LOUIS BOLK INSTITUTE

Depressive Disorders

An Integral Psychiatric Approach

Marko van Gerven MD
Christina van Tellingen MD

BOLK'S COMPANIONS
FOR THE PRACTICE OF MEDICINE

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Publication number: GVO 09
ISBN 978-90-74021-40-1
Price € 10
Postage € 7,50

KvK 41197208
Triodos Bank 212185764
IBAN: NL77 TRIO 0212185764
BIC code/Swift code: TRIONL 2U
For credit card payment visit our website at
www.louisbolk.nl/companions

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Colofon:
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Translation: Sandy Reijnhart and Sherry Wildfeuer
Cover: Fingerprint, Witzenhausen D
Cover painting: Rob Otte, Man
Watercolor painting 2006 Original: 21 x 15 cm

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The Prelude to this Companion; A Word of Thanks

June 2007. I was awaiting heart surgery for a life threatening condition. I was unusually impressionable. During this period, two events occurred. I attended a lecture by Brian Leonard on the relation between the immune system and depression and was struck by his comment about depression research nowadays, which is mostly focused on the brain. As if the body does not play a great part in depressive symptoms. The other event was reading " The Healing Process," written by Guus van der Bie, Tom Scheffers, and Christina van Tellingen. In it, the process of illness was described from the viewpoint of phenomenology and systems biology. The authors developed a model in which illness can be viewed as the result of stagnation in one of four stages of the process of recuperation, as illustrated in the process of wound healing.

My medical problem was solved after a successful surgery, November 2007, but not before I realized something else: how many caring people were surrounding me. After another intense work period, I retired and had time to write this Companion.

In the first place, I have to thank my destiny and its miraculous ways. Inspiration came at the right moment and I had time to realize my ideas. I started working with Guus van der Bie and Christina van Tellingen who encouraged and helped me to work out my initial questions. After finishing a first draft, Christina emerged as co-author. We proved to complement one another in this research.

As I am no longer active in patient care, I have had to revert to former patients of mine, or to ask cooperation from those patients, whom I saw as a supervisor of other psychiatrists. I am very grateful to them for having given me permission to publish their medical histories.

Of a totally different nature was the help given to me by my dear wife Marianne, who never forgot to confront me with the point of view that there is more to life than writing books!

Marko van Gerven

About the Authors

*Marko van Gerven MD (*1947) has worked as a psychiatrist in several hospitals, on acute psychiatric wards, and in private practice. He was one of the founders of the Lievegoed Clinic, an anthroposophic psychiatric hospital in the Netherlands. Marko van Gerven specialized in the treatment of patients with chronic trauma. After his recent retirement, he started teaching art and social therapy students. He is member of the board of the 'Networkuniversity' of the Lievegoed Foundation.

Christina van Tellingen MD (1949) has been a general practitioner since 1982. She has educated medical students, physicians, and therapists in the United States, Canada, and Europe. She teaches medical students and physicians at the University of Witten/Herdecke, Germany. She is a member of the Medical Section of the School of Spiritual Science at the Goetheanum, Dornach, Switzerland.

About the Project

The project *Renewal of Medical Education* aims to produce Companions that demonstrate how the insights of current biomedical science can be broadened by using the Goethean phenomenological method. This method innovates current concepts and expands the understanding of biochemical, physiological, psychological, and morphological factors in living organisms and their development in time and space, and in health, illness, and therapy. The project is commissioned by the Kingfisher Foundation, which aspires the development, application, and publication of the Goethean phenomenological research method in the widest sense, to complement and innovate the accepted scientific view and research method.

BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE complement current medical education, specifically disclosing human qualities in the fundamental biomedical sciences of today.

BOLK'S COMPANIONS FOR THE PRACTICE OF MEDICINE contribute to a scientific phenomenological basis for integrative medicine and integral psychiatry.

Contents

Foreword

Important advancements have been made by regular psychiatry over the past decades, yet not everyone is better, and many patients complain about the side effects of standard medication. Moreover, according to recent reviews, it appears that the effectiveness of the two most important standard treatments, antidepressants and cognitive behavioral therapy (CBT), is lower than thought, when screened for publication bias (Turner et al 2008; Kirsch et al 2008; Cuijper et al 2010). This is all the more reason to keep searching for new treatments and for improvements to the existing ones.

This is also one of the reasons why patients are increasingly turning to complementary and alternative medicine (CAM): from 34% of the American population in 1990 to 42% in 1997 (Eisenberg et al 1998). When our own research showed that this was also true for 43% of the outpatient patients in Groningen, the Netherlands (Hoenders et al 2006), the public mental health authority Lentis decided in 2006 to start a Center for Integral Psychiatry (CIP). Here, alongside standard psychiatric treatments, CAM that has been proven safe and effective is offered additionally as part of an integrated treatment. This was also prompted by the fact that the integral approach to medicine is stimulated by such organizations as the European Parliament and the World Health Organization (EP 1997, 2007; WHO 2003, 2006) and is being successfully implemented by a consortium of 44 academic medical hospitals in North America under the term 'Integrative Medicine' (www.imconsortium.org).

The Lentis CIP consists of an outpatient clinic, a yearly conference, a research group, and a training course (Hoenders et al 2008). Due to the controversy surrounding CAM and the fact that what is needed here is not only an open mind but also a critical spirit in order to arrive at a responsible choice, the CIP recently developed a protocol for the application of CAM in standard mental healthcare (Hoenders et al 2010).

The vision and basic principles of the CIP correspond to those of Marko van Gerven and Christina van Tellingen. In this book, they provide an accurate picture of the limitations

of the DSM-IV. The DSM is indeed a useful instrument for worldwide communication, classification, and scientific research, but there is also the danger of 'cookbook medicine' in which all nuances and profundity disappear. Van Gerven and van Tellingen offer a counterbalance to this danger by providing an interesting and broadening vision of the various biological disturbances that occur during depression according to older as well as more current models. They do this with extreme care. Their classification provides new grounds for more individualized treatment (also called 'personalized medicine'). This is enormously valuable at a time when a one-sided scientific approach threatens to lead to reductionism and the deterioration of psychiatry.

There are clear similarities between this book and the previously described CIP method, such as the intention to offer a more differentiated and complete palette of treatments and to work within a holistic/systemic framework. There are, though, also differences. Van Gerven and van Tellingen place the emphasis on meticulous and differentiated diagnostics, using principles that include functional medicine, and, in addition, base their work on systems biology. The CIP works chiefly on the integration of safe and effective CAM in standard psychiatry, and also advocates a critical open mind for all possible treatments, regardless of the culture or the medical tradition they come from. These two approaches dovetail well with each other.

I hope that this book can make a contribution to more multiform and individualized treatments in the mental healthcare sector, using an innovative mix of findings from recent research along with the best of what the various treatment methods have to offer.

Rogier Hoenders MD, PhD

Acknowledgments

This Companion was written at the Louis Bolk Institute, Driebergen, the Netherlands, under the auspices of the Kingfisher Foundation.
Writing a book is unthinkable without the enthusiastic cooperation of a large group of colleagues and friends. Ronald Baas, Geartsje Boonstra, Milou Dunselman, Jan van der Greef, Onno van der Hart, Rogier Hoenders, Henk Koers, Leo Reidsma, Marjory van Rinkhuyzen, and Anne-Marije Schat gave important contributions to this Companion. It is also a result of the stimulating exchange of ideas with Guus van der Bie, Loes van den Heuvel, Wouter Endel, Kore Luske, and Tom Scheffers, our colleagues in the search to find innovative approaches for medical research using Goethean phenomenology.
This project was made possible financially by generous gifts from the Bernard Lievegoed Fonds, Triodos Foundation, Iona Stichting, Stichting Phoenix, and the Brigitta Rogmanfonds.

Marko van Gerven MD
Christina van Tellingen MD

Preface

"The objective of a causal treatment is to suppress the symptoms as little as possible, to provide as much health-promoting support as possible and to approach the patient with a holistic and multidisciplinary process-related therapy."

Dr. Thomas Breitkreuz, University Hospital, Witten, Germany

Depression is, according to the Diagnostic Statistic Manual (DSM-IV-TR), a heterogeneous diagnosis. The DSM offers no etiological basis and few relevant points regarding effective treatment for depressions of light to moderate severity, in spite of all the guidelines. That patients are told that depression is caused by a shortage of a specific substance in the brain is a grave underestimation of the number of different risk factors that have been discovered. Although each of these separate risk factors plays only a small part in the development of depression, clustering of these risk factors may give plausibly connected groups for the physician searching for an appropriate treatment.

We have found the model of the wound healing process to be the missing link between cause and treatment. The model developed in this Companion links risk factors with treatment methods in a logical relation. What is gratifying here is that this also does justice to the individual's circumstances in the development of a depressive disorder. Such a method complements what is now called integral psychiatry, within which the patient-therapist relationship is central. We hope this Companion offers an improvement in the diagnostics and treatment of the clinically depressed patient with respect to current practice.

1. Introduction

This chapter presnets a bird's eye view of the key elements of this book. First, it discusses the high prevalence of depressive disorders. Then follows a discussion of the dilemma that group-related research is not necessary relevant for the diagnosis and treatment of the individual depressed patient. An alternative is found in larger patterns of risk factor combinations, as is done in systems biology. Therapy may also be approached in this way, based on the model of general physical wound healing.

1.1. Depressive Disorders Today

Depression is, after cardiovascular disease, the most common illness in the Western world. In the Netherlands, the chance that someone would undergo a major depression at least once during his or her lifetime was 15.4 % and 1.6% for dysthymic disorders (Bijl et al 1997). In spite of the increase in material welfare, the prevalence of depression in the general population has increased so sharply that at the moment an estimated 25% of the population runs the risk of developing one or more variants of depression in the course of a lifetime. There is talk of a 'depression epidemic' (Dehue 2008), which, according to Dehue, may also be attributed to smart marketing techniques of the pharmaceutical industry. However, there is more to it. The age at which the initial depression occurs has gone down from 25-30 years old to early adolescence. Moreover, depression appears, more often than was previously believed, to be a chronic condition.

Experiencing a depression has a huge impact on the quality of life:

1. Depressive disorders involve a great deal of suffering for patients and their families, including the risk of premature death (through illness and/or suicide).
2. Depression has an adverse effect on the course of physical illnesses such as cardiovascular disease. This is probably connected with decreased attention to correct medication usage and inability to make changes in lifestyle, but also with the

biological consequences for health. Depression modifies, for example, the coagulation mechanism in thrombocytes with a consequent increased risk of myocardial infarction.
3. The social costs of depression are high due to absenteeism and medical treatment.

1.2. Clustering Risk Factors

In spite of the increase in therapeutic possibilities for the treatment of depressive disorders, the percentage of successful treatments is still small. Treatment is most effective for major depression due to the therapies initiated in the first half of the previous century, such as the use of the 'classical' antidepressants and electroconvulsive therapy. For less serious depression, the outcome of treatment with antidepressants rises barely, if at all, above the placebo level (Fournier et al 2010). The effect of cognitive behavioral therapy, once it is corrected for publication bias, does not seem to be better than placebo (Cuijpers et al 2010).

General treatment outcomes are also disappointing because depression is a 'hodgepodge' concept that does not take into account how it originates and develops. The diagnostic classification by the DSM-IV-TR is, after all, not focused on causal factors. Risk factors for depression have certainly been identified through large-scale population screening, but each of these factors, such as genetic tendencies or dysfunction of the hypothalamus-pituitary-adrenal axis, play only a small role in the development of depression (Beekman and van Marwijk 2008). It is nonetheless possible to arrange the possible risk factors for depression into four causal clusters (McHugh 2006). Treatment according to clustering of causal risk factors could substantially increase the effectiveness of existing treatment possibilities. If depression manifests itself in significant stress situations, this demands, in the first instance, a change in stress management. However, the treatment of a depression in which hereditary components play a major role ('brain disease') justifies a more drug-related line of approach. That could be a first step in gearing the cause and treatment of depression to each other in a more focused manner.

1.3. Functional Psychiatry

An important current attempt to categorize the symptoms of depression stems from functional psychiatry, which makes connections between psychiatric symptoms and disorders in brain function:

1. 'Brooding' can be attributed to insufficient functioning of the hypothalamus-prefrontal-cortex circuit.
2. Sleeping disorders can be related to the 24-hour rhythm of light metabolism.
3. Long-term stress can be related to changes in cortisol management.

Specific treatment suggestions can be derived from these types of connections (Loonen et al 2008). Explaining a symptom from a pathophysiological 'substrate' is the accepted method in somatic medicine. This type of symptomatic approach is based on research of large groups of patients. The above mentioned connections proved to apply to only part of the group of depressive patients.

1.4. Integral Systems Biology

The phenomenological tradition searches to summarize those characteristics of a disease that cluster a set of symptoms. This corresponds with the method used by experienced physicians who apply pattern recognition to establish a diagnosis. They search, in part intuitively, for similarities in the symptoms of the patient with the prototype 'depression' (Hengeveld 2010). The Louis Bolk Institute (LBI) in Driebergen, the Netherlands, has detailed phenomenology for medicine in a number of publications. A series of English-language "Companion" publications takes a phenomenological approach to accompany the study of basic subjects in medical training, such as anatomy, biochemistry, physiology, immunology, embryology, and pharmacology. Bolk's Companion "The Healing Process" (Bie et al 2008) develops a model for understanding pathological progression using the wound healing process. The wound healing process is the prototype of how recovery functions operate in the human organism. During the wound healing process, various phases can be distinguished. Hemostasis, the first phase, takes only a few minutes, while the final recovery phase, the formation of scar tissue, continues for up to a year

after the injury. It is not known how the various phases are navigated. For that reason a metaphor – the term "Organ of Repair" – is used in "The Healing Process." Normally, each phase is successfully completed in sequence. However, stagnation may occur in the recovery process. If the "Organ of Repair" fails, it can become disturbed in the direction of 'dissolving' (for instance increased tendency to bleed) or of 'hardening' (for instance tendency to clot). In this Companion, the clustering of risk groups is related to the model of the wound healing process. This leads to the development of a systems vision for the origin and treatment of depression.

1.5. Overview of this Companion

Chapter 2 discusses various diagnostic and therapeutic models of depression and closes with the presentation of a working model. This model includes the description of four clusters of causes of depression at biological and psychological levels and four related recovery phases, based on the model of the wound healing process. The four risk levels and recovery phases are explored in depth in the chapters 3, 4, 5, and 6 and their mutual relations are examined.

Chapter 3 discusses the cluster disorders of integrative processes, which occur not only in the brain but also in other parts of the body. Integrative processes may work at each of the four levels discussed and are characterized by a different mechanism on the four levels: on level I integrative mechanisms effect heterostasis, on level II allostasis, on level III homeostasis, and on level IV epigenetics plays a role in integrative processes. Integrative processes are characterized as the driving force behind self-regulative recovery mechanisms.

Chapter 4 deals with the cluster disorders of interactive processes as a risk factor. These processes, with the aid of the messenger systems, are responsible for the harmony between the inner world and the outer world. Important messenger systems are the hypothalamus-pituitary-adrenal axis and the immune system. Hormones, neurotransmitters, and cytokines appear to play a leading role as messengers. Allostatic recovery mechanisms ensure the maintenance of a dynamic equilibrium.

Chapter 5 deals with disorders of metabolic processes as a causal cluster of risk factors for

depression. A disturbed monoamine metabolism in the brain plays a major role here, as do physical illnesses. The disruption of homeostatic self-regulation is an important illness-promoting factor.

Chapter 6 deals with disorders due to genetic aspects as a cluster of risk factors and epigenetics as risk factor and recovery possibility of depression, and describes the mechanisms that are involved when depression becomes chronic.

Chapter 7 provides the final working model, a few guidelines for practice, and its application in two cases. This Companion concludes with a table in which the current familiar, researched treatments are listed according to systems level.

2. The Working Model

The problems using the DSM classification for depression are discussed first in this chapter. Then we focus on functional psychiatry, which correlates some depressive symptoms to neurophysiological or anatomical change, similar to the way this is done in somatic medicine. A pragmatic claasification of risk factors is offered in four areas according to McHugh. Parker propoes grouping the severity of depressive disorders in dimensions, with consequences for the pharmacological approach. A systems biology approach tot the healing process allows development of a working model, in which the different perspectives are brought together.

2.1. Depression According to the DSM

If the diagnosis of depression is inadequate, it is understandable that its treatment would also lead to mediocre results. The implementation of the DSM-III in 1980, a classification system for psychiatrists and scientists, has resulted in worldwide agreement on the definition of various depressive disorders. That serves the practice of scientific research. However, a major disadvantage is the less-than-expected reliability of the diagnosis of depression in practice and the lack of a pathophysiological substrate, as is customary in somatic medicine. The classification method according to the DSM (see box) is identical to that of a bird book: phenomenological criteria such as color, size, and feathering are used as distinguishing characteristics. In reference to this, it is a good idea to delve first into what phenomenology means to psychiatry. According to Velleman and De Wachter (2009), the term phenomenology is used in psychiatry in three ways:

1. As an *objective* description of signs and symptoms of psychiatric conditions by a neutral observer (the DSM ideal);
2. As a description of *subjective* experiences (the patient's own story);
3. In referring to a *philosophical* school that originated in the early 20th century (with names such as Husserl, Heidegger, and Merleau-Ponty). In this context, phenomenology is used to designate a pattern, an organizational whole.

The philosopher-psychiatrist Jaspers believed that both the objective and the subjective phenomenological approach could be used in psychiatry, depending upon what one wanted to describe. The researcher mainly had to develop an awareness for which method he needed to use in a specific situation. In a recent opinion piece, Nassir Ghaemi (2009) criticizes the loss of the subjective approach since the introduction of Engel's biopsychosocial model (1977). He characterizes this model as antihuman: Engel was only interested in scientific objectivity, completely ignoring the humanistic side of medicine. Reinstating a pluralistic perspective, as Nassir Ghaemi proposes, is a basic premise in this Companion.

The DSM has a solely objective phenomenological point of view. Yet in spite of the DSM classification, the diagnosis of depression is difficult. Depression has proved to have many different forms of expression. The diagnosis says nothing about the cause, and it predicts no treatment outcomes (Parker 2009). Due to the lack of coupling with an ethiopathological substrate, risk factors will only have bearing on some of the patients with a given form of depressive disorder.
Drugs or psychotherapeutic methods only help some of the patients and, in mild to moderate depressions, are not notably different from placebo (40% effect). Based on these unstable data, generally applicable guidelines are, however, being developed for the diagnosis and treatment of depression.
Even though the DSM does not organize according to etiology, a great deal is known about the causes of depression. Why shouldn't this knowledge be used in diagnostics? If risk factors are bundled on the basis of coordinating patterns, there is an opportunity for more specialized treatment (see box).

2.1.1. Criticism of the DSM Classification

The category of Depressive Disorders in the DSM includes more than 200 clinical pictures. It is problematic that depressive patients with very different etiology and symptoms should, nonetheless, be given the same diagnosis. Also, it is not clear what the influence is of comorbid disorders, such as anxiety disorders, addiction, and

personality disorders, in the recognition and course of depression. These often occur with depression. In addition to comorbidity, the age at which the first depression manifests itself and the degree of recovery from a previous depression are important factors for the course of the disease. An initial depression at a young age and incomplete recovery are related to a more chronic – and therefore less favorable – course (Wilkinson et al 2009). For these reasons, it is logical that explanatory models

Current Classification of Depression According to the DSM (APA 1994)

There are two core symptoms of depression:
1. 'Depressive mood'
2. 'Clear decrease in interests or pleasure.'
For the diagnosis of an episode, one or both of these core symptoms must be present for most of the day and nearly every day for at least two consecutive weeks.

There are seven additional symptoms:

- *Weight change (loss or gain) or change in appetite (increase or decrease)*
- *Sleeplessness or excessive sleeping*
- *Agitation or inhibition*
- *Fatigue or loss of energy*
- *Feelings of worthlessness or excessive or undeserved feelings of guilt*
- *Indecisiveness or concentration problems*
- *Recurring thoughts of death or suicide or a suicide attempt*

In order to diagnose an episode of depression, at least five of the nine symptoms must be present, including one or both of the core symptoms. Current episodes are differentiated in severity: subclinical depression (2-4 symptoms); mild depression (5-6 symptoms); moderate depression (6-8 symptoms) and major depression (8-9 symptoms). Moreover, in order to assess the total clinical picture, the following are also examined: psychotic characteristics; suicidal tendencies; general social functioning; the role of life events; co-morbidity; clinical course; social support; and (previous) response to treatment.

for the development of depression, and studies on the effects of medicinal and psychotherapeutic interventions should only apply to part of the group of patients with depression.
Another problem is that the DSM does not indicate where normalcy stops and depression begins (Praag van 2008). The pharmaceutical industry uses this 'void' to seduce therapists who have little time but who want to satisfy the growing demand of their sub-depressive patients to nonetheless, prescribe antidepressant medication. (Dehue 2008). Moreover, therapists have difficulty making the diagnosis of depression because, in addition to the multiformity of the phenomenon of depression, when interpreting the patient's complaints the quality of the therapeutic relationship is one of the determining factors. Family doctors regularly seem to miss the diagnosis of depression, but there are similar problems with second line healthcare. Thus it takes, on average, 12 years before the diagnosis of depression is made within the framework of a bipolar disorder (Postma and Schulte 2008).

2.1.2. Treatment Consequences within the DSM Model

Antidepressants only score better than placebo in the treatment of depression with vital symptoms and for psychotic depression. The magnitude of response when treating these types of depression with classical antidepressants was, according to studies dating from the 1960s, 60-70%, while the magnitude of placebo response was then 10% (meanwhile risen to 40%). The existing psychotherapeutic treatments for depression are equally effective as antidepressants. Regardless of the treatment method, depression becomes chronic in 25% of the patients (First et al 1996). The evidence-based treatments for depression, such as pharmacotherapy, cognitive behavioral therapy (CBT), and interpersonal psychotherapy (IPT) achieve less positive results in patients with more chronic forms of depression, yet a combination of pharmacotherapy and psychotherapy does lead to better outcomes than one of the treatments by itself (43-48% remission as opposed to 25-32%) (Wiersma et al 2009). It can be concluded from a recent meta-analysis by Kirsch et al (2008) that newer antidepressants are no more effective than placebo. This elicited the remark from Parker (2009) that a stop should be put to research on the effectiveness of antidepressants based on the idea that they could be effective for all types of depression. He also points

to the problem of the biased patient selection within randomized clinical trial (RCT) procedures. The patients who are selected differ greatly from the patients in daily clinical practice. Thus, patients with comorbid psychiatric disorders, such as anxiety or addiction, are barred from participation in the study so that there is too rose-colored an image of the effectiveness of the treatment. Subsequently, however, the treatment guidelines for populations including comorbid disorders are based on such studies.

2.2. Depressive Complaints at Symptom Level: the Approach of Functional Psychiatry

As has already been stated, in the absence of clear biological markers, psychiatry uses phenomenological strategies for profiling clinical pictures (section 2.1.). Functional psychiatry tries to differentiate itself from this by making a connection – at the symptom level – between functional disorders and neurophysiological and/or anatomically explained models (see also 1.3.). Functional disorders have various causes, such as heredity, spontaneous mutations, adverse life events, changes in anatomical structure, or the imbalance of neurophysiological processes. All of the above etiologic factors influence behavior and sensory experience. Conversely, experiences and behavior also influence the neurobiological process.

