Chapter 6
Neurobiological Findings Underlying Personality Dysfunction in Depression: From Vulnerability to Differential Susceptibility

Alberto Botto and Caroline Leighton

Abstract The relationship between temperament as a manifestation of personality and mood disorders comes from Greek antiquity. Throughout history, the relationship between personality and depression has been conceptualized in at least four ways: (1) Personality is a predisposing or vulnerability factor for the development of depression. (2) Personality changes are a consequence of mood alteration resulting from depression. (3) Personality is a subclinical manifestation of depression (affective temperaments). And (4) personality characteristics influence the manner in which depression clinically manifests. Currently, there is a tendency to recover the concept of affective temperaments (depressive, hypertensive, cyclothymic, irritable, and anxious), considering them as subclinical manifestations of some disorder within the affective spectrum. These temperaments have been shown to be universal, with distinctive characteristics and without gender differences. Although in depressive illness there is important evidence regarding both functional and structural neurobiological alterations, much less is known about the biological findings of personality dysfunction in depression. One reason, in part, is that explanatory models are required that integrate various levels of analysis, including the different types of gene-environment relationships. In this chapter, we will review the relationship between personality and depression, then we will describe the main neurobiological findings underlying personality dysfunction in depression, and finally we will analyze the relationship between genes and environment in depression, taking into account the approach of differential sensitivity to environmental stimuli. We will conclude with some recommendations for future research.

Keywords Neurobiology · Personality · Affective temperaments · Depression · Gene-environment relationship

A. Botto (✉) · C. Leighton
Departamento de Psiquiatría y Salud Mental Campus Oriente, Facultad de Medicina, Universidad de Chile, Santiago, Chile

Millennium Institute for Research in Depression and Personality (MIDAP), Santiago, Chile

G. de la Parra et al. (eds.), *Depression and Personality Dysfunction*, Depression and Personality, https://doi.org/10.1007/978-3-030-70699-9_6

6.1 Introduction

Traditionally, it has been considered that personality (i.e., the habitual way of being and behaving of individuals) is composed of two fundamental aspects: the character and the temperament. Character is related to the way we see ourselves and behave based on learning and developing of our psychic life in interaction with others trough socialization. Temperament, on the other hand, is linked to biological based, innate attitudes, behaviors, and reactions to a series of environmental challenges and has genetic and neurobiological correlates that have been linked to critical processes, involving cognition, emotion, and behavior (Coccaro & Siever, 2005). However, for some authors, this distinction is questionable since personality traits would present all the characteristics of temperament, and they prefer to use the terms "personality" and "temperament" as if they were synonymous (Krueger & Johnson, 2008).

The relationship between temperament as a manifestation of personality and mood alterations comes from Greek antiquity (Berrios & Porter, 1995). At the beginning of the last century, Emil Kraepelin (2012) distinguished, within the forms of presentation of mood alterations, the affective episodes that broke into the continuity of life (and that generally came at the margin of external influences), from those manifestations – the so-called fundamental states – that persisted chronically independently of these episodes. These alterations consisted of certain singularities of the psychic life that were characterized by a permanent temperamental disposition before the experiences of life which he called "constitutions" and classified them into the following: depressive ("constitutional depression"), manic ("constitutional excitement"), and 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 ruminations, 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, devoting themselves to their duties with abnegation but being unable to enjoy them. Many of these characteristics are manifested from youth in a more or less constant way, but it can also be the case in which 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. The "manic constitution" or "constitutional excitement" is characterized by a higher-than-average intelligence, with a marked creativity, which can sometimes be altered by a tendency to distractibility and impulsivity, so that these subjects may appear as little reflective and rather superficial. In general, the mood is elevated, with greater self-confidence and high self-esteem, overvaluing their abilities and acting in an arrogant and provocative manner. They tend to be very sociable and communicative, easily adaptable to new situations, and therefore changeable and unpredictable, evidencing a scarce capacity for

planning, which leads them to fleeting choices regarding their occupations and their interpersonal relationships. For the same reason, they usually maintain a conflictive relationship with their environment. There are often mood swings that can alternate with periods of distress and depression. However, in milder cases, they can be bright, vital, charming, and creative individuals close to genius. The "irritable constitution" is a combination of the first two. Individuals show a tendency to extreme oscillation in their moods, being very sensitive to life events. They are combative, unpredictable, and easily offended and can explode into insolence, anger, and aggression. Their mood is changing through periods of anxiety, moodiness, discouragement, and complaints of all kinds. Finally, the "cyclothymic constitution" is presented as a chronic and regular variation of mood in a manic or depressive sense. Unlike the irritable one, the cyclothymic alternates in its moods, appearing in one moment as full of joy and joviality and in another as completely dejected and depressed. These changes can last for weeks or months and can be the early manifestation of a manic-depressive psychosis.

Something similar was described by Kretschmer – with the picnic type in 1925 – and Sheldon – with the endomorphic constitution in 1940 – linking the 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 placed within them depressive psychopaths (Schneider, 1997). The fundamental state of mind of these subjects does not have such a direct relationship with temperament as in the case of hyperthymic psychopaths; however, they also suffer because of a constantly oppressed state of mind and a pessimistic and skeptical conception 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 to a quest for order. These are characteristics of 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 in relations with others. The subject lives in a constant threat between the desire to fulfill and the high level of demands placed on himself, which easily triggers feelings of guilt and inadequacy. However, these temperamental dispositions only constitute the

premorbid personality of depression. In order for the endogenous-melancholic transformation to occur – and thus become the depressive illness – it is necessary to have a special relationship with the lived world, what Tellenbach calls *situational constellations*.

Throughout life, people face two fundamental psychological challenges: (1) maintain close, reciprocal, and meaningful interpersonal relationships and (2) maintain a differentiated, coherent, realistic, and integrated sense of self. Based on these polarities (relationality and self-definition, respectively), 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 that 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, introyective (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). Each personality type is associated with a characteristic interpersonal style that enhances the risk of developing depression and influences the clinical presentation of its symptoms (Luyten, Blatt, & Corveleyn, 2005). Various pathological processes can arise from a disruption of this dialectical relationship at different levels of development and can manifest themselves in a variety of ways as with depression.

Currently, there is a tendency to recover the concept of *affective temperaments* (depressive, hypertimic, 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 clear gender differences, where men scored significantly higher than women for hypertimic and irritable temperaments, while women scored significantly higher than men for cyclotimic, depressive, and anxious temperaments (Vazquez, Tondo, Mazzarini, & Gonda, 2012).

In brief, 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). However, from a neurobiological point of view, the link between personality and depression depends on the approach we use. Thus, in the case of personality understood as a subclinical form of depression, it would be possible to raise the existence of etiological factors with a common

neurobiological correlate, while in the case of the pathoplastic model, the presence of a shared neurobiological disorder would be less probably.

6.2 Neurobiology of Depression

Major depressive disorder has been linked to a series of neurobiological alterations ranging from dysfunction of the monoaminergic system and alteration of the hypothalamic-pituitary-adrenal (HPA) axis to alterations in the inflammatory pathways, mechanisms linked to neuroplasticity, neurogenesis, and even a series of epigenetic modifications (Malhi & Mann, 2018). Among the neurobiological systems investigated in relation to depression, most research has focused on the stress (Gold, 2015; Hammen, 2005) and reward system (Auerbach, Admon, & Pizzagalli, 2014). Genetics models of depression include a long series of genes involved in its etiopathogeny (Hong & Tsai, 2003). Frequently studied, the polymorphism (short or long variant) of the serotonin transporter encoder gene has been associated with depression. Individuals presenting one or two copies of the short allele of the gene have evidenced a higher tendency toward depressive symptoms and clinical depression and more frequent suicidal tendency in the face of adverse vital events than homozygous for the L-variant (Caspi et al., 2003). However, later investigations have failed to replicate the results (Gillespie, Whitfield, Williams, Heath, & Martin, 2005). As to the cognitive functions, depressed patients present a typical alteration of episodic memory (Ilsley, Moffoot, & O'Carroll, 1995), probably due to a hippocampal dysfunction (Bremner, 1999). In addition, the subtypes of depression (atypical versus melancholic) are related to specific alteration patterns (Austin, Mitchell, & Goodwin, 2001). Neuroanatomic and functional studies have shown decreased activity in the orbitofrontal cortex, alterations in the parahippocampal gyrus, and amygdala hyperactivity (Ebmeier, Donaghey, & Steele, 2006; Gillihan et al., 2010).

