24-HOUR MOTOR ACTIVITY AND AUTONOMIC CARDIAC FUNCTIONING IN MAJOR DEPRESSIVE DISORDER

24-UURS MOTORISCHE ACTIVITEIT
EN AUTONOME CARDIALE FUNCTIE
IN DEPRESSIEVE STOORNISSEN

Proefschrift

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Voor mijn moeder,

Om haar te bedanken voor haar liefde
en de wijsheid, kennis en vrijheid
die zij mij heeft gegeven

Contents

Chapter 1

General introduction

1 Introduction

The studies presented in this thesis focus on the spontaneous pattern of motor activity and autonomic cardiac functioning in healthy subjects and patients with a major depression, which is a common psychiatric disorder. The 24-hour pattern of motor activity and the sympathetic and parasympathetic regulation of the cardiovascular system were examined to enlarge the knowledge about the psychomotor and autonomic cardiac dysfunction in major depressive disorder, and to obtain insight in the potential determinants. At the same time, parameters of spontaneous motor behavior and parasympathetic activity were evaluated for their usefulness in providing indirect (peripheral) information about the cholinergic dysfunction in depressed patients.

In this first chapter the characteristics of major depressive disorder are described and a concise overview is given of the role of genetic, psychosocial and neurobiological factors in the etiology of this affective disorder. In addition, developmental strategies, efficacy and pharmacological mechanisms of antidepressant treatments are explained, with special attention to the tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Subsequently, the psychomotor dysfunction in depressed patients, general aspects of the daily pattern of motor activity, the method of wrist-actigraphy, and several factors that may determine the 24-hour motor activity in depressed patients are discussed. Furthermore, the autonomic cardiac dysfunction in depressed patients, the neural short-term regulation of the cardiovascular system, the method of spectral analyses of heart rate (HR) and blood pressure (BP) variability, and the factors that may influence the autonomic regulation in depressed patients are clarified. Finally, the aim of the studies and the structure of the thesis are presented.

2 Major depressive disorder

In the Dutch population between 18-64 year, the lifetime prevalence of all affective disorders (major depressive disorder, dysthymic disorder, and bipolar disorder) is 19.0%, and of major depressive disorder 15.4% (Bijl et al., 1997). The lifetime risk to develop an affective disorder is nearly 2 times higher for women than for men. Major depression is the fourth leading cause of disease burden in the world, and is projected to be the second leading cause in the year 2020 (Murray and Lopez, 1997a, 1997b). According to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) (APA, 1994), the essential feature of a major depressive disorder is a clinical course

that is characterised by one or more major depressive episodes without a history of manic mixed or hypomanic episodes. During a depressive episode subjects have a depressed mood and/or loss of interest and pleasure in nearly all activities. Additionally, depressed subjects may experience several other symptoms such as changes in appetite and weight, alterations in the sleep/wake pattern, disturbances in psychomotor activity, decreased energy, feelings of worthlessness or guilt, cognitive dysfunctions (e.g. impaired concentration and memory) and thoughts of death or suicide. Major depressive disorder is recurrent, but it is also progressive in the sense that successive episodes occur after shorter intervals of remission (Post, 1992; Ormel and Sytema, 1999). Most depressive episodes vary between several weeks and several months, but a minority become chronic (lasting more than 2 years) (Angst, 2000). Depression has a negative impact on social and occupational functioning, and severe symptomatology results in disabilities in the family role and affects the self care (Ormel et al., 1993; Ormel and Sytema, 1999).

2.1 Etiology of depression

The three important factors in the etiology of depression concern genetic, psychosocial and neurobiological factors. There exist a large number of theories about how these different types of factors contribute, alone or by interaction, to the development of a depressive disorder.

2.1.1 Genetic factors

A meta-analysis of studies to the genetic epidemiology of major depression showed that the heritability of major depression is likely to be in the range of 31%-42% (Sullivan et al., 2000). Yet, it is unknown which specific chromosomal areas are involved in major depression (Souery et al., 2000). Probably the genetic component is more related to alterations in the expression of neurotransmitters, receptors and neuropeptides from the DNA matrix than to structural gene changes (see also 2.1.3 Neurobiological factors) (Post, 1992). This principle is also found in the gene-environment interaction theory proposing that genetic vulnerability to major depression comes to expression if an individual is exposed to specific environmental factors such as stress (Sullivan et al., 2000). Furthermore, repeated exposure to stressors and depressive episodes themselves may leave residual traces in gene expression processes that predispose to further occurrences of affective illness (Post, 1992).