In functional psychiatry, depressive symptoms such as brooding and loss of energy and pleasure are linked to function disorders of neuronal circuits in the brain. Sleep disorders are related to disorders in circadian rhythms. Stress-related complaints are connected to physiological changes in cortisol management and are expressed in changes in the Hypothalamus-Pituitary-Adrenal Axis (HPA-axis). Based on these assumed etiologic relations, a rational choice is made for the treatment of the respective function disorder (Loonen et al 2008).

Table 2.1. Examples of the relation between functional disorders and symptoms of depression with therapeutic links (according to Loonen et al 2008)

Biologic functional disorder	Symptom	Treatment
Prefrontal cortex	Anhedonia	Monoamines
Amygdala-hippocampal complex	Brooding	Monoamines, specifically norepinephrine
Circadian rhythms	Sleeping disorders	Melatonin
Hypothalamus-Pituitary-Adrenal-Axis	Stress	Interpersonal psychotherapy

2.2.1. Elaboration of Depressive Symptoms Based on Functional Psychiatry: Biological Risk Factors

Below are five different hypotheses on the biological etiology of depression developed over the past decades, and used in functional psychiatry.

1. The first hypothesis on the etiology of depression originated in the 1960s (Schildkraut 1965) and is called the *Monoamine Hypothesis*. It states that there is a presumed shortage of monoamines in the brain – specifically, norepinephrine and serotonin – that causes a depressed mood.
2. The second hypothesis for the development of depression is based on sleep disorders due to *disorders of biorhythms.*
3. *The third hypothesis is derived from patients with thyroid problems or with Cushing's syndrome, who develop depression more often than expected.* Disorders in the equilibrium between the hypothalamus, the pituitary, and the adrenal cortex or thyroid gland are central here.
4. Because of the close relationship between the HPA-axis and the hypothalamus-pituitary-thyroid axis (HPT-axis) with the immune system, the fourth hypothesis states that depressive disorders are based on *chronic inflammation*. Chronic inflammation

involves illness behavior that closely resembles depressive behavior.

5. The fifth hypothesis is based on the *kindling* mechanism. This hypothesis presumes that kindling is a process such as with epileptic patients whereby, due to chronic subliminal stimuli, there is a steady increase in neuronal activity that ultimately leads to an epileptic seizure in those who are predisposed to them. After the initial depressive episode, often following a traumatic event, the subsequent episodes occur more easily and in reaction to less traumatic events (Loonen et al 2008). Kindling is accompanied by an *altered genetic expression* of Brain Derived Neurotrophic Factor (BDNF), which implies that damage to brain neurons can occur more easily.

Table 2.2. Five models of functional disorders for depressive symptoms and treatment options (according to Loonen et al 2008)

Organic level	Functional disorder	Symptom/sign	Treatment
Internal metabolic	Monoamine metabolism	Norepinephrine and serotonin deficiency	Administering monoamines
Reaction to stress	Deviating biorhythm, deviating sleep architecture	Sleeping disorders	Melatonin Light treatment
	Deviating Hypothalamus-Pituitary-Adrenal-Axis	Changed stress management	Stress reduction, Interpersonal psychotherapy
	Chronic inflammatory state of the immune system	'Sickness behavior'	If possible, treat inflammation Stress reduction
BDNF gene-expression	Kindling	Lowered depression threshold	None

The presumed functional disorders in table 2.2. appear to occur at various biological organizational levels.

1. Monoamine-dysregulation is chiefly based on internal metabolic processes.
2. Disorders of the HPA-axis, the immune system, and deviating sleep architecture are primarily connected to excretion of cortisol or the production of interleukins as a reaction to stress coming from outside the organism.
3. Kindling presumes a gene-environment interaction via transcriptional regulatory networks.

These three different biological levels may be mutually interactive. Thinking in biological systems is, however, not part of functional psychiatry. The relation to the syndromal DSM-IV-TR division is missing in functional psychiatry because it focuses on one symptom at the time.

2.3. Clustering of Psychological Risk Factors and Depressive Symptoms According to McHugh

McHugh (2006) sees four causal clusters as the basis for the development of depression in patients. These clusters link up for further systematic research based on the evolutionary theory, psychology, neurosciences, and genetics.

1. In the first cluster, McHugh describes patients with *life problems* induced by negative experiences leading to depression. These patients lose feelings of hope, solidarity, and inner ambition. Taxing experiences such as mourning, situational anxiety, homesickness, jealousy, or post-traumatic stress thwart any positive assumptions and expectations they have of life. The pathogenic factor is determined by the way the person reacts to traumatic events (*'encountering'*). This type of depression was previously called reactive depression.
2. The second cluster of patients 'chooses' a type of behavior that becomes a relatively fixed but dangerous *lifestyle*. These could be patients with limited capacities, whether or not in combination with addiction. As a consequence of the chosen (stressful) lifestyle they can become depressed. They have become patients because of what they are *'doing'* and how they have become entrapped in their own actions (previously also part of the reactive depression).

3. The third cluster consists of people who are *sensitive to mental stress and agitation* through congenital characteristics. These are defects in one of the congenital psychological dimensions (temperament), such as intelligence, the degree of extrovertedness, and emotional stability. Because of the nature of their temperament, these patients react with more severe anxiety and dejection to taxing events that are a normal part of life. They do not necessarily have neuropathological defects, but because of the way their brain patterns have developed, they see themselves *'to be like this'* (previously called neurotic depression).
4. The fourth cluster includes patients who *'have brain disease,'* disturbing basic psychological functions such as cognition and perception. McHugh includes patients with bipolar disorder, psychotic depression, and depression with vital characteristics (previously called 'endogenous depression'). This group of patients has structural or functional pathology in the brain.

This approach implies that symptoms can be explained on the basis of one or more causes, which can work in favor of the treatment strategy. Moreover, it fits closely with pathogenetic thinking, as is customary among medical colleagues. McHugh bundles these four groups of patients into four summarizing terms in which the clustering of risk factors of depression resounds: 'encountering,' 'doing,' 'being,' and 'having.'
The meaning of these terms can be explained as a dual concept. Having and being indicate a more passive situation: brain disease 'happens' to you, you discover that you have reaction mechanisms that are congenitally determined or a particular temperament. Conversely, when processing negative events, changing your own focus seems reachable.

Table 2.3. Possible causes of depression as a syndrome (according to McHugh 2006)

	Negative Events	Lifestyle	Temperament	Brain Disease
Meeting	+			
Doing		+		
Being			+	
Having				+

If we compare this with the hypotheses of functional psychiatry, McHugh's first cluster of risk factors has no correlate in the classification of functional psychiatry (table 2.2.). The second cluster correlates to van Loonen's stress-related group that has, for example, sleep disorders (deviating biorhythms, deviating sleep architecture), changes in stress management (deviating HPA-axis), and illness behavior (along with a chronic inflammatory state of the immune system). The third cluster of risk factors correlates with a deficiency of norepinephrine and/or serotonin (deviating monoamine metabolism in the brain). McHugh's fourth cluster of risk factors for depression correlates with Loonen's lowered depression threshold and changed transcriptional networks (kindling).

Table 2.4. Relation between biologic risk factors according to Loonen and the clusters of psychological risk factors (according to McHugh 2009)

Biologically disrupting factors (Loonen)	Psychological clusters of risk factors (McHugh)	Characterization by McHugh	Previous designation of depression type
	Life problems, negative events	'Meeting'	Reactive depression
Disrupted HPA-axis, melatonin, deregulated immune system, autonomous nervous system	Damaging lifestyle as cause or consequence	'Doing'	Reactive depression
Disrupted monoamine metabolism, internal metabolic problem	Sensitive to mental stress, anxious temperament	'Being'	Neurotic depression
Disrupted transcriptional networks, genetic predisposition	Brain disease	'Having'	Endogenous depression

2.3.1. Treatment of Depression According to McHugh

Depression is a psychological symptom; just as fever or coughing are physical symptoms. A depressive mood can follow a traumatic event or can be a habitual emotional response of someone with an anxious temperament. Depression can be an accompanying symptom of an addictive intoxication or can be a prominent characteristic of bipolar disorder. McHugh's position is that the key to treatment cannot be found in the symptom – depressive mood – alone, but chiefly in the underlying causes.

1. The cluster 'depressed patients with negative events' benefits from psychological treatment that is focused on dealing with experiences of loss and trauma. Trauma is the most important factor in the development of chronic depression (Adriaenssens 2000).

2. In the 'harmful lifestyle' cluster, one should strive to increase awareness of the choices made in order to create the motivation to instigate change. It is possible, for example, to lift to consciousness – using interpersonally focused psychotherapy – the social consequences of these choices.

3. Cognitive behavioral therapy (CBT) is the first choice for tackling awareness issues and changing habitualized reactions.

4. Patients with temperament problems and 'brain disease' such as depression with psychotic or vital symptoms benefit most from biological interventions such as antidepressants and electroconvulsive therapy (ECT).

Of course, in an individual patient a combination of several factors can occur, such that the chance of developing a depressive episode as well as the chance of it becoming chronic is increased, and the treatment therefore more complex.

2.4. The Classification According to Parker

Parker's classification (2009b) connects with both the phenomenological classification of the DSM, and the etiological classification by McHugh. Based on research, Parker argues that depression with vital characteristics/melancholia and the psychotic depression based on neurobiological data can be differentiated from other forms of depression. In the depression with vital characteristics, genetic and biological causes play a greater role than psychosocial stress factors; there is more often a disturbed HPA-axis; there is a positive reaction to biological treatment (antidepressants, ECT), and a lower placebo rate. Parker argues that, based on this data, this form of depression can be differentiated from other forms. Founded on research, he has instigated the use of a measuring instrument, the "CORE-measure." A high "CORE score" (psychomotor retardation and cognitive problems) indicates a larger number of vital characteristics in the depression:

1. Fewer life events;
2. A compromised reaction-time;
3. Non-suppression on the Dexamethasone (DEX)-suppression test (non-suppression to the administration of a load with dexamethasone is a measurement for a hyperactive HPA-axis);
4. Deviations in the prefrontal cortex and basal ganglia in brain imaging;
5. A deviating dopamine metabolism.

The depression with vital characteristics can then be differentiated on the basis of structural and functional defects of the neural network of the prefrontal cortex to the basal ganglia, expressing itself in depressive moods, cognitive limitations and psychomotor disturbances.

Parker (2009b) concludes his explanation with a structural model in which he combines a dimensional vision (gradual increase of depression) with a categorical classification characterized by an increase of vital and psychotic symptoms. Functionally, he sees the most metabolic deviations in psychotic depression: both dopaminergic and norepinephrinergic (NE-ergic) as well as serotonergic. For melancholia, he postulates that there are NE-ergic and serotonergic defects; and only serotonergic shortages for the remaining depressions.

The significance of this classification lies in the various forms of drug therapy. In psychotic depression, it is preferable to prescribe the combination of an antipsychotic drug along with a NE-ergic antidepressant; for melancholia, a NE-ergic antidepressant; and, for the remaining depressions, a serotonergic antidepressant.

Table 2.5. Classification of depression and therapy (according to Parker 2009). The classification of these disorders fits into the third level of McHugh

	Depression	Motor skills	Psychosis	Therapy
Depressive disorder	+	-	-	Serotonergic
Depressive disorder with vital characteristics	++	+	-	Norepinephrinergic
Psychotic depression	+++	++	+	Serotonergic, Norepinephrinergic, and Dopaminergic

What is interesting in Parker's model is the connection he makes between the severity of the depressive disorder and the various neurobiological factors. His perspective therefore contributes to the working model we are developing. Together with McHugh's clustering of causes, a successful **'systems model'** is created that looks not only at the relation of the separate phenomena to each other but at the relation of systems to each other, as is done in Goethean phenomenology and systems biology.

2.5. The Contribution of the Wound Healing Process to Recovery

The combined categorization into four groups by McHugh, Loonen, and Parker in tables 2.4. and 2.5. corresponds for the most part, interestingly enough, to the phenomenological classification into four recovery phases of healing processes for illnesses in general. The integrating, interactive, metabolic, and maturation phases (Bie et al 2008), are derived from wound healing processes. These four recovery mechanisms are presented below. An elaboration of the connection to the clustering of risk factors by McHugh and others follows in section 2.6., the working model in table 2.7.

1. *The integrative phase.* The first step in wound healing is thrombus formation to effect *hemostasis*, which serves to recover the integrity of the organism (integrative phase), thus aiding its own survival. Disturbances of this acute phase manifest themselves in bleeding or clotting disorders (Chapter 2, van der Bie et al 2008). This recovery mechanism at the biological level describes processes that remind us of McHugh's first group of risk factor clusters at the psychological level. The disturbance there is the inability to integrate acute negative events.
2. *The interaction phase* is the recovery phase in which the wound area starts communicating with the rest of the organism through the immune system and the nervous system. As a consequence of this, *inflammation* occurs and necrotic tissue is cleared away. Disturbances in this phase of healing cause acute infection or chronic inflammation: the interaction with the environment becomes deadlocked (Chapter 3, Bie et al 2008). The disorders of this biological phase correspond to McHugh's second cluster of psychological risk factors, summarized as (damaging) lifestyle choices: patients who have a limited capacity to deal with what happens to them in life derail in reaction to stressful moments.
3. In *the metabolic phase* of the wound healing process, during which new tissue develops and which is vegetative in nature, disturbances are expressed in a shortage or excess of metabolic processes in tissue *proliferation* (Chapter 4, Bie et al 2008). The level of the disorders in this phase corresponds to McHugh's third temperament cluster. Here, disturbances occur because deregulation of metabolic processes in the brain hampers an effective reaction, which is expressed as sensitivity to mental stress.
4. *The maturation phase* is characterized by recovery of the original physical form of

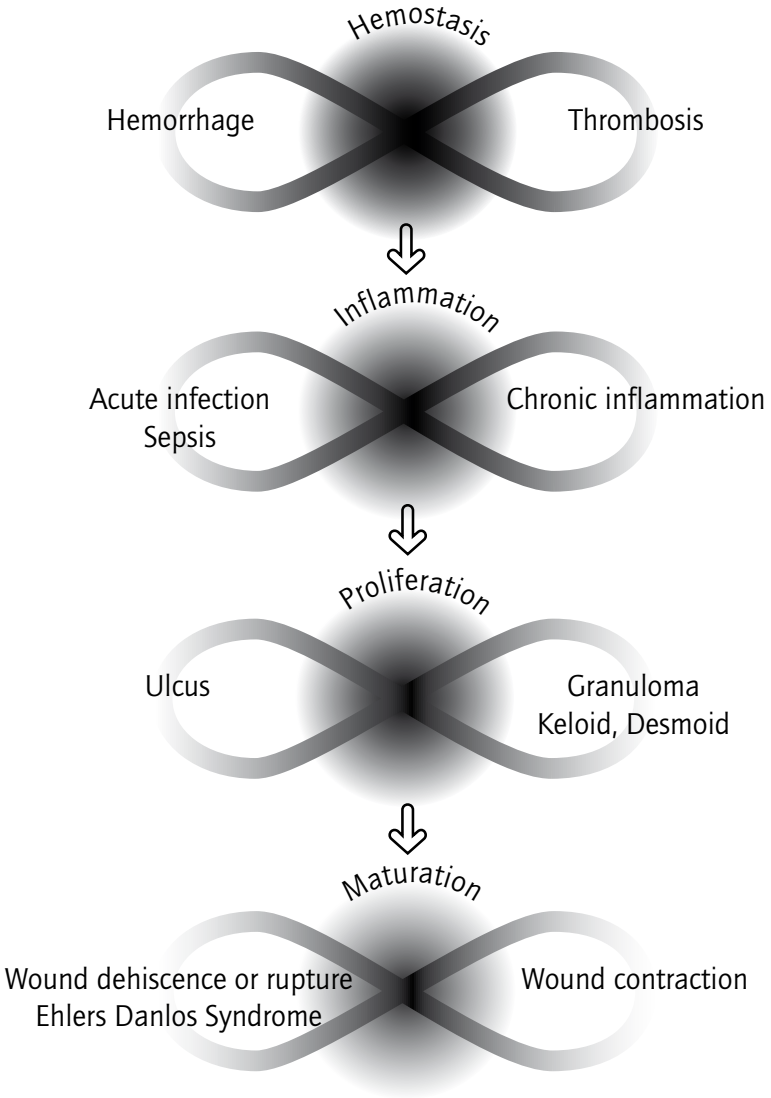

Fig. 2.1. Healthy and disturbed balance in healing proces (Source: Bie van der et al 2008)

the organism or scarring (Chapter 5., Bie et al 2008). Disturbance of this phase of healing is expressed as continuous scar formation or no recovery of the mechanical plasticity of the tissue. This phase reminds us of McHugh's cluster 'brain disease,' in which genetic risk factors hamper recovery at the physical level.

Table 2.6. Four phases of the wound healing process and the clustering according to McHugh (2006), including corresponding recovery mechanisms (according to Bie van der et al 2008)

Phase of wound healing process	Causal clusters for depression/ Biologic factors	Recovery mechanism
Integration	Negative events	Recovery of the integrity of the organism
Interaction	Damaging lifestyle/ Changes in the HPA-axis, immune system, autonomous nervous system, and melatonin rhythm	Recovery of the interaction of the wound area with the rest of the organism
Metabolic	Anxious temperament/ Changes in monoamine metabolism	Restoration of lost tissue in the wound area
Maturation	Brain disease/ Kindling phenomenon	Recovery of the original form of the organism

These four phases of the wound healing process: the integrative, interactive, metabolic, and physical phase, are all coordinated through the self-regulating activity of the organism in which various biological systems levels (2.4.) appear to play a role. Pathology develops if this self-regulation or resilience, the 'Self-regulating ability' in the form of the *'Organ of Repair'* (Chapter 7, Bie et al 2008) fails in one of the four phases. The pathology in question can, in principle derail in two directions: in a dissolving/accelerated or a hardening/decelerated manner. From a systemic perspective, the regulation of the 'Organ of Repair,' or the recovery process, ensures that wound healing proceeds through the various phases correctly.

The recovery of health depends upon whether or not damaging influences can be neutralized by specific brain activity – both psychological and physical – in each phase. Based on this normal recovery mechanism, pathology can be described as deviations in one or more of the essential recovery phases after trauma.

It is probable that the recovery process after psychological trauma is analogous to the recovery of the body after physical trauma.

Symptoms of depression are then a deviation of this process, also manifesting in either a dissolving/accelerated or a hardening/decelerated manner on four different levels of the recovery mechanism. The wound healing process and its possible disorders seem to be a good model for understanding the origin and treatment of depression.

2.6. A Synthesis of Clusters of Risk Factors and Recovery from Depression; A Provisional Working Model

There is a remarkable similarity of the four levels of depressive pathology from McHugh's patient groups clustered according to the nature of psychological risk factors and from Loonen's biologically deviating factors in depression to the four levels of recovery that are directed by the 'Organ of Repair' in recovery processes after physical trauma.

Level I. At the first systems level of wound healing, called the integrative phase, the forming of a thrombus is the acute reaction of an organism to close an open wound and to integrate the wound area into the whole organism.

The burdening factor in acute psychological events ('encountering') is the acute stress that develops in attempting to integrate the traumatic occurrence. Acute stress expresses itself emotionally as the perception of threat, and biologically in the increase of the serum level of the stress hormones epinephrine and cortisol (see table 2.7.). For physical recovery, the resting level of these hormones must be restored. Emotionally, interpretation of the event and, if necessary, a focused action, can offer the support needed to make recovery from the trauma possible. The primary reaction to trauma is, in this phase, at a psychological level.

Flexibility, openness, and trust in one's own abilities are mental health-promoting elements for dealing with negative events (Antonovsky 1979). He sums this up with the term,

Table 2.7. The working model: an integration of levels of causes and the ability to recover from depression

Level	Biologically disrupting factors (Loonen)	Clusters of psychological risk factors (McHugh)	Characterization by McHugh	Previous designation of depression *and Parker's designation*	Recovery process in wound healing (Bie van der et al.)
I Psychological	Acute stress hormones	Life problems, acute negative events	'Meeting'	Reactive	Recovery of integration heterostasis
II Psychological/ Physical	Disrupted HPA-axis, melatonin, deregulated immune system, autonomous nervous system	Damaging lifestyle as cause or consequence	'Doing'	Reactive *Serotonergic (5-HT)*	Recovery of interaction allostasis
III Physical/ Psychological	Disrupted monoamine metabolism, internal metabolic problems	Deviating metabolic brain patterns, temperament problem	'Being'	Neurotic *Melancholia (NE)* *Psychotic (DA)*	Recovery of metabolic balance homeostasis
IV Physical	Disrupted transcriptional regulative networks, genetic predisposition, kindling	Brain disease, structural or functional pathology of the brain	'Having'	Endogenous	Recovery of physical form epigenetic balance

'Sense of Coherence.' In the literature, this integrative ability is also called resilience (see section 3.3.1.). In summary, integrative recovery mechanisms such as *heterostasis* are used to monitor and repair the equilibrium between sociocultural processes and experiences, on the one hand, and behavioral reactions on the other.

Level II. In the second wound healing phase, the second systems level described as the interactional phase, the entire organism is involved in the local wound healing (in reaction to the stress from the wound area). As an expression of this, leukocytes and macrophages appear via the blood at the site of the wound and a catabolic process occurs.
The disorders of the second phase of the recovery process are paralleled as symptoms of depression in dysfunctional behavior of the person involved ('doing', lifestyle choice) in response to external and internal processes. Here, three important 'messenger systems' are active at the biological level, described largely by Loonen: the HPA-axis, melatonin, and the immune system. The interactive phase of recovery forms the mediation between the consequences of chronic psychological stress and the adaptation of the organism to this at a physiological level. In this phase, the mediation between behavior and lifestyle and automatic reactions of anxiety and tension related to the lifestyle are central. This second group of McHugh's patients is characterized as being imprisoned in their own choices. Damaging lifestyle choices and problems in stress management contribute, in this phase, to a more continuous reactivity as the cause of depression, which maintains an *allostatic equilibrium* (see section 3.3.2.), a new equilibrium at an unhealthy level. Disturbance of this recovery process is characteristic of the reactive depression.

Level III. In the third recovery phase of the wound healing process, the metabolic phase, the anabolic metabolism is particularly increased. New tissue grows after the necrotic tissue is cleared away. There is an increase in fibroblast activity. This new growth is stimulated by growth factors. The healing phase that involved the entire organism has been completed. This third phase is localized once again in the wound area itself.
At the third level of risk factors in relation to symptoms of depression, the emphasis – as far as we now know – is on increased metabolic processes in the brain that determine brain patterns (Loonen 2008). In these metabolic processes neurotransmitters play a major role, as well as neurochemical processes and the degree of activity of the cortex and subcortical

areas. This group of patients correlates to McHugh's cluster of metabolic risk factors: they have a dominant temperament position: this is the way they find themselves 'to be.' The overreaction – anxiety or irritability – to daily occurrences in this phase gives the depression a neurotic coloring: *homeostasis* (see section 3.3.3.) is disturbed. Parker's categorical classification of the three types of metabolic monoamine defects has its basis in this cluster.