Traumatic childhood experiences may contribute to the appearance of adult depression, especially among individuals with genetic vulnerability (Risch et al., 2009). It has been suggested that the existence of different neurobiological subtypes of depression may depend on the presence or absence of early adverse events, which would also exert an influence on the response to treatment and the course of disease (Heim, Plotsky, & Nemeroff, 2004). Heim and Nemeroff (2001) have developed an etiopathogenic model of depression proposing that early adverse events, such as trauma or abandonment, trigger a long-term hyperactivation and sensibilization of the corticotropin-releasing factor (CRT) in the central nervous system (CNS), which leads to an increased endocrine, autonomic, and behavioral response to stress (vulnerable phenotype). In this regard, continuous exposure to stressful factors favors the appearance of a number of psychobiological changes, leading to an anxious or depressive clinical disorder. According to Hasler (2010), the clinically most relevant neurobiological hypotheses are as follows: (1) genetic vulnerability, (2) a dysfunction in the hypothalamus-pituitary-adrenal axis, (3) monoamine deficiency, (4) dysfunction in specific brain areas, (5) disequilibrium between neurotrophic and

neurotoxic processes, (6) decreased GABA activity, (7) glutamate dysregulation, and (8) disruption of circadian rhythms. It has recently been suggested that a number of inflammatory processes have a role in the etiopathogeny of depression, both as precipitating and maintaining symptomatology factors. Some inflammatory markers could even prove useful in the diagnosis and prediction of treatment response (Krishnadas & Cavanagh, 2012).

Concerning to attachment theory, depression is thought to respond to a threat to affective bonds (and, in consequence, to our own *self*) in situations of separation, rejection, loss, or failure, leading to an altered awareness regarding the wishes and motivations of ourselves and others (Luyten, Fonagy, Lemma, & Target, 2012). Specifically, insecure attachment has been related to a higher vulnerability to develop depression and suicidal behavior (Grunebaum et al., 2010). Therefore, there is a close relationship between attachment, stress, and awareness in the etiopathogeny of depression (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008).

Even though the first evolutionist hypotheses on the origin of depression were proposed years ago, they remain controversial to date (Nettle, 2004). Nesse (2000) developed a series of arguments in favor of the adaptive value of depression, where discouragement and its associated symptoms contribute to the management of inappropriate or potentially harmful situations, communicating the need for help, or acting as a signal of submission in social conflicts involving hierarchy when no chance exists of becoming victorious. On the other hand, a number of situations have been proposed to provoke different patterns of depressive symptoms aimed at solving the specific challenges posed by each situation (situation-symptom congruence hypothesis). Blame, rumination, fatigue, and pessimism tend to be associated to failure, while crying, sadness, and a need for social support are frequent after social losses (Keller & Nesse, 2006).

6.3 Neurobiology of Personality Traits in Depression

The neurobiology of temperament has been studied in several ways, including behavioral genetics, neuropsychopharmacology, molecular genetics, psychophysiology, and neuroimaging. Based on the affective neuroscience approach, Davis and Panksepp (2011) propose that the affective foundations of personality are found in the sub-neocortical "limbic" and "reptilian" areas of the central nervous system, where the most important evolutionary "roots" of personality would be based on six primary-process subcortical brain emotion systems (SEEKING, RAGE, FEAR, CARE, GRIEF, and PLAY). These systems would generate a type of affective valence within the brain in order to face the survival challenges that our ancestors faced for millennia. However, in humans, these "primary" systems are elaborated during development by "secondary" conditioning and "tertiary" thinking and self-reflection. More recently, it has been proposed to add to the study of personality neuroscience a perspective founded in the study of network maps of brain

connectivity, which has been called the connectome paradigm (Markett, Montag, & Reuter, 2018).

In his seminal studies on the biological basis of personality, Eysenck (1963) postulated that personality is the result of an interplay between two dimensions: on the one hand introversion/extroversion and on the other hand stability/instability (also called emotionality or neuroticism). According to Eysenck, neuroticism was linked with intense emotional reactions to various stimuli which was associated with the activity of the autonomic nervous system, especially the sympathetic system. Furthermore, he proposed that extroversion would be linked to a rapid rise in cortical inhibition, its low dissipation, and its relatively high level (the opposite would be true of introversion). The brain structures related to these processes of excitation and inhibition would be the ascending reticular formation, an alternative pathway for ascending impulses from the periphery to the brain cortex. This proposal was reviewed by Gray (1970), who proposed that the physiological basis of introversion would consist not only in the activity of the ascending reticular system but also in the negative feedback loop, involving the orbitofrontal cortex, the medial septal area, and the hippocampus. Gray proposes that there are two major neurobehavioral systems that underlie behavior: the behavioral activation system (BAS), related to response of reward signals, and the behavioral inhibition system (BIS), which is particularly sensitive to punishment signals (for a complete review of neural correlates of these models, see (Kennis, Rademaker, & Geuze, 2013)). Some decades later, Siever and Davis (1991) proposed that the psychobiology of personality disorders could be formulated as a dimensional model based on the major psychiatric syndromes (from Axis I of DSM-III-R). Thus, they proposed the existence of four psychopathological dimensions: (1) *cognitive/perceptual organization*, (2) *impulsivity/aggression*, (3) *affective instability*, and (4) *anxiety/inhibition*. Alterations in each of these dimensions could occur on a *continuum* ranging from mild manifestations linked to personality to severe manifestations of a clinical syndrome, such schizophrenia or depression. Thus, each dimension was associated with the following: (1) Axis I disorder, (2) Axis II disorder, (3) biological indexes, (4) personality traits, and (5) defenses and coping strategies. For example, *affective instability* dimension was related with major mood disorders (Axis I); borderline and histrionic personality disorders (Axis II); neurobiological alterations related to REM latency, response to cholinergic and catecholaminergic challenges; personality traits, such environmental reactivity and transient affective changes; and finally, with defensive strategies such avoidance, compulsion, and dependent behaviors. Another prominent attempt to develop a psychobiological model of personality is that of Cloninger, Svrakic, and Przybeck (1993), who proposed a model of personality structure and development that accounts for the dimensions of both temperament and character. According Cloninger, the four temperamental dimensions (novelty seeking, harm avoidance, reward dependence, and persistence) are independently inherited, manifest early in life, and involve preconceptual biases in perceptual memory and habit formation. For its part, character dimensions mature in adulthood and influence personal and social life through learning about self-concept and correspond to self-directedness, cooperativeness, and self-transcendence.

Another model of personality classification that has been widely used is the so-called five-factor model (FFM), which states that personality is ordered hierarchically in a series of traits that can be summarized in five general characteristics: neuroticism, extraversion, conscientiousness, agreeableness, and openness to experience (Goldberg, 1990, 1993). Combining some of the previous models, more recently Whittle, Allen, Lubman, and Yucel (2006) have proposed that specific areas of the prefrontal cortex (dorsolateral prefrontal cortex, anterior cingulate, and orbitofrontal cortex) and limbic structures (amygdala, hippocampus, and nucleus *accumbens*) are related to three fundamental temperamental dimensions: negative affect, positive affect, and constraint. The authors propose that negative affect (manifested by inhibition, avoidance, and punishment sensitivity) is related to a circuit that links limbic-subcortical structures (like amygdala and ventral anterior cingulate cortex) involved in automatic processing of affective states with right hemisphere structures (hippocampus, dorsal anterior cingulate cortex, and dorsolateral prefrontal cortex) related to executive processes and involved with the integration of cognitive processes, affective input, and effortful regulation of affective states.

Based on Gray's psychobiological model, it has been hypothesized that depression would be associated with decreased BAS and/or heightened BIS sensitivity (Depue & Iacono, 1989). In addition, studies have linked high levels of harm avoidance and low levels of self-directedness in patients with depression compared with healthy controls (Celikel et al., 2009). Analyzing the patterns of neural activity in relation to various personality syndromes, using the functional magnetic resonance imaging paradigm in chronic depressive patients, Taubner, Wiswede, and Kessler (2013) found a positive correlation between a high score in "emotional-hostile-externalizing personality" and increased activity in the orbitofrontal cortex, ventral striatum, and temporal pole, areas that, as we saw, are directly linked to emotional processing. From the perspective of connectivity and network level correlates of personality (ranging from associations between single brain areas to whole-brain connectivity), the most studied traits have been neuroticism and avoidance (Markett et al., 2018), which have been associated with differential patterns of functional connectivity, originating in the amygdala and its subregions (neuroticism) and in the anterior insula (harm avoidance).

Unlike psychotic depression or melancholic depression (which has a recognizable genetic, neurobiological, and clinical profile), there are a number of so-called "atypical" or non-melancholic depressive conditions that have a marked reactivity to stressful life events and are related to personality styles and coping strategies (Parker, 2000). Moreover, personality styles can directly influence the level at which the individual is exposed to certain types of stressors, which could trigger the appearance of depressive states and be linked to the recurrence of the depressive disease (Liu, 2013). These personality styles can be determined by genetic variables and influence exposure to certain environments in what is known as gene-environment correlation (see below). Parker and Crawford (2007) have developed a model based on the notion of spectrum, where they propose that certain neurobiological processes shape personality styles, which are accentuated when the individual is stressed or depressed, and determine the clinical characteristics of

non-melancholic (atypical) depression. The authors describe six dimensions of personality (anxious worrying, perfectionism, personal reserve, irritability/snappiness, social avoidance, and rejection sensitivity), each of which presents a specific pattern of symptoms and coping responses. An interesting aspect of this model is that it not only contributes to the understanding the role of personality in origin and clinical presentation of depression but also supports the importance of the differential indication of treatment, emphasizing the importance of psychotherapeutic interventions for the management of the personality in cases of non-melancholic depressions.

