General introduction and outline
The existence of life on Earth is fuelled by light from the sun. Sunlight is the dominant source of energy, directly by photosynthesis, or indirectly via the food chain. Sunlight heats the environment and allows for photic vision, in a daily rhythm following the earth rotation. Sunlight, in the broadest sense, is the total frequency spectrum of electromagnetic radiation given by the sun. On earth, sunlight is filtered through the atmosphere, and solar radiation is obvious when the sun is above the horizon, during daytime, and also in summer near the poles at night, but not at all in winter near the poles. When the direct radiation is not blocked by clouds, it is experienced as sunshine, combining the perception of bright white light (sunlight in the strict sense) and warming heat. When it is blocked by the clouds or reflects off of other objects, it is experienced as diffuse light.

Light
Light is only a small part of the total electromagnetic radiation spectrum that is emitted by the sun. Humans are capable of perceiving light in two modes: 1) via visual photoreception, by the rods and cones from within the retina, which provides us with a spatiotemporal image of the environment; 2) via nonvisual photoreception, which affects the circadian system. This distinct set of ganglion cells in the inner retinal layer was demonstrated to project to the suprachiasmatic nucleus (SCN). Furthermore, studies determining the action spectrum show that blue-green light (450-500 nm) is the most potent in shifting the phase of the circadian rhythm, indicating melanopsin is (one) of the crucial circadian photoreceptors.

Hypothalamic clock
The biological clock is located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus, on top of the optic chiasm. From the optic chiasm it receives direct neuronal projections originating from the retina comprising a pathway from the retina to the SCN, which is called the retino-hypothalamic tract. The notion that the biological clock is located in the SCN came from experimental studies in which the SCN from animals are lesioned, resulting in the loss of behavioural, endocrinological, and physiological circadian rhythms. If SCN is isolated in vitro it continues to show a 24-hour electrical activity. Follow-up experiments transplanted embryonic SCN tissue back in the animals with destructed SCN tissue, showed that transplanted animals returned to day-night activity rhythm again.

The mammalian biological clock
generates the circadian (circa dies = day length is approximately 24 hour) rhythms in physiology and behaviour, estimated in humans to a mean of 24 hours and 18 minutes.\(^{16}\) Under normal conditions the various rhythms run in synchrony with each other and with the natural periodic changes of the environment, e.g. the light-dark cycle. This light-dark cycle acts as the dominant Zeitgeber, or synchronizer, of the internal rhythms resulting in a stable phase relationship between the circadian rhythms and the environment.\(^{17}\)

**Neurotransmitters and the SCN**

Although the SCN is a small nucleus (not even 1 mm\(^3\)), it contains over 10 000 neurons that are packed tightly together, with a heterogeneous neuron population containing multiple neurotransmitters, of vasopressin, vasoactive intestinal polypeptide (VIP), gastrin-releasing peptide (GRP), neurotensin (NT) and histidine isoleucine (PHI) prevail. Many more neurotransmitters have already been reported, e.g. somatostatin, gamma-aminobutyric acid (GABA),\(^{16, 19}\) calbindin, thyrotrophin-releasing hormone, corticotrophin-releasing hormone, angiotensin II, enkephalin, substance P, neuropeptide Y (NPY), dynorphin, cholecystokinin, calcitonin gene-related peptide, and galanin.\(^{20}\) Interestingly, of all these neurotransmitters, only for VIP a clear circadian rhythm in production has been demonstrated.\(^2\) There has been a considerable progress in the understanding of the input, output,\(^{21}\) and oscillation machinery which consists of gene-protein-gene feedback loops, where proteins can downregulate their own transcription and stimulate the transcription of other clock proteins.\(^{22}\)

One of the most important outputs of the SCN might be the hypothalamic-pituitary-adrenocortical axis (HPA axis), which is the neuro-endocrine axis running from the paraventricular nucleus (PVN) to the neuropituitary releasing neuropeptides like AVP. From the PVN also corticotropin releasing hormone (CRH) is produced which mediates the pituitary to produce adrenocorticotropic hormone (ACTH), and consequently the adrenocortex to produce cortisol (Figure 1.1, p. 15).

