# Sensorimotor Modulation of Mood and Depression

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By

Resit Canbeyli

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# FOREWORD

Depression is one of the most prevalent and devastating psychopathologies humanity faces, as its toll on individuals and societies is getting alarmingly more costly by each passing year (WHO (World Health Organization) 2018; World Health Assembly 2012). While there is a tremendous effort by clinicians and researchers to discover more efficient therapies for depression and, just as importantly, to prevent its occurrence, there is no algorithmic cure for the pathology nor any indication that we are close to a state of understanding to achieve such a goal. Despite the grim situation at present, there is reason for optimism in the long run for treatment and, just as importantly, for the prevention of depression due to increased concerted efforts by clinicians and researchers. Interested readers will find a large number of books that document the progress in this area, ranging in scope from those with a clinical perspective to others dealing with the neurobiology and pharmacology of the psychopathology. In this context, the tenure and approach adopted by the present book must be emphasized. The book is not meant as a clinical guide to the treatment of depression nor does it purport to provide a definitive insight into its pathogenesis. Instead, as will be evident, starting with the introductory chapter, the book will provide strong evidence that a comprehensive assessment of both the etiology and therapeutics of depression requires an integrative view of how affect and mood are modulated by peripheral as well as central mechanisms. The main thrust of the present book can be briefly summarized as follows: sensorimotor stimulation, via the five sensory modalities (vision, audition, olfaction, touch and gustation) as well as the motor system, is capable of modulating mood and depression. This means that, depending on several parameters, peripheral-bottom-up-sensorimotor stimulation can have the diametrically opposite effects of alleviating or aggravating mood and depression in humans and animals. Moreover, depression, in turn, can modulate sensorimotor function, mostly in the negative direction, impairing sensory processing in all sensory modalities, as well as altering motor behavior.

The main thrust of the present book is that sensorimotor stimulation has direct affective consequences, which may accrue over time and circumstances to modulate mood and depression. A major reason for writing this book is

the fact that, despite the vast accumulation of evidence supporting the critical contribution of sensorimotor stimulation to mood, there has been, so far, no integrative/comprehensive view to synthesize these findings with what we already know about the pathogenesis and therapeutics of depression, based on the centralist/top-down view that the brain is and should be the main target of any effort to understand and cure the pathology. One reason that such a bottom-up view has been missing from the established theoretical and, to a lesser extent, practical approach to depression is the overwhelming emphasis on the central mechanisms—a point taken up in the introductory chapter. The other reason is due to the rather historically inconsistent approach to the intricate relation between sensation and emotion, evident in the history of psychology and neuroscience. This claim may seem too strong for many readers who are familiar with more recent interest in those fields for understanding and applying emotional approaches to therapy. Neverthless, it is justified not just on the basis of the historically inconsistent approach to the relationship between sensory data and affect, but also due to the fact, which will be clear from the following chapters, that interest in that relationship has not translated into a coherent, integrative framework for the subject until very recently, when the present author argued for such an approach in three review articles published, approximately, over a decade (Canbeyli 2010; 2013; 2022).

Since the main thrust of the present book is the sensorimotor modulation of mood and depression, it is critical to assess and to document how such peripheral stimulation comes to engender mood changes that may, in the long run, have the diametrically opposite effects of inducing or alleviating depression. Leaving the latter issue of detailed documentation to the subsequent chapters, it is important to briefly highlight a few landmarks in how views on the relation between sensation and emotion/affect have fared, roughly, over the last century and a half. For that purpose, an important starting point is a revolutionary idea, advanced by Gustav Fechner (1801–1887), in Germany, before psychology was established as a scientifc discipline in the second half of the nineteenth century. In his seminal 1860 book, *Elemente der Psychophysik* (*Elements of Psychophysics*), Fechner equated in a formula—the first of its kind— the sensory/psychological impact of the physical intensity of sensory stimulation: S=klogI, where k is a constant, S stands for the psychological effect engendered by a sensory stimulation, with a physical intensity, I, such as perceived loudness for auditory stimulation or brightness for photic stimulation. While the validity of the Fechnerian equation was later questioned by S. S. Stevens (Stevens 1961), what truly matters, even today, as a guiding beacon, is Fechner's

revolutionary idea that sensation, and the physical stimulation that induces it, can be expressed together and equated by means of a psychophysical equation. The main message behind this formula, which finds resonance in the main theme of the present book, is the all-important view that the physical aspect of sensory stimulation has a measurable/quantifiable psychological impact. In fact, the present book goes beyond the psychophysical equivalence to assert and to document the mood modulatory impact of sensorimotor stimulation in humans and animals.

Studies after Fechner developed the notion that sensory stimulation has a lawful impact on our psychology. An important issue in this context is how we have moved from a rather mechanistic approach, in Fechner's psychophysics, to the present realization that what and how we sense, through our sensory modalities, and how we move, by means of the motor system, have profound implications for emotion, mood and affect. This has not been a short, straight journey, but a few important developments along the way will be discussed to show how the rather mechanical psychophysical view can be transformed into an integrative framework that explains how sensorimotor stimulation can modulate mood and depression.

The next important development in this area, after Fechner's formula, came from a prominent scientist whose studies and whose establishment of an institute in Leipzig Germany have been considered the official inauguration of psychology as a scientific discipline: Wilhelm Wundt (1832–1920). In fact, it is common to begin the history of experimental ("physiological") psychology in 1879, on the occasion of the establishment of the physiological psychology institute in Leipzig. Wundt's introspective psychology aimed to discover the immediate impact of sensory input in trained experimenters who were expected to introspect and describe the unmediated impression they had upon being exposed to such inputs. Wundt and several prominent German psychologists, at that time, were trying to delienate the fundamental sensory elements with the aim of arriving at laws or principles that were necessary and sufficient to build perceptions. In a nutshell, their methodology paralleled that of chemists who synthesize new chemical compounds from atoms—fundamental elements of physics and chemistry (Reisenzein 1992; Shanker 2015).

In retrospect, scientific history does not look favorably upon the Wundtian approach of building percepts from sensory elements. One major reason was the devastatingly brilliant experiments by Gestalt psychology, mainly by the Gestaltist Max Wertheimer (1880–1943) and colleagues, demonstrating that the whole is different from the sum of its parts and that knowing all of its

elements separately did not guarantee and predict the full psychological experience of the whole. Wundt's elementism, therefore, lost its appeal to many psychologists at a time when psychology had begun to show a remarkably rapid growth in the universities in Europe and, particularly, across the ocean in the USA.