Despite the above, there is still much to know about the biological basis of personality in depression. For example, although the relationship between stress, alterations in HPA axis, and the hippocampus is relevant in the pathogenesis of depression, there is no strong evidence regarding the link between these alterations and personality that can be categorically linked to depression (Foster & MacQueen, 2008). In relation to monoaminergic systems, the evidence is also contradictory. Both for dopamine (a neurotransmitter linked to the reward system, which in turn has been linked to extroversion) and serotonin (linked to neuroticism), the results have not been sufficiently consistent, and this is probably because the study of the relationship between monoamines, personality traits, and depression requires a more complex approach that includes the analysis of neural circuits linked to complex behaviors (Shao & Zhu, 2020). Discrepancies in studies of the biological basis of personality in depression are likely to be due, at least in part, to the fact that depression is a multidetermined clinical phenomenon that requires study from diverse perspectives. In that sense, one particularly interesting area is the research of the relationship between genes and the environment.

6.4 Gene-Environment Relationship in Depression

Recent decades have witnessed a clear shift in the study of psychopathology from models emphasizing either genetic (Hong & Tsai, 2003) or environmental (Brown & Harris, 1978) factors to models incorporating various relationships between the genome and the environment (Dick, 2011; Rutter, 2007; Uher, 2008), including cultural variables and gene-culture coevolution (Chiao & Blizinsky, 2010; Way & Lieberman, 2010).

Every human being is unique, despite sharing over 99% of genetic material with the rest of the human species. The answer of what makes us distinctively different from other human beings lies in the continuous reciprocal interaction between the environment and our biology. Such gene-environment relations are thought to result from both gene-environment correlations (rGE) and gene-environment interactions (GxE). Recent theoretical models stress the fact that a person's relationship with his environment from the moment of conception can be assumed to play a crucial role in this uniqueness (Heim & Nemeroff, 2001, 2002; Nemeroff, 1998). The inheritance of our personality traits is polygenic and needs environmental factors to express itself. In order to illustrate how this relationship between the environment

and genes can operate, we will proceed to briefly explain how genes function. Genes contain the information for protein synthesis (coding genes) or a noncoding RNA (RNA genes). They consist of a promoter region (sequence that regulates gene expression) and then the sequence that is transcribed. One way to induce variation in genetic structure is through polymorphisms. Polymorphisms are variations in the DNA sequence by substitution, deletion, or insertion. Not all genetic polymorphisms lead to an alteration in the sequence of a protein or its expression levels, i.e., many are silent and have no phenotypic expression. Genetic polymorphism is the presence in the same population of two or more alleles at a locus, with a significant frequency, where the minimum frequency is usually 1%. Polymorphisms that affect the coding or regulatory sequences, and therefore significantly change the structure of the protein or the mechanism of regulation of its expression, can give rise to different phenotypes. It is the differences in sequence that, together with environmental differences, contribute to phenotypic divergence. They are part of the biological foundations of plasticity and differential response to environmental stimuli and serve as an example to explain the relationship between genes and environment in the etiopathogenesis of mental disorders. Therefore, we are not all affected equally by the environment. The phenotype can be defined as a set of morphological, functional, biochemical, behavioral, and other characteristics of a living being, i.e., expression of the genotype according to a certain environment.

The genome regulates gene expression basically through three mechanisms, all of which are closely intertwined: (1) based on the regulation of transcription factors that bind to the promoter sequences, (2) epigenetic modification mechanisms, and (3) control of accessibility to promoters determined by the degree of chromatin condensation.

An example of polymorphism, which induces a different response in the carrier according to the environment it is related to, is the polymorphism of the promoter region of the serotonin transporter gene (5HTTLPR), and being one of the most studied, many of the examples and investigations that we will describe refer to it. The polymorphism is an insertion/deletion of 44 bp that determines two allelic variants, a short allele (S) with 14 repetitions and a long one (L) with 16 repetitions. The short form has been associated with less than 40% of gene expression compared to the long allele, resulting in decreased expression of the transport protein in the neuronal membrane. This results in a slower performance of the serotonin transporter and an increase in the availability of serotonin in the synaptic space. This has been associated with certain personality traits, such as neuroticism and with greater vulnerability to anxious depressive conditions.

6.4.1 Gene-Environment Correlation (rGE)

Research on gene-environment correlation (rGE) explores the role of genes in the exposure to environmental factors (Kendler & Eaves, 1986; Kendler et al., 1995). rGE refers to the tendency of individuals to select and generate their environment

based on genetic features that influence behavior, thoughts, and feelings. It explains why some people attract certain situations into their lives that actively create stress, while others create satisfying lives, depending on their personalities, which, in turn, depend in part on their genes (Plomin, DeFries, McClearn, & Rutter, 1997). Three types of rGE have been described in the literature: (a) passive, (b) reactive, provocative or evocative, and (c) active or selective (Jaffee & Price, 2008).

(a) Passive rGE refers to the situation in which children inherit from their parents not only a genetic constitution but also the environment in which they are raised (i.e., they inherit intellectual curiosity and the means to satisfy it). The association between genetically related individuals is a requirement for passive rGE.
(b) Evocative, provocative, or reactive rGE refers to the tendency of certain genetically influenced behaviors or temperamental features to elicit certain types of responses from people within their environment, (e.g., a child with a difficult temperament is more likely to elicit negative parenting behaviors). Fighting with your partner may cause someone to become depressed, but it's equally possible that people who are prone to depression tend to trigger arguments with significant others, questioning the direction of the effect.
(c) Active or selective rGE refers to the active generation of certain environments based on genetic tendencies. This refers to the association between genetic features of the individual and the environmental niches that the individual selects or generates (e.g., a child with intellectual curiosity will tend to find intellectually rich environments, while a child with behavioral disorder will seek peers with similar behaviors; that is, people who are more extroverted may seek very different social environments from those who are shy and withdrawn) (Plomin et al., 1997).

6.4.2 Gene-Environment Interaction (GxE)

Gene-environment interaction (GxE) refers to an individual's genetic sensitivity to environmental factors. Explains why people respond differently to environmental factors, some becoming depressed and others becoming stronger, after being exposed to similar life events (Plomin et al., 1997). Until relatively recently, GxE were thought to be rare in psychiatry, but research over the past decades has proven its existence both for medical diseases, (Morales & Duffy, 2019; Raby, 2019) as for mental disorders, shifting research toward a focus on GxE (Moffitt, Caspi, & Rutter, 2005; Rutter, 2010). One of the earliest studies of GxE was reported by Kendler and colleagues (Kendler et al., 1995), who found that stressful life events increased the risk of developing depression more in people with a high genetic risk for depression (i.e., with a twin with depression) than in people with a low genetic risk for depression (i.e., with a twin without depression). This study overthrew the concept of reactive or endogenous depression, because those individuals with a greater genetic risk for depression were shown to be also more reactive to negative environmental

events. In 2003, Caspi and colleagues (2003) published a groundbreaking study, which reported that carrying the short allele of the 5HTTLPR gene interacted with both early and recent negative events to predict depression and suicidal thoughts. Yet, findings have not always been consistent. Two meta-analyses (Munafo, 2012; Risch et al., 2009), for instance, failed to corroborate an interaction between the 5HTTLPR gene and stressful life events in predicting depression. By contrast, a meta-analysis by Uher and McGuffin (Uher, 2014) did find evidence for an interaction between the 5HTTLPR gene and adversity in predicting depression. Differences between these studies' conclusions may be due to differences in their methodology and inclusion criteria. But it is clear that there still is controversy regarding the role of GxE and rGE in psychiatric disorders.

There is now increasing consensus that most common psychiatric disorders, such as depression and anxiety, are best explained as complex disorders, involving dysfunctions in several biological systems in interaction with environmental factors. Gene-environment correlations and interactions are not mutually exclusive. A polymorphism may correlate with some traits that generate changes in the environment (mediation model) and at the same time interact with the environment to generate a new result (moderation model). An example of such a mediational model is the finding that the short allele of the 5HTTLPR gene has been shown to correlate with neuroticism (Greenberg et al., 2000; Sen, Burmeister, & Ghosh, 2004), which in turn has been shown to be related to a tendency to have a negative interpretation bias related to life events (John & Gross, 2004) and therefore a more pessimistic and depressive interpretation of life events (correlational explanation with a mediation model of the relationship between the HTTLPR gene and depression). But this same polymorphism can be associated with the environment in an interaction model, that is, through the moderation of environmental effects. Studies suggest that carriers of the short 5HTTLPR gene allele may interact with negative life events to predict higher levels of depression (Caspi et al., 2003), but they may also interact with social support to lower levels of depression more than noncarriers of the short 5HTTLPR gene (Kaufman et al., 2004; Kim et al., 2014).