2.1.2 Psychosocial factors

Impaired social relationships, stressful life events, cognitive dysfunction, economic status and personality are all psychosocial factors that are associated with major depression. However, it is difficult to make general statements about the etiological role of these factors, because the number of theories of psychosocial factors underlying depression is large, and they all use different concepts. To illustrate, Street et al. (2001) made a single framework for the psychosocial determinants of depression based on 29 theories with 99 concepts in total. Additionally, it is difficult to unravel the cause and consequence in the relationship between psychosocial factors and depressive disorder. Psychosocial factors are often integrated in multifactor models for the origin of major depressive disorder. The above mentioned gene-environment theory is one example. Another example is provided by the biosocial personality model of Cloninger, which comprised originally three genetically independent temperament dimensions: Harm Avoidance, Novelty Seeking, and Reward Dependence (Cloninger, 1987; Cloninger et al., 1993, 1994). Cloninger developed the Tridimensional Personality Questionnaire (TPQ) to measure these personality traits. Later on a fourth temperament dimension, Persistence, emerged from normative studies (Cloninger et al., 1993). The temperament dimensions are theorised to have predictable patterns of interaction with specific classes of environmental stimuli and to be related to single monoamine systems. However, the next chapter about neurobiological factors makes clear that the suggested link between temperament and specific neurotransmitters is an oversimplification (Tuinier and Verhoeven, 1995; Verhoeven and Tuinier, 2001). A high score on Harm Avoidance, which is the tendency to respond intensely to signals of aversive stimuli, is predicted to increase the susceptibility to depression (Cloninger, 1994). Presumably, individuals high in Harm Avoidance learn to inhibit behavior to avoid punishment, novelty, and nonreward: they tend to be cautious, fearful, tense, apprehensive, and passive. Individuals low on this dimension tend to be carefree, relaxed, daring, courageous, and composed. So far, the predictive value of Harm Avoidance for developing major depressive disorder has not been established in longitudinal studies, but many studies have found increased Harm Avoidance scores in depressed patients in comparison to healthy subjects (Brown et al., 1992; Joffe et al., 1993; Hansenne et al., 1999; Marijnissen et al., 2001).

2.1.3 Neurobiological factors

With respect to the origin of major depression, neurobiological factors are most frequently studied. Disturbances in various neurotransmitter and neuroendocrine systems (e.g. monoaminergic system, cholinergic system, glutamatergic system,

GABAergic system, hypothalamic-pituitary-adrenal (HPA) axis, hypothalamic-pituitary-thyroid (HPT) axis) are considered to be responsible for depressive mood and other symptoms of major depression, such as psychomotor dysfunctions, alterations in sleep, and cognitive dysfunctions. The major hypotheses about the neurobiological basis of depression are the monoamine hypothesis and the HPA axis hyperactivity hypothesis. In contrast, less attention has been paid to the etiological role of the cholinergic system in depression.

Monoamine hypothesis

The monoamine hypothesis was postulated in the 1960s and assumes that the neurobiological basis of depression is a deficit of one or more monoamine neurotransmitters (serotonin, noradrenaline, and/or dopamine) in synaptic clefts of the central nervous system (Bunney and Davis, 1965; Van Praag et al., 1970; Schildkraut, 1965). This hypothesis was based on the sequence of findings in the 1950s that depletion of central monoamine stores by reserpine, an antihypertensive drug, was followed by symptoms of depression (Muller et al., 1955; Shore et al., 1955) and that elevation of monoamine levels by iproniazid, a drug for tuberculosis, and imipramine, developed as tranquilliser, had an antidepressant effect (Kline, 1961; Kuhn, 1958). The latter agents were considered to establish their effect by inhibition of the metabolising enzyme monoamine oxidase (MAO) and the transporter-mediated reuptake of serotonin and noradrenaline from the synaptic cleft respectively. Two important limitations of the original hypothesis are the inconsistent findings about a dysfunctional metabolism of monoamine neurotransmitters, and the delay of clinical improvement after raising monoamine levels by antidepressant treatment (see review Verhoeven and Tuinier, 1999; Hirschfeld, 2000; Leonard, 2000). Recent neurobiological research at the cellular and molecular level suggests that there are dysfunctions in the pre- and postsynaptic receptors of the monoamine system due to changes in postsynaptic cellular signal pathways with the G protein as component, and in the gene expression of neuronal proteins via nuclear transcription factors (Leonard, 2000). The G protein plays a central role in coupling membrane receptors to various intracellular effector systems (Holsboer and Barden, 1996).