**The SCN in aging**

Hoogendijk et al\(^{23}\) showed with aging, circadian rhythm changes (e.g. fragmented sleep-wake patterns) go together with an (also age-related) decreased SCN activity. This may be related to the decreased light input via a less photosensitive optic system in elderly people. The age-related decreased SCN activity may thus be a risk factor for the elderly to develop circadian rhythm-related disturbances and hyperactivity of the HPA axis\(^{24}\) due to dysinhibition of CRH neurons, which, in
itself, is also a risk factor for depression. Moreover, sleep disturbances frequently result in decreased self-sufficiency in terms of decreased activity during the day (ADL), emotional instability (depression), decreased concentration (cognition) and sleeping during the day or drowsiness (social isolation).

Major depressive disorder

Epidemiology of depression
About 13-14% of the older population suffer from depressive complaints that require clinical attention, and the prevalence of a major depressive disorder varies around 1.8%. Depression is one of the most important diseases in developed countries, only second to ischaemic heart disease as reported by the World Health Organisation. Depression is number four cause of disease burden and causes the largest nonfatal burden, accounting for almost 12% of all total years lived with a disability worldwide. In the coming decades non communicable diseases such as unipolar major depression and heart disease will rapidly replace infectious diseases and malnutrition as the leading causes of disability and premature death in developed as well as in developing countries. In the Netherlands the percentage of the population over the age of 65 years will increase from 14.8% in 2008 to 23.3% in 2040. The vast majority of depressions in older people start late in life. Epidemiological studies have shown that the prevalence of MDD in women is between 1.5 and 3 times higher than in men. Depression does not manifest itself in single episodes, but recurrences are very common and substantial numbers of patients experience extended periods with subsyndromal symptoms and co-occur with anxiety disorders.

Diagnosis of major depression
The diagnosis of major depression is based on an evaluation of symptoms. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) is the most widely accepted classification system of mental disorders, providing specified criteria for each specific mental disorder. The key symptoms of major depressive disorder are a depressed mood and a loss of interest or pleasure. For the diagnosis of depression, at least 1 of these symptoms is required, together with 4 (or more) additional symptoms that should all have been present for at least 2 weeks and have caused clinically significant distress or impairment in functioning (see Figure 1.2, p. 17). Almost all patients with depression complain of fatigue or reduced energy and about 80% complain of trouble in sleeping. Many patients have decreased appetite and weight loss.
**Fig. 1.1** Circadian neuro-system. The biological clock moderates the neuro-endocrinology of stress. Legend: ↓ = stimulates / activates; ● = inhibits / blocks; SCN, suprachiasmatic nucleus; PVN, paraventricular nucleus; RHT, retinohypothalamic tract; IGL, intergeniculate leaflet; CRH, corticotropine releasing hormone; ACTH, corticotropin; AVP, arginine vasopressine, DHEA(S), dehydroepiandrosterone(sulphate); GR, glucocorticoid receptor; MR, mineralocorticoid receptor.
Other patients have increased appetite, weight gain and excessive need to sleep. These patients are classified in the *DSM-IV* as having atypical features. Feelings of worthlessness or excessive guilt and a diminished ability to think or concentrate are other common symptoms. Often, there is generalized psychomotor retardation, although psychomotor agitation is also seen. Suicidal ideation is present in about two thirds of all patients with depression.

As only 5 out of 9 symptoms are required for the diagnosis of major depression, the clinical presentation can vary substantially. Not only the severity may vary, there are also various subtypes. Melancholic-type depression is associated with worse mood in the morning, early morning awakening, significant anorexia and / or weight loss.

*Pathophysiology of major depression*

The pathophysiology of depression is largely unknown. Depression is considered a complex, heterogeneous multifactorial disorder with genetic, neurobiological and psychosocial correlates. The pathophysiology may involve a deregulation of a number of neurotransmitter systems, including the serotonin, norepinephrine, dopamine, acetylcholine, and gamma-aminobutyric acid systems. There is also evidence of alterations of several neuropeptides, including corticotropin-releasing hormone. In some patients with depression, hormonal disturbances have been observed, including elevated glucocorticoid secretion (e.g. elevated urinary free cortisol levels or dexamethasone nonsuppression of plasma cortisol) and blunted growth hormone, thyroid-stimulating hormone, and prolactin responses to various challenge tests. Functional brain imaging studies document alterations in cerebral blood flow in limbic and paralimbic regions and decreased blood flow in the lateral prefrontal cortex. Depression beginning in late life is associated with alterations in brain structure, including periventricular vascular changes. None of the changes are present in all individuals with a major depression. Nor is any particular disturbance specific to depression.