6.5 Psychopathology Models on Gene-Environment Relationship

The potential interactions between genetic, neurochemical, and cognitive factors have only recently been demonstrated. The combination of findings from behavioral genetics and cognitive neuroscience opens new opportunities to integrate research results. It is suggested that a comprehensive study of the psychological and biological correlates of mental disorders may grant a new way to understand how we get mentally ill (Beck, 2008). Since the last decade, investigators propose that the future of clinical research and therapeutic efforts should focus on the study of processes of vulnerability (Corveleyn & Blatt, 2005). It becomes especially urgent to

accommodate these new proposals and integrate biological, psychological, and environmental findings if we look at the results of meta-analytic review about the effectiveness of treatments with empirical support (Gaynes et al., 2008; Kirsch, 2019; van der Lem, van der Wee, van Veen, & Zitman, 2012; Westen, Novotny, & Thompson-Brenner, 2004). Because the low rates of response to treatment, researchers agree on the need to change research strategies to target from the beginning the question of which patients require what type of treatment (e.g., pharmacotherapy or psychotherapy, brief or long term) being necessary to then identify dimensions related to patient treatment.

In the 1990s, empirical studies on the interaction between genes and environment began in psychiatry. These investigations were designed to determine vulnerable to stress phenotypes. They conclude that some people carrying particular polymorphisms are more vulnerable to the effects of stressful environment.

6.5.1 Diathesis-Stress Model/Vulnerable Phenotype Model

The diathesis-stress model of mental diseases proposes that stress activates a latent predisposition or diathesis, which then manifests itself as some form of psychopathology. This model assumes that a predisposition is necessary but not an enough condition for the development of a mental disorder and that the interaction with stress activates the diathesis to increase the risk of developing a mental disorder (Zuckerman, 1999). Originally, the predisposition was presumed to be a genetic condition that was observable in certain biological traits; since then, the concept of diathesis has been expanded to include factors such as cognitive or social predispositions (Abela, 2001; Monroe & Simons, 1991). Under this broader concept, biological and psychological traits can be considered diathesis, i.e., the necessary precursors to develop the disorder. As such, in this theory, stress vulnerability is a predisposition or diathesis. This extension of the concept of vulnerability to stress has some conceptual problems, for example, a negative cognitive scheme that makes an individual more vulnerable to stress and anxiety can itself be influenced by genetic, social, or both (Zuckerman, 1999).

Stress not only can be defined as "a specific response of the body to a demand" (Lanfumey, Mongeau, Cohen-Salmon, & Hamon, 2008) but also can be described as "any environmental internal external change, or altering maintenance homeostasis" (Leonard, 2005). Its role as a risk factor for presenting psychopathology has been extensively studied. For this purpose, stress can be subdivided into three categories: acute stress, chronic stress, and stress in early life.

In the diathesis-stress model, events that occur within the previous year of onset of the disorder are considered stressors or acute stress. Generally, life events that involve loss or humiliation have proved depressogenic (OR: 5.64) (Kendler, Karkowski, & Prescott, 1999). Mild chronic stress studies have shown in animals and humans that stress is related with neurobiological changes, like those seen in depressed individuals (Grippo, Beltz, & Johnson, 2003; Tennant, 2002). Finally,

stress in early life, such as childhood trauma (physical, sexual, or emotional abuse) and alterations in attachment, has shown to produce permanent biological changes that confer increased vulnerability to psychopathology (Gutman & Nemeroff, 2003; Heim & Binder, 2012; Heim et al., 2008) and even different response to treatment, responding better to psychotherapy than drugs on chronic depressed women with a history of trauma (Nemeroff et al., 2003).

The distinction between early or remote and recent events is important for this model. This distinction is equally important for the psychoanalytic theory, where it is considered that childhood events are predisposing factors for mental disorders in adults. Prior to the 1990s, stress was considered as a nonspecific and continuous concept, measured as high or low levels. The predisposition to stress was assumed as a threshold, below which the disorder is not expressed, no matter how severe was the stressor, and above which the disorder is expressed if you have sufficient levels of stress to activate the latent predisposition (Monroe & Simons, 1991). The vulnerable phenotype model, instead, incorporates the concept that early adverse experience can have lifelong effects on physical and psychological functioning and become a vulnerability or diathesis for mental disorders. The vulnerable phenotype model illustrates independent and interactive effects of genes and early environment in the development of the phenotype of the individual (Rutter et al., 1997). The GxE interaction is implicit in the stress diathesis model and the vulnerable phenotype model. Adverse childhood experiences can exacerbate genetic vulnerability to stress. This can result in a phenotype that is hypersensitive to future exposures to stress and has an increased risk of developing psychopathology. Early social support and coping styles interact with the genetically determined temperament (Scarr & McCartney, 1983) and can act as buffers against the effect of early adversity in the development of the phenotype. Evidence from animal and human studies supports the model of vulnerable phenotype, suggesting that early adversity induces neurobiological changes and that these changes inhibit the ability of the central nervous system to regulate stress and emotions. This deregulation is accompanied by an increase in the rate of psychiatric disorders (Claes, 2004; Heim & Nemeroff, 2002; Shea, Walsh, Macmillan, & Steiner, 2005). Individuals carrying the vulnerable genotype are more sensitive to adverse environments presenting a worse outcome than noncarriers of the vulnerable genotype. The latter are considered resistant to negative environments (resilient).

The problem of the diathesis-stress model is that it is limited by its focus on stress, which excludes other aspects of the environment that may interact with biological factors. As it was conceptualized to explain psychopathology, the focus is on environmental stressors that can contribute to the development of mental disorders, leaving out environmental factors that can prevent, delay, or treat mental disorders and promote resilience and health. This is the case of the polymorphism of the promoter region of the serotonin transporter (5HTTLPR) gene, which the short allele variant would be more vulnerable to stressful environments. This model of psychopathology, in recent years, has shifted, including positive aspects of the environment and considering these "vulnerable" alleles as "prosocial or plastic" alleles, that is, more sensitive to both negative and positive environment. The model changes from

vulnerability to stress to different sensitivity to the environment. That is, if the relationship between genotype and environment shows that carriers of the short allele of the serotonin transporter are more sensitive to environment. That is, the influence of the environment to predict symptoms is stronger on plastic allele carriers.

6.5.2 Differential Susceptibility to Environment

Over recent years, investigators have reported about the relationship of certain genes, especially the serotonin transporter gene and increased sensitivity to environmental events. Taylor, Way, and Lieberman (Way & Lieberman, 2010; Way & Taylor, 2010) have proposed the hypothesis that these polymorphisms predispose to greater social sensitivity, i.e., they would be prosocial genes, while Pluess and Belsky (Belsky et al., 2009; Belsky & Pluess, 2009) proposed that these kinds of genes confer differential susceptibility to the environment and would be plastic genes, malleable by the environment (Fox, Zougkou, Ridgewell, & Garner, 2011). Previously, Ellis and Boyce (Ellis & Boyce, 2008), from an evolutionary perspective, proposed the model of biological sensitivity to context. Bringing together their theories, they proposed that these genes confer differential sensitivity to environment. Therefore, health and illness depend on the interaction between environmental and biological factors. That is, the genes (as biological factors) would give us more or less sensitivity to environmental factors, and the environment, as if it's positive or negative, would shape the individual, for worse or for better.

Unlike the vulnerable phenotype model, in which the presence of the short allele HTTLPR gene confers susceptibility to adverse environmental factors, in this model, the presence of this allele may provide greater sensitivity to the environment. This means that the short allele actually increases the sensitivity to the environment more generally, so exposition to adverse environments leads to worse outcomes, while supporters and positive environments lead to advantages (Bakermans-Kranenburg & van, 2015; Homberg & Lesch, 2011; Perez-Perez et al., 2018; Stocker et al., 2017). This model includes the previous models of stress diathesis and vulnerable phenotype but takes a more integrated vision of the environment (not only the negative aspects). "It seems that these models (diathesis stress and vulnerable phenotype) are only half the story" (Way & Taylor, 2010). The serotonin transporter gene has been the most studied gene as plastic, known by its interaction with stress (environment) to develop psychopathology. Taylor's study (2006) on prediction of depressive symptoms, according to early family environment and recent life events, showed that homozygotes short allele carriers, when they described a family atmosphere of low-risk and low number of recent stressors, presented the lower depressive symptoms rates of the sample, whereas if they described a high-risk family environment and many recent stressful events, they had the highest depressive symptoms rates of the sample. This indicates that individuals homozygous for the short allele are more sensitive to life events, both positive and negative ones, than the other genotypes. Way & Taylor (2010) studied whether the

nature of recent life events influences this interaction. He distinguished recent events between social events (i.e., end of romantic relationship, conflict with family or friends, death of a loved one) and nonsocial events (receiving a low grade, job loss, car accident). He noted that the relationship between genotype SS, life events, and depression remains significant for recent social events, but it was lost for recent nonsocial events, supporting the subtle difference between prosocial alleles instead of plastic alleles that he proposed. For individuals carrying the short allele, social support appears to be an important factor in maintaining their well-being. Kilpatrick et al. (2007) observed that subjects homozygous for the short allele that were exposed to a hurricane had no greater risk for depression than those homozygous for the long allele, when they had a good perceived social support. However, if they perceived a bad social support, they had 4.5 times greater risk of depression. Kaufman (Kaufman et al., 2004) found that social support moderated the risk for depression associated with the short allele and child abuse. Children with a history of abuse and SS genotype reported higher levels of depression. Maltreated children with the SS genotype and an absence of positive support had depression scores that were approximately twice as high as those of maltreated children with the SS genotype and positive social support. The authors conclude that the availability and frequency of social support may promote resilience even in children with high genetic vulnerability to depression and who have experienced adversity in childhood.

