resemble a depressive episode', and that *the decision about whether a major depressive episode (or just a normal response to the loss) is present 'inevitably requires the exercise of clinical judgment based on what the clinician knows about the individual in question and the individual's cultural norms for the expression of distress in the context of loss*'" (Maj, 2013, pp. 89f; italics added).

We suggest that this back and forth in American psychiatric taxonomy shows the inevitable need for the clinician to go beyond the merely descriptive diagnosis of depression and take into account the context of its causation. And this can be generalized. Sound clinical thinking always seeks to relate diagnosis with etiology, since this is the basis for the indication of a treatment adapted to the particular conditions of each patient. In that sense, as Ratcliffe (2015) suggests following Max Weber's ideas, the clinical construct we call depression consists of an "ideal type." As such, it serves as a starting point from which to begin clinical work. Thus, its value should not be placed on its character of truth but fundamentally on its heuristic power.

Consider, for example, the case of a depressive patient whose main comorbidity is a serious personality pathology. Evidence shows that, if the underlying personality disorder is not treated psychotherapeutically, depression treatment will fail (Leichsenring et al., 2011; see Chap. 15). This is especially important in the case of *introjective depressions* (Blatt, 2004; Luyten et al., 2005a). The same is true when depression occurs in subjects who have had a traumatic childhood or adolescence. According to the Adverse Childhood Experiences (ACEs) study, a collaboration between Kaiser Permanente and US Centers for Disease Control and Prevention, exposure to one or more maltreatment-related ACEs accounts for 54% of the population attributable risk for depression (Dube et al., 2003; Teicher et al., 2016). The German LAC depression study found that more than 80% of its sample of chronically depressed patients who were in long-term psychoanalytic or cognitive-behavioral therapy had experienced severe trauma in their childhood (Leuzinger-Bohleber et al., 2019; see Chap. 5). The importance of considering early adversity in the diagnosis of depression seems to be increasingly evident, especially because of its relevance to prognosis and response to drug treatment. Using a high-dimensional dataset consisting of resting state functional connectivity measured by functional MRI, clinical questionnaire scores, and various biomarkers, in a sample of 134 subjects (67 depressive subjects and 67 controls), Tokuda et al. (2018) found that the presence of child abuse trauma was a key point in resistance to treatment with selective serotonin reuptake inhibitors. Of course, we still know little about the etiopathogenetic mechanisms of this relationship. Still, we think there are sufficient reasons to state that, in the diagnosis of depression, it is unavoidable for the clinician to weigh the relative importance of the multiple causal domains, since this will allow him or her not only to establish a good therapeutic alliance with the patient and his or her family but also to plan a treatment adapted to each particular case. And this brings us to the issue of clinical judgment in psychiatry.

16.4 Clinical Judgment: The Process Linking Diagnosis to the Etiology of Depression

The issue of the usefulness of clinical judgment in the clinical decision-making process is an old concern in the philosophy of medicine (Engelhardt Jr., 1979; Feinstein, 1967). Moreover, the discussion about the relationship between theoretical (scientific) reason and practical reason (clinical judgment) is as old as Greek philosophy. If we put ourselves in the place of the clinician who is interacting – in the "here and now" of the clinical interview – with his or her patient trying to arrive at a diagnosis and an indication for treatment, it is easy to realize that it is not just a matter of putting the patient's condition in some box of the taxonomic system in question. The clinician needs to *predict* how the patient will react to such a diagnosis or indication – and this prediction is a matter of practical wisdom, not theoretical reasoning. Practical reasons intend to answer, based on a number of

alternatives – none of which have yet been realized – which is the best, in terms of what needs to be done. Therefore, it is not a question of fact and its explanation but of value: What is preferable to do? (Jiménez, 2009a, b). It is important to note that theoretical and practical reasons are one and the same, but with different applications. Therefore, there cannot be a radical opposition between scientific knowledge (evidence-based medicine) and practical wisdom (clinical judgment). The clinical art consists precisely in being able to combine both in the service of patients.

While the discussion initially linked clinical judgment to scientific (statistical) clinical evidence, the discussion soon became polarized into antagonistic positions. In fact, the pioneers of the evidence-based medicine movement placed great importance on professional expertise in the clinical decision-making process: "*External clinical evidence can inform, but can never replace, individual clinical expertise*, and it is this expertise that decides whether the external evidence applies to the individual patient at all and, if so, how it should be integrated into a clinical decision" (Sackett et al., 1996, p. 72; italics added).