In daily clinical practice the role of stressful environmental factors in the aetiology of depression has been acknowledged. Epidemiological studies have confirmed that severe life events and chronic difficulties contribute to development and course of depression. Environmental factors have been shown to interact with pre-existing genetic vulnerabilities. Known risk factors for late-life depression are bereavement, sleep disturbance, disability, prior depression and female gender. Other psychosocial risk factors are life events, on-going difficulties and lack of social context.
Fig. 1.2 DSM-IV-TR Criteria for the diagnosis of a major depressive disorder

Major Depressive Episode

A. Five (or more) of the following symptoms have been present during the same
2-week period and represent a change from previous functioning; at least one of the symp-
toms is either (1) depressed mood or (2) loss of interest or pleasure.
(1) depressed mood most of the day, nearly every day, as indicated by either subjective
report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
(2) markedly diminished interest or pleasure in all, or almost all, activities most of the day,
early every day (as indicated by either subjective account or observation made by others)
(3) significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of
body weight in a month), or decrease or increase in appetite nearly every day
(4) insomnia or hypersomnia nearly every day
(5) psychomotor agitation or retardation nearly every day (observable by others, not merely
subjective feelings of restlessness or being slowed down)
(6) fatigue or loss of energy nearly every day
(7) feelings of worthlessness or excessive or inappropriate guilt (which may be delusion al)
nearly every day (not merely self-reproach or guilt about being sick)
(8) diminished ability to think or concentrate, or indecisiveness, nearly every day (either by
subjective account or as observed by others)
(9) recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation with out a
specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.

C. The symptoms cause clinically significant distress or impairment in social, occupational,
or other important areas of functioning.

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug
of abuse, a medication) or a general medical condition (e.g., hypothyroidism).

E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved
one, the symptoms persist for longer than 2 months or are characterized by marked
functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psy-
chotic symptoms, or psychomotor retardation.

Diagnostic criteria for major depressive disorder

A. Presence of a single Major Depressive Episode

B. The Major Depressive Episode is not better accounted for by Schizoaffective Disorder and is
not superimposed on Schizophrenia, Schizophreniform Disorder, Delusional Disorder, or
Psychotic Disorder Not Otherwise Specified.

C. There has never been a Manic Episode, a Mixed Episode, or a Hypomanic Episode. Note:
This exclusion does not apply if all the manic-like, mixed-like, or hypomanic-like episodes
are substance or treatment induced or are due to the direct physiological effects of a general
medical condition.
The HPA axis, involved in the stress response, is thought to play a role in both the etiology and pathophysiology of depression. In patients with depression, abnormalities have been described at all levels of the axis, including high plasma, saliva and urinary cortisol levels, increased adrenal gland volumes which are often normalized by treatment with antidepressants.

Animal studies have shown that intracerebral CRH injection results in ‘depression-like symptoms’. In earlier studies it was shown that this activation is due to hyperactivity of CRH neurons of the hypothalamic paraventricular nucleus. Moreover, it has been shown that these CRH neurons are also hyperactive in normal aging. Therefore, the age related hyperactivity of the CRH neurons, resulting in high plasma cortisol levels, may represent a risk factor for depression. Normally, the CRH neurons are inhibited by: 1) negative feedback via cortisol binding at the glucocorticoid receptor; and 2) the SCN, the clock of the brain, which is mainly entrained by the environmental “Zeitgeber” daylight through the optic nerve. In depression, however: 1) the glucocorticoid receptor is hypothesized to be resistant to cortisol due to genetic factors; and 2) the metabolism of the SCN is disturbed in depression. Hofman and Swaab showed that AVP in the SCN reduces with aging. Lucassen et al further showed, in rats, that light counteracts the age-related loss of AVP, which is a sign of reactivation.