Unfortunately, when elementism was shown to be a fruitless approach to study sensation and perception, a fundamental tridimensional view of emotion based on sensation, developed by Wundt, was also cast aside for a long time; namely, that such emotion due to sensory stimulation was a mixture of three dimensions of feeling; pleasure vs displeasure, excitement vs inhibition (tranquillization), and tension vs relaxation (Blumenthal 1975; Reisenzein 1992). Many theories of emotion have been advanced since Wundt's time, but his view stands alone in strongly positing an emotional quality to sensory data. The extension of such a view that includes—unlike Wundt's approach-—animals would dovetail with the thesis of the present book that sensory stimulation in humans and animals has an affective component that may be accumulated or dissipated, over time, depending on several factors, including the state of the organism, and the quality, intensity, frequency (intermittency) and duration of sensorimotor stimulation.

An important lesson to be learned from investigating the development of overarching issues in psychology and neuroscience is the time lag between the slow progress in realizing that a phenomenon is critical and worth studying in depth, and the beginning of the investigations in earnest. This is nowhere more dramatically seen than in the case of sensory modulation of mood and depression. There is no doubt that humans were always aware of the positive mood modulatory effects of fragrances, tactile stimulation in the form of gentle caresses, pleasant music, esthetically pleasing visual artifacts, and tasty food. One can also imagine easily that negative mood can be induced by offensive smells, rough tactile stimulation, cacophonous music, unaesthetic visual items, and unsavory food. Until recently, these observations were not converted to immediate scientific inquiry and did not form the basis of an integrated approach to elucidate the mood modulatory impact of sensory stimulation.

It should be pointed out that the psychological and neurobiological underpinings of the relation between sensory stimulation, emotion and mood have been targets of genuine objective research, with some astounding discoveries, only relatively recently. As the reader will find out in the subsequent chapters, psychology and neuroscience dwelled on the affective aspect of vision, audition, olfaction, touch, and gustation much

later than on the mechanisms underlying the all important sensory processing related to sight, hearing, smelling, touching, and tasting. Just to give two examples, which will be dealt with in detail in the appropriate chapters, later, mechanisms for affective vision and touch were discovered decades later than the basic mechanisms for sight and discriminative touch.

An important driving force in the accelerated research in this field has been the realization that mood disorders, in general, and depression, in particular, now, pose overwhelming global health issues, a point that will be considered in more detail in the introductory chapter. Additionally, the development of animal models to study various pathologies, prominently including depression, has been a source of fundamental information, providing the means to explore the underlying neurochemical and neurophysiological mechanisms of mood and depression.

The following chapters will provide ample evidence—mostly with human data—to demonstrate the significant effects of sensorimotor stimulation in regulating mood. Before delving into the details in those chapters, it may be important to touch upon a few landmark discoveries with animals that have shaped how we think about the importance of sensory stimulation for affect. While there are many important events along the way, three important insights gained since the beginning of the nineteenth century will be briefly discussed: Ivan Pavlov's (1849–1936) work with neuroticism; the development of the learned helplessness; and behavioral despair models of depression.

## Pavlov and the Neurotic Dog

A major development in understanding the full implication of reflexive behavior, first proposed in detail by René Descartes (1596–1650), occurred considerably later, in the early twentieth century, with Pavlov's seminal work on classical (Pavlovian) conditioning. Briefly, Pavlov showed that several pairings of an initially neutral ("conditioned") stimulus (CS) with an unconditioned stimulus (US) that always elicited a specific response eventually resulted in the conditioned stimulus also eliciting a similar response (Fanselow and Wassum 2016; Pavlov 1927). This was the basis of reflexive learning that drew a great deal of interest and inspired a variety of experimental approaches from psychologists and neuroscientists. Importantly, for subsequent developments in this field and more germane to the thesis of the present book, Pavlov showed that emotional reactions in dogs could be induced by what initially looked like a mechanical discrimination task involving a circle ($CS^+$), always paired with food, and

an ellipse ($CS^-$), never paired with it (Gantt 1944; Karn 1940). Pavlov was able to teach a dog to respond (salivate) to the circle and not to do so to the elliptical $CS^-$. After some initial errors, the dog could distinguish and respond to the circular $CS^+$ but not to the elliptical $CS^-$. What made this experiment so different from most of the others in Pavlov's laboratory was the fact that, once the distinction was well learned, Pavlov began to gradually make the elliptical stimulus approach the shape of the circular one. As long as the two CSs were still distinguishable, the dog responded properly but started making more errors when the CSs began to look more alike. A critical point was reached when the ellipse was very difficult to distinguish from the circle. At that point, the experiment took on a new character in that, instead of passively making more mistakes, the dog began struggling from its harness, and showed signs of irritability and emotional distress. This experiment showed, dramatically, that learning, sensory information, and emotions are not only intricately related but, under certain circumstances, can form the basis of psychopathology.

## Learned Helplessness

While Pavlov's work with the neurotic dogs was greeted with interest, it did not quite result in the development of an animal model for studying affective behavior. One study did just that; an important seminal development in animal models of depression first began in 1967 from what was planned as a learning experiment with classical conditioning. Seligman and colleagues (Maier and Seligman 1976, 2016; Overmier and Seligman 1967; Seligman and Maier 1967) exposed dogs to several shocks they could instrumentally terminate (the escapable shock group) and others to shocks they had no control over (the inescapable shock group). The escapable group dogs could not prevent shocks but could terminate them by pressing a panel. Equality (density and duration) of shock treatment for both groups was assured by yoking the two such that the inescapable shock group received the same pattern of shocks that the escapable group received. The two groups were, then, tested in a second phase of the experiment where they could avoid a shock by running to the safe side of a platform. The radically different reactions of the two groups opened a new era in animal research on helplessness and depression because while the dogs in the escapable group from Experiment 1 could learn to escape and, later, avoid shocks in the second phase, the inescapable group simply stayed passively in the experimental chamber and accepted the shocks without making any efforts to escape. The experimenters called this phenomenon learned helplessness. Since the initial experiment, the paradigm has been applied with variations

with dogs and rodents. Such studies conducted with many animal species and with a variety of escapable and inescapable aversive stimulation have indicated that a transient helplessness—akin to a depressive state—can be induced and its consequences measured by means of cognitive or emotive tests. The paradigm has also been applied, with considerable modification, to human subjects with aversive stimulation such as loud tones or unpleasant situations such as unsolvable puzzles (Abramson *et al*. 1978; Cemalcilar *et al*. 2003; Hiroto and Seligman 1975). For the last several decades, there has been a large number of studies cataloguing the negative impact of inducing learned helplessness or depression-like state in animal models of depression, as will be evident from the following chapters.