Level IV. At the fourth stage of wound healing, the maturation phase, the tissue in the wound area is restructured. The activity of blood vessels and fibroblasts decreases; collagen is introduced according to the pattern of mechanical stress lines at the wound location.
In the fourth cluster of depression risk factors, we see the consequences of the failure of *transcriptional regulative networks* as in BDNF (Stel van der 2009). These are an expression of gene-environment interaction (see section 3.3.4.). The field of tension between molecular genetics and environmental influences on the activating and deactivating of genes (*epigenetics*) is central here. The quality of the parenting and of the environment may also contribute to whether or not an adverse hereditary tendency will be expressed. The patients with depression in this fourth group are those who, according to McHugh, are afflicted with brain disease. *Kindling* plays a significant pathogenetic role here (see table 2.7.).

Depression can develop in patients characterized by McHugh's clustering of psychological risk factors or by Loonen's biological factors if recovery processes are disrupted in any of the four levels corresponding to wound healing phases: heterostasis, allostasis, homeostasis, or genetic/epigenetic balance.

There is a transition in the four levels from conscious control to control based on genetic networks. The more physical the level of the phase in question, the less conscious the process, and the less chance that change based on conscious control is successful. At the fourth level, coercive treatments such as antidepressant drugs or electroconvulsive therapy (ECT) are often the most effective.

Symptoms can develop starting from a conscious level (I and II) towards the unconscious/ biological levels (III and IV) or the other way around.
A *psychosomatic* development of symptoms of depression can, for example, stem from avoidant behavior (I) and lead, subsequently, to damaged self-esteem, which in turn can cause feelings of inferiority (II) with, ultimately, alterations at the metabolic level that lead to the development of a depressive clinical picture at level III. Giving up negative lifestyle habits, such as smoking or alcohol abuse, and changing the style of dealing with problems (II) can help prevent symptoms of depression from becoming chronic. It is intriguing that a successful cognitive treatment (level I) – including 'mindfulness-based cognitive therapy' (MBCT) – can normalize the blood circulation of the prefrontal cerebral cortex (IV) so that ruminating on negative thoughts stops, which contributes to the recuperation from depression.
The converse process, the *somatopsychological* development of depression, is also well known. Physical illness or a genetic predisposition (IV) can lead to depression, such that it is difficult to discover what is an immediate consequence of the illness itself and what can be attributed to the depression that occurs along with it. At the level of disturbance of metabolic processes, antidepressants are used to restore the supposed shortage of serotonin or norepinephrine and thus to bring the metabolism of the brain back into equilibrium (Parker 2009).

Based on this provisional working model, in which a disturbance on four levels of recovery can be placed alongside four clusters of risk factors for depression at the biological and psychological levels, we will examine what the currently known views and insights are in the coming chapters. Following that, therapeutic insights as a consequence of this model will be discussed, using the self-healing ability of the patient as optimally as possible (see table 2.8.).

Table 2.8. Working model of systems levels in relation to therapeutic options

	Causal cluster/ risk factors for depression	Functional reaction	Recovery processes	Treatment, recovery
I	Negative events	Acute stress hormones, epinefphine	Integration	Trauma-oriented psychotherapy, EMDR, CGT, focused on *heterostasis*
II	Damaging lifestyle	Reactions in sleep architecture, HPA-axis, and immune system	Interaction	Melatonin, light therapy, stress reduction (IPT, CGT, MBCT) focused on *allostasis*
III	Anxious temperament	Disorder of monoamine metabolism	Recovery of metabolic patterns	Antidepressants, CGT, focused on recovery of *homeostasis*
IV	Brain disease	Structural and metabolic changes in the brain	Maturation in wound healing, improvement of structural and functional brain pathology	Antidepressants, ECT, favorable socio-cultural conditions i.c. *epigenetic factors*

2.7. Discussion

The manner in which risk factors affect someone is always a result of the equilibrium between stress and congenital or acquired characteristics. Various risk factors influence the basis from which one reacts to a negative event.

Integration of negative events begins immediately after 'encountering' them and is a process that takes time. Those who have difficulty integrating negative events constantly experience problems that can result in depression. These problems pile up due to insufficiently successful integration. It leads to the loss of the feeling of connectedness with others and of the desire to strive for a positive life. Acute stress demands an answer at the psychological level, for which active adjustment and learning processes are central (reestablishing heterostasis). Reassurance may lead to a normalization of the elevated secretion of epinephrine and cortisol (*level I*).

If the stress continues, the consequences can become more extensive biologically. Disruption in the HPA-axis, the immune system, and the rhythm of melatonin excretion may occur *(level II)*. A changed equilibrium develops (allostasis) with, in time, an allostatic load that is often enhanced by negative lifestyle choices adopted by the patient in an attempt to decrease the consequences of the load (alcohol, smoking, eating too much with an excess of fatty foods).

The following phase in the development of depression due to insufficient integration of stress sees a disturbance of the homeostasis of metabolic processes in the brain. As a consequence of this, chronic stress alters the activity of the cortex and subcortical areas. If there is a question of congenital variations in the metabolism, disturbances of the homeostatic mechanism can occur more easily (anxious temperament). This is an example of *level III.*

Finally, genetic factors and transcriptional regulative networks also determine the ability to react to stress. There are a number of genetic predispositions that cause a depressive reaction to occur more readily. However, the stress of repeated depressive episodes contributes to the increasingly smaller role of external factors in the occurrence of the following depression. The depression then takes on the characteristics of what McHugh calls a brain disease *(level IV)*, and kindling starts to play a role (Loonen 2008).

On all four levels, epigenetic factors play a role in the expression of the genetic predisposition or in the prevention of kindling phenomena.

3. Integrative Processes

This chapter depicts the integrative processes active at the four different described systems levels. It is noteworthy that starting from the level of the physical body, the degree of self-awareness increases.

3.1. Systems Levels

Integrative balancing processes are essential in processing negative events. Neuroscience focuses on the brain when explaining integrative abilities. Where in the brain does integration occur?

Systems level I One used to think that specific areas in the brain were responsible for sensory, motor, and intellectual coordination. Now we know that it is the neural networks that are activated at different places and simultaneously in different brain systems as a thought, an emotion, or an action occurs. Integration is not bound to one area of the brain.

Systems level II Outside the brain, other systems play a role in integrating the processes following psychosocial stress. Messenger systems such as the autonomous nervous system, the HPA-axis, and the immune system (the psycho-neuro-immune system) constantly mediate between impressions from the inner and the outer world to achieve adaptation to change.

Systems level III Metabolic processes also regulate integrative mechanisms. The degree of health has great influence on integrative capacities. A high fever can easily limit the ability to think about things. The condition of the body plays an important role in regulating the brain. Damasio (1995) states that every morning the perception of the condition of our organs, muscles, and tendons is translated into the feeling of vitality. Servan-Schreiber describes the heart as an important integrating organ. The heart's nervous system adjusts itself on the basis of perceptions, and then changes it own 'memories.' The heart produces,

among other things, epinephrine (in reaction to stress), oxytocin ('the love hormone') and natriuretic peptide to regulate blood pressure. These hormones work, as does the autonomous nervous system, directly on the brain and form, together with the heart, an emotional brain (Servan-Schreiber 2005) (see also section 4.6.).

Systems level IV This level of integration occurs between the outer world and the genome. By 'outer world' we mean the environment of the body, thus also including the uterus for the fetus.

The entire body is involved in integrative processes. For a successful adaptation to life, the four levels of integration are active simultaneously. Integration occurs at both conscious and unconscious levels, and disturbances of integrative functions can lead to depression.
It is good to realize that there is also a time dimension to integration. In the previously-mentioned wound healing process, a coordinated sequence in time determines the events starting with clot formation and ending with the formation of scar tissue. In this chapter, integrative processes behind the four systems levels are discussed, with a focus on the importance of developmental processes in time.

Table 3.1. Integrative processes on four systems levels

Integrative systems level	Brain/Consciousness
	Messenger systems/behavior
	Temperament/heart/metabolic processes
	Genotype/Transcriptional regulative networks

3.2. Self-Regulation per Systems Level: Resilience

The quality of self-regulation determines the possible adaptation to changed circumstances. There are different forms of self-regulation, set in motion by external circumstances.

1. Flexible solutions to the demands that life sets are instrumental in attempting to reach

a state of resilience (*heterostasis*);
2. Adaptation can lead to *allostasis*: a new metabolic equilibrium or different behavior;
3. Buffer capacity is necessary for maintaining *homeostasis* in the metabolism. Adaptation is here within narrow boundaries such as, for example, in body temperature regulation;
4. *Epigenetic adaptation* acts via the transcriptional regulative networks of the genome.

In the model sketched in table 3.1., health occurs when the various systems − based on diverse mechanisms of self-regulation − are brought into equilibrium. Thus, a tense situation can lead to a reaction by the messenger systems. At that moment, stress hormones (glucocorticoids and catecholamines) play an important role in activating the body to manifest appropriate behavior. After the passing of the immediate situation, during which resilience plays an important role in the successful acute adjustment, rest returns and the stress hormone levels are normalized. Similarly, a feeling of malaise upon waking that originates from the lack of physical well being can be overcome by making the decision to take a half-hour walk. These self-regulating mechanisms function in part subconsciously and in part may be influenced by the individual's own will.

When adaptation falls short, it can be important to seek out the level on which this occurred. If 'ruminating' is a prominent symptom of the depression, this can be the consequence of discouragement and lowered self-esteem caused, for example, by a performing artist's recurring stage fright. The recurring acute stress of performing can ultimately lead to an overburdening of the messenger systems and, subsequently, to brooding and loss of pleasure within the framework of depression. The obvious solution is to reduce this overburdening through a form of psychotherapy or mindfulness. If the overburdening of the messenger systems can be successfully reduced, then the person in question can be expected to recover from the depression.

Just as resilience can be approached at the systems level, it can also be approached as a time process: Becoming 'stuck,' or conversely 'over-accelerating,' leads to functional disorders. With affective disorders, a differentiation can be made between 'hardening' (chronic depression) and 'dissolving' (maniform) mood components. Table 3.2. shows that each systems level has its own regulation (see also figure 2.1.).

Table 3.2. Examples of adaptation through integrative processes per systems level

	Systems level	Integration mechanism
Integration	Brain/Consciousness	Sense of coherence / heterostasis
	Messenger systems/behavior	Allostasis
	Temperament/heart/metabolic processes	Homeostasis
	Transcriptional regulative networks	Epigenetic factors

3.3. Resilience at the Four Levels

3.3.1. Sense of Coherence: the Integrative Level During Crisis and Heterostasis

The Sense of Coherence is mentioned here as an example of the highest level of integration. It is also the highest level of consciousness. Antonovsky, the medical sociologist, was the instigator of research into *salutogenesis* (the study of how people remain healthy) in contrast to the more common *pathogenesis* (how people become sick). One of the studies within the framework of his research on the effect of stress was concerned with the psychological and physical health of a group of post-menopausal women born between 1914 and 1923 (Antonovsky 1979). Half the group appeared to be in good health. Part of this group had, as young adults, experienced the horrors of the concentration camps during World War II. To his surprise, nearly a third of the women in this subgroup appeared, in spite of their past, to be in good psychological and physical health. He hypothesized that these women must possess protective factors to make that possible. Antonovsky believed that these protective factors determine how people deal with ever-present stressors.
He argued that people have *general resistance resources*, such as individual strengths, cultural stability, money, and social support. These sources of resilience play a role in whether one avoids stress or actively deals with it. Alongside these more general characteristics, through interviews he uncovered flexible individual characteristics that he

summarized under the term: *Sense of Coherence* (SOC).
Going through consistent experiences in the course of growing up leads to a perception that life is understandable and predictable (*comprehensibility*). A proper balance of being challenged, being allowed to make mistakes, and being able to relax helps in learning to see oneself as competent (*manageability*) and to have faith in oneself. Active involvement in one's own upbringing and not experiencing indifference from the parents/guardians leads to a sense of *meaningfulness*. A strong sense of meaningfulness, the most important part of these three aspects of SOC, leads to the idea that a crisis can be a challenge, which can be met with a cognitive strategy instead of an emotional (anxiety-ridden) reaction.
The SOC develops as the fruit of the upbringing and other circumstances during roughly the first thirty years of life (Antonovsky 1979).

Table 3.3. The components of the sense of coherence, SOC

Comprehensibility	Ability to create overview
Manageability	Trusting one's ability to be able to find a fitting reaction
Meaningfulness	One's own contribution matters

An important question is whether or not the SOC can develop further, after the personality has been formed. Can people profit from successful experiences? According to research on adult heroin addicts, this is possible. During the addiction period, their SOC was extremely low, while after being 'clean' for a few years it had risen to a level that is average for adults (Franke 1997).
Antonovsky wonders what the mechanism is behind this flexible adjustment. The systems biologist von Bertalanffy (1968) differentiates between homeostasis and heterostasis. Homeostasis maintains a set value within narrow boundaries (such as body temperature during changing outside temperatures). Heterostasis implies that radical physiological and psychological adjustments can be made to changing external circumstances. This can cause the development of completely new behavior. For people who must continually adjust to changing circumstances, this is a precondition for successful coping.
Pathogenetic thinking assumes that crisis is an exceptional and undesirable situation.

Antonovsky feels that that is a misconception of reality. Crisis is everywhere; it is part of life. If you believe that crisis – and the tension stemming from it – should not be there, as in pathogenetic thinking, you will lack the proper attitude for coping with challenges. This leads to a potentially dangerous, passive adjustment to changing circumstances, in which one of the consequences can be that the individual becomes increasingly dependent upon, for example, a medical-technological model. *Salutogenesis* as a movement is, for Antonovsky, an answer to the passive, helpless position of the patient due to the major increase in technological support. Heterostasis is a dynamic adjustment to changing circumstances in which change, differentiation, evolution, negative entropy (the entropy that an organism exports in order to keep its 'disorder/chaos level' low), creativity, self-realization, and emergence (the development of new characteristics within complex systems) each play a role. *Salutogenetic thinking* demands the active participation of patients in their own treatment. 'Narrative-based medicine,' in which the patients learn to transform radical events into their own story, is an example of active participation, which results in an improvement in both physical and psychological health (Pennebaker and Seagal 1999). The patient learns to bring positive and negative emotions into equilibrium, and arrives at new insights when telling or writing his own story. The therapist makes the patient his central focus by concentrating on his subjective experiences. The insight that the patient develops, based on his own story, subsequently leads to a strengthening of the feeling of meaningfulness, which enhances the positive feelings he has about himself.

In contrast to what was expected, the SOC does not decrease with physical illnesses such as cancer or rheumatoid arthritis. It does, however, decline with psychosomatic illnesses, substance dependence (most strongly with heroin dependence), and depression with an anxious temperament, with high correlation values between .60 and .85 (Franke 1997).

We may conclude that the degree of coherence is a better predictor of psychological disorders than of somatic disease. A decreased SOC is a risk factor for symptoms of depression (see also 6.4.2.).

Table 3.4. Various assessments of the meaning of crisis

Pathogenetic thinking	Crisis incidental and undesirable; passive attitude
Salutogenetic thinking	Crisis inherent to life; active development

3.3.2. Allostasis: Stress and the Interactive System

At the end of the 1990s, the endocrinologist McEwen introduced the concept of 'allostasis.' Allostasis is the ability to maintain dynamic stability during processes of change. 'Allostatic load' is the toll that must be paid for the adjustment to long-lasting stress. Important allostatic systems are the autonomous nervous system, the HPA-axis, the cardiovascular system, the metabolic system, and the immune system. Stress plays an important causal role in affective disorders and places a burden on interpersonal relationships. The secretion of stress hormones varies with the diurnal rhythm, coordinated through the light-darkness cycle and the sleeping-waking rhythm. The time of the day that stress hormones are measured is, therefore, significant. In the morning, there is normally a serum cortisol peak, while the lowest point of the cortisol level in the serum falls in the middle of the afternoon (McEwen 1998).

Table 3.5. Overview of systems involved in allostasis

Allostasic systems level	Autonomous nervous system
	HPA-axis
	Cardiovascular system
	Metabolic system
	Immune system

The ways in which we evaluate a situation and experience our own state of health are the two most important factors in reaction to stress. The taxation leads first to a behavioral response, influenced by hereditary factors, animal defense mechanisms, temperament,

personality style, and SOC. The physiological response, such as heart palpitations or an increased serum cortisol level, is also part of the total behavioral response. The *allostatic load* is partially determined by whether or not habituation occurs. A genetic predisposition for high blood pressure, for example, can hinder habituation to recurring everyday stress because of blood pressure symptoms.

The general state of health and the ability to deal with stress directly influence one another. Illness can hinder the ability to effectively adjust to stressful situations, and tension within the family can increase the incidence and severity of insulin-dependent diabetes. Chronic stress, characterized by lack of energy, fatigue, irritability, demoralization, and hostility, appears to contribute to the development of insulin resistance. Such continuing stress leads to an increase in abdominal fat and can contribute to *cardiovascular disease* and *diabetes* (McEwen 2000), which can in turn indirectly increase the chance of depression.

Stress response under normal circumstances has a beginning and an end. Defects on either side can lead to pathology. Increased blood pressure in reaction to recurring acute stress can elicit atherosclerosis and a heart attack. The non-occurrence of habituation when speaking in public can contribute to the development of an anxiety disorder. Persistent stress response subsequently leads to allostatic load.

Such a load can, in women with a previous history of depression, lead to osteoporosis and forgetfulness through the consequences of a chronic moderately increased serum cortisol level. If, however, there is insufficient cortisol secretion in reaction to stress, then the body compensates by producing inflammatory cytokines. It is suspected that this could be one of the mechanisms triggering the development of fibromyalgia and chronic fatigue.

Another well-known example of allostatic load is the stress that chronic depression places on the cardiovascular system. As a consequence of continuing depression, an increase in the reactivity of fibrinogen and blood platelets develops. This increases the risk of a *myocardial infarction*.

In chronic stress caused by early childhood trauma, depression, PTSD, or Cushing's disease, damage can occur in the neurons of the *hippocampus*, where a high concentration of cortisol receptors can be found. Damage of the hippocampus through a hyperactive HPA-axis can lead to apoptosis. This damage expresses itself as degeneration of the verbal and contextual memory. The latter form of memory is important for adequately dealing with emotions.

From these examples, it becomes clear that the consequences of allostatic load ultimately effect functional and anatomic changes, even at the metabolic level.
In conclusion, McEwen (2000) points to the possibility of quantifying the allostatic load in chronic stress.

Table 3.6. Quantitative approach of allostatic load (according to McEwen 2000)

Measurement	System load
Systolic/diastolic blood pressure	Cardiovascular system
Waist-hip ratio	Glucocorticoid activity
Serum HDL/cholesterol	Atherosclerosis
HbA1C	Glucose metabolism
Serum DHEA-S	HPA-axis activity
Nightly cortisol in urine	HPA-axis activity over the past 12 hours
Nightly NE and epinefphine in urine	Activity sympathetic nervous system over the past 12 hours

Life history, compounded from genome, early childhood, living and working environment, family relationships, eating habits, the amount of physical activity, the quality of sleep, and other lifestyle factors, is expressed in the body's metabolism, behavior, and in the resilience that one possesses during one's lifetime. Various parameters of allostatic load, such as blood pressure, arteriosclerosis, and an increase in the cortisol level are coupled with an increased incidence of depression.

3.3.3. Homeostasis: Frailty as an Example of Depletion of the Buffer Capacity of Metabolic Systems

During aging, the propensity to develop various diseases increases, and the functional capacity of the body decreases. Physical and cognitive dysfunctions are strong, independent predictors of mortality. The existence of these dysfunctions, even before there is serious illness or invalidity, is termed '*frailty*.' Frailty indicates that the buffer capacity of various metabolic systems has decreased. The definition of frailty, according to Medline, reads: "Frail elderly persons are individuals who are lacking in general strength and are unusually susceptible to disease or to other infirmity."

The speed of walking speed and problems with equilibrium are used as the indicators for frailty. These two functions appear to work synergistically. Mobility problems are a strong predictor of morbidity, admittance to a hospital or nursing home, falling incidence, and mortality. The ability to walk well is, in the history of mankind, a basic condition for survival. Many metabolic systems work together to accomplish walking (Fried et al 2009). For these reasons, walking defects are a good first indicator of a decreased 'buffer capacity' of the metabolic system (Ferrucci 2009). Along with functional defects in walking and equilibrium, interleukine-6 (IL-6) appears to be a good quantitative measure of frailty. IL-6 is increased during functional decrease of muscle mass. The muscle breakdown is connected to the catabolic effect of IL-6 on muscle metabolism (Ferrucci 2009).

Frailty appears to be related – in a non-linear manner – to *the number of abnormally functioning physiological systems* and not to any specific defect within one system. This outcome follows the rules of systems biology: when a critical level of homeostatic dysregulation within physiological systems is passed, other normally functioning systems also start to dysfunction. For this reason, the systems imbalance will not improve if only one system is treated unless this system is at the origin of a negative cascade. The number of chronic illnesses, independent of the system in which the illnesses originate, is also a predictor of frailty.

3.3.3.1. The Relation between Depression and Frailty

With depression among the elderly, it is striking that although the recovery percentage is, indeed, equal to that of other age groups, the percentage of patients who have recurring bouts of depression is much higher. This is further complicated by the continued existence of cognitive problems outside the depressive episodes. It indicates that there is a relation between frailty and depression. From research by Jonge de et al (2004) something similar emerges: Depressed elderly people appear to have problems adjusting *psychologically* to somatic disease. Permanent cognitive deficiencies are an additional factor affecting the abilities of coping, adaptation, and resilience. They introduce the term 'psychosocial frailty' to describe this situation.
Two other approaches to the concept of frailty, as discussed in an informative overview by Katz (2004), place more emphasis on the somatic side of depression.

1. The first approach is by Brown et al (2000). They see frailty abnormalities as *subclinical vascular defects.* Vascular damage in the anterior part of the brain leads primarily to depression and, in the posterior part, to walking and equilibrium problems. The combination of these two doubles the risk. They warn that falling incidents are interpreted too easily as side effects of an SSRI instead of as a vascular incident.
2. The second approach based on *immunology* comes from the above-mentioned Fried group (2009). Frailty would be the somatic component of depression, in which other signs of depression, such as mood deviations and negative thoughts are missing ('depression without sadness'). Typical characteristics of depression, such as exhaustion, spontaneous weight loss, slowing down, and passivity are seen here as characteristic of frailty. Depression as well as frailty can explain muscle loss in old age.

In summary, Katz bundles these models into two pathways which can lead from frailty to depression. The first path proceeds via vascular disease, leading to ischemia of the brain and subsequently to depression. The second pathway proceeds via the immune system, leading to depression via systemic infection. There is, of course, also interaction possible between vascular disease and infectious processes. Although frailty is not identical to depression, it can be a step on the road towards the development of a depression at

the metabolic level (level III). Depression at this systems level develops through the loss of homeostasis and the loss of connection between various biological systems because the buffer system can no longer absorb the metabolic changes. In view of the fact that motor disorders are seen as an important indicator for frailty, it is interesting that running or, in any case, taking a good, half-hour walk every day is a proven effective treatment (Bosscher 1993).
The maintenance of homeostasis in the body is an integrative function at the metabolic level. This function is diminished in elderly patients, and frailty occurs as the expression of a changed metabolic equilibrium that develops in old age. Neuroticism in childhood increases the chance of chronicity and also of frailty in old age (see also 6.4.2).