Some depression symptoms seem to be related to circadian rhythms, such as early morning awakening and diurnal variation in mood (depression worst in the morning). Although circadian rhythm-related symptoms, such as sleep-wake disturbances, are common in aging and frequently respond to light treatment, the effect of light treatment for depression has never been studied in the elderly.

Moreover, in seasonal affective disorders, and also in healthy controls, mood fluctuates with the circannual rhythm, which is also driven by the SCN. Light therapy is known to stimulate the SCN and to improve circannual rhythm-related mood disturbances. In depression not only antidepressants, but also stimulation of the SCN may beneficially inhibit the hyperactive CRH neurons (see Figure 1.3, p. 20).

The beneficial effect of BLT in seasonal affective disorder (SAD) is well accepted, with early onset of action, and mild adverse-effect profiles. Results of controlled BLT trials in nonseasonal MDD are promising, but inconclusive, especially with respect to efficacy in elderly patients with MDD. Reviews emphasize the need for further study because of the great diversity of study designs and the relatively small sample.
sizes. Riemersma-van der Lek et al showed that bright light attenuated the development of depressive symptoms in elderly residents of group care facilities. To our knowledge, double-blind placebo-controlled randomized clinical trials (RCTs) of sufficient sample size to evaluate the efficacy of BLT in elderly patients diagnosed with major depressive disorder have not been performed, although some studies suggested BLT might have favourable effects.

Finally, non-pharmacological interventions (e.g. light treatment) lack the serious adverse events of tricyclic antidepressants, which are normally used if a patient does not respond to SSRI. This is an important advantage, since the elderly are known to be especially susceptible to adverse events, such as positional hypotension and, consequently, falls and hip fracture causing decreased physical self-sufficiency and social isolation.

**Chronobiopsychosocial approaches to depression**

MDD is frequently accompanied by symptoms suggestive of circadian dysfunction, such as altered sleep-wake patterns, diurnal mood swings, energy level, and often, endocrine dysfunction.

Several hypotheses have been put forward in attempts to relate biological rhythms to the pathogenesis of MDD. These include the desynchronization theory, the phase advance hypothesis, the two-process model of sleep regulation, biological rhythm amplitude reduction, dysrhythmia, and loss of appropriate entrainment. These theories have led to studies that have yielded a considerable amount of empirical data relating circadian rhythm disturbances to MDD. Nevertheless, a considerable amount of wanted investigations are still lacking. For instance, actigraphy studies in elderly MDD with a sufficient sample-size have never been performed, although elderly with MDD are thought to be at increased risk for diurnal motor activity rhythm disturbances, and sleep fragmentation disturbances. Actigraphy not only allows for the analysis of diurnal motor rhythm, but also for sleep analysis.

In humans circadian rhythms are largely endogenously generated by the suprachiasmatic nucleus (SCN), and synchronized with the environment via Zeitgebers. The dominant Zeitgeber is light, but also the social environment is able to entrain circadian rhythms, e.g. via exposure to sunlight when one goes outdoors. Also, non-photic social Zeitgebers like daily activities, mealtimes, or social interactions entrain circadian rhythms. McClintock et al described
**Fig. 1.3** Hypothesis concerning the effects of light on HPA axis in MDD.