## Behavioral Despair

There are, now, several animal models of depression using different stressful manipulations to induce depression-like behavior for the purpose of not just probing its underlying central neurobiological mechanisms, but also finding neurochemical and behavioral remedies for such induced depression (Nestler and Hyman 2010; Schulz *et al*. 2006; Sun and Alkon 2003; Unal and Canbeyli 2019; Willner 1995; Yan *et al*. 2010). Two of these methods will be explicitly dealt with at this stage because they have been employed very often in the relevant literature and are referred to in the present book: behavioral despair and the tail suspension test. Behavioral despair, as an animal model of depression, was proposed by Porsolt in seminal articles that enabled researchers to probe the central mechanisms of depression and to screen for potential antidepressants (Porsolt *et al*. 1977a; 1977b; 1978). Briefly, the model, usually using rats, is based on two forced swim tests—the initial induction test, for fifteen minutes, and the test swim, for five minutes—separated by twenty-four hours. A large number of studies have discovered that the immobility in the second swim test is significantly longer than that in the first five minutes of the induction test. This increase in the immobility has been interpreted as behavioral despair, or depression-like behavior, and can be alleviated by antidepressant treatments. The second model, usually with mice as subjects, consists of a six minute tail suspension test followed usually by a forced swim test (Steru *et al*. 1985). In both models, the depressive-like behavior in the form of immobility is often accompanied by anhedonia (Cryan *et al*. 2005). More recently, the forced swim models of depression have been shown to affect not just immobility but also to reduce struggling and swimming (Cryan *et al*. 2002). Furthermore, there is good evidence that these behaviors are related to the impaired central neurotransmission, mainly in the noradrenergic

and serotonergic systems, respectively (Detke *et al*. 1995; Klemm 1989; Yamada *et al*. 2004).

The relevance of the preceding brief account of a few landmarks in psychology and neuroscience to the main theme of the present book will be evident, below, from the treatment of the five sensory modalities and the motor system. At this stage, however, it is important to emphasize that any evaluation of the etiology and therapeutics of depression has to take into account the critical contribution of sensorimotor input from the periphery. Equally important and relevant to the approach espoused in the present book is the realization that depression is an ailment afflicting not just humans, but can be induced, in some form, in animals as well. Special attention devoted to animal research on depression in the following chapters is predicated on the firm view that animal models of depression have provided and will continue to provide valuable information and insights into the psychopathology.

The following chapters will deal with sensory modalities and the motor system to document the wealth of data showing the intricate and critical involvement of each in the modulation of mood and depression. Each chapter will also provide robust evidence that lowered mood and depression, in turn, can modulate sensory reception and perception. Emphasis on the bidirectional nature of sensorimotor activity and depression is an important aspect of the present book and provides the basis of the view espoused, here, that the depressed person lives and labors with not just a modified nervous system, but also an altered sensorimotor apparatus. This reciprocal relation between depression and altered sensorimotor functions can lead to a vicious cycle causing further complications for therapeutically improving mood and alleviating depressive symptoms. It is instructive and certainly surprising to note, at this point, that the reciprocity between depression and sensorimotor function has not been studied adequately nor has it, so far, become a major target of research in its own right.

# INTRODUCTION

With sufferers estimated to be over 300 million in the world, depression is a major health burden for individuals and societies (Whiteford *et al*. 2015; WHO 2016; 2018) and is predicted to become the leading cause of disability by 2030 (World Health Assembly 2012). On an individual basis, depression is a debilitating illness not just impairing mood, motivation, cognitive function, sleep, and dietary patterns, but also contributing to co-morbidity in several major somatic diseases, increasing the risk for diabetes, cancer, cardiovascular, respiratory, and metabolic ailments, among others (Hare *et al*. 2014; Pinquart and Duberstein 2010; Vancampfort 2015a; 2015b). According to two different, but related, studies, depression lowers life expectancy by approximately ten years (Walker *et al*. 2015), increases the risk of mortality by 1.52 times (Cuijpers *et al*. 2014) and is also a high risk factor for suicide, particularly among the young (Hawton *et al*. 2013; WHO 2018).

To many clinicians and researchers, depression is not a single disorder but a heterogeneous illness with a constellation of symptoms, possibly with different causes and underlying pathologies, that can be subsumed under melancholic, atypical, suicidal, reactive, anxious, etc., depressive types (Goldberg 2011; Kunugi *et al*. 2015; Lamers *et al*. 2010; Lee *et al*. 2010). With such a constellation of dysfunctions, it is perhaps not surprising that, despite concentrated efforts, research on the neurobiology of mood disorders has, so far, not covered any biomarker pathognomonic to depression and diagnosis is, therefore, primarily based on symptoms derived from feelings and experiences as reported by the patient.

There are currently two main psychiatric diagnostic systems used globally that directly affect the global clinical categorization and treatment, as well as neuroscientific research, of depression; namely the Diagnostic and Statistical Manual of Mental Disorders (abbreviated as the DSM system) and the International Classification of Diseases (ICD-11). The World Health Organization (WHO 2019) has a guideline for medical professionals in the form of the Mental and Behavioural Disorders Section of the International Classification of Disease (ICD-11), which also includes guidelines for diagnosing depression. The ICD-11 is an all encompassing guideline, covering major diseases and pathologies, meant for medical professions

with heterogeneous specializations in medicine, due to diverse educational systems, sociocultural, and socioeconomic backgrounds.

Designed as a diagnostic system, in the early 1950s, the DSM has undergone several major revisions, over several decades, with the culmination of the current version, DSM-5, launched in 2013 and modified as the DSM V-TR, in 2022 (Clark *et al*. 2017; First *et al*. 2015; Regier *et al*. 2009; 2013; Widiger and Clark 2000; Wilson 1993). The DSM system defines depression based on depressed mood, loss of interest or pleasure, feelings of guilt or worthlessness, changes in appetite or weight, changed energy/fatigue psychomotor disturbances, sleep disturbances, impairment in concentration or attention, and suicidal thought. Diagnosis of depression is contingent upon the presence of at least five of these symptoms for two weeks, one of which has to be either depressed mood or reduced interest or pleasure not due to any obvious mood debilitating event such as divorce, loss of a job, etc. It is obvious that a diagnosis based on such a constellation of symptomatology lacks the precision usually found in the diagnoses of other medical ailments, such as in cancer or cardiovascular diseases, and contains symptoms that may present opposite tendencies. For example, sleep disturbance in depression may present as oversleeping or undersleeping, while psychomotor symptoms may be manifested as retardation or agitation. In fact, it has been calculated that the manifestation of these symptoms may result in several hundred permutations that will still be considered under the rubric of "major depression" (Kim and Park 2021; Shankman *et al*. 2020). Nevertheless, the categorical approach to depression, adopted by DSM-5, has been embraced not just by practitioners in the USA, where it originated, but by a large number of clinicians and researchers throughout the world.