Individuals carrying more plastic alleles may be more sensitive to the detection of biological and socially relevant information from the environment, which is a critical function for social interaction and emotional functioning. The association of increased amygdala reactivity and short allele 5HTTLPR genotype has been demonstrated both with scary faces and with other negative emotions, like anger and grief (Dannlowski et al., 2008), and with positive emotions, such as joy (Domschke et al., 2006), both in healthy population and patients with depression and panic disorder. This indicates, again, sensitivity to socially relevant information rather than only specific threat keys (Canli & Lesch, 2007). Several studies on cognitive function, especially on voluntary attention and working memory in healthy individuals, have shown that carriers of the short allele perform better (Anderson, Bell, & Awh, 2012; Enge, Fleischhauer, Lesch, Reif, & Strobel, 2011). Studies on emotional biases have shown that carriers of the S allele have a strong tendency toward negative material, especially related to threat (Beevers, Wells, Ellis, & McGeary, 2009), and greater difficulty disengaging from emotional, positive, and negative stimuli (Beevers, Gibb, McGeary, & Miller, 2007; Beevers et al., 2011; Fox, Ridgewell, & Ashwin, 2009), and this was even observed in a meta-analysis (Pergamin-Hight, Bakermans-Kranenburg, van Ijzendoorn, & Bar-Haim, 2012). While plasticity can operate toward negative and positive information, attention would respond more to negative bias, maybe related to neuroticism trait related to this polymorphism. Studies in healthy volunteers submitted to learning paradigms show greater and faster learning in short allele carriers (Fox et al., 2011).

Cultural factors may also come into play here. For instance, some GxE seem quite robust in Western cultures but have not been replicated in Eastern cultures (Leighton, Botto, Silva, Jiménez, & Luyten, 2017). Further, GxE may also differ

along the course of development, with some interactions observed at some points during development but not during other developmental stages, and some may be gender dependent.

Unlike the vulnerability model, the differentiated sensitivity to the environment is a model that includes an evolutionary perspective, which considers the potential disadvantages and advantages of individual differences. This evolutionary perspective may be better able to explain the observation that many of the genetic variants included in studies of GxE candidate genes in psychiatry are "common" variants (i.e., have a high frequency in the general population). If there were genetic variants associated exclusively with an increased risk for the development of psychopathology in the presence of adversity, it could be expected that the frequency of these genes would decrease over time (and that the genetic variants associated with resilience would increase). However, this has not been observed; many of these variations are very frequent. It is thought that this type of genetic variation could allow faster adaptation to environmental changes and favor the reproduction of the species.

6.6 Conclusions

Regardless of whether we call it "personality," "temperament," or "character," clinically it is evident that there are certain typologies regarding the way of being and behaving of individuals that are determined by a mood tone and that do not constitute (either by their intensity or their quality) a characteristic mood disorder (manifested by lack of reactivity, an episodic and recurrent course, and with complete interepisodic restitution). Despite the abundant research on the various personality types and their associated traits (both normal and pathological), little is known about the biological basis of these traits. In the case of the relationship between personality and mood disorders, this is especially evident. This may have several explanations. Firstly, it should be noted that, unlike phenomena such as delirium or hallucinations, sadness and depressed mood are part of a set of emotional experiences that are present in everyone's daily life and, therefore, can be difficult to classify immediately as pathological. Another important aspect relates to the diagnosis of depression. We know that there are different clinical subtypes of depression that, under the perspective of a spectrum, can be considered from more chronic, more reactive, and less recurrent manifestations (and, therefore, more linked to personality) to less reactive, more episodic, and recurrent depressions, which would have a more evident genetic and biological component and, therefore, less related to personality (Ghaemi, Vohringer, & Vergne, 2012). It is important to note that many of the personality traits involved in depression have also been associated with other disorders, such as anxiety disorders (Kotov, Watson, Robles, & Schmidt, 2007), so it is difficult to attribute a specificity to them; rather, they would be a general risk factor for various forms of psychopathology. In addition, it's known that personality is not a stable construct but varies throughout life, which can influence how you approach your study scientifically if not considering a life cycle perspective.

As summarized by Klein, Kotov, and Bufferd (2011), the study of the relationship between personality and depression may have a number of implications for research and clinical practice: (1) personality traits associated with the expression and regulation of emotional experiences could be considered as intermediate phenotypes and therefore contribute to a more focalized study of the genetic and biological basis of depression; (2) the study of personality may be useful to distinguish subgroups of depressive disorders that differ in their etiopathogenesis and developmental trajectories; (3) the analysis of the relationship between personality and depressive disorders may facilitate the understanding of the proximal processes involved in the emergence of mood disorders; (4) the study of personality traits may guide in the indication of treatments and predict the therapeutic response; (5) the identification of personality traits that could be considered at risk would allow the development of prevention strategies in the most vulnerable population.

Finally, we now know that the psychosocial environment (including psychotherapeutic interventions) produces modifications in the central nervous system and many of these can be mediated by epigenetic mechanisms (Jimenez et al., 2018). These processes influence the entire life cycle and can act as a molecular bridge between nature and nurture. Therefore, it is necessary to have studies that analyze the relationship between personality and depression from multiple perspectives, having a comprehensive view that integrates the various types of relationships between genes and the environment, including models that, beyond vulnerability, consider the perspective of differentiated sensitivity to environmental stimuli (Leighton et al., 2017). Moreover, as McNaughton (2020) recently suggests, research on explanatory models of personality constructs and the relationship between personality traits, basic emotions, and their disorders should take an evolutionary approach, starting with the study of conserved neutral-level modulators and only then invoke emergent, higher order (i.e., cognitive or behavioral disfunctions) explanations.

References

Abela, J. R. (2001). The hopelessness theory of depression: A test of the diathesis-stress and causal mediation components in third and seventh grade children. *Journal of Abnormal Child Psychology, 29*(3), 241–254. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11411786

Akiskal, K. K., & Akiskal, H. S. (2005). The theoretical underpinnings of affective temperaments: Implications for evolutionary foundations of bipolar disorder and human nature. *Journal of Affective Disorders, 85*(1–2), 231–239. https://doi.org/10.1016/j.jad.2004.08.002

Anderson, D. E., Bell, T. A., & Awh, E. (2012). Polymorphisms in the 5-HTTLPR gene mediate storage capacity of visual working memory. *Journal of Cognitive Neuroscience, 24*(5), 1069–1076. https://doi.org/10.1162/jocn_a_00207

Auerbach, R. P., Admon, R., & Pizzagalli, D. A. (2014). Adolescent depression: Stress and reward dysfunction. *Harvard Review of Psychiatry, 22*(3), 139–148. https://doi.org/10.1097/HRP.0000000000000034

Austin, M. P., Mitchell, P., & Goodwin, G. M. (2001). Cognitive deficits in depression: Possible implications for functional neuropathology. *The British Journal of Psychiatry: The Journal*

of Mental Science, 178, 200–206. Retrieved from http://bjp.rcpsych.org/content/178/3/200.full.pdf

Bakermans-Kranenburg, M. J., & van, I. M. H. (2015). The hidden efficacy of interventions: Genexenvironment experiments from a differential susceptibility perspective. *Annual Review of Psychology, 66*, 381–409. https://doi.org/10.1146/annurev-psych-010814-015407

Beck, A. T. (2008). The evolution of the cognitive model of depression and its neurobiological correlates. *The American Journal of Psychiatry, 165*(8), 969–977. https://doi.org/10.1176/appi.ajp.2008.08050721

Beevers, C. G., Gibb, B. E., McGeary, J. E., & Miller, I. W. (2007). Serotonin transporter genetic variation and biased attention for emotional word stimuli among psychiatric inpatients. *Journal of Abnormal Psychology, 116*(1), 208–212. https://doi.org/10.1037/0021-843x.116.1.208

Beevers, C. G., Marti, C. N., Lee, H. J., Stote, D. L., Ferrell, R. E., Hariri, A. R., & Telch, M. J. (2011). Associations between serotonin transporter gene promoter region (5-HTTLPR) polymorphism and gaze bias for emotional information. *Journal of Abnormal Psychology, 120*(1), 187–197. https://doi.org/10.1037/a0022125

Beevers, C. G., Wells, T. T., Ellis, A. J., & McGeary, J. E. (2009). Association of the serotonin transporter gene promoter region (5-HTTLPR) polymorphism with biased attention for emotional stimuli. *Journal of Abnormal Psychology, 118*(3), 670–681. https://doi.org/10.1037/a0016198

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry, 14*(8), 746–754. https://doi.org/10.1038/mp.2009.44

Belsky, J., & Pluess, M. (2009). Beyond diathesis stress: Differential susceptibility to environmental influences. *Psychological Bulletin, 135*(6), 885–908. https://doi.org/10.1037/a0017376

Berrios, G., & Porter, R. (1995). *A history of clinical psychiatry*. London, UK: The Athlone Press.