Schematic illustration (adapted from Boa et al.\(^{110}\)) of an impaired interaction between the decreased activity of AVP-vasopressin neurons (AVP) in the suprachiasmatic nucleus (SCN) and the increased activity of corticotropin-releasing hormone (CRH) neurons in the paraventricular nucleus (PVN). The hypothalamo-pituitary-adrenal (HPA) system is activated in depression and affects mood, via CRH and cortisol. Zhou et al. showed evidence that in the SCN in postmortem brains of people with depression expression of AVP is reduced.\(^{52}\) Hofman and Swaab showed that AVP in the SCN reduces with ageing.\(^{53}\) The decreased activity of AVP neurons in the SCN of people with depression is the basis of the impaired circadian regulation of the HPA system in depression.\(^{111}\) Moreover, animal data have shown that AVP neurons of the SCN exert an inhibitory influence on CRH neurons in the PVN.\(^{112}\) In people with depression, stress acting on the HPA system results in a disproportionately high activity of the HPA system because of a deficient cortisol feedback effect due to the presence of glucocorticoid resistance. AVP neurons in the SCN react to the increased cortisol levels and subsequently fail to inhibit sufficiently the CRH neurons in the PVN. Such impaired negative feedback mechanism may lead to a further increase in the activity of the HPA system in depression. Both the elevated CRH and cortisol levels contribute to depression.\(^{113}\) Lucassen et al. further showed, in rats, that light counteracts the age-related loss of AVP, which is a sign of reactivation.\(^{54}\) At present, SCN stimulation is indeed mostly a model to explain effects of BLT in (non-seasonal) depression.\(^{56,114}\) Antidepressant medication generally inhibits the activity of CRH neurons in the PVN.\(^{115}\) ACTH, corticotropin.
a phenomenon whereby a group of women living together experienced synchronization of their menstrual cycles, and Bogdan et al described that the alteration of Muslim's daily activities during Ramadan was associated with a change in the diurnal secretion patterns of several hormones, including cortisol. It appears that changes in the daily activity patterns in the social environment can have important effects on biological rhythms.

The social Zeitgeber/Zeitstörer theory hypothesizes psychosocial factors, such as life events, chronic stress or lack of social support systems may decrease circadian rhythm regularity, not only via ‘the psychologically threat’, but also via disrupting social routines, which cause disruptions in the regularity of our circadian rhythms in vulnerable individuals (see Figure 1.4, p. 22). Healthy elderly people have been repeatedly shown to display elevated social rhythm regularity than younger adults. This has been hypothesized to be an adaptation to blunted circadian rhythmicity associated with aging. Depressed individuals as well as patients with remitted depression display lower social rhythm regularity, and in elderly individuals with bereavement related depression social rhythm regularity was lower than in elderly individuals without depression, reflecting deteriorating daily life structure, and the need the need for stronger Zeitgebers.

Grandin et al proposed that MDD patients require stronger or more frequent social zeitgebers than healthy controls to influence their biological rhythms due to weaker circadian rhythmicity and less responsivity of the SCN in MDD. Congruent with this view is that patients with depression find social interactions less enjoyable and less intimate compared to normal controls. The effect of social support on social rhythm disruptions has never been studied. Also, social rhythmicity has never been studied in relation to treatment of MDD.

Outline of the Thesis
Chapter 2,3 and 4 cover the experimental section of the thesis. Our hypotheses were twofold. First, we expected BLT to lower depressive symptoms. Second, we expected this to be mediated by improved circadian functioning, as indirectly indicated by enhanced sleep and hormone rhythms. Therefore, we designed (Chapter 2) and conducted (Chapter 3) a double-blind placebo-controlled RCT that included assessment of SCN function from cortisol profiles, evening melatonin rise and actigraphic sleep estimates. Chapter 4 examines the effects of BLT on social rhythmicity and describes how social rhythm stability contributes to the prediction of treatment response.
**Chapter 5 and Chapter 6** cover the case-control studies from the randomized controlled trial. **Chapter 5** examines if and how social rhythmicity and social support are interconnected in major depression in a case-control design. **Chapter 6** is a case-control study on the diurnal and social rhythm disturbances and subjective sleep quality analysis and actigraphic sleep parameter estimates in an actigraphy study comparing elderly major depression with healthy controls. **Chapter 8** elaborates on this introduction and outline by a review in Dutch on chronotherapeutics in depression. This chapter aims to situate BLT with a evolving repertoire of chronotherapeutics, and further the range of evidence based indications for BLT is growing.

**Fig. 1.4** Scheme of the Social Zeitgeber/Zeitstörer hypothesis. In this theory, Ehlers, Frank and Kupfer proposed that depressive episodes arise as a consequence of life events and difficulties, particularly those which involve separation or loss such as death, divorce, loss of job, moving, etc., disturbing social Zeitgebers (external cues that function to entrain biological rhythms) which, in turn, derail social routines and, in turn, their biological circadian rhythms. Ultimately it is postulated that chronic disruption of social and biological rhythms can lead to the onset of depression symptoms and in ‘vulnerable’ individuals, affective episodes.
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