It can be said that the DSM system, which started in the early 1950's with DSM-I and has been modified several times since, has been, increasingly, the backbone of the medical profession's approach to the diagnosis and treatment of depression. Generally speaking, the DSM system is considered to provide a framework to clinicians, for consistent diagnosis, and a template to researchers, for investigating mood disorders in both humans and animals. While this has been considered progress, in the sense of providing a consistent approach to depression, the DSM system does not reveal any fundamental insights into the underlying causal mechanisms. The restrictive nature of the diagnostic method and the fact that it is based on categorical as opposed to dimensional classification of symptoms are considered shortcomings (Hyman, 2010; Lilienfeld and Treadway 2016).

Partly because of these shortcomings and partly due to the increasing realization that the diagnostic categories do not seem to be matched with the relevant neurobiological and genetic findings related to depression, a new approach to psychiatric disorders, including depression, emerged from several years of evaluations, spearheaded by the National Institute of Mental Health (NIMH) in the USA, culminating with the launching of the Research Domain Criteria (RDoC) initiative in 2013 (Cuthbert and Insel 2013; Insel 2014; Insel *et al*. 2010). Rather than having a diagnostic thrust, as in the DSM and ICD systems, the RDoC is a complementary project promoting basic translational neuroscientific and genetic research on the diagnosis and therapeutics of depression. Instead of categories, the RDoC evaluates the full dimensional range of the symptomatology relied on in diagnosing depression, emphasizing that the symptoms are engendered by underlying central mechanisms, some of which are continuously distributed without clear demarcations marking normal from pathological (Cuthbert and Insel 2013; Fluyau 2018; Lilienfeld and Treadway 2016).

In addition to the diagnostic tools mentioned above, there are a few psychometric scales clinicians use to assess different dimensions of depressive state, as well as the progress in therapy; prominent among which are the Hamilton Depression Rating Scale (HDRS) (Hamilton 1960), Beck Depression Scale (BDI) (Beck *et al*. 1961), and the Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg 1979).

## Views on the Underlying Causes of Depression

The current thinking on the pathogenesis and therapeutics of depression covers a vast ground, from pyschological factors to neurochemical dysfunction. While the present book cannot delve into such a large number of hypotheses on the pathogenesis of depression and the diverse therapeutic techniques, a few of the prominent views that have shaped these approaches will be briefly discussed, as they are also relevant to the sensorimotor view of depression, elaborated in the following chapters. The etiology of depression is highly complex and, despite extensive investigations since the late nineteenth century, is not fully understood. Nevertheless, considerable progress has been made on several fronts to show that depression is particularly closely associated with central dysfunctions involving the monoaminergic neurotransmission system, stress, neurotrophic factors, adult neurogenesis, and inflammation.

Among the many proposed hypotheses related to the pathogenesis of depression, the most prominent one is based on the monoaminergic system

dysfunction, particularly related to the neurotransmitters serotonin (5-HT), noradrenaline (NA) and dopamine (DA). Over the last three quarters of a century, a great deal of evidence from clinical practice and basic research, including studies with animal models, suggests that monoaminergic dysfunction may be a primary factor in the onset and maintenance of affective and cognitive symptoms associated with depression (Hamon and Blier 2013; Hirschfeld 2000; Lopez-Munoz and Alamo 2009). As a result, several classes and generations of monoaminergic drugs have been designed for the pharmacotherapeutics of depression, including MAO inhibitors (common antidepressants) and culminating in the relatively new types of drugs based on selective serotonin and noradrenaline reuptake inhibitors.

In addition to the monoaminergic theory of depression, several factors that may contribute to the pathogenesis of depression, not necessarily conflicting with and possibly supporting the neurochemical dysfunction view, have been proposed. Prominent among these are the views that stress, neurotrophic factors, neurogenesis, and neuroinflammation critically contribute to the pathogenesis of depression.

A vast accumulation of data, over several decades of clinical practice and research with animal models, indicates that stress and emotional dysregulation may induce depression in both humans and animals. A common pathway by which long-term and even acute stress can induce depression is through the overactivation of the HPA (hypothalamic-pituitary-adrenal) axis, which increases glucocorticoids (e.g., cortisol) secretion and consequently compromises the structural and functional integrity of the fronto-limbic networks (Lee *et al*. 2022; Tian *et al*. 2014; Yuan and Hou 2015).

In addition to the monoaminergic theory, and related to the stress hypothesis, there is, in depression, a deficiency of the brain derived neurotrophic factor (BDNF). The deleterious impact of stress on the hippocampus and the production of neurotrophic factors, including BDNF and transforming-growth-factor-b1 (TGF-b1), has led to the neurotrophic hypothesis of depression (Altar 1999; Caraci *et al*. 2018; Jaggar *et al*. 2019). In fact, there is downregulation of BDNF, as well as expression of BDNF genes, in animal models of depression (Berry *et al*. 2012; Smith *et al*. 1995) and a decrease in BDNF, as well as BDNF receptor gene expression, in depressed patients (Angelucci *et al*. 2005; Tripp *et al*. 2012).

Until relatively recently, there was a dogmatic view that no new creation of nerve cells (neurogenesis) was possible. However, starting with early

observations, first characterized in rodents in the 1960s by Altmann (Altmann 1969; Altmann and Das 1965), neurogenesis is, now, known to continue in adult life, albeit limited in numbers and restricted to only a few structures in the brain: particularly, the dentate gyrus of the hippocampus, the subventricular zone, and the olfactory bulb (Bernier *et al*. 2002; Lepousez *et al*. 2013; Pierce and Xu 2010; Yuan *et al*. 2011). Studies with animal models of depression indicate that acute and chronic stress and depressogenic treatments impair (Drew and Hen, 2007; Gould *et al*. 1992; Vaidya *et al*. 2007), whereas antidepressants (Malberg *et al*. 2000; Mirescu and Gould 2006), as well as electroconvulsive shock with antidepressant effect in animal models of depression, promote neurogenesis (Giacobbe *et al*. 2020; Madsen *et al*. 2000). Furthermore, experimentally impairing neurogenesis can abolish the ameliorative effects of antidepressants, while decreased neurogenesis is observed in diverse models of depression (Eisch and Petrik 2012; Salmina *et al*. 2021).