Clinical judgment refers to the cognitive/affective process that allows healthcare providers to arrive at a conclusion based on objective and subjective information about a patient. Clinical judgment is developed through practice, experience, knowledge, and continuous critical analysis. It extends into all clinical areas: diagnosis, therapy, communication, and decision-making (Kienle & Kiene, 2011). Clinical judgment can involve both automatic, intuitive reasoning and analytic, reflective reasoning. These types of reasoning are not mutually exclusive: healthcare providers might switch their judgment strategy based on the circumstances they encounter. Further, because the cognitive processes involved in clinical judgment are complex, they are prone to various cognitive errors, such as faulty heuristics/cognitive biases and affective influences (Cascella, 2020). Clinical reasoning and clinical judgment are goal oriented, aimed at clinical action. Such judgments are often made with clinicians working with imperfect information and uncertainty of prognosis and therapeutic effectiveness. Uncertainty arises from lack of evidence, conflicting interpretations of evidence, inability to access evidence in a timely manner, concerns about the application of aggregate statistical data to individual cases, and lack of clarity regarding patient preferences and values. In this sense, clinical judgment has a strong ethical component and is based more on practical wisdom than on abstract knowledge. A good example of this is the discussion of when to make the diagnosis of depression and when to make the diagnosis of bereavement (Maj, 2013). Another example is GPs' use of clinical guidelines at the primary level of care: they make decisions based on criteria other than those suggested by evidence-based medicine.

These examples, as well as others showing the problematic reception of clinical guidelines by mental health professionals, show that clinicians cannot dispense with etiological theories when diagnosing and indicating treatment. A merely descriptive symptomatic diagnosis, i.e., one that disregards the causal context and the consideration of the psychosocial circumstances of the patient, is a "soulless" diagnosis, which probably prevents the activation of the patient's commitment and collaboration. It has been suggested that science is a tool rather than the soul of medicine and

that medicine is neither a science nor an art. It is a distinctive, practical endeavor whose particular way of knowing qualifies it to be that impossible thing, a science of individuals (Montgomery, 2005).

Critical self-reflection enables mental health practitioners to listen attentively to patients' distress, recognize their own errors, refine their technical skills, make evidence-based decisions, and clarify their values so that they can act with compassion, technical competence, presence, and insight. Explicit clinical knowledge is readily taught, accessible to awareness, quantifiable, and easily translated into evidence-based guidelines. Tacit knowledge, however, is usually learned during observation and practice; includes prior experiences, theories in action, and deeply held values; and is usually applied more inductively. Mindful practitioners use a variety of means to enhance their ability to engage in moment-to-moment self-monitoring, bring to consciousness their tacit personal knowledge and deeply held values, use peripheral vision and subsidiary awareness to become aware of new information and perspectives, and adopt curiosity in both ordinary and novel situations. In contrast, mindlessness may account for some deviations from professionalism and errors in judgment and technique (Epstein, 1999).

16.5 Case Formulation

During our teaching career, we have always recommended to psychiatrists and psychologists in training to finish the diagnostic process with a case formulation. Although case formulation is not something routinely practiced by mental health professionals, we believe that carrying it out on a regular basis is good clinical practice. Case formulation is a framework or "picture" that informs a choice of psychopharmacological and/or psychological treatments, thus providing a bridge between diagnostic assessment and treatment phases to guide treatment options; in contrast, purely using psychiatric diagnosis to guide treatments limits individualized care. Using a case formulation approach, irrespective of diagnostic classification, offers flexibility by linking assessment and interventions (Rainforth & Laurenson, 2014). Case formulation is a method of integrating multiple judgments about etiology, the patient's reasons for consulting an expert, and symptomatology, providing a template to assist clinicians in deciding which problems are paramount and require treatment interventions. Furthermore, it suggests a theoretically based explanation of the information obtained from assessment, which offers a hypothesis about the cause, nature, and maintaining factors of presenting problems (Bieling & Kuyken, 2003; Persons, 2005; Westmeyer, 2003).

In psychiatry and psychology, there is currently no single, integrated way to arrive at a case formulation. As case formulation is especially useful in choosing the type of psychotherapeutic treatment that best suits each particular patient, all psychotherapy orientations have developed case formulation models in line with their own ideologies. Thus, there are psychodynamic (Bernardi et al., 2016; Le Feuvre & Halasz, 2011; Mace & Binyon, 2005, 2006; McWilliams, 1999), behavioral

(Kaholokulaa et al., 2013), and cognitive-behavioral case formulation models (Boschen & Oei, 2008; Kuyken et al., 2005), as well as some transtheoretical ones (Bergner, 1998; Restifo, 2010; Ridley et al., 2017). In this chapter, we will not go into the details of each of these models; instead, we refer the reader to the specialized literature.