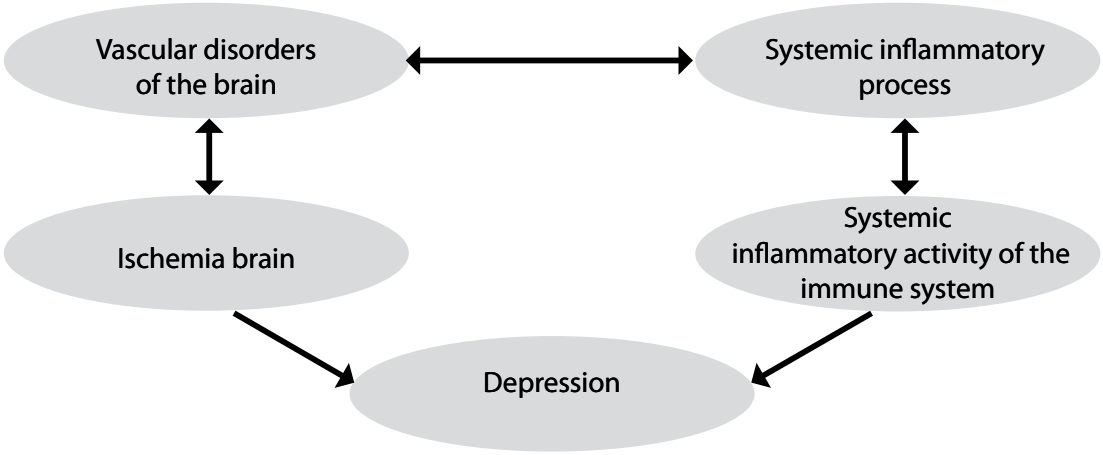

Figure 3.1. Schematic representation of paths to depression according to Katz (2004).

3.3.4. Plasticity: Integration at the level of brain disease

The final form of adaptation to external circumstances is achieved via epigenetic factors. The consequence of this is that the genome can develop into various phenotypes, initiated by outside influences. There is a 10% chance that children of a mother with schizophrenia will also get this disease. Placement with a good quality adoption family, however, reduces

the child's chance to develop schizophrenia to 1%, which is the percentage that applies to the general population (Alanen et al 1963). Thus, favorable developmental circumstances decrease the genetic chance for schizophrenia (phenotype). This is discussed further in 6.6.

Unfortunately, the reverse is also true. Epigenetic changes, for example by switching off genes through methylation or 'chromatic remodeling' by which the DNA is folded differently, does not lead directly to mutation of the genetic material. Nonetheless, it appears that epigenetic changes in animals over many generations have a stable survival. Hormonal changes, caused, for example, by environmental stress, can change the response of genes that are regulated by these hormones later in life. This can, in turn, also influence other hormones. Thus, a greater sensitivity for cortisol increases can develop.

Adaptation through epigenetics is a form of plasticity. *Plasticity* makes adaptation in various developmental steps easier.

When inheriting acquired behavioral characteristics, the two parents can, via the mechanism of 'imprinting,' ensure still other phenotypical variations. An 'imprinted' gene from one of the parents can cause the normal methylation at conception to be partially released so that recessive characteristics from one of the parents can gain the upper hand (Crews and McLachlan 2006). The combination of genes that are or are not activated determine, for example, whether a person has Prader-Willi syndrome or the syndrome of Angelman, both based on a defect in chromosome 15. In the first case, there is a paternal and in the second a maternal gene defect (Bos 2008).

Genetic activity influences to a significant degree the developmental steps from conception to adulthood. There is no immediate causal connection between genetic influences and behavior. Genes have, namely, only a direct effect at the molecular level. Therefore, various steps must be taken to go from genes to behavioral changes. Johnston and Edwards (2002) call this a developmental systems theory. They talk about a complex network of interactions among molecular, cellular, physiological, behavioral, and environmental influences.

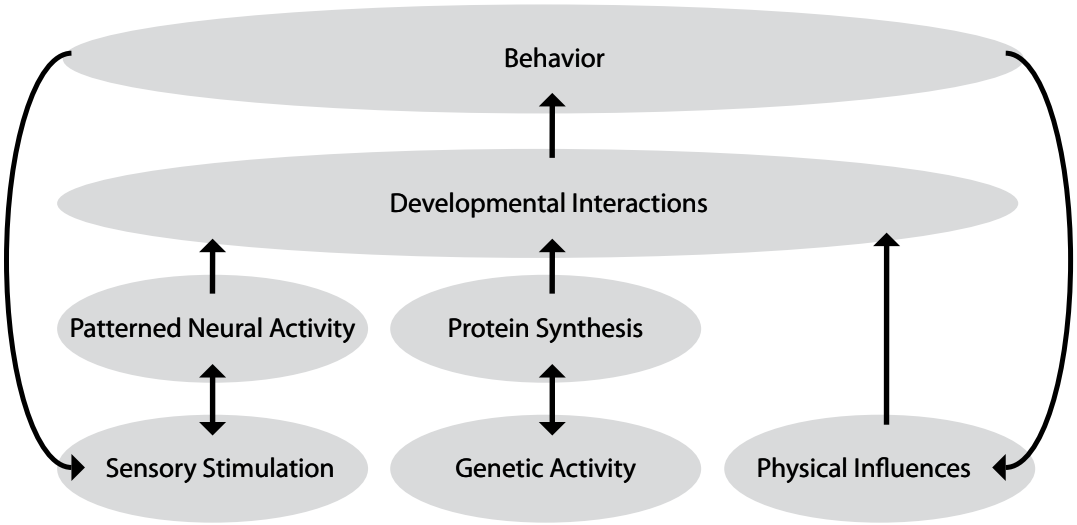

Figure 3.2. The model of behavioral development. The immediate effect of sensory stimulation becomes apparent in the pattern of neuronal activity. Conversely, functions such as attention and orientation influence the way in which the stimuli are processed. The immediate consequence of genetic activity is protein synthesis. The proteins that have been formed can react on the genes. (Taken from Johnston and Edwards 2002).

3.4. Self-regulation in Time

3.4.1. The Developmental Model of Depression

The inability to consciously integrate crises is, of all risk factors, the most important factor in the development of depression. The circumstances during one's lifetime in which loss of self-determination occurs are in no way specific for depression alone but also apply to other psychiatric disorders such as anxiety disorders, which include post-traumatic stress disorder, and physical illnesses.

In the developmental model of depression, various risk factors culminate at different times, which undermine the self-regulating mechanism so that integration is lost.

1. In early childhood, risk factors for depression include a lack of warmth, a feeling of lack of control over one's immediate behavior, experiencing trauma, and the loss of a parent. A recent review of large-scale prospective studies with a duration of at least ten years by Weich et al (2009), confirms this. Abuse during childhood is a predictor for depression and anxiety disorders at a later age, including post-traumatic stress disorder (PTSD). The absence of the mother in early childhood appeared to have value as a predictor for suicide attempts in adolescence. These results were independent of socio-economic factors and mediating factors such as the child's behavioral problems and stressful circumstances within the family.
2. Neuroticism, lack of self-esteem, early anxiety, and behavioral disorders are risk factors for the development of depression in early adolescence.
3. For the development of depression in late adolescence, predictors include a low educational level, youth traumas, lack of social support, and substance abuse.
4. In adulthood, divorce, a previous episode of depression, marital problems, socially aggravating events, and behavioral disorders are predictors for depression.
5. In old age, the most important risk factors for the development of depression are frailty, mourning, sleeping disorders, functional limitations, physical illnesses, cognitive disorders, loss of social contacts, and previous episodes of depression (Lampe et al 2008).

Various risk factors mutually influence each other. Thus a high genetic risk is associated with neuroticism, disorders within the context of the family, sexual abuse, and loss of a parent (Kendler et al 2002 and 2006). Via statistical analysis, these authors arrive at three different pathways that lead to depression:

A. An 'internalizing pathway' in which neuroticism and early anxiety disorders are determining factors;
B. An 'externalizing pathway', in which behavioral disorders and substance abuse are paramount.
C. The 'adversity pathway,' which is the most common pathway. This includes disturbed family situations, childhood sexual abuse, loss of a parent, low educational level, lifetime trauma, loss of social support, divorce from the partner, and life events in the year before the appearance of the major depression.

Of course, combinations of these pathways are also possible.
The authors conclude that depression is a 'final common pathway' made up of divergent developmental pathways. In addition to life circumstances, neurobiology (temperament and childhood anxiety) plays an important role. They point out the importance to the therapist of knowing the *patient's individual life history* so as to include the abundance of determining factors in the ultimate diagnosis.

3.5. Therapeutic Possibilities

In the wound healing model discussed in Chapter 2., a time sequence could be ascertained. Four stages can be differentiated that develop in sequence over time: The phase of thrombus formation, the inflammation phase, the proliferation phase, and the maturation phase. Self-regulating processes coordinate each of these phases. Self-regulation is described as "the coordination and integration of the various phases of the healing process and the ability to be able to regulate the various phases through metamorphoses of conscious processes in metabolic activity and back again" (Bie van der et al 2008). Generally, self-regulation progresses well. We associate this with health and the ability to resist disease. How self-regulation comes about is complex and thus far not sufficiently clear. The term self-regulation is no more than a metaphor that, however, does make it clear that there must be a complex coordinating system.
In passing through the various levels, self-regulation continually adopts different forms. The four phases in the wound healing process each have their own task within the whole. When one phase has been gone through successfully, the following can begin. Thus, for example, the first phase – the integrative or thrombus-forming phase – is characterized by the tendency to protect the organism from the outside world. There, the equilibrium between hemostasis and hemorrhaging tendencies plays an essential role. At each of the four levels, a disturbed self-regulation in the wound healing process leads to one of two types of illnesses: excess hardening or excess dissolving (see fig. 2.1.).
This dichotomy is detailed in the table below for mood disorders. Depressive disorders are affiliated with an excess of 'hardening,' and maniform disorders with an excess of dissolving tendencies.

Table 3.7. Overview of hardening (depressive) and dissolving (maniform) tendencies (according to Whybrow 1998).

	'Dissolving'			'Hardening'	
	Mania	Hypomania	Normal	Minor Depression	Major Depression
Bipolar I disorder				■	■
Bipolar II disorder				■	■
Unipolar mania					
Unipolar depression				■	■
Hypomania					
Dysthymia				■	
Cyclothymia				■	
Temperament					

Elementary therapeutic approaches may be derived from this division into excessive 'hardening' or excessive 'dissolving' tendencies. In depressive disorders, the focus of healing lies on 'getting moving,' 'adding light,' and, 'warming' that which has become 'hardened.' Breaking through automatic negative thoughts can be an example of 'getting moving.' Light therapy is a tried and true treatment with season-related depression. Evoking enthusiasm and interest can be a task for creative therapy in the sense of 'warming.'

Conversely, maniform disorders require focusing on 'adding structure,' and dampening the excess activity. An important job for nurses is to limit the manic patient's excessive crossing of boundaries in order to facilitate more social behavior. Medically, tranquilizers are successfully used to handle excessive agitation and insomnia. If both sides – hardening and dissolving – play a role at the same time, 'enhancing the balance' is

a logical motto. Table 3.7. makes the various levels of disturbed equilibrium visible. These occur between the regulation of emotion and memory, on the one hand, and vital functions on the other (Whybrow 1998).

3.6. Discussion

Four different integrative mechanisms – *heterostasis, allostasis, homeostasis, and epigenetic factors via transcriptional regulative networks* – were described in this chapter. Each of these represents a different manner of self-regulation. The risk factors described by McHugh, Loonen, and Parker that were grouped in Chapter 2 are compensated for by specific self-regulative mechanisms per level. An overloading or shortfall of this regulation can have health consequences. With the aid of the history of the patient, a beginning development toward depression can be interpreted as originating from the failure of self-regulation in one of the four systems described above. In the course of time, other levels can also become overburdened and contribute to the symptomatology. Therapists often start treating depression based on the current symptomatology but tend to lose sight of the developmental history of the symptoms and with that miss important causes of depression. With a systems-oriented view, it is possible to make a current diagnosis and also contribute to the developmental history of a depression (see also sections 7.2.1. and 7.2.2.).

4. Interactive Processes

Chronic stress reactions play an important role in the development of depression. This chapter examines the role of three different messsenger systems. Light metabolism is also discussed in thsi chapter, because sleep disorders play a prominent role in depression and light metabolism is also determined by the interaction with the world "outside".

4.1. Introduction

In this chapter, we will examine how depression develops in relation to the three messenger systems: the HPA-axis, the immune system, and melatonin metabolism. These systems are part of the interactive systems level and play an important role in the regulation of stress. We will study how depression develops if protective factors at this level, such as the ability to integrate stress, lifestyle, and personality characteristics are inadequate – in other words, if the *allostatic load* becomes too great (section 3.3.2.). To this purpose, the activity of these three messenger systems will be described in detail.
Some patients with depression have an abnormally functioning stress system. The non-normalization of the **HPA-axis** (section 4.2.) that occurs as a result of this leads to a considerable increase in the chance of recurring depression. In particular, among patients with recurring depression there is also increased activity in the **immune system** (IS) (section 4.4.). Affective disorders increase the chance of these patients to develop autoimmune disease because there is a long-lasting pro-inflammatory status of the immune system. Monitoring the equilibrium between these various systems is an important task for the interactive system.
The relation between **light metabolism** and sleeping in connection to depression will be discussed in section 4.5.
The HPA-axis provides a *psychosomatic focus* to stress reactions. Via the sensory nervous system and the brain (hypothalamus and pituitary gland), the adrenal gland is activated during acute stress (epinephrine). This results in a physiological condition that makes action, fighting, fleeing, or freezing possible. The IS also enters into an increased state of

activity.
Conversely, in *chronic stress,* the influence of cortisol dominates. Because of that, the body retains nutrients and the IS then enters into a decreased state of activity. The direction of the IS reaction is *somatopsychic*.

4.2. The Hypothalamus-Pituitary-Adrenal Axis hormones

The HPA-axis is part of the psycho-neuro-endocrine system that regulates the stress response. Anatomically, the HPA-axis is formed by the hippocampus (which contains many receptors for glucocorticoids), the hypothalamus, the pituitary gland, and the adrenal gland.
The hypothalamus produces corticotropin releasing hormone (**CRH**) that regulates the production of adrenocorticotropin (**ACTH**) in the *frontal lobe of the pituitary gland*. **ACTH** is essential for the functioning of the HPA-axis. In its turn, it ensures the secretion of cortisol (a glucocorticoid) by the adrenal cortex as well as epinephrine from the adrenal medulla.
Cortisol is a regulating hormone of carbohydrate metabolism and is released during both physical and psychological stress. Cortisol ensures that glucose is released to supply the energy needed for the adaptation to stress and also breaks down proteins. Hormones such as cortisol play an important role in the maintenance of homeostasis within the carbohydrate system (Tellingen 2001). Peripherally, cortisol is also correlated with muscle breakdown, which releases glucose, which in turn is necessary for the adaptation to more intensive stress. Centrally, the glucocorticoid receptors (GR) in the brain (receptors for cortisol) are activated in stress, which are not only dispersed in the limbic system but throughout the entire brain. This activation leads to a change in neurotransmission in the brain and has consequences for behavior.
The hormone ACTH, which the pituitary produces during stress, also stimulates the medulla of the adrenal gland. This starts the secretion of the catecholamine **epinephrine** from the adrenal marrow, which activates animal defense mechanisms (fighting, fleeing, freezing, submission). The hormone epinephrine influences autonomous functions such as blood pressure and heart rate. Specifically autonomous or neurovegetative functions such

as eating, sleeping, growth, and libido are inhibited by epinephrine.
The *posterior lobe of the pituitary gland produces* – under the influence of CRH – another hormone that plays a role in stress management: **vasopressin.** In its function as a hormone, vasopressin regulates the urine concentration in the kidneys by returning water from the ultrafiltrate to the blood. As a neurotransmitter, it plays a role in the regulation of aggression, blood pressure, and body temperature.
Other hormones that play a role in stress are the mineralo-corticoids, such as **aldosterone**, from the adrenal cortex which in their function as hormones regulate the concentration of salts in the body, especially sodium. Via aldosterone's effect primarily in the limbic system, the 'resting state ' is maintained in the brain.
Norepinephrine (NE) is produced during stress in the brainstem as a neurotransmitter and contributes to the above-mentioned animal defense mechanisms.

4.2.1. Prefrontal Cortex and Hippocampus in HPA-Axis Hyperactivity

The prefrontal cortex (PFC) plays a role in the assessment of the chance of reward or punishment during threatening situations, influences the affect based on internal and external circumstances, and facilitates complex cognitive functions. The PFC also influences the amygdala, the NE-nuclei in the brainstem, and the HPA-axis. Cortisol decreases PFC-function by a blockade of the GR. One of the problems of depressive patients is that because of this blockade blood circulation in the PFC decreases, which explains the cognitive disorders that are part of depression, such as rumination, memory disturbances, and concentration problems. The GR decrease both quantitatively and qualitatively and cause permanent hyperactivity of the HPA-axis.
In depressed patients there is, in addition to decreased blood circulation of the PFC, also a decrease of white matter in the frontal lobe, with negative consequences for the associative networks at that location (associated with decreased overview and creativity). That can also be a good explanation for memory problems associated with depression. Increasing cortisol levels lead, through positive feedback, to activation of further cortisol secretion.
Elevated cortisol eventually leads to cell death of neurons in the brain, particularly in the hippocampus where there is a high concentration of GR.

4.2.2. Hyperactivity of the HPA-Axis and Corticotropin Releasing Hormone

Hyperactivity of the HPA-axis can be attributed to hypersecretion of CRH.
In laboratory animals, CRH administered centrally to the brain causes behavior that strongly resembles that of depressed patients, including the changes in sleep pattern, libido, appetite, and activity patterns.
Depressed patients have an increased concentration of CRH in the spinal fluid, an elevated CRH-mRNA in the paraventricular nucleus of the hypothalamus, and a decreased ACTH-response to intravenously administered CRH. In the frontal cortex of suicide deaths, a downregulation of CRH-receptors has been reported. In view of the behavioral effects of CRH, depressed patients are differentiated into melancholic (CRH-expression is too high) and atypical (CRH-expression is too low) (Gold and Chrousos 2002). CRH hyperactivity is more a symptom that occurs during an episode of depression (state characteristic) than a permanent change (trait) outside of the depressive episodes. This applies particularly to patients with a serious depression with or without melancholic/ psychotic characteristics. After successful treatment for 6 months with antidepressants, the CRH-level in the spinal fluid is normalized, while patients with recurring depression maintain an elevated CRH and shift over to a permanent change (trait-situation).

Patients with depression can have a disturbed Dexamethasone-CRH test, a challenge test that is a good measure for the activity of the HPA-axis. If, after provocation with dexamethasone, an abnormal amount of CRH is produced, resulting in an elevated cortisol level in blood or saliva, this is an indication of a hyperactive HPA-axis.

An elevated CRH is only found in some patients with depression (circa 50%), and CRH elevation is also possible without signs of depression, so that measuring this value only appears to be meaningful within the patient's total clinical picture. First-degree relatives of patients with a major depression and bipolar disorder have been found to have hyperactivity of the HPA-axis but no symptoms. This is attributed to genetic variations (polymorphisms of the GR) (see also section 6.3.4.).

Prenatal stress, early developmental trauma, and chronic stress can also lead to

hyperactivity of the HPA-axis, including CRH (Claes 2008). Moreover, abnormal lifestyle characteristics play a role in elevating the *allostatic load* of stress. There are indications that this latter category of patients has an increased chance of developing autoimmune disease along with depression.

Table 4.1. Overview of causes for an elevated CRH

Increased CRH	Cause
	Recurring depression
	As trait: asymptomatic with polymorphism GR
	As state caused by prenatal stress, early developmental trauma, chronic stress

4.2.3. Cortisol in HPA-Axis Hyperactivity

Cortisol has significant interactions with other neurotransmitters, neuropeptides, and brain circuits that are associated with depressive symptomatology. Most patients with a depressive disorder appear, however, to have no hypercortisolemia during cross-sectional research. Unlike in Cushing's disease, in which there is a continuously high cortisol level, one can also find circadian fluctuations in some patients with depression (namely, an elevated cortisol level at night and an accentuation of the cortisol morning peak). Cortisol elevation is mainly found in a subgroup of patients with depression, namely those with psychotic depressions.

4.2.4. The Limbic System: HPA-Axis hyperactivity versus Brain Derived Neurotrophic Factor

Within the limbic system, the hippocampus (HC) and amygdala are specifically responsible for the regulation of emotions. Via the amygdala, both the HPA-axis and the locus coeruleus

(LC) (the most important NE-ergic center in the medulla oblongata) can be activated. NE stimulates the CRH secretion, after which there is a further increase in cortisol.
Volume and activity of the HC decrease during depression. This change is partially brought about by hypercortisolemia, more so in longer duration of the disease. Glucocorticoids such as cortisol inhibit neurogenesis, cause dendrite atrophy, limit the survival capacity of neurons during epileptic seizures, and cause neuron death. The right amount of glucocorticoids is necessary for optimum memory performance; if there is an excess (or shortage), memory processes are disrupted (Kloet et al 1999).
The decrease in HC volume can restore itself with treatment to an important degree in depressed patients and in Cushing patients when the cortisol level decreases. The depressive mood, memory loss, and sleep disorders of patients with Cushing's disease have a positive correlation to the plasma cortisol level.

Brain derived neurotrophic factor (BDNF) is one of the growth factors that regulate neuronal cell differentiation from stem cells. It fulfils an important role in the maintenance of neuronal networks. Stress and depression can lead to a fall in the level of BDNF and therefore contribute to the volume reduction of the hippocampus. Antidepressants and ECT promote the genetic expression of BDNF and induce the outgrowth of dendrites and neurons in the hippocampus from local stem cells (Timmerman and Zitman 2004) (see also 6.3.2.).

4.3. Pain Symptoms and Depression

Both pain and emotions have a common neurobiological basis in the thalamus, hypothalamus, anterior cingulate cortex, insula, and PFC. Physical pain is a symptom that is often seen in people with depression (65%). Sorrow in healthy people is associated with less release of endogenous opiates than in a neutral condition. This also applies to patients with depression. Decreased opiate secretion and increased CRH concentration correlate positively.
There is a connection between the severity of the depressive episode and the presence of pain symptoms, irrespective of comorbid somatic conditions. Moreover, depressive patients without symptoms of pain still appear to have a lowered pain threshold and pain tolerance

level. On the other hand, patients with chronic pain often suffer from comorbid psychiatric conditions, including depression (13-85%). In them, the severity of the depression is related to the subjective degree of pain. When depression and pain occur together, the treatment outcome for both complaints is influenced negatively.
The stress hormone system and the endogenous opiate system interact inversely in regulating the emotions. A traumatic history is associated with a deviating pattern of endogenous opiate secretion in the above-mentioned regions of the brain. The secretion of endogenous opiates appears to be an important common indicator for pain and emotions (Houdenhove 2008).