Blatt, S. (2005). Therapeutic implications. In *Experiences of depression. Theoretical, clinical and research perspectives* (pp. 255–295). Washington, DC: American Psychological Association.

Blatt, S. (2008). *Polarities of experience. Relatedness and self-definition in personality development, psychopathology, and the therapeutic process*. Washington, DC: American Psychological Association.

Blatt, S. (2015). Depression. In P. Luyten, L. Mayes, P. Fonagy, M. Target, & S. Blatt (Eds.), *Handbook of psychodynamic approaches to psychopathology* (pp. 131–151). New York, NY: The Guilford Press.

Blatt, S. J., & Luyten, P. (2009). A structural-developmental psychodynamic approach to psychopathology: Two polarities of experience across the life span. *Development and Psychopathology, 21*(3), 793–814. https://doi.org/10.1017/S0954579409000431

Bremner, J. D. (1999). Does stress damage the brain? *Biological Psychiatry, 45*(7), 797–805. Retrieved from http://www.biologicalpsychiatryjournal.com/article/S0006-3223(99)00009-8/abstract

Brown, G., & Harris, T. (1978). *Social origins of depression. A study of psychiatric disorder in women*. New York, NY: Free Press.

Canli, T., & Lesch, K. P. (2007). Long story short: The serotonin transporter in emotion regulation and social cognition. *Nature Neuroscience, 10*(9), 1103–1109. https://doi.org/10.1038/nn1964

Caspi, A., Sugden, K., Moffitt, T. E., Taylor, A., Craig, I. W., Harrington, H., … Poulton, R. (2003). Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386. Retrieved from http://search.ebscohost.com/login.aspx?direct=true&db=a9h&AN=10422967&lang=es&site=ehost-live

Celikel, F. C., Kose, S., Cumurcu, B. E., Erkorkmaz, U., Sayar, K., Borckardt, J. J., & Cloninger, C. R. (2009). Cloninger's temperament and character dimensions of personality in patients with major depressive disorder. *Comprehensive Psychiatry, 50*(6), 556–561. https://doi.org/10.1016/j.comppsych.2008.11.012

Chiao, J. Y., & Blizinsky, K. D. (2010). Culture-gene coevolution of individualism-collectivism and the serotonin transporter gene. *Proceedings of the Royal Society B: Biological Sciences, 277*(1681), 529–537. https://doi.org/10.1098/rspb.2009.1650

Claes, S. J. (2004). Corticotropin-releasing hormone (CRH) in psychiatry: From stress to psychopathology. *Annals of Medicine, 36*(1), 50–61.

Cloninger, C. R., Svrakic, D. M., & Przybeck, T. R. (1993). A psychobiological model of temperament and character. *Archives of General Psychiatry, 50*(12), 975–990. https://doi.org/10.1001/archpsyc.1993.01820240059008

Coccaro, E., & Siever, L. (2005). Neurobiology. In J. Oldham, A. Skodol, & D. Bender (Eds.), *Textbook of personality disorders* (pp. 155–169). Arlington, TX: American Psychiatric Publishing, Inc.

Corveleyn, J. L. P., & Blatt, S. J. (2005). *The theory and treatment of depression: Towards a dynamic interactionism model*. Leuven, Belgium: Leuven University Press.

Dannlowski, U., Ohrmann, P., Bauer, J., Deckert, J., Hohoff, C., Kugel, H., … Suslow, T. (2008). 5-HTTLPR biases amygdala activity in response to masked facial expressions in major depression. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 33*(2), 418–424. https://doi.org/10.1038/sj.npp.1301411

Davis, K. L., & Panksepp, J. (2011). The brain's emotional foundations of human personality and the affective neuroscience personality scales. *Neuroscience and Biobehavioral Reviews, 35*(9), 1946–1958. https://doi.org/10.1016/j.neubiorev.2011.04.004

Depue, R. A., & Iacono, W. G. (1989). Neurobehavioral aspects of affective disorders. *Annual Review of Psychology, 40*, 457–492. https://doi.org/10.1146/annurev.ps.40.020189.002325

Dick, D. M. (2011). Gene-environment interaction in psychological traits and disorders. *Annual Review of Clinical Psychology, 7*, 383–409. https://doi.org/10.1146/annurev-clinpsy-032210-104518

Domschke, K., Braun, M., Ohrmann, P., Suslow, T., Kugel, H., Bauer, J., … Deckert, J. (2006). Association of the functional -1019C/G 5-HT1A polymorphism with prefrontal cortex and amygdala activation measured with 3 T fMRI in panic disorder. *The International Journal of Neuropsychopharmacology/Official Scientific Journal of the Collegium Internationale Neuropsychopharmacologicum (CINP), 9*(3), 349–355. https://doi.org/10.1017/s1461145705005869

Ebmeier, K. P., Donaghey, C., & Steele, J. D. (2006). Recent developments and current controversies in depression. *Lancet, 367*(9505), 153–167. https://doi.org/10.1016/S0140-6736(06)67964-6

Ellis, B. J., & Boyce, W. T. (2008). Biological sensitivity to context. *Current Directions in Psychological Science, 17*(3), 183–187.

Enge, S., Fleischhauer, M., Lesch, K. P., Reif, A., & Strobel, A. (2011). Serotonergic modulation in executive functioning: Linking genetic variations to working memory performance. *Neuropsychologia, 49*(13), 3776–3785. https://doi.org/10.1016/j.neuropsychologia.2011.09.038

Eysenck, H. J. (1963). Biological basis of personality. *Nature, 199*, 1031–1034. https://doi.org/10.1038/1991031a0

Foster, J. A., & MacQueen, G. (2008). Neurobiological factors linking personality traits and major depression. *Canadian Journal of Psychiatry, 53*(1), 6–13. https://doi.org/10.1177/070674370805300103

Fox, E., Ridgewell, A., & Ashwin, C. (2009). Looking on the bright side: Biased attention and the human serotonin transporter gene. *Proceedings of the Royal Society B: Biological Sciences, 276*(1663), 1747–1751. https://doi.org/10.1098/rspb.2008.1788

Fox, E., Zougkou, K., Ridgewell, A., & Garner, K. (2011). The serotonin transporter gene alters sensitivity to attention bias modification: Evidence for a plasticity gene. *Biological Psychiatry, 70*(11), 1049–1054. https://doi.org/10.1016/j.biopsych.2011.07.004

Gaynes, B. N., Rush, A. J., Trivedi, M. H., Wisniewski, S. R., Spencer, D., & Fava, M. (2008). The STAR*D study: Treating depression in the real world. *Cleveland Clinic Journal of Medicine, 75*(1), 57–66.

Ghaemi, S. N., Vohringer, P. A., & Vergne, D. E. (2012). The varieties of depressive experience: Diagnosing mood disorders. *The Psychiatric Clinics of North America, 35*(1), 73–86. https://doi.org/10.1016/j.psc.2011.11.008

Gillespie, N. A., Whitfield, J. B., Williams, B., Heath, A. C., & Martin, N. G. (2005). The relationship between stressful life events, the serotonin transporter (5-HTTLPR) genotype and major depression. *Psychological Medicine, 35*(1), 101–111.

Gillihan, S. J., Rao, H., Wang, J., Detre, J. A., Breland, J., Sankoorikal, G. M., … Farah, M. J. (2010). Serotonin transporter genotype modulates amygdala activity during mood regulation. *Social Cognitive and Affective Neuroscience, 5*(1), 1–10. https://doi.org/10.1093/scan/nsp035

Gold, P. W. (2015). The organization of the stress system and its dysregulation in depressive illness. *Molecular Psychiatry, 20*(1), 32–47. https://doi.org/10.1038/mp.2014.163

Goldberg, L. R. (1990). An alternative "description of personality": The big-five factor structure. *Journal of Personality and Social Psychology, 59*(6), 1216–1229. https://doi.org/10.1037//0022-3514.59.6.1216

Goldberg, L. R. (1993). The structure of phenotypic personality traits. *The American Psychologist, 48*(1), 26–34. https://doi.org/10.1037//0003-066x.48.1.26

Gray, J. A. (1970). The psychophysiological basis of introversion-extraversion. *Behaviour Research and Therapy, 8*(3), 249–266. https://doi.org/10.1016/0005-7967(70)90069-0

Greenberg, B. D., Li, Q., Lucas, F. R., Hu, S., Sirota, L. A., Benjamin, J., … Murphy, D. L. (2000). Association between the serotonin transporter promoter polymorphism and personality traits in a primarily female population sample. *American Journal of Medical Genetics, 96*(2), 202–216.

Grippo, A. J., Beltz, T. G., & Johnson, A. K. (2003). Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiology & Behavior, 78*(4–5), 703–710.

Grunebaum, M. F., Galfalvy, H. C., Mortenson, L. Y., Burke, A. K., Oquendo, M. A., & Mann, J. J. (2010). Attachment and social adjustment: Relationships to suicide attempt and major depressive episode in a prospective study. *Journal of Affective Disorders, 123*(1–3), 123–130. https://doi.org/10.1016/j.jad.2009.09.010

Gutman, D. A., & Nemeroff, C. B. (2003). Persistent central nervous system effects of an adverse early environment: Clinical and preclinical studies. *Physiology & Behavior, 79*(3), 471–478. https://doi.org/10.1016/s0031-9384(03)00166-5. PMID: 12954441.