16.6 Conclusion: Towards a Staggered Depression Diagnostic Process

The following points summarize the conclusions that support the recommendation of a sequential diagnostic process for depression (Botto et al., 2014):

1. There is a broad consensus that psychiatric disorders are etiologically complex conditions; therefore, in order to understand them, it is necessary to have a model that, without leaving aside conceptual and empirical rigor, is pluralistic, integrative (Kendler, 2005), and informed by close collaboration with other branches of science (Musalek et al., 2010).
2. Diagnosis in psychiatry assumes the existence of multiple views or approaches (positivist, phenomenological, or hermeneutic) that involve, on the part of the practitioner, different levels of cognitive, affective, and personal commitment (Fuchs, 2010). The diagnostic process culminates in a negotiation between the patient's and the therapist's subjectivity (Stanghellini, 2010). However, we know that diagnosis also depends on the sociocultural context and the structure of the health systems that operate in dialogue with families, the mass media, and local administrations (Kirmayer, 2001).
3. Therefore, one of the challenges for the development of new nosological systems consists in incorporating variables that make it possible to refine diagnoses, integrating neuroscientific evidence with clinical findings in order to establish groups of disorders with shared criteria – and possibly also with common etiologies or vulnerabilities – based on genetic risk, family association, neural substrates, biological markers, and endophenotypes (Kupfer & Regier, 2011).
4. At present, the medical model of causality, focused on simple biological essences, has proved insufficient to capture the nature of mental illness; on the contrary, its adequate conceptualization requires multiple explanatory perspectives that also consider the interaction of its elements at different levels (Kendler, 2012). Therefore, despite the undoubted efforts to develop quality clinical recommendations, we consider that current guidelines do not fully incorporate the complexities inherent to the diagnosis of depression.

5. Since mental illnesses are not mono-causal entities, an atheoretical and categorical classification, based on observable behaviors and symptoms that do not consider etiopathogenesis, is insufficient to account for the complexity and richness of the clinical phenomenon we call depression. Instead, psychiatric diagnosis should incorporate an approach that integrates clinical observation with causal hypotheses (Luyten & Blatt, 2007).
6. Depression is now considered to be part of the group of affective illnesses. According to Kraepelin, this group (which he labeled *manic-depressive illness* and which includes the current bipolar illness and unipolar depression) is mainly characterized by the *recurrence* of mood episodes rather than by their *polarity*. Furthermore, in both mania and depression, a fundamental clinical feature is psychomotor alteration (activation vs. retardation). Especially in the case of mania, life events may be irrelevant and mood changes secondary and epiphenomenal (Ghaemi, 2013). Unlike the DSM series, for Kraepelin, the bipolar or unipolar courses represent subtypes of the same illness and not two separate clinical entities. The rationale for these assumptions is based on the observation that the most frequent presentation of this illness is mixed states, in which it is not possible to distinguish a polarity. In fact, at present, the evidence supporting a categorical distinction between bipolar and unipolar illness is quite weak; in contrast, scientific research supports the notion of a broad *affective or manic-depressive spectrum* (Ghaemi, 2019). This phenomenon has important implications for our approach to etiopathogenic analysis, classification, and indication of treatments.
7. Historically, multiple classifications of depressive states have been proposed, from the classic division between *exogenous* (somatic origin), *endogenous*, and *reactive* depressions to *melancholic*, *non-melancholic*, and *atypical* depressions (Parker, 2000), through a series of intermediate states. Recently, Ghaemi et al. (2012) has proposed a classification that recognizes a spectrum of depressive manifestations ranging from the most chronic and less severe pole (*neurotic* depression) to the most episodic and severe pole (*melancholic* depression), through *pure* depression and *mixed* depression (see Chap. 1 in this book).
8. The relationship between personality and depression is another important issue. As mentioned in Chap. 1, there are several ways to understand this association. For practical purposes, we will consider two fundamental aspects because, in our opinion, they have greater empirical support and a clear clinical correlation. The first is the notion of *affective temperaments*. From a psychopathological point of view, they represent mild variations of the manic-depressive illness, which are present all the time, forming part of the basic personality of the individual. According to the predominance of emotional states, they are classified as *hyperthymia*, *dysthymia*, and *cyclothymia*. Secondly, authors have advanced the notion of personality as a predisposing factor for the development of depressive symp-

toms, as in the case of *typus melancholicus* described by Tellenbach (1974) or the *anaclitic/introjective* polarity described by Blatt (2004). In the latter case, it is also possible to apply the pathoplastic model, which states that the manifestations of depression are shaped by certain personality traits (see Chap. 1).