An important avenue of research, along with and related to those on neurotrophic factors and neurogenesis, involves the investigation of the effects of neuroinflammation and oxidative stress in the pathogenesis of depression (Anderson and Maes 2014; Czarny *et al*. 2018; Hashimoto 2015; Maes 1999; 2008; Miller *et al*. 2009; Miller and Raison 2016). While the precise mechanism for the role of inflammation is not known, there is evidence that depressed patients display increased levels of proinflammatory cytokines, such as tumor necrosis factor-α (TNF- α) and interleukin-6 (IL-6), compared to healthy controls (Dowlati *et al*. 2010; Kohler *et al*. 2017; Liu *et al*. 2020).

## Need for New Therapeutic Approaches to Depression

Despite insights gained by the aforementoned approaches, depression still looms large as a global health threat and urgently requires a more thorough understanding of its pathogenesis and more effective treatment methods (Kessler 2012; Kessler and Bromet 2013; Malhi and Mann 2018). Despite a great deal of progress made in clinical work and basic research, success in treating depression is not guaranteed and lags behind the positive developments in the treatment of many other medical disorders. By way of comparison, thanks to both clinical and basic research, mortality due to heart disease has declined steadily in the last half a century, despite an increase in population, while there has not been a substantial improvement in mortality or prevalence rates for mental disorders (Kessler *et al*. 2005). However, for a fair comparison with progress in other areas of medicine,

dealing for instance with ailments involving the heart, the kidneys or the lungs, it must be pointed out that depression involves not only the brain, the most complex organ in the body, but also the sensorimotor system, as this book will argue. Nevertheless, the reasons for the lack of satisfactory state in diagnosing and treating depression must be critically assessed to provide a solid basis for future progress.

While the DSM, based on self-reported symptoms and prescribed categories, has provided a useful framework for clinicians, its drawbacks have also contributed to the slow progress in therapy and research related to depression. As pointed out, earlier, since the categories used to arrive at a diagnosis are not causally buttressed in underlying genetic or neurobiological mechanisms, there can be differences in diagnosis by different clinicians, who lack biomarkers for more informed and consistent conclusions. Moreover, the potential variance in self-reports by patients with different educational and cultural backgrounds can increase the likelihood of misdiagnosis. Unresolved issues with diagnosis, however, are only part of the current problems with the therapeutics of depression; another major setback is often the failure of pharmacotherapeutic interventions (Kraus *et al*. 2019; Lecrubier 2007). Although various types of psychotherapy are available, pharmacotherapy with antidepressants is the first option for the treatment of depression. Despite the fact that several types of antidepressants are available, selection, among these, is a major problem in itself, in the absence of biomarkers or predictors of treatment response, and success in treatment is, still, by no means assured (Akil *et al*. 2018; Blackburn 2019; Johnston *et al*. 2019; Trivedi *et al*. 2006). Regardless of the choice of antidepressants, less than half of the patients achieve remission following an initial treatment with an antidepressant, and remission rates are low, even with a subsequent treatment (Gaynes *et al*. 2009; Rush *et al*. 2006; Thase *et al*. 2005; Trivedi *et al*. 2006). Moreover, in many cases, the efficacy of monoaminergic antidepressants is marginal and comes with a cost of side effects and financial burden (Kirsch 2009).

Before considering the merits of the bottom-up sensorimotor view of mood regulation, the rationale behind the current emphasis on the top-down centralist approach must be addressed. Despite progress in understanding the depressive state in animals, as to how it is induced and can be cured (Czeh *et al*. 2016; Hao *et al*. 2019; Krishnan and Nestler, 2011; Menard *et al*. 2016; Unal and Canbeyli 2019), depression is mainly considered a human affliction and a health burden involving the brain, due to neurochemical and neurobiological dysfunctions. Moreover, depression in humans involves higher cortical functions including rumination (Gotlib and

Joormann 2010; Hamilton *et al*. 2015). Thus, the main thrust of clinical work and basic research has been based on the central origin and therapeutics of depression. As a result, configurations of the symptomatology of depression, ranging from anhedonia to psychomotor retardation, have been interpreted as centrally generated dysfunctions, the ill effects of which filter down to the periphery. This emphasis on the centralist top-down approach has not only promulgated but, in turn, has also found support from clinical applications of pharmacotherapeutic methods (Carreno and Frazer 2017**;** Krishnan and Nestler 2010; Matveychuk *et al*. 2020), and various invasive and noninvasive centrally applied electrical/magnetic and vagal stimulation techniques (Andrade *et al*. 2010; Askalsky and Iosifescu 2019; Conway and Xiong 2018; Dandekar *et al*. 2018; Kisely *et al*. 2018**;** Singh *et al*. 2019).

In contrast to the top-down view of depression, three review articles, over approximately a decade (Canbeyli 2010; 2013; 2022), advanced the diametrically opposite, but complementary, view—sensorimotor modulation of mood and depression—that stimulation via the sensory modalities (vision, audition, olfaction, touch and gustation) and physical exercise has the power to alleviate or aggravate depressive symptoms, depending on several parameters, such as intensity, frequency, duration, and quality of stimulation or physical exercise. The papers marshalled ample evidence to suggest that a bottom-up approach to depression could not only figure in the therapeutics of depression, but may also provide clues as to its pathogenesis. Since the initial review in 2010, there has been a growing body of new evidence expanding the scope and empasizing the relevance of the bottom-up approach for a more thorough evaluation of depression. The main reason for the present book is not to show, by any means, that the top-down approach to depression is inappropriate but to emphasize the fact that, while necessary, it is not sufficient for a full account of the pathogenesis and therapeutics of depression. Let us briefly summarize the three main points that the top-down view of depression is grounded on. First, it is firmly based on the proposition that depression arises from a neurochemical/neurobiological dysfunction. Second, it is primarily a human affliction and principally involves the brain. Third, as a result of the preceeding two assumptions, all the variety of symptoms due to depression are the consequences of a central dysfunction that may find reflections in the periphery. Thus, along with the cerebral impairments, such as impaired cognitive functions or excessive rumination, peripheral changes in a large number of functions—related to ambulation, gate, dietary habits, and a variety of sensory impairments to be taken up in detail in the following chapters—are considered malfunctions filtered to the periphery via, and due to, the central dysfunction.