Hammen, C. (2005). Stress and depression. *Annual Review of Clinical Psychology, 1*, 293–319. https://doi.org/10.1146/annurev.clinpsy.1.102803.143938

Hasler, G. (2010). Pathophysiology of depression: Do we have any solid evidence of interest to clinicians? *World Psychiatry: Official Journal of the World Psychiatric Association (WPA), 9*(3), 155–161. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2950973/pdf/wpa030155.pdf

Heim, C., & Binder, E. B. (2012). Current research trends in early life stress and depression: Review of human studies on sensitive periods, gene-environment interactions, and epigenetics. *Experimental Neurology, 233*(1), 102–111. https://doi.org/10.1016/j.expneurol.2011.10.032

Heim, C., & Nemeroff, C. B. (2001). The role of childhood trauma in the neurobiology of mood and anxiety disorders: Preclinical and clinical studies. *Biological Psychiatry, 49*(12), 1023–1039. https://doi.org/10.1016/s0006-3223(01)01157-x

Heim, C., & Nemeroff, C. B. (2002). Neurobiology of early life stress: Clinical studies. *Seminars in Clinical Neuropsychiatry, 7*(2), 147–159.

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: Insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33*(6), 693–710. https://doi.org/10.1016/j.psyneuen.2008.03.008

Heim, C., Plotsky, P. M., & Nemeroff, C. B. (2004). Importance of studying the contributions of early adverse experience to neurobiological findings in depression. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 29*(4), 641–648. https://doi.org/10.1038/sj.npp.1300397

Hirschfeld, R. M. (2013). Personality and mood disorders. In M. Keller (Ed.), *Clinical guide to depression and bipolar disorder. Findings from the collaborative depression study* (Vol. First, pp. 135–140). Washington, DC: American Psychiatric Publishing.

Homberg, J. R., & Lesch, K. P. (2011). Looking on the bright side of serotonin transporter gene variation. *Biological Psychiatry, 69*(6), 513–519. https://doi.org/10.1016/j.biopsych.2010.09.024

Hong, C., & Tsai, T. (2003). The genomic approaches to major depression. *Current Pharmacogenomics, 1*, 67–74.

Ikeda, M., Tanaka, S., Saito, T., Ozaki, N., Kamatani, Y., & Iwata, N. (2018). Re-evaluating classical body type theories: Genetic correlation between psychiatric disorders and body mass index. *Psychological Medicine, 48*(10), 1745–1748. https://doi.org/10.1017/S0033291718000685

Ilsley, J. E., Moffoot, A. P., & O'Carroll, R. E. (1995). An analysis of memory dysfunction in major depression. *Journal of Affective Disorders, 35*(1–2), 1–9. Retrieved from http://www.jad-journal.com/article/0165-0327(95)00032-I/abstract

Jaffee, S. R., & Price, T. S. (2008). Genotype-environment correlations: Implications for determining the relationship between environmental exposures and psychiatric illness. *Psychiatry, 7*(12), 496–499. https://doi.org/10.1016/j.mppsy.2008.10.002

Jimenez, J. P., Botto, A., Herrera, L., Leighton, C., Rossi, J. L., Quevedo, Y., … Luyten, P. (2018). Psychotherapy and genetic neuroscience: An emerging dialog. *Frontiers in Genetics, 9*, 257. https://doi.org/10.3389/fgene.2018.00257

John, O. P., & Gross, J. J. (2004). Healthy and unhealthy emotion regulation: Personality processes, individual differences, and life span development. *Journal of Personality, 72*(6), 1301–1333. https://doi.org/10.1111/j.1467-6494.2004.00298.x

Kaufman, J., Yang, B. Z., Douglas-Palumberi, H., Houshyar, S., Lipschitz, D., Krystal, J. H., & Gelernter, J. (2004). Social supports and serotonin transporter gene moderate depression in maltreated children. *Proceedings of the National Academy of Sciences of the United States of America, 101*(49), 17316–17321. https://doi.org/10.1073/pnas.0404376101

Keller, M. C., & Nesse, R. M. (2006). The evolutionary significance of depressive symptoms: Different adverse situations lead to different depressive symptom patterns. *Journal of Personality and Social Psychology, 91*(2), 316–330. https://doi.org/10.1037/0022-3514.91.2.316

Kendler, K. S., & Eaves, L. J. (1986). Models for the joint effect of genotype and environment on liability to psychiatric illness. *The American Journal of Psychiatry, 143*(3), 279–289. Retrieved from http://search.proquest.com.ezproxy.puc.cl/docview/220469699?accountid=16788

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *The American Journal of Psychiatry, 156*(6), 837–841.

Kendler, K. S., Kessler, R. C., Walters, E. E., MacLean, C., Neale, M. C., Heath, A. C., & Eaves, L. J. (1995). Stressful life events, genetic liability, and onset of an episode of major depression in women. *The American Journal of Psychiatry, 152*(6), 833–842.

Kennis, M., Rademaker, A. R., & Geuze, E. (2013). Neural correlates of personality: An integrative review. *Neuroscience and Biobehavioral Reviews, 37*(1), 73–95. https://doi.org/10.1016/j.neubiorev.2012.10.012

Kilpatrick, D. G., Koenen, K. C., Ruggiero, K. J., Acierno, R., Galea, S., Resnick, H. S., … Gelernter, J. (2007). The serotonin transporter genotype and social support and moderation of posttraumatic stress disorder and depression in hurricane-exposed adults. *The American Journal of Psychiatry, 164*(11), 1693–1699. https://doi.org/10.1176/appi.ajp.2007.06122007

Kim, J. M., Stewart, R., Kim, S. W., Kang, H. J., Kim, S. Y., Lee, J. Y., … Yoon, J. S. (2014). Interactions between a serotonin transporter gene, life events and social support on suicidal ideation in Korean elders. *Journal of Affective Disorders, 160*, 14–20. https://doi.org/10.1016/j.jad.2014.02.030

Kirsch, I. (2019). Placebo effect in the treatment of depression and anxiety. *Frontiers in Psychiatry, 10*, 407. https://doi.org/10.3389/fpsyt.2019.00407

Klein, D. N., Kotov, R., & Bufferd, S. J. (2011). Personality and depression: Explanatory models and review of the evidence. *Annual Review of Clinical Psychology, 7*, 269–295. https://doi.org/10.1146/annurev-clinpsy-032210-104540

Kotov, R., Watson, D., Robles, J. P., & Schmidt, N. B. (2007). Personality traits and anxiety symptoms: The multilevel trait predictor model. *Behaviour Research and Therapy, 45*(7), 1485–1503. https://doi.org/10.1016/j.brat.2006.11.011

Kraepelin, E. (2012). *La locura maníaco-depresiva*. Madrid, Spain: Ergon.

Krishnadas, R., & Cavanagh, J. (2012). Depression: An inflammatory illness? *Journal of Neurology, Neurosurgery, and Psychiatry, 83*(5), 495–502. https://doi.org/10.1136/jnnp-2011-301779

Krueger, R. F., & Johnson, W. (2008). Behavioral genetics and personality: A new look at the integration of nature and nurture. In O. P. John, R. W. Robins, & L. A. Pervin (Eds.), *Handbook of personality: Theory and research* (3rd ed., pp. 287–310). New York, NY: Guilford.

Lanfumey, L., Mongeau, R., Cohen-Salmon, C., & Hamon, M. (2008). Corticosteroid-serotonin interactions in the neurobiological mechanisms of stress-related disorders. *Neuroscience and Biobehavioral Reviews, 32*(6), 1174–1184. https://doi.org/10.1016/j.neubiorev.2008.04.006

Leighton, C., Botto, A., Silva, J. R., Jiménez, J. P., & Luyten, P. (2017). Vulnerability or sensitivity to the environment? Methodological issues, trends, and recommendations in gene–environment interactions research in human behavior. *Frontiers in Psychiatry, 8*, 106. https://doi.org/10.3389/fpsyt.2017.00106

Leonard, B. E. (2005). The HPA and immune axes in stress: The involvement of the serotonergic system. *European Psychiatry: The Journal of the Association of European Psychiatrists, 20*(Suppl 3) (Journal Article), S302–S306.

Liu, R. T. (2013). Stress generation: Future directions and clinical implications. *Clinical Psychology Review, 33*(3), 406–416. https://doi.org/10.1016/j.cpr.2013.01.005

Luyten, P., Blatt, S., & Corveleyn, J. (2005). Towards integration in the theory and treatment of depression? The time is now. In J. Corveleyn, P. Luyten, & S. Blatt (Eds.), *The theory and treatment of depression. Towards a dynamic interactionism model* (Vol. First, pp. 253–284). Leuven, Belgium: Leuven University Press.

Luyten, P., Fonagy, P., Lemma, A., & Target, M. (2012). Depression. In A. Bateman & P. Fonagy (Eds.), *Handbook of mentalizing in mental health practice* (Vol. First, pp. 385–417). Washington, DC: American Psychiatric Association.