4.4. The Immune System in Stress

Like the HPA-axis, the IS is important in the interaction between body and mind and in the maintenance of health. The detection of a pathogenic factor (an antigen such as a virus or bacteria) occurs here entirely unconsciously. Immune reactions in lymph nodes and spleen and the production there of messenger molecules such as cytokines prove subsequently to have consequences not only within the IS but also in the brain, for example through their effect on serotonin management.
In addition to this path from the IS to the brain, the brain communicates with the autonomous and endocrine nervous system via the HPA-axis, the Hypothalamus-Pituitary-Thyroid-axis (HPT-axis) and the Hypothalamus-Pituitary-Gonad-axis (HPG-axis). The brain is also linked to lymphatic tissue via the efferent peripheral nervous system and via receptors for neurotransmitters on the surface of immune cells. This entire area forms the terrain of psycho-neuro-immunology.
Within the IS, three different adaptive responses can be distinguished: Observation, adaptation, and finally, the effect of the entire process (Bie 2006). There is a similarity between these three functions and the functions of the hormones in the HPA-axis. Observation occurs in the cortisol receptors in PFC and HC for the HPA-axis; adaptation is regulated in the hypothalamus by CRH secretion; the effect manifests itself in an elevated cortisol secretion. Thus, the immune system and the HPA-axis function in this sense in a similar manner.

Table 4.2. Perception, adaptation, and effect of stress at the interactional level

Perception	Cortisol receptors in PFC and HC
Adaptation	CRH secretion in hypothalamus
Effect	Elevated cortisol

4.4.1. Changes in the Immune System during Depression

In depressed people, the hyperactivity of the IS also results in an increased chance of cardiovascular disease. Those who are burdened by traumatic experiences and depression have decreased Natural Killer (NK) cell activity and a decrease of other cellular immune responses. The severity of the depression in reaction to stressful experiences is correlated with the decrease in NK activity.
The decrease of NK activity improves when the depression is in remission. Lifestyle can be an aggravating factor here. The combination of depression and smoking provides a greater decrease in NK activity than smoking or depression alone. This can explain the combination of smoking and depression with a greater prevalence of cancer.
The pro-inflammatory state in patients with a depressive disorder also leads to higher concentrations of granulocytes and activated T-lymphocytes.
In the group of patients with recurring depression, there is a transition to a permanent pro-inflammatory state. In addition, there is an enhanced macrophage activity and T-cell activation.

4.4.2. Influence of Corticotropin Releasing Hormone on Immune Response

In animal studies, it appeared that IgM and IgG specific antibody responses were considerably reduced when CRH was administered to rat brains during active immunization. The administration of the cytokine IL-1 into the brains of laboratory animals, which ensures a central production of CRH, leads to the suppression of antibody response. In humans with stress or depression and subsequent endogenous CRH

production, immune response is also weakened, leading to the failure of immunological protection (Gool et al 2008).

4.4.3. Sympathetic Nervous System and Immune Response

Lymphoid tissue is innervated by NE-ergic nerve cells, and lymphocytes have α-adrenergic receptors. Moreover, it is also known from in vitro studies that catecholamines and neuropeptide Y (NPY, a neurotransmitter) suppress the cellular and innate immune responses. Both patients with depression and those under stress had an increase of NPY in the peripheral blood. NPY is negatively correlated with NK activity, irrespective of the level of circulating catecholamines. NPY appears to play a key role in the immune changes during depression and stress. Moreover, α2-adrenergic receptor activation plays a major role in changes in inflammatory response and endothelial activation, together with an increase of chemotaxis. Such activation can lead to the occurrence of arteriosclerosis and cardiovascular disease (Irwin 2008). In aging, there is an increase in the sympathetic output which results in a decreased cellular response and an increase in infectious diseases.

Table 4.3. Weakened immune response due to neuropeptide Y (NPY) and catecholamines via the peripheral adrenergic nervous system and α-adrenergic receptors on immune cells. This supports development of a pro-inflammatory state, both in the body and in the brain

Perception	Autonomous nervous system and α-adrenergic receptors on immune cells
Adaptation	NPY↑, Catecholamines↑, NK-cells ↓
Effect	Pro-inflammatory state, depression, cardiovascular disease, inflammatory disease

4.4.4. Sickness Behavior in Systemic Disease

'Sickness behavior' caused by, among other things, cytokines (CK) or fever, presents itself as a decrease in spontaneous activity, decrease in social and explorative behavior, decrease in sexual activity, loss of appetite, and an increased need for sleep. At the same time, there is a decreased sensitivity for pleasure stimuli and increased sensitivity for pain stimuli. The mechanisms that are involved are the same when fatigue and a depressed mood develop in affective disorders, somatic illnesses, or in hard to explain medical complaints like chronic fatigue (Gool et al 2008).
Sickness behavior can be largely explained by the effect of CK and other messenger molecules of the IS and is equated with the behavioral aspects of depression. This is the source of the chronic inflammation hypothesis that depression could be the result of the influence on the central nervous system of peripheral messenger molecules from the IS such as complement factors, chemokines, and CK.
CK play a role in both the specific and the non-specific IS.

1. Pro-inflammatory CK from the non-specific IS, such as IL-1, IL-6, and TNF-α are released immediately after contact with the pathogen and mainly play a role in non-specific immunity. Secretion of these proteins will initiate the inflammatory process and effect fever.
2. The CK of the specific immune system are divided into two groups:
   a) Th-1 CK (IL-2 and IFN-γ) are involved in the immune response to intracellular pathogens such as viruses
   b) Th-2 CK (IL-4 and IL-10) are involved in humoral resistance, when B-lymphocytes produce antibodies, specifically, in bacterial infections.

Table 4.4. Perception, adaptation, and effect of pathogen or stress within the immune system

Perception	Pathogen, stress
Adaptation	Complement factors, Cytokines (IL-6, TNF-α, Th1, and Th2)
Effect	Sickness behavior

4.4.5. Communication between the Immune System and the Brain

There are various paths along which the IS and the brain communicate with each other:

1. The *neural route*. The vagal afferent nerves probably play an important role in the information transfer from the IS to the brain. Transecting the vagus nerve in laboratory animals preceding the administering of lipopolysaccharides (LPS) blocks the behavioral component of sickness behavior, but not the elevation in temperature. LPS are present in the outer layer of Gram-negative bacteria and cause severe immune reaction.
2. The *CK-mediated route*. When injecting laboratory animals with LPS, there is a massive production of pro-inflammatory CK, such as IL-1, IL-6, and TNF-α through macrophages. The brain is affected via areas where the blood-brain barrier is missing (circumventricular areas). In the brain, the CK interact with specific receptors on neurons and microglia and induce the formation of other CK. CK circulating in the bloodstream can probably promote the formation of secondary messenger substances in the endothelium of the blood vessels in the brain (prostaglandins, NO), which diffuse into the brain. There are LPS receptors at the blood-brain barrier, leading to local synthesis of pro-inflammatory CK.
3. The *indoleamine-2,3-dioxygenase (IDO)-mediated route.* IDO is an enzyme that breaks down tryptophan in the intestines and the lungs. Tryptophan, as an essential amino acid, is needed for the synthesis of proteins and is also the precursor of the neurotransmitter serotonin. IDO activity is positively influenced by pro-inflammatory CK, in particular, IFN-γ, and immune activation accelerates the breakdown of tryptophan. In the liver, tryptophan is broken down by tryptophanpyrolase.
   Peripherally available tryptophan is transported across the blood-brain barrier actively (with other Large Neutral Amino Acids such as tyrosine and valine). Tryptophan is converted to serotonin inside neurons. Peripheral activation of IDO leads, in the brain, to lower serotonin production. The primary decomposition product of tryptophan is kynurenine. The further breakdown of kynurenine under the influence of IDO results in neurotoxic metabolic products, leading to damaged neurons and cell death. This has sparked the **neurodegeneration hypothesis** of depression under the assumption that IDO can play a significant role in nerve damage.

4. *Other routes.* Treatment with IFN-γ influences the central activity of MAO, which, among other functions, breaks down serotonin. MAO also breaks down certain protein-splitting enzymes (endo- and exopeptidases), and is involved in the breakdown of peptides with a signal function such as bradykinine, thyreotropin releasing hormone (TRH), and CRH (see also section 5.2.5.). IFN-γ also has depression as a side effect when used, for example, in the treatment of chronic hepatitis C.

Table 4.5. Communication routes of the immune system to the brain

Route	Effect
Neural	Stimulation of vagus nerve by CK
CK	Induction of NO and prostaglandins by CK in vascular endothelium in the brain
IDO	Decreased availability of tryptophan, causing a lack of serotonin
Other	Regulating activity MAO and peptidases

4.4.6. Changes in the Brain during Inflammation Processes

Inflammation leads, via the peripheral immune system, to changes in the brain:

1. Through CK production (in the projection area of the vagus nerve)
2. Through hyperactivity of the HPA-axis (CK activation of GR)
3. Through the production of vasopressin (an increase causes vasoconstriction in the brain)
4. Through pro-inflammatory CK, which changes monoaminergic neurotransmission (serotonergic and NE-ergic transmission decrease)

In addition, sensitization to pro-inflammatory CK occurs and cross-sensitization between immunological stress factors (administering of CK or LPS) and psychological stress factors leads to more severe reactions of the HPA-axis (Gool et al 2008). A negative lifestyle will

certainly add to these developments.
Longitudinal research in humans has established a connection between child abuse and autoimmune diseases in adulthood. This could be the expression of a changed (allostatic) balance of the IS through psychological stress (Danese et al 2007).

4.4.7. Behavioral Effects of Pro-inflammatory Cytokines in Humans

In patients infected with a general pathogen (for example, Epstein-Barr virus), it has been demonstrated that the severity of sickness behavior correlates positively with the serum concentration of various pro-inflammatory CK. For this reason, it is obvious that administering CK as a treatment can be linked to an increased risk of depression. CK are given as intramuscular or intravenous eradication therapy for various diseases: IFN- (multiple sclerosis), IFN-α (chronic viral hepatitis to prevent cirrhosis of the liver or liver carcinoma; in combination with ribovarine during kidney cancer metastasis, M. Behcet). CK are ineffective if given orally since they are glycoproteins. The goal of the intramuscular or intravenous therapy is to eradicate the virus.
IFN-β probably has no psychiatric side effects. IFN-α mainly causes depression (40% of the patients, including those without a previous psychiatric history) in addition to sleep disorders, anxiety, slowed information processing, delirium, mania, suicide, and psychosis. IFN-α induces sickness behavior and also depression. Antidepressants are effective in the treatment of these depressions and are given prophylactically (Gool et al 2008).
In practice it is not possible to differentiate between sickness behavior within the framework of physical disease and a depression. If a physically ill patient displays symptoms that meet with the DSM-IV-TR criteria for depression, it is recommended to accept this diagnosis as a co-morbid disorder and to treat it accordingly (see also 5.3.).

4.4.8. Autoimmune Disease and Affective Disorders

Patients with mood disorders more often have an autoimmune reaction against the **thyroid** than those without a mood disorder. Autoantibodies against thyroidperoxydase (TPO) or

thyreoglobuline (Tg) are more common for both patients with a vital depression and for those with a bipolar disorder. This is coupled with the occurrence of more hypothyroidism in bipolar disorders (Kupka et al 2002). There are indications that autoimmunity against the thyroid is more common among children of parents with a bipolar disorder as compared with controls (Hillegers et al 2007).
People with **diabetes** have more depressive episodes than the average population and there is also a higher prevalence of diabetes mellitus in patients with mood disorders. Antibodies against glutamate decarboxylase (GAD65), the most important type-1-diabetes antigen in the islets of Langerhans, are more common among patients with a bipolar disorder than among healthy controls (Padmos et al 2004).
In summary, there are indications that both organ-specific and generalized autoimmune disease occur more frequently with affective disorders. The findings on active macrophages and pro-inflammatory CK in relation to mood disorders have led to the formulation of the macrophage theory of depression (Smith 1991; Maes 1997). According to this theory, an excessive secretion of monocyte- and macrophage CK can be held responsible for the symptoms of depression. Both the non-specific immune system (elevation at mRNA-level) and the specific immune system (activation of T- and B-cell systems) are in an activated state in patients with affective disorders.
According to some researchers, (Leonard and Myint 2006) a connection can be made between depression and dementia. Arguments for this include the fact that 50% of the **Alzheimer's cases** are preceded by a depression and both are associated with inflammatory symptoms in the brain. Moreover, chronic autoimmune diseases, such as **rheumatism**, occur more often among those with depression than in people without depression.

4.4.9. Child Abuse

In prospective research within the framework of the Dunedin Multidisciplinary Health and Development Study, proof was found for a causal connection between various forms of child abuse in early childhood and a tendency for inflammation in adulthood, also measured in an elevated (and clinically significant) acute phase C-reactive protein (CRP)-level. It was discovered that reporting more than one traumatic event in childhood

increased the risk of hospitalization for an autoimmune disease – as compared with those who had not reported such events – 70% in Th1 autoimmune diseases such as **idiopathic myocarditis** and 100% for **rheumatoid arthritis** (Dube et al 2009).
Possible explanatory mechanisms are that the HPA-axis in these cases ultimately produces insufficient cortisol or that the IS becomes relatively insensitive for cortisol (glucocorticoid resistance), so that abnormal immune activation can occur.
The upregulation of the HPA-axis and the IS – possibly connected to lifestyle problems – could also provide an explanation for the common occurrence of depression in patients of old age with a previous history of child abuse. In another prospective study at the University of Wisconsin, it was discovered that in particular depression in the mother was a predictor for high cortisol levels in her child in the fourth year of life (Houdenhove van 2008).

4.5. Sleep

During sleep, a dynamic equilibrium between sympathetic and neuroendocrine activity is present. From observational studies of patients with depression, it appeared that the subjectively experienced quality of sleep and problems falling asleep were negatively correlated to the NK cell activity and positively correlated to an increase in inflammatory markers. This relation did not apply to other symptoms of depression, such as somatization, weight loss, cognitive disorders, or diurnal variations (Irwin et al 2003).
There is also a relation between depression and an elevated IL-6 with an increase in the time necessary to fall asleep and more REM-periods (Motivala et al 2005). Supported by the fact that patients with primary insomnia displayed the same inflammatory disorder, the **hypothesis** can be put forward that **sleep disorders** play a role in the deregulation of immune cells and their function (Irwin 2008).
Structural lack of delta sleep periods in patients leads to a sharp increase of the sympathetic and pro-inflammatory activity (elevated IL-6, TNF-γ, and CRP, which has particular consequences for cardiovascular and inflammatory disease).

4.5.1. The Physiology and Psychology of Sleep

The function of sleep is presumably to facilitate growth and recovery (Loonen 2008). There is a *physiological* side to sleep because a myriad of growth-promoting factors, such as growth hormone, prolactin, and the sex hormones are secreted then. This also applies to such growth factors as BDNF in the brain. The *psychological* side to sleep possibly has to do with facilitating psychological growth. During sleep, dreams occur which can have a function in the integration of impressions that were incurred during the day and in the development of long-term memory. Lifestyle problems can slow down – or even prevent – such processing.

A number of cycles take place during sleep. As the night progresses, sleep becomes increasingly superficial, the cycles become shorter, REM-sleep is longer and one can also wake up a few times. In the beginning of the night, growth hormone is secreted; after a few hours the secretion of TSH replaces this.

At the end of the sleep period, the production of TSH stops and that of ACTH starts. The hypnogram is influenced to an important degree by age and medication. Newborn babies sleep sixteen hours a day, half of which is taken up by REM-sleep. Late in life, deep sleep (stage-4) occurs less or even not at all. Also, the number of sleep cycles decreases and the number of sleep interruptions increases (Loonen 2008).

4.5.2. The Neurobiology of Some Sleep Disorders

Sometimes insomnia can be a biorhythm disorder, such as in elderly people with dementia which may have a dysfunctional 'brain clock.' This happens in delayed sleep phase and advanced sleep phase syndromes: The normal sleep phase has been pushed backwards or forwards, respectively. These sleep disorders react well to treatment with light and/or melatonin.

1. A sleep disorder whereby the patient *cannot fall asleep* is often connected to an elevated activity level (elevated dopamine level, hyperactive adrenergic locus coeruleus), or *restless leg syndrome* (RLS), which strongly resembles acathisia. Benzodiazepins, which

enhance the effect of GABA, are prescribed for these symptoms. Relaxation exercises and cognitive behavioral therapy are intended to bring about a decrease in adrenergic activation.

2. In sleep disorders whereby the patient *cannot stay asleep*, the problem is not only frequent awakening episodes but sleep architecture is generally disturbed and there is insufficient stage-4 sleep. The latter can also be caused by sleep apnea syndrome. In the latter group, there are symptoms of fatigue and sleepiness during the day, just as with *paroxysmal leg myoclonus disease* (PLMD) or nocturnal myoclonus. These last two conditions can be treated with dopamine agonists. For nocturnal myoclonus, anticonvulsants such as clonazepam also help.
3. Finally, there are *parasomnias*. In anxiety disorders, the activity of the locus coeruleus complex easily becomes too great and one awakens during REM sleep (possibly the explanation for nightmares connected to PTSS). Prazosine, an α1-adrenergic antagonist, specifically reduces nightmares, as does cyproheptadine.

Narcolepsy is the daily occurrence of irresistible attacks of sleepiness during the day. During these attacks, acute REM sleep occurs.

4.6. Discussion

In one group of depressed patients, one or more of the messenger systems function at an abnormal level. Ultimately, this has negative consequences for the adaptation to stress and leads to loss of health, including the occurrence of more depression.
Within the brain, the above-named changes lead to subnormal functioning of the PFC. It is known that antidepressants as well as psychotherapeutic interventions can lead to an improvement of the depression and, at the same time, better blood supply to the PFC.
Stressful events 'happen' to us, admittedly; however, we may also inwardly keep them alive. We do this through self-reproach or by having feelings of guilt about our 'stupid' behavior during important moments, by attributing to ourselves a position of power or powerlessness, and by connecting taxing events with the further course our life will be taking. For these reasons, Luyten et al (2009) recommend *narrative therapy* as an answer

to breaking through the vicious circle of stress. They do point out that the therapist must then be narrative-competent. This means that he has the ability to listen to stories, interpret them, and help 'metabolize' them. The essential condition that must be added here is time for the patient!

In addition to the brain's function in sleep, the HPA-axis is kept in equilibrium through what Servan-Schreiber (2005) calls the *heart-brain* from level III (see 3.1.). He points out that the heart has a close relation to the *emotional brain*, which is chiefly approachable via the body and less via the consciousness.

The heart has its own nervous system, which has its own observations. It produces various hormones (including epinephrine and the 'love hormone' oxytocin) that exert a direct effect on the brain. The heart also has a powerful electromagnetic field, for which the meaning and the influence on other organs have not yet been clarified. 'Heart-focused mindfulness' and heart coherence are capable of improving the hyperactivity of the sympathetic nervous system and the fragility of the IS.

This brings us to the final point: Premature aging. In this chapter, we mentioned an increase of sympathetic activity, a decreased cellular activity in the IS, and an increase in inflammatory activity in patients with depression. These are also processes that can be found in aging. In this sense, the combination of stress and depression leads to signs of premature aging. This aging is characteristic of people with chronic depression along with the increased risk of cardiovascular disease and dementia.

As described earlier in section 2.6., there appears to be a connection between the messenger systems of level II, life style problems, and the phenomenon of allostasis in interactive processes that we also know from the wound healing process. Lifestyle problems increase the allostatic load. How a depression develops at this level can well be explained from the phenomenon of chronic stress and the allostatic load that it imposes. Monitoring the equilibrium between these various systems is an important task for the interactive system.

5. Metabolic Processes

This chapter researches metabolic disturbance in relation to the development of depression. The many metabolic processes in the body are normally in a state of homeostasis. Genetic factors can disturb the homeostasis. An anxious temperament, a damaging lifestyle, and traumatic experiences can further influence it.

Monoamine metabolism is an important element in brain physiology that strongly affects the networks of the brain. Some patients who have a disturbed homeostasis of monoamine metabolism manifest measurable symptoms of depression. In some patients with depression, a shortage of monoamines was found. Other depressed patients express an anxious temperament with increased tension and agitation and do not display pathophysiological disorders. Physical illnesses and medication use for these illnesses can also provoke depression through disturbance of the homeostasis if these decrease the buffer capacity that allows the homeostatic balance to absorb deviations (see also section 3.3.3.).

5.1. Neurotransmitter Systems and Depression

The monoamines norepinephrine or norepinephrine (NE), serotonin, and dopamine ensure neurotransmission in the smaller neurotransmitter systems in the brain that regulate, in turn, the larger neurotransmitter systems of the brain (glutamate, acetylcholine, and gamma-amino-butyric acid) and the neuroanatomical structures connected to them. The function of the larger systems comprises analysis, selection, and storage of sensory input, as well as initiating, coordinating, and monitoring these systems on behalf of the motor output of the brain. The smaller neurotransmitter systems each have a different task: NE ensures short-term action through fast acceleration; dopamine maintains the motivation for higher activity in the long term; while serotonin induces rest and relaxation so that conditions are created for recovery (Loonen et al 2008).

Serotonergic and NE-ergic antidepressants influence neurotransmission. Moreover, they also have an effect on *gene expression*, such that the amount of brain derived neurotrophic factor (BDNF) and glucocorticoid receptor (GR) are changed (Stel 2009)(see section

6.3.2.). As a result of antidepressant use, BDNF can stimulate the hippocampus to develop new brain tissue.

The explosion in the development of antidepressants since the 1950s is based on the monoamine hypothesis that deficiencies of **monoamine metabolism** exist in the brain during depression. This hypothesis is the oldest bio-scientific explanation for the development of depression, but it has never been proven. The first antidepressant, phenelzine, was based on delaying the breakdown of monoamines with monoamine oxidase (MAO). Later, NE-ergic and serotonergic antidepressant drugs appeared on the market. These drugs are still being used, and MAO inhibitors have receded to second place in the guidelines for the treatment of depression due to their side effects, except in the treatment of atypical depression (section 5.2.5.).

Owing to their broad effect, the monoamine-related drugs are not only used for depression. Anxiety disorder and other stress-related disorders also respond to them. These conditions are often seen as comorbid disorders of depression.

5.2. Monoamines

Monoamines can be amino acids or other small compounds with one amine-group. Monoamines are converted from the amino acids α-keto-glutarate and glutamate in transamination reactions after which they can be changed more to fit their many tasks in the organism. Serotonin is formed from the amino acid tryptophan, while the catecholamines dopamine, epinephrine, and NE are formed from tyrosine.

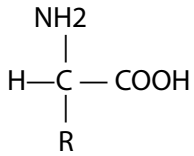

Figure 5.1. General amino acid structural formula. R represents the amino-acid-specific side chain

Monoamines can be biologically active by themselves or, as amino acids, can be a *structural component* of proteins. The biological activity includes their function as

neurotransmitters that chemically support the transport of the electrical impulse from the axon of one neuron to the dendrite of the next neuron, as, for example, with serotonin, NE, and dopamine. Diverse monoamines mediate in establishing consciousness.
They also may have a *hormonal* function within or outside of the central nervous system, as, for example, with epinephrine (Tellingen van 2001).

Peripheral Activity of Some Monoamines

Epinephrine causes the blood pressure to rise and can also cause flushing.
The pain and local inflammation from bee or other insect stings are caused by serotonin and histamine.
The stimulating effect of coffee is due to the stimulating effect it has on the metabolism of the monoamines both in the brain as well as in the metabolism.
Cocaine and LSD imitate the effect of catecholamines in the brain and peripherally have the same sympatico-mimetic effect.

These examples make it clear that neurotransmitter substances have important tasks, both centrally and peripherally.
The metabolism of different monoamines and amino acids varies with the sleeping-waking rhythm and circadian rhythms play an important role. Serotonin and dopamine are mainly produced during the day in the brain stem.