9. Depression is a complex, etiologically multi-determined, and clinically heterogeneous disorder which can be reached through various pathways, whose psychopathological manifestations are related to personality, and which depends on the interaction between genetic and environmental factors throughout a person's development (Luyten et al., 2005b). Regardless of the etiopathogenic mechanism involved in its origin and the various forms it can take, depression remains phenomenologically consistent across manifestations, personality styles, and sociocultural contexts (Parnas, 2012). Furthermore, we consider that depression is an affective disorder that is clinically defined by a psychomotor disturbance (retardation) – manifested by a decrease in mood, anhedonia, and low self-esteem – and which is associated with certain personality traits such as increased self-criticism and perfectionism. This symptomatic nucleus can be reached by various routes (environmental, neurobiological, characterological) with different degrees of interaction (Bleichmar, 2005). Depending on the way these pathways are related, depression can take various forms: *psychotic, melancholic, or mixed* (predominance of biological factors); *neurotic* (predominance of characterological elements); *pure* (combination of reactivity with biological factors); *anaclitic/introjective* (personality, configuration of attachment styles); etc. This model allows us to refine diagnoses, better plan treatments, and determine prognosis.

Consequently, we propose a diagnostic approach to depression consisting in a sequential process (Table 16.1) that must answer a series of questions whose final objective will be to determine *why this individual is depressed at this precise moment* (Parker & Manicavasagar, 2005). We conclude that the diagnosis of depression should be one of exclusion, having previously ruled out bipolarity, medical illness, and other psychiatric disorders such as substance abuse and comorbid illnesses.

Table 16.1 Recommendations for the diagnostic assessment of depression

Step	Recommendation	Questions
1	When depression is suspected, the practitioner should explore the presence of psychomotor disturbance (retardation) associated with the symptomatic triad: low mood, anhedonia, and low self-esteem with self-reproach. Then, medical causes and bipolarity must be ruled out, placing such symptoms within the *affective spectrum* (*manic-depressive spectrum*) through the study of family history, history of hypomania, recurrence, reactivity, and clinical profile. Finally, the practitioner must define the presence of clinical subtypes of depression: melancholic, pure, mixed, and neurotic	Does the patient have depression?
		Is his or her depression of organic or psychiatric origin?
		Is his or her depression of a bipolar type?
		Which subtype of depression is it?
2	Once the existence of depression has been confirmed and classified according to the above recommendation, the physician should consider the presence of an *affective temperament* and how the patient's personality influences the clinical presentation (*anaclitic/introjective*) and the eventual response to treatments. The history of childhood trauma should be studied at this point	Does the patient have an affective temperament?
		What type of personality organization predominates in the patient: anaclitic or introjective?
		In what way has the personality determined, conditioned, or perpetuated the symptomatology?
		Does the patient have a history of childhood trauma?
		How does the trauma influence the patient's symptoms, indication for treatment, and prognosis?
3	Explore the triggering situations and the relational context in which the symptoms develop (experiences of loss, separation, failure, humiliation), along with their degree of reactivity	What is the nature of the situation to which the patient is reacting or from which he is "defending" himself?
		What has been the cost of the problem for the patient?
		What consequences could a psychological or emotional change have for the patient's life?
4	Consider the patient's social and cultural environment and its relationship with the health systems involved	How does the patient's environment, culture, social setting, and health systems influence the occurrence of symptoms, their persistence, or the response to interventions?
5	Establish a diagnosis and a differential indication of treatments consisting in a process of "negotiation" between the patient's own etiopathogenic theories, his or her treatment expectations, and the clinician's judgment about the nature of the problem. Consider a clinically informed treatment indication for both pharmacotherapy and psychotherapy. Also, consider the positive evidence regarding combined treatments.	What will be the "working hypothesis" that will guide the decision-making between the patient and the therapist?
		Which treatment is best suited to this particular patient?
		What results are expected from the treatment?
6	Finally, the clinician should consider depression as a disorder that can be reached from various interrelated pathways (biology, personality, environment, etc.) and that, depending on the way these combinations occur, presents clinically through several subtypes whose differentiation has diagnostic, prognostic, and therapeutic implications	How did this particular patient become depressed?

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