Malhi, G. S., & Mann, J. J. (2018). Depression. *Lancet, 392*(10161), 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2

Markett, S., Montag, C., & Reuter, M. (2018). Network neuroscience and personality. *Personal Neuroscience, 1*, e14. https://doi.org/10.1017/pen.2018.12

McNaughton, N. (2020). Personality neuroscience and psychopathology: Should we start with biology and look for neural-level factors? *Personal Neuroscience, 3*, e4. https://doi.org/10.1017/pen.2020.5

Moffitt, T. E., Caspi, A., & Rutter, M. (2005). Strategy for investigating interactions between measured genes and measured environments. *Archives of General Psychiatry, 62*(5), 473–481. https://doi.org/10.1001/archpsyc.62.5.473

Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin, 110*(3), 406–425. Retrieved from http://psycnet.apa.org/journals/bul/110/3/406/

Morales, E., & Duffy, D. (2019). Genetics and gene-environment interactions in childhood and adult onset asthma. *Frontiers in Pediatrics, 7*, 499. https://doi.org/10.3389/fped.2019.00499

Munafo, M. R. (2012). The serotonin transporter gene and depression. *Depression and Anxiety, 29*(11), 915–917. https://doi.org/10.1002/da.22009

Nemeroff, C. B. (1998). The neurobiology of depression. *Scientific American, 278*(6), 42–49.

Nemeroff, C. B., Heim, C. M., Thase, M. E., Klein, D. N., Rush, A. J., Schatzberg, A. F., … Keller, M. B. (2003). Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proceedings of the National*

Academy of Sciences of the United States of America, 100(24), 14293–14296. https://doi.org/10.1073/pnas.2336126100

Nesse, R. M. (2000). Is depression an adaptation? *Archives of General Psychiatry, 57*(1), 14–20.

Nettle, D. (2004). Evolutionary origins of depression: A review and reformulation. *Journal of Affective Disorders, 81*(2), 91–102. https://doi.org/10.1016/j.jad.2003.08.009

Parker, G. (2000). Classifying depression: Should paradigms lost be regained? *The American Journal of Psychiatry, 157*(8), 1195–1203. https://doi.org/10.1176/appi.ajp.157.8.1195

Parker, G. B., & Crawford, J. (2007). A spectrum model for depressive conditions: Extrapolation of the atypical depression prototype. *Journal of Affective Disorders, 103*(1–3), 155–163. https://doi.org/10.1016/j.jad.2007.01.022

Perez-Perez, B., Cristobal-Narvaez, P., Sheinbaum, T., Kwapil, T. R., Ballespi, S., Pena, E., … Barrantes-Vidal, N. (2018). Interaction between FKBP5 variability and recent life events in the anxiety spectrum: Evidence for the differential susceptibility model. *PLoS One, 13*(2), e0193044. https://doi.org/10.1371/journal.pone.0193044

Pergamin-Hight, L., Bakermans-Kranenburg, M. J., van Ijzendoorn, M. H., & Bar-Haim, Y. (2012). Variations in the promoter region of the serotonin transporter gene and biased attention for emotional information: A meta-analysis. *Biological Psychiatry, 71*(4), 373–379. https://doi.org/10.1016/j.biopsych.2011.10.030

Plomin, R., DeFries, J., McClearn, G., & Rutter, M. (1997). *Behavioral genetics*. New York, NY: W. H. Freeman.

Raby, B. A. (2019). Asthma severity, nature or nurture: Genetic determinants. *Current Opinion in Pediatrics, 31*(3), 340–348. https://doi.org/10.1097/mop.0000000000000758

Risch, N., Herrell, R., Lehner, T., Liang, K. Y., Eaves, L., Hoh, J., … Merikangas, K. R. (2009). Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: A meta-analysis. JAMA: The Journal of the American Medical Association, 301(23), 2462–2471. https://doi.org/10.1001/jama.2009.878

Rutter, M. (2007). Gene-environment interdependence. *Developmental Science, 10*(1), 12–18. https://doi.org/10.1111/j.1467-7687.2007.00557.x

Rutter, M. (2010). Gene-environment interplay. *Depression and Anxiety, 27*(1), 1–4. https://doi.org/10.1002/da.20641

Rutter, M., Dunn, J., Plomin, R., Simonoff, E., Pickles, A., Maughan, B., … Eaves, L. (1997). Integrating nature and nurture: Implications of person–environment correlations and interactions for developmental psychopathology. *Development and Psychopathology, 9*(02), 335–364. Retrieved from https://doi.org/10.1017/S0954579497002083

Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype greater than environment effects. *Child Development, 54*(2), 424–435.

Schneider, K. (1997). *Psicopatología clínica*. Madrid, Spain: Fundación Archivos de Neurobiología.

Sen, S., Burmeister, M., & Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 127B*(1), 85–89. https://doi.org/10.1002/ajmg.b.20158

Shao, X., & Zhu, G. (2020). Associations among monoamine neurotransmitter pathways, personality traits, and major depressive disorder. *Frontiers in Psychiatry, 11*, 381. https://doi.org/10.3389/fpsyt.2020.00381

Shea, A., Walsh, C., Macmillan, H., & Steiner, M. (2005). Child maltreatment and HPA axis dysregulation: Relationship to major depressive disorder and post traumatic stress disorder in females. *Psychoneuroendocrinology, 30*(2), 162–178. https://doi.org/10.1016/j.psyneuen.2004.07.001

Siever, L. J., & Davis, K. L. (1991). A psychobiological perspective on the personality disorders. *The American Journal of Psychiatry, 148*(12), 1647–1658. https://doi.org/10.1176/ajp.148.12.1647

Stocker, C. M., Masarik, A. S., Widaman, K. F., Reeb, B. T., Boardman, J. D., Smolen, A., … Conger, K. J. (2017). Parenting and adolescents' psychological adjustment: Longitudinal mod-

eration by adolescents' genetic sensitivity. *Development and Psychopathology, 29*(4), 1289–1304. https://doi.org/10.1017/s0954579416001310

Taubner, S., Wiswede, D., & Kessler, H. (2013). Neural activity in relation to empirically derived personality syndromes in depression using a psychodynamic fMRI paradigm. *Frontiers in Human Neuroscience, 7*, 812. https://doi.org/10.3389/fnhum.2013.00812

Taylor, S. E., Way, B. M., Welch, W. T., Hilmert, C. J., Lehman, B. J., & Eisenberger, N. I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological Psychiatry, 60*(7), 671–676. https://doi.org/10.1016/j.biopsych.2006.04.019

Tellenbach, H. (1976). *La Melancolía. Visión histórica del problema: endogeneidad, tipología, patogenia y clínica*. Madrid, Spain: Morata.

Tennant, C. (2002). Life events, stress and depression: A review of recent findings. *Australian and New Zealand Journal of Psychiatry, 36*(2), 173–182. https://doi.org/10.1046/j.1440-1614.2002.01007.x

Uher, R. (2008). The implications of gene-environment interactions in depression: Will cause inform cure? *Molecular Psychiatry, 13*(12), 1070–1078. https://doi.org/10.1038/mp.2008.92

Uher, R. (2014). Gene-environment interactions in severe mental illness. *Frontiers in Psychiatry, 5*, 48.

van der Lem, R., van der Wee, N. J., van Veen, T., & Zitman, F. G. (2012). Efficacy versus effectiveness: A direct comparison of the outcome of treatment for mild to moderate depression in randomized controlled trials and daily practice. *Psychotherapy and Psychosomatics, 81*(4), 226–234. https://doi.org/10.1159/000330890

Vazquez, G. H., Tondo, L., Mazzarini, L., & Gonda, X. (2012). Affective temperaments in general population: A review and combined analysis from national studies. *Journal of Affective Disorders, 139*(1), 18–22. https://doi.org/10.1016/j.jad.2011.06.032

Way, B. M., & Lieberman, M. D. (2010). Is there a genetic contribution to cultural differences? Collectivism, individualism and genetic markers of social sensitivity. *Social Cognitive and Affective Neuroscience, 5*(2–3), 203–211. https://doi.org/10.1093/scan/nsq059

Way, B. M., & Taylor, S. E. (2010). Social influences on health: Is serotonin a critical mediator? *Psychosomatic Medicine, 72*(2), 107–112. https://doi.org/10.1097/PSY.0b013e3181ce6a7d

Westen, D., Novotny, C. M., & Thompson-Brenner, H. (2004). The empirical status of empirically supported psychotherapies: Assumptions, findings, and reporting in controlled clinical trials. *Psychological Bulletin, 130*(4), 631–663. https://doi.org/10.1037/0033-2909.130.4.631

Whittle, S., Allen, N. B., Lubman, D. I., & Yucel, M. (2006). The neurobiological basis of temperament: Towards a better understanding of psychopathology. *Neuroscience and Biobehavioral Reviews, 30*(4), 511–525. https://doi.org/10.1016/j.neubiorev.2005.09.003

Zuckerman, M. (1999). *Vulnerability to psychopathology: A biosocial model*. Washington, DC: American Psychological Association.