5.2.1. Serotonin and Depression

Serotonin, the rest and relaxation neurotransmitter – also called 5-hydroxytryptophane (5-HT) – is produced from tryptophan in the cells of the rostral and caudal raphe nuclei in the medulla oblongata. These nuclei have projections to the PFC, cingulate cortex, thalamus, hypothalamus, HC, amygdala, and the basal ganglia. Thus the areas that are considered important in the development of depression are all provided with serotonergic connections.
Decreased activity of the serotonergic system – the collective term for the serotonergic nuclei and their connections – is associated with an increased level of anxiety, suicidal

tendencies, irritability, temper explosions, and impatience. These symptoms often precede an actual depression. Giving a tryptophan-poor diet to volunteers leads, among 40% of the participants, to a decreased concentration of serotonin in the brain and a downward trend in mood. Patients who were recovering from their depression with a serotonergic antidepressant relapsed into melancholy and anxiety when eating a tryptophan-poor diet. Such a relapse did not occur if the patient was treated with a NE-ergic antidepressant and then followed such a diet. These findings correspond to a decreased concentration of serotonin breakdown products in the spinal fluid (such as 5-hydroxyindolacetate) in patients with a depressive disorder.

With this type of depressive disorder there is, in addition to serotonin deficiency, also hypofunction of postsynaptic 5-HT1a-receptors (Lesch et al 1996) that is not completely normalized after complete clinical recovery. At the same time, there is an increased 5-HT2a-receptor-binding capacity in depressed patients. Treatment with antidepressants leads to decreased expression of the 5-HT2a-receptors, parallel to the beginning of the clinical effect. Both serotonergic antidepressants and electroconvulsive therapy increase serotonergic neurotransmission in the brain. Atypical antidepressants, such as mianserine and mirtazapine enhance the effect of the Selective Serotonin Reuptake Inhibitors (SSRI's). Chronic stress also leads to an increase in the 5-HT2a-receptors and a decrease of the 5-HT1a-receptors (Celada et al 2004). The relation between depression, anxiety, and stress appears to be profound. Just as with permanent changes in the stress-axis and the immune system after recuperation from a depression (see 4.4.), a permanent metabolic disturbance may occur in anxiety and stress possibly related to temperament problems, which in time contribute to recurrence of the depression or to a decreased capacity to recover.

The breakdown of serotonin was discussed in section 4.4.5.3.

Table 5.1. Overview of factors that cause variations of the serotonergic system (according to Loonen et al 2008; Timmerman and Zitman 2004). AD = antidepressant

Cause of serotonin deficiency	Symptom	Decrease	Increase	Therapy
Tryptophan deficiency due to inflammation or chronic stress	Increased anxiety, suicidal tendency, depressive mood	5-HT 1a receptors	5-HT 2a receptors	Serotonergic AD
				Addition of atypical AD, mianserine or mirtazapine ECT

5.2.2. Norepinephrine and Depression

The most important NE secreting nucleus is the locus coeruleus, also located in the medulla oblongata. From this center there is projection to any number of areas in the diencephalon, the mesencephalon (such as the thalamus, the hypothalamus, the HC, and the septum), and the cortex cerebri. The NE-ergic neurons in the diencephalon are involved in emotional and neuroendocrine response. Dopamine is converted to NE in the NE-ergic neurons with the aid of dopaminebetahydroxylase. Because antidepressants enhance the NE-transmission when administered, it was thought that a deficiency of NE was part of the pathophysiology of major depression. Peripherally, however, a hyperactivity of NE was demonstrated in depression, which was most pronounced in patients with a melancholic depression and with hyperactivity of the HPA-axis. It is less clear whether or not there is also NE hyperactivity in the central brain. Inertia and motor inhibition are

important symptoms that are related to a possible cerebral deficiency of NE. Moreover, cognitive disorders are correlated to the NE-ergic system (Timmerman and Zitman 2004). Such disorders can manifest as a medical condition or as a temperament problem that constitutes a permanent part of the psyche of the patient.

Table 5.2. Overview of possible consequences norepinefphine deficiency

Norepinefphine	Symptom	Decrease	Increase	Therapy
	Cognitive disorders	Possibly central	Possibly peripheral	NE-ergic AD

5.2.3. Dopamine and Depression

It is presumed that the dopaminergic (DA-ergic) system chiefly plays a role in psychotic depression and manias. It is suspected that both with mood disorders and psychoses, deficiencies within the DA-ergic system play a role in the development of some symptoms of depression and, in particular, with anhedonia.

5.2.4. Summary Monoamines

The significance of the monoamines serotonin, norepinephrine, and dopamine corresponds to Parker's dimensional and categorial division described in 2.4. He determined that in depressive disorders there is mainly a deviating *serotonin* metabolism; in melancholia and depression in which striking motor changes also play a role, there is an imbalance of the *serotonergic and NE-ergic metabolism*; if psychotic symptoms play a prominent role, there is *serotonergic, NE-ergic, and DA-ergic* imbalance. Based on this, he advocates the use of a serotonergic, NE-ergic, or NE-ergic and DA-ergic antidepressant for the respective forms of depression.

Table 5.3. Different symptoms due to lack of various monoamines (after Parker 2009)

Monoamine	Effect
Serotonin	Anxiety, suicidal tendencies, irritability, depressive mood
Norepinephrine	Inertia, motor inhibition
Dopamine	Psychotic symptoms, anhedonia

5.2.5. Monoamine Oxidase Inhibitors and Depression

The effect of phenelzine and tranylcypromine is based on decreasing the activity of the enzyme monoamine oxidase (MAO). The enzyme breaks down serotonin and NE. A decrease in activity of this enzyme leads to higher concentrations of the above-named monoamines. This explanation is used to clarify the antidepressant effect of MAO-inhibitors. Because the MAO-inhibitors that are already present in the organism are inactivated, problems arise with the breakdown of tyramine (see 5.2.) in such foods as wine, blue cheeses, chocolate, and herring. Ingesting these products together with MAO-inhibitors can lead to a dangerously high blood pressure, due to the peripheral hypertensive effect of dopamine. A tyramine-poor diet is, therefore, required. The consequence is that this drug has become second choice, except for atypical depression.

5.2.6. Anhedonia: The Prefrontal Cortex and Monoamines

Anhedonia – lack of lust for life – is, according to the DSM, one of the two core symptoms for depression. Loonen (2008) poses that depression, as a 'lust for life disorder,' can be the consequence of a dysfunction of the PFC. Anatomically, there are two separate areas with different functions in the PFC.

1. In the *dorsolateral PFC,* hypoactivity is associated with apathy (lust for life disorder) and cognitive dysfunctioning.
2. Hypoactivity in the *ventral and orbital PFC* areas results in the continuation of emotional response by lack of inhibition of limbic structures in the diencephalon (causing increased anxiety and irritability).

Serotonin suppresses the DA-ergic nerve cells in the mesencephalon and inhibits the terminal synapses in the prefrontal cortex, so that more dopamine becomes available there and leads to an improvement in both initiative (dorsolateral PFC) and reward perception (mesial PFC and nucleus accumbens). The effect is a decrease of listlessness.
Serotonin also causes a downregulation of the adrenergic locus coeruleus complex. Because of this, the possibility for the HC to initiate a flight response is reduced and the anxiety level decreases.

Table 5.4. Corrective role of increased serotonin (according to Loonen et al 2008)

Serotonin	From Nucleus Raphe to Hippocampus	Recovery of emotional response
Serotonin via NE	Generated in the Locus Coeruleus	Recovery of emotional response
Serotonin via DA	Generated in the dorsolateral prefrontal cortex, mesial prefrontal cortex, and Nucleus Accumbens	Improvement in initiative and motivation

5.2.7. Brooding: the Amygdala-Hippocampal Complex

The amygdala-hippocampal complex appears to be generally related to the disorder of brooding. Within the HC, sensory information is categorized according to 'old,' 'new,' or 'unexpected.' On the basis of this categorized information, the HC then directs the amygdala (the alarm center). The amygdala is, depending upon the information it receives,

activated ('danger') or, conversely, inhibited if it receives more neutral information. Because the HC has connections to the PFC, the cognitive side of the protection mechanism is also switched on in danger, but a bit later than the amygdala.
Chronic depression can result in both neuronal cell death and dysfunctioning of the HC (see sections 3.3.2., 4.2.1., 4.2.4., and 4.4.5.3.). This leads to a chronic state of hyperarousal and anxiety.
Serotonin has a protective, relaxing effect when stimulating the 5-HT1a-receptors and it suppresses the effects of the stress receptors, the GR. Moreover, serotonin increases BDNF, which is important for regeneration of the stem cells located in the HC. If, ultimately, the amygdala is inhibited by the HC, then there is a greater chance of a cognitive response to the event, instead of a reflexive one. This improves the emotional state, decreases ruminating on negative thoughts and on negative, anxiety-ridden expectations. Such a mechanism can explain the effectiveness of the combination of an SSRI with CGT in brooding. (Loonen et al 2008).

Table 5.5. The effect of combined serotonin and cognitive behavioral therapy (CGT) for brooding (according to Loonen et al 2008)

Serotonin and CGT	Improvement in function HC, inhibition amygdala	Decrease in ruminating, negative expectations, and anxiety Strengthening of cognitive schemata

5.3. Depression in Patients with a Physical Disorder

Mara
In the midst of a busy life with small children, the forty-year old Mara was bothered by dark thoughts, lack of lust for life, and thoughts of death. She could no longer put things into perspective. Carrying out her daily tasks cost her an increasing amount of energy. Gradually, due to loss of appetite she lost a few kilos. After three months of brooding she

started to have increasing symptoms of nausea. Although nobody really believed in the possibility of physical illness, her family doctor sent her to an internist, just to make sure. The specialist found indications for the presence of a swelling in the gallbladder/liver area. After emergency surgery, there proved to be a large, isolated gallstone in the gallbladder. The depression disappeared after she recovered from the procedure. Metabolic disturbances apparently evoked the depression.

Patients with a physical illness often have metabolic abnormalities. These can also effect a change in the functioning of brain networks, as in Mara's case (see above) and lead to a depression. The point prevalence of depression among those (often elderly people) who are physically ill varies from 4-26% and is higher than in the population of healthy elderly people. The diagnosis of a depression with a physical illness is no easy task. The symptoms of depression can *overlap* with the physical illness, or be an *expression of the stress* that coping with the disease elicits, or the physical illness and the depression can simply exist *alongside each other.* For these reasons, as we mentioned before, an inclusive approach is taken in hospital psychiatry: All of the symptoms that fit a depression are attributed to depression, irrespective of the overlap with physical disease symptoms such as fatigue, lack of energy, or sleeping problems. This approach is in keeping with that of the DSM (no causal diagnostics) and is supposed to decrease the chance of underdiagnosis. It is then referred to as a somatogenic depression.

Depressive disorders that occur at a later age can be seen as a reaction to previous somatic disorders, such that not necessarily the depressive mood, but physical symptoms such as loss of energy and passivity are the primary symptoms.

In spite of this inclusive method of diagnostics, the diagnosis of depression is missed in more than 50% of physically ill patients (see also 4.4.7.).

The depression with physical disease does not essentially differ from a depression with a psychiatric origin. Thoughts of death due to a potentially life-threatening illness are, of course, different. Decreased interest in activities or pleasure can, in physically ill patients, also be explained by the nature and severity of the physical symptoms.

In hospital psychiatry, apathy, particularly for neurodegenerative disease, is described as a separate syndrome and treated with amphetamines without there being any question of a depression (Leentjens 2008).

5.3.1. Depression and Heart Disease

Heart patients are afflicted with depression relatively often (20-30%) (see also section 3.3.2.). The presence of depression leads to higher morbidity and mortality from the underlying heart disease. Depression appears to decrease the variability of the heart rate. The heart rate is subject to the consequences of subtle changes in the sympatico-vagal impulse. Decrease in the variability of the heart rate is an expression of an increase of the tonicity of the sympathetic autonomic nervous system. That forms an important cause of ventricular rhythm disorders and increased morbidity in patients with heart disease. In addition, depression can activate the clotting mechanism by an increase in serotonin-induced aggregation of blood platelets and thereby increase the chance of thrombosis. Patients with depression appear to develop twice as much stomach fat as their non-depressed peers. The stress that goes hand in hand with depression causes an increased cortisol level that in turn is responsible for an increase in fat storage: a risk factor for cardiovascular disease. The elevated cortisol level can also explain the activated state of the immune system in cardiac disease (Vogelzangs et al 2009) (section 4.4.1.).
Depression increases cardiac mortality by a factor of 4. After bypass surgery, depression is the most important predictor of cardiac complications in the first 12 months. Mortality due to depression is, in the 5-year period after bypass surgery, increased by a factor of 2 (van Melle et al 2004).

5.3.2. Depression and Other Physical Conditions

Approximately 25% of cancer patients are afflicted with depression, but some forms of cancer have much higher rates, such as pancreatic and oropharyngeal cancers.
In neurological syndromes, depression is particularly prevalent with Parkinson's disease, dementia, multiple sclerosis, cerebrovascular disorders, and brain trauma.
There is a relation between the degree of hyperglycemia with diabetes mellitus and the occurrence of depression (8-27%).
Disorders of the thyroid and parathyroid gland, as well as HIV (AIDS), are associated with depression.

5.3.3. Iatrogenic Depression through Medication Usage

In addition to illnesses themselves, nearly all medications used in the treatment of physical illness can induce depression. This is particularly the case for anti-hypertensive drugs (β-adrenergic blockers, calcium channel blockers), cholesterol lowering drugs, anti-arrhythmic drugs, glucocorticoids, antimicrobial drugs, centrally effective pain medication, anti-Parkinson drugs, and anticonvulsive medication (Reus 2008).
It cannot be ruled out that in the long term even antidepressants can have negative side effects. In a large-scale observational study, it was found that the use of certain antidepressants, such as the tricyclic antidepressants (TCAs) and a select group of serotonergic and NE-ergic reuptake inhibitors (SSNRIs), correlate to more strongly deviating cholesterol values, more abdominal fat, decreased heart rate variability, elevated heart rate, and hypertension. (Penninx and Dyck Van, 2010). To date, however, no differences have been demonstrated in cardiovascular mortality between patients who use these antidepressants and those taking a placebo (van Melle et al 2007; Glassman 2008).

5.3.4. Treatment of Depression Associated with Physical Illness

The effectiveness of the treatment with antidepressants for this type of depression is limited. Some drugs can be relatively contraindicated, such as TCAs in heart rhythm disorders or hyperglycemia, or MAO-inhibitors in hypoglycemia (Reus 2008). For heart patients, antidepressants appear to be most effective if prior to the heart disease there was an episode of depression which was treated successfully with these drugs. Sertraline and citalopram are effective and safe for depressed patients with congestive heart failure. These drugs contribute to an increase in compliance. According to a recent large-scale review, antidepressants seem to work better than a placebo for this type of depression (Cochrane 2010). Cognitive therapy and physical activity can also improve the symptoms of depression with physical illness.
Whether or not all treatments are equally effective, until recently no study has shown that improving the depression also leads to improved cardiac outcomes. However, in a recent study (COPES, Davidson et al 2010) a 'stepped care' treatment for mild to

moderate depression was given to patients with acute coronary syndrome, starting after 3 months of observation and lasting for 6 months. The outcome provided more patient satisfaction about the recommended treatment and also, in contrast to the previous conclusion, a trend towards lower cardiac mortality and morbidity (4% instead of 16%) in comparison to the traditional treatment group with symptoms of depression, in which the depressive symptoms were not treated. At the same time, the reverse statement is clearly demonstrable: Depressed patients who do not react to a treatment for depression have an increased risk of negative cardiac events and would prognostically only be helped by an intensification of the cardiac treatment (Lichtman et al 2008). We do not have an intelligible explanation of how depression develops in physical illness.

5.4. Discussion

Metabolic deviations as a consequence of changes in monoamine metabolism − through temperament, physical illness, drug addiction, or medication use − is a separate area among the factors that promote the occurrence of depression. Recovery may be achieved by intervention with antidepressants when monoamine metabolism is disturbed. Other methods, such as cognitive behavioral therapy, however, also appear to be able to readjust the recuperation mechanism. The term somatogenic depression was used to indicate both the origin and the different coloring of this category of depression. Various types of depression demand different forms of antidepressant medication (serotonergic, a combination of serotonergic and NE-ergic, or even a combination of serotonergic, NE-ergic, and dopaminergic drugs (section 2.4.).

Recently, the term *metabolic depression* has also come into use (Vogelzangs et al 2008). In the elderly, the combination of metabolic disturbance (obesity, high cholesterol levels in the blood, hypertension, and hyperglycemia) and depression leads to poorer chances of recovery from the depression.

An interesting example of the treatment of metabolic disturbance in patients with coronary artery disease and post-traumatic stress disorder (PTSD) is the influence of *forgiveness* on the sympathetic nervous system (Waltman et al 2009). The study dealt with 17 veterans with a myocardial perfusion deficit at the moment they re-experienced their

trauma in military service. During a period of 10 weeks of psychotherapeutic treatment, they were supported in learning to forgive the perpetrators. The process of achieving forgiveness appeared to significantly improve coronary circulation. The clinically relevant improvement of myocardial perfusion was maintained for 10 weeks after treatment. This is an example of how a changed mental attitude can correct metabolic abnormalities. The authors suspect that stress increases sympathetic activity so that the pulse accelerates, blood pressure increases, and arterial vasoconstriction occurs. Conversely, positive feelings lead to a decrease in the metabolic energy requirement of the heart and decreased vasoconstriction. These examples demonstrate that a chronic disturbance of metabolic functions plays an important role in maintaining depression, which can also explain its vital characteristics; and that a change of temperament can correct metabolic disturbances, at least temporarily.

6. Brain Disease, Genetics, Epigenetics, and Chronicity

This chapter deals with the causes of depression related to having a physical "brain impairment". An important consequence of defects at this level is that the initiation of repair processes of depression often makes a more compelling external therapy necessary.

6.1. Introduction

Brain disease is the collective term that McHugh uses to include genetic processes and those mechanisms leading to chronic depressive disorders (section 2.3.). At this systems level IV, recovery processes are characterized by epigenetic factors. This includes the developmental impact of positive and negative conditions from the environment on the transcriptional regulative networks. These networks contain the genetic encoding. It is the area from which kindling (see 6.3.2.) originates. The object of this chapter is to study the extent to which this is a separate area for the origin of depression.

Sven, 35 Years Old, Overcomes the Fate of Heredity

In bipolar disorder, we know the phenomenon of anticipation. This refers to the situation that the time between mood episodes becomes shorter in the course of life, but also that the disease is more severe than in the previous generation. It is suspected that the kindling mechanism also plays an important role here. The variability of the expression of genetic material (plasticity) is a factor as well (see 3.3.4.).

Sven's father was diagnosed with bipolar disorder and Sven himself had, indeed, more frequent and more serious episodes. Sven has been off mood stabilizers (lithium carbonate) for his bipolar disorder with psychotic characteristics for around six years now. He does notice mood swings, but has learned to pay attention to them on time, to slow down if necessary, and to follow the signals his wife gives him. In the past, in desperation during a depressive episode, he jumped from a high place in a serious suicide attempt. By some miracle, he survived. After that he was troubled by a number of manic episodes with psychotic characteristics. He has managed now to not simply be at the mercy of heredity, but an active effort is necessary for

this. Along with the use of lithium carbonate for a number of years, (treatment at level IV of the model), working in a carpentry shop (change of lifestyle, level II) counterbalanced a tendency to have thought patterns that quickly become illusory. To supplement his psychiatric treatment, he took various training courses focused on learning to better deal with his mood swings (level I and II). When he felt that he could do that well enough, six years ago he stopped taking the lithium carbonate, after which he had a single, one day long, manic relapse. With short-term use (less than one week) of an antipsychotic drug (level IV), this relapse could be suppressed. In his previous history it is significant that his father was also alcohol-dependent and that his youth was characterized by instability in his family of origin. In comparison to his father's bipolar disorder, the course of Sven's disease was more serious (measured by the number of hospitalizations, more marked mood swings, and the occurrence of a serious suicidal attempt). Nonetheless, he has, for the most part, freed himself from the impact of the bipolar disorder.

6.2. Genetic Factors

6.2.1. Genetic Risk and Environmental Factors

The *genetic risk* for family members of patients with a major depression rises in first-degree relatives with a factor 1 to 2.8 in different studies in comparison to immediate first-degree relatives of families without major depression. This increase is, based on studies of twins and adopted children, ascribed for the most part to genetic factors. The heritability, defined as the degree to which individual genetic differences contribute to the development (or not) of depression, is estimated at 40%. The remaining 60% of the vulnerability for major depression can be attributed to events in one's life history. In bipolar disorder, the role of heredity is estimated to be considerably higher (60-93%).

The role of *environmental factors* becomes clear in a study of young mothers with depression. They appear to have less eye contact with the baby and a lower sensitivity for recognizing and reacting to their baby's behavior. This decreased sensitivity leads in some mothers to

a hostile or intrusive style of communicating with their child and in others to a passive and disengaged style. Children of mothers with depression are more inclined to develop an insecure attachment of the avoidance type.
First-degree relatives of adults who were depressed as children have twice as much chance to develop a unipolar depression. The various genetic regions that possibly play a role in the occurrence of depression are not specific for depression. Sex-linked psychopathological characteristics have, however, been clearly demonstrated. Males tend to display early neuropsychiatric developmental disorders such as autism, attention deficit disorder, hyperactivity disorder, and disorders in language development, while females are more often afflicted with disorders that manifest themselves in adolescence, such as mood disorders, anxiety, and eating disorders. Genetic factors play a role in these differences, alongside the increased risk through certain *life events* such as sexual abuse (Nolen and Boks 2004).

6.3. Endophenotype between Genotype en Phenotype

Because there is no unequivocal relation between psychiatric diagnosis (or phenotypes) and genetic predisposition, the search is for endotypes: measurable biological components that are midway between the condition (phenotype) and the genotype (Swets et al 2009). The *tryptophan depletion test* and the combined *dexamethasone/CRH test* (4.2.2.) are examples of such measurements. In both, a decreased level is related to increased stress sensitivity. Because tryptophan is the precursor of serotonin, decreased availability of tryptophan through genetic variations leads to decreased availability of serotonin in the brain. The DEX-CRH test is an example for measuring disruption of the 'stress axis,' the HPA-axis discussed in Chapter 4.

6.3.1. Epigenetic Changes

Through gene-environment interaction, the environment determines whether or not a person's genetic vulnerability manifests itself. One example of this type of epigenetic change is the influence of child abuse on permanent changes in the HPA-axis (McGowan et al

2009), leading to permanently changed reactions to stress. Depression based on changes in the stress system is a common complication of child abuse. These permanent changes in the HPA-axis can be found with help of an abnormal DEX-CRH test in these individuals. Since, in addition, changes in the HPA-axis are often combined with chronic changes in the immune system (Loonen et al 2008) stress should be differentiated in:
1. *Acute stress* in reaction to negative events
2. *Chronic stress* as a source for the developing depression
3. *Physical and/or sexual abuse, particularly in childhood.*

Increased stress sensitivity develops through the combination of stress with genetic factors. From these examples it may be clear how strongly the expression of genetic factors is determined by the quality of upbringing.