While the top-down approach to depression views the periphery from a central perch and bias, the present book provides not just a different, but also a complementary view, which is necessary to have a critically integrated approach to the pathogenesis and therapeutics of depression. The bottom-up sensorimotor view is grounded in the fact that while depression finds its expression in the brain, it is a pathology involving the whole body. As such, depressive symptoms do not just arise via a unidirectional stream of influences emanating from the brain, but are products of the interaction between central and peripheral (dys)functions. In light of this broadened view, the book will emphasize, for the sensory modalities and the motor system, the fact that sensorimotor stimulation can not only modulate mood and depression, but, in turn, it can be altered because of the depressed state. Therefore, an important aspect of the present thesis is the bidirectional nature of the relation between peripheral input via sensorimotor activation and depression. Perhaps the most important reason for considering the proposed bottom-up view of depression as an integral part of understanding and treating depression is the strong evidence cited in the following chapters that sensorimotor stimulation is capable of improving mood and alleviating depression. This is in sharp contrast to the top-down view that considers peripheral symptoms of depression as consequences of the central dysfunction. To put it strongly, the peripheral state of a person depressed, or not, is not just a passive outcome due to centrally engendered phenomena, but provides active channels, via the sensory modalities and the motor system, the means to modulate mood and depression.

The following chapters will provide a wealth of data confirming the relevance of the sensorimotor modulation of mood and depression in understanding the pathogenesis and therapeutics of the pathology. At this stage, three major supportive arguments are in order to provide a framework for understanding the rationale for and the critical importance of the bottom-up view of depression. First, it is important to establish the fact that the brain is not only the source but also the recipient of information that matters in the pathogenesis and therapeutics of depression. To appreciate the relevance of the peripheral/sensorimotor input to emotion and mood, consider the profound paradox posed by the almost impenetrable status of the brain by external means, thanks to the mechanisms that protect it, and, yet, its continual accessibility to sensorimotor stimulation throughout the day. The brain is not only encased by the protective skull, but is also cushioned by the meninges, as well as protected by the cerebrospinal fluid efficiently absorbing physical insults that otherwise could cause lasting damage. The blood-brain barrier and the immune system constitute further protective measures that reduce the chances of damage by internal and external threats.

In contrast to these overwhelming protective measures, the brain is also, paradoxically, the most accessible organ in the body to external stimulation, thanks to the sensory modalities. The motor system also provides ambulation that will add variety to the sensory input encountered from one instance to the next. It is with this understanding that the present book will show how the "sensory windows" and the motor system provide constant stimulation that not only constitutes the raw material for perception, but **is** also the affective basis for modulation of mood. Just to show how the central and the peripheral systems do work and feed into each other, consider the potential stress and fear instigated by an encounter with a potentially dangerous situation. There is a vast literature that has worked out, in great detail, how the brain will assess such danger by means of the HPA axis and the central mechanisms reacting to the fearsome situation by means of the "fight or flight" or the "freeze or flee" aspects of motoric behavior. Humans and animals, however, do not experience such fear and face critical decisions unless there is a threat perceived through the sensory systems. For example, imagine the fear of someone in the presence of a roaring and threatening lion. Now, place a clearly visible strong cage around the lion and you now have, perhaps, the relaxed experience of a zoo visitor!

A second point that distinguishes the present bottom-up approach is that the available diagnostic systems consider the configuration of symptoms without taking into account or probing the developmental trajectory of these symptoms over time. The bottom-up view, on the other hand, shows how the ameliorative or debilitating effects of sensorimotor stimulation develop over time, thus, providing insights into the progressive trajectory of these effects.

Third, related to the two salient features of the bottom-up view of depression is the fact that modern living, particularly in urban areas, has a direct and growing negative impact on mood and depression. An increasingly important factor in the steep global rise of mood disorders is the cumulative detrimental effects of the global change in lifestyles due to modern age; there is, now, compelling evidence that the negative consequences of modern living contribute to the increased prevalence of depression throughout the world. Needless to say, technological advances in the last several decades have made life easier for many, lenghthened life expectancy, and provided creature comforts, previously only enjoyed by a priviledged few. Nevertheless, such benefits have come with a price tag, due to the negative consequences of the rapid transition from more traditional lifestyles to those brought about by urbanization, the competitive business landscape, and environmental pollution. Thus, many people, now,

live in noisier environments, cope with polluted air and water, are forced to travel longer to work, and have to settle for unhealthy meals due to the pressure of time. Contributing to all these negative enchroachments of modern lifestyle is the fact that most people also have to work, study, or produce under more stressful and competitive conditions than just a few decades ago (Firth *et al*. 2019; Jacka *et al*. 2012; Lopresti *et al*. 2013; Sarris *et al*. 2014). The following chapters will document how these lifestyle developments impact the sensorimotor system, to modulate mood and depression.

The following six chapters deal with the mood modulatory effects of visual, auditory, olfactory, tactile, and gustatory stimulation, as well as the affective contribution of the motor system in the form of physical exercise. The subsequent chapter emphasizes the potential importance of multisensory, as opposed to unisensory, stimulation in modulating mood and depression. The final, concluding, chapter provides an integrated summary of the critical features of the sensorimotor modulation of mood that will provide a springboard for future research on the essential contributions of the bottom-up approach for understanding and treating depression.

# VISION

## Introduction

Antoine Lavoisier (Antoine-Laurent de Lavoisier 1743–1794), considered the father of modern chemistry, having paved the way to the chemical revolution that took place in the nineteenth century, listed light among the chemical elements he considered as the building blocks of chemical compounds (*Traite Elémentaire de Chimie—Elementary Treatise on Chemistry* 1789). It is perhaps easy to understand this inclusion as a scientific misjudgment due to Lavoisier's high regard for light as an agent in chemical processes. On the other hand, it is also possible to appreciate Lavoisier's enthusiasm because of the fundamental importance of light in the lives of living organisms; in a sense, for the chemistry of life. Since Lavoisier's times, scientists have gone on studying light in various scientific disciplines, particularly in physics, chemistry, and biology. More recently, neuroscience has delved into the mysteries of light not just because of its agency in sight, but also due to its still unfathomed contribution to emotion and mood. To illustrate one aspect of the complex but appreciable impact of light and sight on our psychology and health, let us briefly examine a well-controlled study on the differential effects of recovering from surgery when patients are housed in rooms either with a view of a brick wall or a natural scene with trees (Ulrich 1984). Over an approximately ten-year period, the study examined, in twenty-three patients who had undergone a specific surgery (cholecystectomy), the health consequences of spending the post-operative period in rooms with a wall view or a natural view with trees. In an exquisitely controlled study, patients were matched as much as possible by age, sex, body weight, and smoking habits, while the rooms were matched by floors and, even, when possible, by wall colors. The results were highly impressive in that, in comparison to patients in the wall-view group, those who spent the recuperative period in rooms with tree views needed significantly fewer moderate and strong doses of analgesics and, importantly, had shorter post-operative hospital stays. A later study that confirmed and extended the results of the Ulrich (1984) report (Beauchemin and Hays 1996), more directly relevant to the topic of this book, reported that depressed patients who stayed in sunny rooms had a significantly shorter hospitalization (16.9 days) than those in "dull" rooms with considerably less sunlight (19.5 days).

This book aims to provide a framework for evaluating the effects of peripheral stimulation, via the five senses and the motor system, on mood and depression. The first sensory system we will take up is vision, which provides sight, with paramount importance, for humans and many other species. We will deal with the fact that, in addition to this all-important function, the visual system is also profoundly involved in mood and depression. An important aspect of photoreception by the visual system, which is all too obvious to us in the modern world, is light. In addition to its agency in sight, light is also critically involved in mood regulation. The mood modulatory impact of light in our lives is dependent on several photic parameters, such as intensity, quality (color), and duration, as well as two other parameters relevant to the availability of daily and seasonal daylight: namely, seasonality and latitude**.** In this context, it is important and instructive to emphasize the fact that all living entities on earth are bound by a daily light schedule, dictated by the revolution of the Earth around its axis as well as by its annual journey around the Sun. These two factors impose, on most terrestrial organisms, daily (circadian) and seasonal (circannual) rhythms that dictate daily and annual adaptations. The picture is further complicated by the fact that geographic, specifically latitudinal, location also imposes many restrictions due to local climate and the availability of sunlight throughout the day and the year. As the reality of life on Earth imposed certain restrictions on living creatures, evolutionary forces and solutions have enabled organisms not just to survive but to thrive under these conditions. Deliberation on the complex evolutionary mechanisms at work, in this context, is certainly beyond the scope of the present book. However, two related phenomena emanating from the interactions between terrestrial realities and evolutionary organismic solutions will be directly addressed, below, as they are critical in our understanding the means by which mood is modulated by vision and light for humans, as well as many for animals: biological rhythms and the biological clock.

## Light Stimulation Can Modulate Mood and Depression

As the two experiments cited above suggest, light stimulation has beneficial effects on health, in general, and mental health, in particular. Clinical as well as basic studies over several decades have elucidated parametrically the affective benefits of light stimulation and have also provided the equally important evidence that impaired photic reception, due to environmental conditions or visual impairment, results in lowered mood and even in depression (Espiritu *et al*. 1994; Jean-Louis *et al*. 2005; Kripke *et al*. 2004;

Rosen *et al*. 1990). These findings, elaborated below, are supported by animal studies that have, additionally, provided the means to probe into the neurobiological foundations of mood regulation by means of photic stimulation, or its lack (Bedrosian *et al*. 2011; Molina-Hernandez and Tellez-Alcantara 2000; Prendergast and Nelson 2005; Yilmaz *et al*. 2004).

Modulation of mood by light exposure is a globally experienced phenomenon, as evinced by the contrast in how most people generally feel during the dark days of winter and the bright days of summer. Moreover, at northern latitudes, with decreased illumination, lowered mood, fatigue, and impaired asleep are often reported (Imai *et al*. 2003; Kegel *et al*. 2009; Leppamaki *et al*. 2004; Potkin *et al*. 1986; Saarijarvi *et al*. 1999**).** A major aspect of the difference in seasonal mood derives from the fact that winter has long nights and short days, characterized as dark (D) and light (L) phases of the daily light cycle. In fact, it is known that low levels, or inadequate light stimulation, due to reduced sunlight throughout the year can aggravate depression in depressed patients and induce depressive symptoms in an otherwise healthy population (Booker *et al*. 1991). Studies also confirm the depressive effects of reduced photoreception as a result of low or inadequate ambient light (Espiritu *et al*. 1994; Jean-Louis *et al*. 2005; Kripke *et al*. 2004; Park *et al*. 2007).

What these and other studies, to be discussed below, indicate is that inadequate exposure to sunlight may be a critical factor in lowered mood and exacerbated depressive symptoms. An important clue in this respect is provided by a study (Hebert *et al*. 1998) reporting that, at a latitude of approximately 45$^{o}$ N, the mean daily duration of time awake for twelve young adults was similar in winter and summer: 14.9 h and 14.6 h, respectively. Because these durations are comparable, mood impairment, generally felt in the winter compared to summer, is likely due to the differences in photoreception in the seasons. In fact, people spend more time outdoors in the summer, when sunlight intensity may range from 25,000 lx on a cloudy day to several times that on a sunny day with clear skies. In contrast, intensity of artificial light indoors is usually below a thousand lx. Support for the view that natural sunlight can have beneficial affective effects comes from studies showing that mood was improved, in seasonally depressed patients, by exposure to sunlight in the morning for one hour per day for a week (Wirz-Justice *et al*. 1996), or to four hours over five to seven days in post menopausal women (Youngstedt *et al*. 2004). Importantly, the latter study also reported that window coverings that allowed more sunlight to enter bedrooms was associated with less depressive mood.

An important systematic remedy to reduced light reception due to latitudinal or seasonal restrictions is to provide individuals with artificial light stimulation. Indeed, exposure to artificial bright light can have an ameliorative effect on mood in nonclinical populations; in Finland, repeated exposure, in the winter, to at least one hour of light has been shown to reduce depressive symptoms in healthy office workers with or without winter-related negative mood symptoms (Partonen and Lonnqvist 2000). Similarly, another Finnish study (Leppamaki *et al*. 2002) with nonclinical subjects indicated that bright light exposure (2500 lx to 4000 lx), combined with exercise, over an eight-week period, significantly reduced depressive symptoms compared to exercise alone in a normal ambient illumination (400 lx to 600 lx).