6.3.2. Kindling, Anticipation, and Sensitization

The combination of kindling, anticipation, and sensitization was, particularly in bipolar disorder but also with unipolar depression, introduced as an explanatory model for the chance of recurrence over time. With these types of depression, recurrence appears to occur more quickly in reaction to less strong stress factors. Ultimately, spontaneous episodes can occur without a clear provocation.

Kindling is a concept taken from the world of epilepsy. It is assumed that, long before the first epileptic seizure occurs, a chronic source of stimulation is present in the brain. These chronic stimuli lead to the clearing of a 'path' in the brain where, ultimately, the stimulus threshold for the occurrence of a seizure is lowered. Probably, epigenetic change also plays a role here. This means that after the first seizure, the next one occurs more easily. *Kindling* could also explain acceleration of the cycle in bipolar disorder as well as an increase in the severity of the episodes. The equilibrium shift, resulting in an increased likelihood of relapse, could be provoked by repeated stress, episodes of illness, and substance abuse (see also Chapter 4., lifestyle problems). A decrease in the protective brain-derived neurotrophic factor (BDNF) could play an important role in this increase, both genetically and in reaction to

environmental factors. BDNF as protein and BDNFmRNA are responsible for the recovery and growth of neurons. The amount of BDNF is positively influenced by mood stabilizers and antidepressants (Post 2007) (see also 4.2.4. and 5.1.) but also by physical activity (Binder and Scharfman 2004).

An as yet unexplained phenomenon is the existence of *anticipation* in bipolar disorder (section 6.1.). Anticipation is the phenomenon that the time between mood episodes becomes shorter in the course of life and that each succeeding generation is afflicted with a more serious form of the disease (earlier onset and higher frequency of hospitalizations).

Sensitization is the increasing sensitivity for stressful circumstances, such that *cross-sensitization* can also develop. With this, a psychological stimulus can lead to increased biological reactivity (a psychosomatic manner of reacting). The underlying mechanism is not clear. Because sensitization can continue for a long time, one assumes that this mechanism plays a role in the phenomenon that a less stressful situation can induce the next episode of depression more easily (Monroe and Harkness 2005; Post 2007).

6.3.3. The Serotonin Transporter Gene (SERT Gene)

Another example of an endophenotype is the expression of the SERT-gene. The consequences of child abuse increase the sensitivity for stress in the gene for the serotonin transporter (SERT). Moreover, it appears that the SERT-gene, with two long alleles, leads to more serotonin production than forms with one or two short alleles. In practice, that leads to less chance of anxiety and depression (Claes 2008a).
In prospective research by Caspi et al (2003) three groups of patients were studied: one group carried two long alleles, one a short and a long allele, and the third group had two short alleles. From this, it emerged that, without important setbacks, the risk of depression during a two-year period in the three groups was 10%. If, however, there were negative events during that period, the chance of depression rose to 16% among the carriers of two long alleles, 30% for carriers of one short and one long allele, and 40% for carriers of two

short alleles.
It is suspected, based on corresponding findings with other stress-related psychiatric conditions such as alcohol dependence and eating disorders, that the SERT-gene influences the psychological coping mechanism of the individual with stress factors. In contrast to this assumption, there is a large-scale meta-analysis by Risch et al (2009) on the relation of the SERT-gene to depression. From that study, it appears that there is no separate 'depression gene' and that the SERT gene – alone or in combination with stressful circumstances – is not associated with an increased risk of depression in both sexes. The chance of depression cannot therefore be attributed only to variations of the SERT-gene. It seems too simple to expect that the SERT-gene test, which is already commercially available, will make a meaningful contribution to correctly predicting an increased risk of depression in people who have previously experienced such an episode.

Table 6.1. Chance of depression with variations of SERT-gene: from a prospective two-year study on the occurrence of negative events (Caspi et al 2003)

Variations in SERT-gene	Percentage chance of depression after 2 years with negative events
Two long alleles	16%
One long and one short allele	30%
Two short alleles	40%

6.3.4. Glucocorticoid Receptor Gene

The glucocorticoid receptor gene is a second example of a gene that contributes to stress sensitivity by its direct influence on the functioning of the HPA-axis. There are polymorphisms that have been described as affecting the resting level of cortisol secretion, while others have an effect on the negative feedback of the HPA-axis. If the activity in this axis is too high, it could explain depression, while if it is too low it could explain Chronic Fatigue Syndrome (CFS) (Claes 2008b). Here, as well, there is increased stress sensitivity

with depression. In section 4.2.2., we already discussed the existence of genetic variations in the glucocorticoid receptors in the brain.

6.3.5. Chromosome 22q11 Deletion

Heterogeneity within the endophenotypes emerges from various psychiatric phenotypes that are associated with the absence (deletion) of locus 22q11 on chromosome 22. The absence of this locus can lead to a wide range of clinical pictures such as childhood autism, ADHD, or an affective psychosis in adulthood (GWAS Consortium 2009).

In summary, it can be said that no unequivocal endophenotypes have as yet been found.

6.4. Heredity in Relation to the Course of Depression

Hereditary factors play a role in the age at which the first depressive episode manifests itself and heredity can influence the course of the depression in the following generation.

6.4.1. Age and Course of Depression in Relation to Heredity

The first episode of depression manifests itself, on average, at around 30 years of age; for women, a bit earlier (29) than for men (32). The median age for the recognition of symptoms leading to the development of a depressive episode in patients who have come for treatment is around 25 years old (Spijker 2008).

Half of the patients with depression recover within three months, whether or not they have been treated, and after a year approximately 80% of the patients are no longer depressed. After that, the recovery curve is nearly flat. This course resembles the fourth and final maturation phase in wound healing, which can take up to a year (compare 1.4.). Because the chance to recover after a year is much smaller, it would be more logical to refer to

chronic disease at that time instead of after two years, which is the accepted timeframe in the DSM-IV-TR.

The long-term course of the disease is impressive. After twelve years' follow-up, it appears that adult patients who had one or more depressive episodes have experienced a clinically relevant level of depressive symptoms during nearly 60% of that time (Spijker et al 2002). On various occasions these patients were given a wide variety of diagnoses from the group of affective disorders in the DSM-IV-TR.
In the elderly, the course of the disease is even worse. Only 23% of a group of elderly patients with depression that was followed intensively for six years recovered completely. Among 44%, there was a fluctuating but adverse course of the disease, while the remaining 32% remained chronically depressed for six years. This can also be linked to the *frailty* of old age (3.3.3. and 3.3.3.1.).

6.4.2. Chronicity and Recurrence in Relation to Heredity

Negative experiences in youth (level I) and neuroticism as a child (level III) are, among patients hospitalized with depression, predictors for a longer duration of the disorder. Vulnerability due to previous psychiatric or other chronic conditions such as physical frailty (3.3.3.1.) is associated with a more chronic course of the depression. Longer-lasting previous episodes of depression are predictors for a longer duration of subsequent depressive episodes. For women, prolonged difficulties in life as well as the lack of social support appear to be linked to the persistence of a depression. Also, the severity of a depressive episode and comorbidity with symptoms of anxiety are predictors of chronicity. In view of the fact that selection takes place since the group with the most unfavorable prognosis receives more intensive treatment, it is not known what role the treatment of depression plays in shortening its duration (Spijker 2008). The presence of residual symptoms after recovery from a depressive or manic episode increases the chance of recurrence in patients with a bipolar disorder by a factor 3 (Judd et al 2008). The question remains unanswered whether or not this includes various subgroups, and if in the group with residual symptoms suboptimal medication levels played a role (Meintjes and Schoevers 2009). It is clear that depression can be a chronic condition.

An important predictor for recurring depression is the experience of a previous episode. Every new episode of depression increases the chance of a relapse by 16% (Solomon et al 2000).

Johan

Johan is now 45 years old. From the age of 32 he experienced a seasonal and severe depression every winter. He describes the onset as follows: Normally he feels light and relaxed when he wakes up. However, at the onset of an episode of depression – always in the autumn – shortly after this pleasant feeling, he is overtaken by heaviness and tension that obstruct his speech, slow down his movements, and cause pain throughout his entire body. After a few weeks other symptoms appear, such as a depressed mood, lack of pleasure, passivity, brooding, skepticism, memory problems, sleep problems, loss of appetite, and pronounced mood fluctuations during the day. Towards evening he is better able to accomplish things than during the day. Towards spring, the depression gradually improves. The use of antidepressants (amitryptiline), light therapy, omega fatty acids, vitamins, and intensive exercise decrease all these symptoms to a tolerable level, but they do not disappear. The level remains so high that it is impossible to work.

There was no clear inducing factor for the first episode and there is no recognizable genetic load. Johan does have an elevated stress level when he must give presentations on his work at scientific conferences. From the moment the date for a presentation is known, symptoms such as anxiety, palpitations, perspiration, dry mouth, sleeping problems, and difficulty speaking start to appear. These anxieties demand a great deal of energy and spoil his work pleasure. The first memory of these kinds of anxieties goes back to when he was 4 years old. There was tension within his family of origin, particularly when his father hit or threatened him or the other family members. The father's behavior was especially bad when he had been drinking. Johan then felt so paralyzed that he could no longer speak well. When the marital tension ran so high that the father left, the mother started to lean on him, as the eldest son, for help with financial matters and with the younger children.

Alongside the problems that Johan is going through with respect to relapses and partial therapy response, the physical abuse and emotional neglect in his family of origin is significant for a possible changed stress system. It is also conceivable that Johan demands too much of

himself in some of his roles. Could these factors play a part in eliciting depression, even if the depressions are characterized by vital characteristics and the presence of a season-bound pattern? It is not impossible that the transcriptional regulative networks have also changed.

6.5. Comorbidity of Depression

The prevalence of anxiety disorders in population studies is considerably higher among people with depression than among people without depression. The percentage of anxiety disorders in people with depression is more than 40%, for which the least taxing phobias are most common (20%), followed by generalized anxiety disorder (15%), social phobia (13%), panic disorder without agoraphobia (11%), and finally, panic disorder with agoraphobia (3%). Genetically, depression is most linked with generalized anxiety disorder and neuroticism. There is an interdependence of these three diagnoses with single nucleotide polymorphisms of the glutamate decarboxylase (GAD-1) gene, which plays a role in the synthesis of GABA. GABA has a dimming effect on the brain. For percentages of the comorbid disorders of depression, see table 6.2.

With these figures, it must be kept in mind how problematic the differentiation between the symptoms of a general illness and that of depression is. Depression increases the chance of coming down with a physical illness later in life, as has been proven for myocardial infarction, type-II-diabetes, and arthritis (Zitman 2008). Here, too, the question arises concerning the variability of expression of genetic material (3.3.4.).

Table 6.2. Comorbidity of depression in a population study (according to Zitman 2008)

Comorbid disorders	Percentage occurrence with depression
Specific phobia	20%
Generalized anxiety disorder	15%
Social phobia	13%
Panic disorder without agoraphobia	11%
Panic disorder with agoraphobia	3%
Personality disorder	31%
Disorder of alcohol use	40%
Nicotine dependence	30%
Disorder of use of other substances	17%
Heart disease	17-27%
CVA	14-19%
Alzheimer's	30-50%

6.6. Discussion

Transcriptional regulative networks appear to form their own system whereby external factors, such as upbringing, war, and hunger also determine in the long run whether or not phenotypes develop that increase the chance of depression. It also becomes clear that activating protective factors can contribute to a more favorable course of seemingly fixed dynamics such as anticipation in bipolar disorder. This is linked to the plasticity of transcriptional regulative networks (6.3.).

Suomi (2006) determined that functional polymorphism of the SERT-gene makes some apes vulnerable to maternal neglect while others are not. Moreover, it appeared that genetically

anxious apes who are raised by good ape mothers could themselves become good mothers, in contrast to genetically anxious apes who are raised by anxious mothers. If one adds these findings to the discovery of lifelong vulnerability for stress as a consequence of epigenetic changes caused by child abuse, this emphasizes the significance of a favorable child-rearing atmosphere as one of the important conditions for a positive development from of genotype to phenotype. A harmonious upbringing together with a healthy present situation forms an important recovery mechanism at this fourth level of physical risk factors.

Also notable is the positive influence of Mindfulness Based Cognitive Therapy (MBCT) and Cognitive Behavioral Analysis System of Psychotherapy (CBASP) on the improvement of chronicity of depression. Both treatments combine various psychotherapeutic visions (MBCT 2008; Wiersma et al 2009). Moreover, short-term cognitive group therapy appears to have a favorable effect on the reactivity of the depression or on ruminating, and therefore appears to reduce the chance of recurrence for patients who have already had four previous episodes. A subgroup of patients who had their first depression at a young age would be less easy to affect in this way. This can be understood based on the view that their depression is more a 'brain disease' and less a reaction to environmental stress (Bockting et al 2009).

Everyone agrees that rigorous treatment of residual symptoms is important in reducing the risk of recurrence. In the long term, maintenance treatment with antidepressants does not protect the majority of the patients from a recurrence. In conclusion, there is no immediate genetic treatment for mood disorders. It is also not possible to do preventive testing on young children for the risk of depression. After all, the depression gene does not exist (Risch et al 2009) and the existence of a specific endophenotype has not been proven.

7. Method and Summary

This chapter contains all the previously cited information in a final working model, which can be used in diagnosis and in the development of a treatment plan for patients with depression. As an illustration, two cases have been worked out with the aid of this model. This is followed by examples of current developments within medical science that work towards a more integral vision of diagnostics and treatment. As an appendix we have included tables which arrange the current tested treatments for depression according to the levels in the working model. Hopefully this will help in daily practice.

7.1. Establishing an Individual Diagnosis

In Chapter 2, the model for diagnosis and treatment of depressive disorder was introduced. The clustering of risk factors (McHugh) is different per system level, just as are the functional systems (Loonen) and the self-regulative processes (Bie van der et al) connected to it. The self-regulative processes are, as developed in Chapter 3, active at every level. It is probable that every level has a different self-regulating mechanism: heterostasis, allostasis, homeostasis, and epigenetic factors through transcriptional regulative networks.
It is not clear how the balance between risk factors and recovery processes is maintained: for this reason the authors of 'The Healing Process' (Bie et al 2008) employed the metaphor 'Organ of Repair'. Distinguishing risk factor levels and related functional systems as well as the possible consequences for the other levels is significant for an appropriate choice of treatment. For the authors of this Companion, it has become clear that the relation between biological and psychological risk factors and recovery mechanisms needs to be further explored and developed. In figure 7.1., the working model from Chapter 2 is presented in an augmented version. Each cluster of physical and psychological causes is, in fact, held in equilibrium by two self-regulative processes.

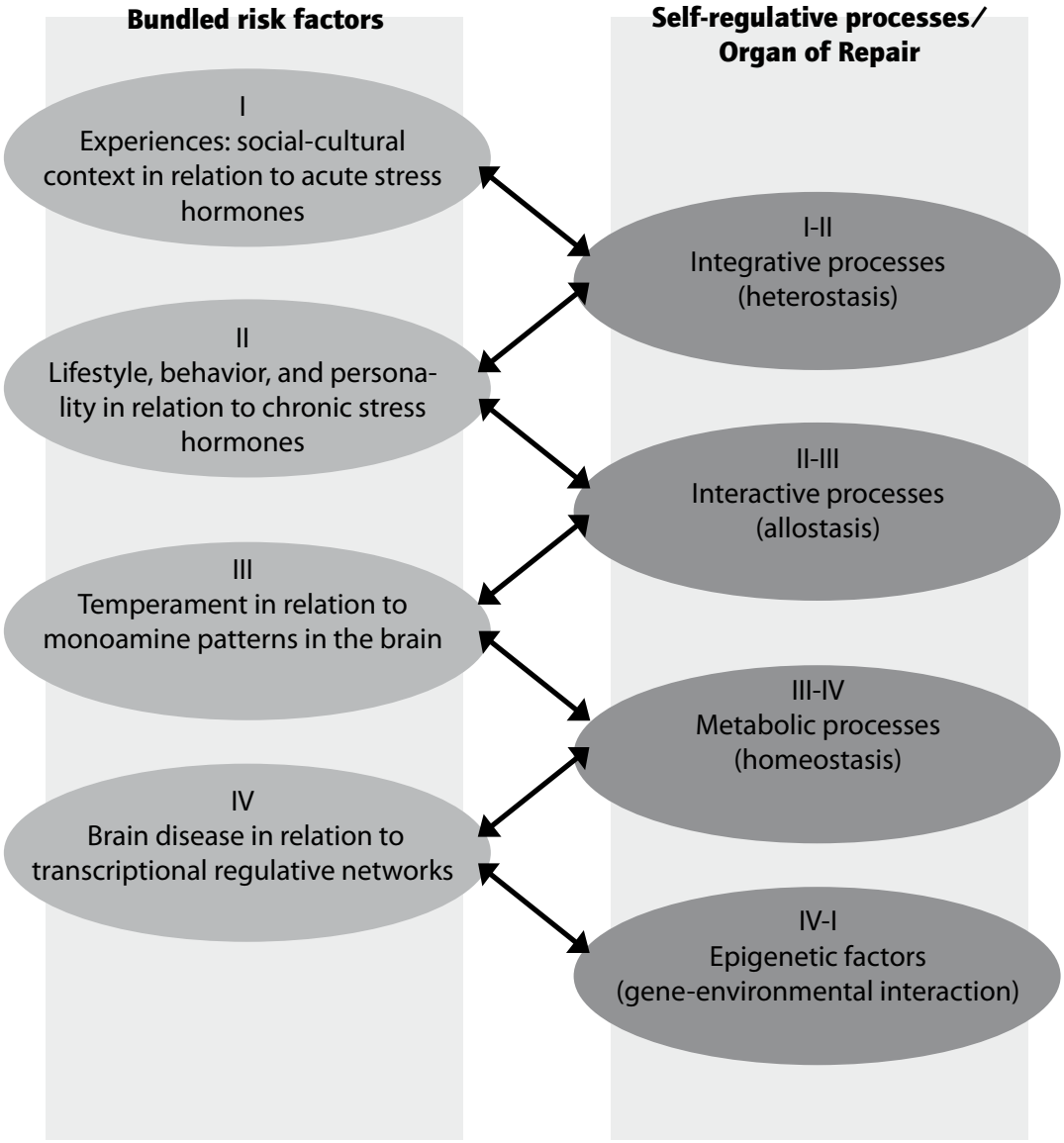

Figure 7.1. The interaction between the syndromal causal classification of depression (according to McHugh, 2009) in relation to the functional classification (according to Loonen 2009) and the recovery processes according to the phenomenological method (Bie et al 2008)

In order to establish a diagnosis and treatment, the following principles are employed:

1. The diagnosis is, in first instance, made at syndromal level. Thus, more than one causal cluster can be involved. This first step is in keeping with the diagnostic method within the current DSM classification. The biography (level I) and an investigation of psychological factors and lifestyle particulars (level II) individualize the first diagnosis, along with the somatic anamnesis (III) and family details (IV).
2. Based on these data, an assumption can be made as to which causal clusters are (and were) involved in the development of the current depression. It follows from the developmental line whether there is a *psychosomatic* or a *somatopsychological* development of the symptomatology. In a psychosomatic dynamic, the *point of departure* for the treatment lies in connecting to and strengthening the integrative and interactional processes. In a somatopsychological dynamic, metabolic processes are the basis for therapy. The approach using the dimensions as illustrated in table 7.2., also belongs to this second diagnostic step.
3. The question is put: Is there is a hardening/decelerating dynamic in which healing is slowed down or remains stuck at a certain stage or, conversely, a dissolving/accelerating development? Chronicity indicates a hardening dynamic. An acute episode of depression or hypomanic or manic episodes have a dissolving tendency. A long-lasting depressive episode or also bipolar disorder can lead to chronicity or hardening, based on the above-described mechanism of kindling, sensitization, and anticipation. Chronicity is the consequence of the involvement of the lower two levels of risk factor clusters (levels III and IV), and demands a more inclusive therapeutic effort. There is less spontaneous recovery.
4. The degree of severity of the depression determines, along with its duration, the level at which the treatment must first be started. Severe depressions demand, in the first instance, a coercive approach, for the purpose of safety and immediate general improvement. Nonetheless, even in more serious depressions, an assessment can be made as to whether the patient be placed in a more passive role or whether a greater appeal can be made to the patient's own efforts.

7.2. Case Studies

7.2.1. Anna

Anna is a now 63 year old woman who has been a widow for sixteen years. After the death of her husband she began to suffer from increasingly longer depressive episodes; the current one has been going on for 8 months. There have never been psychotic symptoms. She is suffering from a general depressive mood and loss of pleasure. She also complains about fatigue, loss of concentration, and brooding.
Fortunately, she still maintains a hopeful perspective for the future and has no thoughts of death. She is desperately trying to cheer herself up, but cannot seem to find her footing so that she has the feeling that she is barely keeping her head above water. Due to her loss of appetite, she has lost a good deal of weight. She had severe sleeping problems, which ultimately led to total insomnia. Anna has always had problems with feelings of inferiority and self-reproach, which have now increased considerably. Moreover, she has the feeling that she is made up of two parts: a lower part starting at the diaphragm with abdominal pains and a heaviness in her legs, and an upper part with no sensation whatsoever, where she feels that she is not even there. In particular, when people she cares about leave – or in some situations in which she already felt powerless – she feels like she is retreating to the level of a young child with corresponding behavior and thought patterns. It is accompanied by severe anxiety. As a child, she learned to control herself trying not to irritate her mother. She believes that others do not notice her depression. In addition to an estimated ten episodes of depression of increasing duration, over the past few years there have been subsequent episodes with an elevated level of energy, spending sprees, much talking, and less need for sleep. A few years ago, she had a serious myocardial infarction. She smokes 15 cigarettes per day.
With respect to her past, she says that during WW II her father died six weeks before her birth from an infectious disease. Her mother, who was always unstable, completely lost her bearings and neglected her and her older sister. Also, her mother physically abused her children, and her then live-in stepfather sexually abused Anna. On top of that, she was once raped outside the family setting and another time was molested. She had been a naturally

cheerful and adventurous child who, however, had to learn to suppress her rebellious nature in order not to antagonize her mother. The suppression of emotions is a theme that has remained with her up to the present. She has not had individual psychotherapeutic treatment for the events from her past.

Interpretation of Anna's Case

Try to differentiate between Anna's current symptoms and the development of her symptoms over time. Then divide the symptoms and the developmental steps according to system level: integrative system, I; interactional system, II; metabolic system, III; and genetic factors or chronicity, IV.

For the *symptoms in the here and now*, the classification is as follows:

Level II: depersonalization, decreased self-esteem, anxiety, sleeping problems, smoking;
Level III: depressive mood, anhedonia, exhaustion, cognitive problems, decreased appetite, hypomania;
Level IV: chronicity, myocardial infarction.

With respect to the *developmental history*, the classification looks like this:

Level I: widow, regression, death of father, emotional neglect in family of origin, sexual abuse in family of origin, rape and molestation outside of own family;
Level II: her need for control, suppression of own feelings;
Level IV: recurring episodes of depression, myocardial infarction.

The actual symptoms mainly play a role at the metabolic level (III), and there were a number of serious traumas in the development (level I). Along with the question of whether there is a bipolar II disorder, the current symptomatology demands, in the first instance, an effective treatment of the present protracted depression (level III-IV), certainly also in view of the ongoing and increasing chronicity. In addition to medication, the chronicity could perhaps be decreased with mindfulness therapy (level I), which could also break through the sensitization (level IV). Mindfulness therapy can help reduce negative thoughts as well

(level II). Running could be an interesting option for stimulating the metabolic processes (III). Depression together with smoking increases the risk of another myocardial infarction. Running could also increase her chance to stop smoking. Professional psychotherapy could contribute to recovering the buried spontaneity (III), help her to start a mourning process (I) for the many losses she has suffered and, at a later stage, perhaps help her integrate the various traumatic experiences. However, it is no less important to strengthen Anna's social embedding, to help her find a new perspective for her life (I-II).

Since the *causes* appear in the interaction between levels I and III/IV, the treatment begins first with stabilization (III/IV), in order, via an adequate mourning process (I), to arrive at a new insight of herself (II), which can augment the lifestyle changes. And indeed, lithium treatment for level III/IV has improved her condition considerably.

7.2.2. Frederieke

Frederieke is a 60 year old woman who was hospitalized in a psychiatric clinic 4 weeks ago with her first depression. She looks thin and somewhat boyish, her appearance is in keeping with her age; she is light-footed and soft-spoken. She does not give the impression that she is depressed; there is no psychomotor retardation. It is striking that during the major part of the interview her chest area appeared immobile. Thus far, antidepressants and tranquillizers have had no positive effect. The depressive mood has been going on for two years and has led to absenteeism from work. Along with her depressed mood she is also afflicted with vague feelings of anxiety and panic every evening when attempting to fall asleep, which also appear when she focuses her attention on her restricted breathing. She has serious problems falling asleep, headaches, and is not able to focus when reading, a problem for which the ophthalmologist cannot find an explanation. She does greatly enjoy taking care of her grandchildren once a week. She is often tired.
With respect to her previous history, she says that she is the eldest in a family of six children. As a baby, she had infantile eczema and severe symptoms of asthma, for which she had to be hospitalized as a young child. She was often short of breath at night, so that she also did not get enough sleep. What is curious is that she cannot remember being anxious, but

does remember that she never woke her parents because "they couldn't do anything about it anyway." Her asthma gradually disappeared as she reached elementary school age. In the final years of elementary school, she was belittled by a teacher. She never talked about that, either. She does know that she already had low self-esteem at the time, something that she has never been able to get rid of. In spite of these problems, she was a cheerful child who was always integrated in the group. When she was 24 years old, her first husband was killed in an accident. Frederieke was then a few weeks pregnant. It was a huge shock for her, and her trust that things will turn out well was shaken. She later remarried, is happy about that and had three more children. She derived a great deal of joy from motherhood. After the children ceased to need so much care, she started doing secretarial work until she was no longer able to continue. As a result of her symptoms of depression, she started to attend workshops where she dealt with her experience of loss. This also confronted her with her ever-present tension, lack of self-confidence, and strong control issues.

Interpretation of Frederieke's Case

Frederieke's *symptoms of the here and now* seem to be much less chronic in nature than for instance Anna's, although the existence of a dysthymic disorder cannot be ruled out:

Level I: no improvement with antidepressants and tranquillizers;
Level II: restricted breathing, headaches, feelings of anxiety and panic, problems falling asleep, slight build, and 'lightness';
Level III: cognitive problems, depression, and fatigue have been going on for two years.

In reference to the *developmental history* of the symptoms:

Level I: an initial episode of depression, probably in reaction to the realization of the significance of suffering a loss, lack of parental emotional support as a child, loss of first husband, and loss of (administrative) work;
Level II: chronic asthma, over-compensation, feelings of inferiority.

This leads to the following interpretation of her depression.

Standard medicinal therapy for Frederieke does not seem to fit with the reactive element of her depression. The treatment could, in the first instance, take a psychotherapeutic line of approach, focused on integrating her experience of loss. Then, one could look at level I to see how the talents that she has can be used to improve her social contacts. An 'inward journey' could subsequently help her to discover the various aspects of her inner world – and not only the negative ones. Artistically oriented professional psychotherapy would be very fitting here. Sleep could be improved with physical exercise and better 'exhaling' at the end of the day by keeping a journal and doing relaxation exercises.

Summary Thus, the mapping out of the various levels in these two cases gives an overview of the manifold symptoms and provides a handle for the realization of a treatment plan.

7.3. Systems Biology and Personalized Medicine

Van der Greef and Hankemeier (2009) discern a continuum of general homeostatic dynamics with resilience (general health promotion) on one side and on the other side disease management focussed on the symptoms. As long as the maintenance of homeostasis is effective through the activation of self-regulation, the person remains healthy. Interventions may be applied by the person himself or by the therapist. These are focused on supporting the resilience, such as stress reduction, change of lifestyle, meditative exercises. During an acute depressive episode or in chronicity, there may be a changed, allostatic equilibrium, which is a reason for prescribing coercive medication. 'Personalized Medicine' can, according to van der Greef and Hankemeier, be in keeping with a biological basis, where many 'biomarkers' can be mapped out like a fingerprint in order to make visible the process of loss of general homeostasis and the change in self-organization. They see similarities with how ancient healing methods such as Chinese or Ayurvedic medicine have an effect on the individual patient. Western medicine has taken the approach of 'disease management.' The drugs that have resulted from it are not individualized; they are validated by group studies. With the aid of such techniques as 'metabolomics', 'proteonomics,' and 'transcriptomics' – all systems biological diagnostic techniques – the diagnostics in Western medicine can certainly be individualized, and it

can be investigated which drugs have the most effect on the patient in question.

From their systems biology study of Chinese medicine, it can be concluded that thus far non-proven healing methods appear to be relevant and effective with this technique. Thus, Wietmarschen (2009) discovered, based on studies with modern biomarkers that the Chinese forms of diagnostics of rheumatism corresponded to systems biological subtypes. Van der Greef and Hankemeier argue: "the integrating of systems-based molecular phenotyping with diet, psychology, and environmental aspects into a 'total package' for one's way of life is a requirement for a revolution in healthcare."

Their method is also focused on following the individual patient in order to assess whether or not the treatment is helpful. It will certainly take years before such an approach becomes common practice, but the direction of development is clear: more effective medicine should focus on the individual and as much as possible be based on the patient's own powers of recuperation.

7.4. Integral Psychiatry

Depression demands an integral approach, as every therapist knows. We have, however, already seen in Chapter 2. that in the biopsychosocial model (Engel 1977) the subject has disappeared. This model is not based on an explicit systems vision. If the individual is put at the core of treatment, then one is quite definitely confronted with non-conventional systems of medicine. These systems are based not only on the physical or biological factors that form the basis of disease. In addition, they take into account the role of complex, non-linear processes and the idea that consciousness can have non-local effects on health and disease. Current scientific models of brain functioning are not able to explain the role of consciousness in healing processes.
Integral psychiatry is based on the following (Hoenders et al 2010):

(a) Optimization of the therapeutic relationship
(b) An open yet critical attitude towards all therapeutic disciplines and systems on the

basis of *evidence-based medicine*
(c) Focus on the promotion of health and well-being
(d) Treatment in a *healing environment* based on a holistic vision

In integral medicine, health is seen as an expression of complex interactions among physical, biological, psychological, and spiritual factors arranged in multiple hierarchical levels in time and space (Bell et al 2002; Reilly 2001). The call for non-conventional treatments has grown because conventional antidepressants appear to have a limited effectiveness, and the risks inherent in these drugs are often greater than the desired therapeutic effects (Keitner 2004). However, it is important to realize that there is no coherent, integrating theory of integrative psychiatry, just as there is no single practical, clinical method to evaluate collective treatment methods. It is striking that research of standard antidepressants is based on a presupposed mechanism of effectiveness before a drug is allowed onto the market or is reimbursed by insurers or the government, while the situation is reversed for complementary treatments. In that case there is already a clinical practice, and later research is done on the safety and comparative effectiveness of these specific non-conventional healing methods. Another difference is that biomedical research is preferably based on one drug that treats all symptoms. In non-conventional methods, often a system of treatments in which the various treatments synergetically support each other, is used, so that the whole produces a better result than the sum of its parts.

For that matter, there is also a variety of standard treatments for which practice-based research is more suitable than a double blind randomized controlled study (Fønnebø et al 2007). When research is based on the individual patient, there is a central methodological place for the schooled, phenomenological clinical judgment of the experienced therapist with respect to pattern recognition and pattern application (see also: Baars 2009).

7.5. The Summarized Model for Diagnosis and Therapy of Depression

Table 7.1. summarizes the elements that form the basis for a establishing a diagnosis that focuses on the individual and aids in developing an individual treatment plan. In the table the four different levels are categorized.

In table 7.2., four different dimensions are indicated with which the symptoms can be refined. Three different 'brain systems' are described, which help direct the various levels: the central brain, the emotional brain, and the 'unconscious' brain. The latter includes the immune system and different hormones.

The Appendix comprises four tables that specify a possible division of therapeutic interventions, arranged according to the four described levels of effectiveness.

Table 7.1. Summarized model for diagnosis and treatment of depression

Risk factor	Systems dynamics	Resilience	Integral psychiatric treatment
Reaction to negative events	Integrative	Heterostasis	Spiritual or bioenergetic treatment
Damaging response patterns	Interactional	Allostasis	Life style changes
Sensitivity to anxiety, stress, agitation	Metabolic	Homeostasis	Biochemical therapy
Brain disease	Genetic	Epigenetics	Biomechanical therapy

Table 7.2. Supplementary dimensions

Somatopsychic		Psychosomatic
Dissolving		Hardening
Disease management		Self-regulation
Unconscious brain	Emotional brain	Central brain

Appendix

Appendix of overview tables with researched treatment methods for depression. (T) stands for the level of evidence from the Trimbos Institute, Netherlands (2007). (L) level of evidence according to Lake (2007). (L&S) level of evidence according to Lake and Spiegel (2007).
For explanation of the levels of evidence, see below.

A. Table of Integrative Treatment

Treatment	Verification Level
EMDR	
Narrative Therapy	
Bibliotherapy	2(T)
Self-Management	1-3(T)
Counseling	3(T)
Psychosocial Interventions	3-4(T)
Art Therapy	3(T)
Attentive Listening to Music	3(L)
Spirituality, Religiosity: Decreased Risk of Major Depression	1(L&S);2(L)
Therapeutic Touch: Decreased Severity Depressive Mood	3(L)
Qigong: Improvement General Well-Being	3 (L&S)
Problem Solving Therapy for Mild Depression	1 (T)
Psychoeducation Group	1 (T)
Internet Psychoeducation	3 (T)

B. Table of Interactional Treatment

Treatment	Verification Level
Light Therapy: 10.000 Lux; not only for Seasonal Depression	3 (T); 3 (L)
Dimmed Green, Blue, Red Light for Winter Depression	3 (L)
Vitamin D for Winter Depression	3 (L)
High-Density Negative Ions for Winter Depression	3 (L)
IPT	1 (T)
CBT	1 (T)
Stress Reduction/Relaxation	4 (T)
Antidepressants	1-3 (T)
Benzodiazepines	1 (T)
Melatonin	
Thyroid Hormone	
MBCT	2 (L&S);1-2 (L)
Yoga	2 (L&S); 1-2 (L)
Heart Coherence Training with EEG-Biofeedback	2 (T) 2 (L)
St. John's Wort for Light to Moderate Depression	1 (L&S) ; 2 (L)
Sleep Deprivation	1 (T)
Running Therapy	2 (T)

C. Table of Metabolic Treatment

Treatment	Verification Level
Antidepressants	1 (T)
S-Adenosylmethionine, wheter or not synergetic with conventional antidepressants	1 (L)
Vitamin B6, B12, Folate, C, D, E as synergetic therapy	2 (L)
Omega-3 Fatty Acids	1 (L&S); 2-3 (L)
Diet: Restricted coffee and sugar, more fatty fish and sustaining foods	1 (L&S); 3 (L)
Ayurvedic Herbs	3 (L)
5-Hydroxytryprophan	2-3 (L)
L-Tryptophan	2-3 (L)
Acetyl-L-Carnitine	2-3 (L)
Inositol	2-3 (L)
Dihydroepiandrosterone (Mild to moderate depression)	2-3 (L)
Cortisol Reducers: Ketoconazol, Aminogluthemide, Metyrapon	3 (L)
ECT	
TMR	
CBT	1 (T)
MBCT	
CBAT	
Mindfulness	
Acupuncture	3 (L)
Classical Homeopathy	2 (L&S);3 (L)
Hyperthermic Baths	3 **
Lithium addition for TCA	1 (T)
T3 addition	2-3 (T)
Acupuncture: for women Other	1 (L&S) 3 (L&S)

D. Table of Genetic Factors in Treatment

Treatment	**Verification** Level
Parenting	
Religion	
Favorable Social-Economic Circumstances	
Physical Activity	2 (T) 1 (L)
CBASP	***

Clarification of the Classification used by the Trimbos Institute, Netherlands, of Multidisciplinary Guidelines for Depression (2007)

For articles concerning prevention or therapy

A1 systematic reviews that deal with at least a few studies of A2-level, which are consistent with the results of separate studies;
A2 good quality randomized comparative clinical studies (randomized, double-blind controlled trials) of sufficient size and consistency;
B randomized clinical trials of poor quality or insufficient size or other comparative study (non-randomized, comparative cohort study, patient-control-study);
C non-comparative study;
D opinion of experts, for example, members of the work-group.

Level of the conclusions

1 based on a minimum of 1 systematic review (A1) or at least 2 studies that are independent of each other at level A1 or A2
2 based on at least 2 studies carried out independently of each other at level B

3 based on 1 study at level A2 or B or study/studies at level C
4 published opinion of experts or opinion of work-group members.

Clarification of the Classification used by James Lake (2007)

Since the above therapy tables also include treatment methods for depression from integral psychiatry, we will quote from the excellent book by Lake on integral psychiatry and cite the criteria on which he bases quantitative and qualitative studies (Lake, page 75, 2007).

Level 1. Substantial proof of evidence. The method is in use and is effective.
The results of systematic reviews are convincing or they are very suggestive or there are three or more rigorously organized double-blind RCT's. There is also support from a representative group of professionals who practice the treatment method in question.
Level 2. Provisional proof of evidence. The method is in use and is probably effective.
The results of systematic reviews are very suggestive, but are either not totally consistent, or there were too few studies for review, or three or more rigorously organized double-blind RCT's provide strong indications but are not completely consistent. There is support from a representative group of professionals for the type of treatment in question.
Level 3. Provisionally effective. The method is used and is perhaps effective.
There are fewer than three well organized studies or three or more less well organized studies. The results of the studies or case reports are limited and inconsistent and there are too few qualitatively good studies on which a systematic review or meta-analysis can be carried out. The treatment is in use but remains controversial. There are, however, a sufficient number of professionals familiar with the treatment.
Level 4. Refuted. In spite of the fact that the treatment is used in practice, there is no scientific evidence that supports its use.

Lake notes that, in this way, all forms of medicine can be categorized according to proof ofevidence. He points out that the double-blind RCT is the gold standard in biomedical research. However, the cohort study is the gold standard for clinical judgment.

Clarification of the Classification used by Lake and Spiegel (2007)

Appendix A in this publication is a table in which scientific evidence concerning the effectiveness of complementary and alternative medicine is categorized according to the following criteria:

Level 1. Accepted use of a therapy for depression based on a systematic review or on three or more RCT's.
Level 2. Use of a method that is based on consistent results of open trials or fewer than three RCT's.
Level 3. The use of the method is supported on the basis of consistent experiences but there have been few or no studies.

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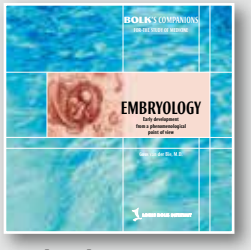

Embryology
Early development from a Phenomenological Point of View

Guus van der Bie, M.D.
Publicationnumber GVO 01

Can we give a scientific basis to our feeling that humans have unique human features? Are the human mind and the human organism 'nothing but' another variation of animal life? Can we find answers for the questions that satisfy both head and hart?
How these quetions are answered depends on the scientific method we use: the current scientific method to learn about biological facts and the phenomenological method to understand more about the meaning of these facts.
Early embryological development can teach us about the unique and characteristic qualities of the human being.
The result is, for example, a possibility to understand the relation between consciousness, psychology, and behavior and the shape of the body.

Biochemistry
Metabolism from a Phenomenological Point of View

Christina van Tellingen, M.D.
Publicationnumber GVO 02

Biochemistry offers insight into the continuous changes within the human organism. But can we maintain awareness of the coherence of the (changing) organism as we study the details? How can the many processes be understood as prototypical aspects of a unique organism?
The scope of the answers to these questions can be enhanced by using a combination of the current scientific method and a phenomenological method developed specifically to research the coherence of processes within living organisms. The current scientific method is used to discover biological facts. The phenomenological approach helps us in finding the meaning of the facts.
What emerges is a new grasp of the interrelations between biological processes, consciousness, psychology, and behavior.

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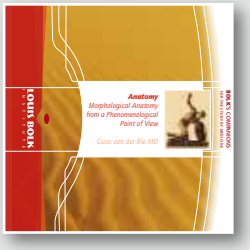


Anatomy
Morphological Anatomy from a Phenomenological Point-of View

Guus van der Bie, M.D.
Publicationnumber GVO 03

Can we give a scientific basis to our feeling that the human being has unique human features? Are the human mind and the human body 'nothing but' another variation of animal life? Can we find answers for these questions that satisfy both our head and our heart?
How these questions are answered depends on the scientific method we use. In this publication two methods are used: the current scientific method to learn about anatomical facts and the phenomenological method to understand the meaning of these facts.
Human morphology can then be understood as an expression of the unique and characteristic qualities of the human being.
This results in new possibilities for understanding the relation between consciousness, psychology, behavior, and morphological aspects of the body.

Physiology
Organphysiology from a Phenomenological Point of View

Christina van Tellingen, M.D.
Publicationnumber GVO 04

Can physiology give more insight into the living human organism than the mere facts reveal at first? Is the level of activity the same for all organs? Are the vital qualities at work in organs unique for organisms and limited to biological activity? Can we find a scientific basis to research the coherence between organ systems?
By enhancing the current scientific method with phenomenological points of view we can find meaning in the facts and understand them as an expression of life itself. The phenomenological method makes the relation between organs visible and comprehensible. It approaches scientific facts from the point of view of their coherence and can give totally new insights this way.
What emerges is a grasp of the interrelations between biological processes, consciousness, and nature.

Immunology
Self and Non-self from a Phenomenological Point of View

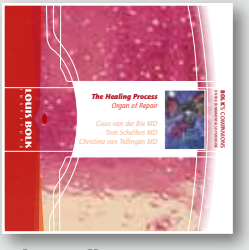
Guus van der Bie MD
Publicationnumber GVO 05

Why write this new booklet on immunology when there are already so many excellent texts on the subject? This Companion is about questions such as: why is it that the immune system functions as one organ? What coordinates the immunological functions?
Here, an attempt is made to develop a viewpoint to answer these questions. By using a phenomenological approach, the factual knowledge obtained through reductionism is placed in a larger perspective.
The concept that is presented in this Companion is derived from the functioning of organisms, observed in the way that was introduced by Goethe in his phenomenological method. This also includes the acquisition of insight into the holistic concept behind the immune system. Moreover, the organism as a whole can then be seen as an expression of the same concept.

Pharmacology
Selected Topics from a Phenomenological Point of View

Christina van Tellingen MD
Publicationnumber GVO 06

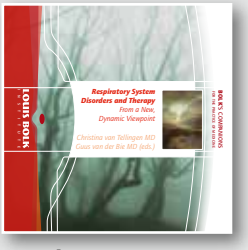
Pharmacology gives us insight into the way organic processes change when foreign compounds are introduced into the organism. Pharmacology is a changeable subject, depending on the needs and knowledge of the time. Can we find an inner coherence in the manifold ways compounds influence organisms? What should such a framework be based on? How can we understand the effect on human consciousness that most compounds have?
We can enhance the scope of the answers to these questions by using a combination of the current scientific method and a phenomenological method. It illuminates the known facts about the activity of compounds in organisms, and provides the means to find their significance.



The Healing Process
Organ of Repair

Guus van der Bie MD
Tom Scheffers MD
Christina van Tellingen MD
Publicationnumber GVO 07

After finalizing the series BOLK'S Companions for the Study of Medicine for the moment, this module on The Healing Process introduces a new series of BOLK'S Companions that studies the Practice of Medicine. In it, we research the healing process itself. There proved to be an enormous volume of scientific literature on the subject. It is easy to loose oneself in the countless details included in the descriptions of this process.
The phenomenological method of systems biology makes it possible to examine physiological and pathological processes in terms of the processes themselves. This results in a characterization of the various phases of the wound healing process. Out of this, new insights into the origin of health and disease emerged that also offer possible leads for medical practice.



Respiratory System
Disorders and Therapy
From a New, Dynamic Viewpoint

Christina van Tellingen MD
Guus van der Bie MD (eds.)
Publicationnumber GVO 08

In this Companion, the experience of three of our own patients with asthma and pneumonia is used as backdrop for our study of airway disorders. Nearly all of us have had some experience with respiratory disease, given that colds, flus, sinusitis, and bronchitis are so common. Most physicians and therapists know people with asthma and pneumonia from own experience and will readily recognize the descriptions we provide.
The experience with these patients leads us through a study of airway disease which eventually opens up to a wider view with new insights and innovative avenues of treatment for respiratory disorders in general.
Our research has alerted us to the part rhythm plays in the healthy respiratory tract and in the treatment of its disease. Rhythm, consequently, is the subject of the final paragraphs of this Companion.

Wholeness in Science
A Methodology
for Pattern Recognition
and Clinical Intuition

Guus van der Bie MD

How do you develop clinical intuition? How do physicians gain practical knowledge about disease?

The above questions are vital for medicine. Diseases do not merely concern a partial defect, they recreate the life of the patient. At the hand of Pfeiffer's disease, the author shows that experienced physicians conceive of diseases as integrated concepts, which they can apply to the individual situation of the patient. Their clinical intuition is a form of pattern recognition and pattern recognition supports the ability to recognize an integrated 'whole.'

The practical exercises of this Companion allow readers to train and expand their ability of pattern recognition through Goethe's methodology. Clinical intuition, as experiential knowledge, appears to be a skill that can be actively developed.

For ways to order the Companions see inside of front cover or check our website: **www.louisbolk.org/companions**

Depressive Disorders

An Integral Psychiatric Approach

'This book describes clearly how a systemic approach, recognizing the coherence and interconnectedness of symptoms, can provide a richer image of the diagnostic fingerprint in depressive disorders. This becomes the basis for individualization in therapy. The patient's role and the quality of the patient/therapist relationship are essential constituents of treatment. The book presents an excellent overview of various scientific perspectives in the field of depressive disorders. Case studies illustrate how the enriched diagnostic fingerprint leads to an improved therapeutic approach in practice.

This book should be required literature in medical school. It is also a source of knowledge for all mental health care workers, especially those who are active in the field of depressive disorders.'

Professor Dr. Jan van der Greef,
Professor of Analytical Biosciences at
Leiden University, Scientific Director of
Systems Biology Research at TNO.

'This book inspires and facilitates an individual approach to patients with depressive disorders, and aids therapists in finding ways to support the patient's recovery process!'

Anne-Marije Schat,
psychiatry resident at
Utrecht University Medical Center

the natural source of knowledge