Instead of natural sunlight, phototherapy, in the form of exposing depressed patients to artificial bright light for approximately one hour either early in the morning or evening, is effective in alleviating the depressive symptoms of patients suffering from seasonal (Avery 1998; Lewy *et al*. 1982; Oren and Terman 1998; Pjrek *et al*. 2020) and nonseasonal depression (Even *et al*. 2008; Kripke 1998; Mackert *et al*. 1991; Pail *et al*. 2011; Trinh *et al*. 2021). Several studies suggest that morning exposure to bright light is more efficacious in alleviating depression than evening exposure (Avery *et al*. 1990; Eastman *et al*. 1998; Lewy *et al*. 1998; Terman *et al*. 1989; 1998). Moreover, in addition to being utilized as monotherapy, phototherapy has also been administered as an augmentation to pharmacotherapy (Al-Karawi and Jubair 2016; Guzel Ozdemir *et al*. 2015; Niederhofer and Klitzing 2012). In fact, bright light therapy as an adjuvant with pharmacotherapy has been shown to be more effective in the treatment of depression than pharmacotherapy alone. Reviews of studies using bright light treatment along with various pharmacotherapies have indicated that phototherapy improves the treatment of major depression compared to pharmacotherapy alone (Penders *et al*. 2016; Tao *et al*. 2020). Successful treatment with bright light exposure is especially critical in the perinatal stage of pregnancy, when pharmacotherapy is counterindicated (Bais *et al*. 2020; Epperson *et al*. 2004; Garbazza *et al*. 2022; Wirz-Justice *et al*. 2011).

Complementing the findings with humans, animal research has provided important data for the mood alleviating effects of light stimulation. For instance, a study by Molina-Hernandez and Tellez-Alcantara (2000) showed, in male rats, that a thirty-day exposure to a long day (15 h L: 9h D) has an antidepressant effect, as measured by reduced immobility in a forced swim test. Importantly, the ameliorative effect of light treatment was comparable to thirty days of treatment with the antidepressants clomipramine or

desipramine. Other studies indicate that even shorter exposures to light, during the dark phase of a daily 12h L: 12h D light schedule, have a protective effect on depression in the rat. For instance, Yilmaz *et al*. (2004) showed, in female rats, that a single 12-h light exposure, replacing the dark phase of a 12h L: 12h D, 24 h lighting cycle, has an antidepressant effect, as measured by behavioral despair. Subsequent studies showed that short light pulses of 30 min (Schulz *et al*. 2008), or even 10 min, duration (Iyilikçi *et al*. 2009), delivered late in the dark phase of the 12h L: 12h D cycle, have ameliorative effects in behavioral despair.

## A Unique Type of Depression (Seasonal Affective Disorder) and a Special Type of Therapy (Phototherapy)

Subsequent chapters will document that auditory, olfactory, tactile, and gustatory stimulation can also affect mood and depression. While humanity has had a long history of experiencing the emotional consequences of sensory engagement in those modalities, realization that such stimulation may have modulatory effect on mood and depression unfolded over a long period, without any demarcation line showing when research began to fundamentally change our approach to appreciating the beneficial contribution of these modalities to affect. Such is not quite the case with the contribution of visual research in our thinking about mood and depression. To be sure, good and long exposure to sunlight has been a desirable condition for mental health, even in ancient times, long before the advent of a scientific understanding of how these were related (Geoffroy *et al*. 2018). While the history of research on visual modulation of mood is as old as those for other sensory systems, as will be evident from subsequent chapters, it can be said that phototherapy deserves a special place in psychiatry and neuroscience because several important discoveries, in roughly the last half-century, brought together pieces of a puzzle that have now contributed to our current understanding of how light, or its deficiency, affects mood and depression. Along with the discovery of the endogenous biological clock and a third type of retinal ganglion cells, to be discussed later, an important piece of the puzzle was the advent of phototherapy, in the 1980s, based on the observation that a subset of depressed patients displayed recurrent depressive symptoms in fall and winter, with remission in spring and summer (Rosenthal *et al*. 1984). This disorder is characterized as seasonal affective disorder (SAD) and is now defined in the DSM-V as a diagnostic subtype of major depressive disorder with seasonal pattern. Since the 1980s, what had started as a special treatment with bright light for a specific type of depression has burgeoned into an important means of

treating SAD, as well as non-seasonal depression (Dong *et al*. 2022; Golden *et al*. 2005; Lam *et al*. 2006; Perera *et al*. 2016).

An important insight into the mood ameliorative agency of light therapy was provided by the observation, in some patients suffering from SAD or from non-seasonal depression, that there was often a misalignment between the biological rhythms and the sleep-wake cycle. This provided an important avenue of research on the potential affective roles of the biological rhythms and the major biological clock in the brain that regulates these rhythms on a daily (circadian) and seasonal (circannual) basis: namely, the suprachiasmatic nucleus (SCN) whose simultaneous discovery, initially in the rat brain, by two laboratories antedated the beginning of phototherapy for SAD by approximately a decade (Moore and Eichler 1972; Stephan and Zucker 1972a; 1972b). Subsequent research has shown the presence of the SCN in the brains of other mammalians, including humans (Morin 1994; 2006; Weaver 1998). The SCN is considered the master clock as it can generate, in the absence of external cues, a daily rhythm, with an approximately twenty-four-hour clock. The solar day is approximately twenty-four hours, while the human circadian period, dictated by the SCN, is slightly longer, thereby, requiring resetting of the biological clock on a daily basis so that the large number of hormonal and behavioral rhythms, including the sleep-wake cycle, are kept in lockstep unison, a state known as eurhythmia. The main agent, depicted as Zeitgeber ("time giver"), that can reset (entrain) the SCN is light. While a few other factors, including social cues, can entrain the SCN, daily transitions from dark to light in the morning and the reverse in the evening are the major factors that provide the basis for the daily eurhythmic functioning of the biological rhythms via the SCN. Moreover, regular seasonal changes of the relative lengths of the day (light) and night (dark) portions of the day provide the basis for the SCN to regulate biorhythms on a yearly basis (Morin 1994; 2005; Van Esseveldt *et al*. 2000). Photic information is relayed to the SCN from the retina directly, via the retinohypothalamic tract, and indirectly, via projections from the intergeniculate leaflet in the lateral geniculate area of the thalamus and from the dorsal raphe nuclei as well (Hannibal and Fahrenkrug 2006; Moore 1973; Moore and Card 1994; Shen and Semba 1994). These inputs provide the means for the SCN, which has extensive connections in the brain, to regulate biological rhythms as well as to modulate affect in response to light input. The SCN connects with constituents of the fronto-limbic circuitry involved in mood and mood disorders, such as the amygdala, the bed nucleus of the stria terminalis, the paraventricular nuclei of the hypothalamus and the thalamus, as well as with the frontal cortical areas (Vrang *et al*. 1995; Watts *et al*. 1987; Watts and Swanson 1987).