HPA axis hyperactivity hypothesis

The first indication of a hyperactivity of the HPA axis in depression also dated from the 1950s, when plasma cortisol levels, generally released by stress, were observed to be increased in depressed patients (Board et al., 1956; Gibbons, 1964). Later on, it was found that depressed patients had no or a reduced suppression of cortisol secretion by the adrenal cortex in response to the glucocorticosteroid

dexamethasone, an exaggerated cortisol secretion in responses to the adrenocorticotropic hormone (ACTH) released by the pituitary, and a hypersecretion of the corticotropin-releasing hormone (CHR) by the hypothalamus, which stimulates the release of ACTH (Holsboer and Barden, 1996; McQuade and Young, 2000). Hypercortisolaemia in other disorders than depression, e.g. Cushing's disease, and corticosteroid manipulations are known to impair cognitive and emotional functions (Holsboer and Barden, 1996; McAllister-Williams et al., 1998; McQuade and Young, 2000). These dysfunctions probably originate from neurodegenerative and neural plastic effects of cortisol in the hippocampus (McQuade and Young, 2000; Reid and Stewart, 2001). In depressed patients changes in the hippocampal function due to hypercortisolaemia can explain memory and learning deficits and may be responsible for the induction and maintenance of depressive mood (Reid and Stewart, 2001). The HPA axis hyperactivity is thought to be the result of a dysregulated feedback inhibition by endogenous corticosteroids due to an impairment of the glucocorticoid receptor (GR) system in HPA-axis tissues (hypothalamus and pituitary) and the hippocampus (De Kloet et al., 1996; Holsboer, 2001; Pariante and Miller, 2001). This impairment may be related to reduced GR gene expression caused by genetic factors and/or chronic stress. At the moment, there are unequivocal data that support the concept of an improvement of the GR function underlying the mechanism of action of antidepressant treatments (Holsboer, 2001).

Cholinergic dysfunction

The cholinergic system with acetylcholine as neurotransmitter is one of the important neurotransmitter systems in the central and autonomic nervous system (Guyton, 1991; Hyman and Nestler, 1993; Powley, 1999). Acetylcholine is synthesised from choline and the acetyl coenzym A by the enzyme choline acetyltransferase. In contrast to monoamines, acetylcholine is inactivated through enzymatic degradation by the enzym acetylcholinesterase in the synaptic cleft within a few seconds. Free choline is then actively taken up by a specific transporter protein in the cholinergic nerve terminals, where it is again acetylated to form acetylcholine. In 1972 Janowsky and colleagues proposed that depression is a manifestation of central cholinergic predominance. This hypothesis was based on the finding that in animals central acting cholinomimetics (cholinergic agonists and cholinesterase inhibitors) produce behavioral inhibition (including reduced motor activity) and decreased self-stimulation. In human, the central cholinesterase inhibitor physostigmine and other central cholinomimetics induce depressive mood accompanied by lethargy, apathy, drained feelings, and motor retardation (Janowsky et al., 1972; Janowsky and Overstreet, 1995). Central cholinergic activation also results in changes in the rapid

eye movement (REM) sleep (including decreased REM movement and increased REM density), which are similar to the changes in REM sleep observed in depressed patients (Janowsky et al., 1994; Janowsky and Overstreet, 1995). These findings suggest that symptoms of depression are linked to increased presynaptic cholinergic function. Further support for an etiological role of the cholinergic system in depression is provided by the exaggerated responses of depressed patients to cholinomimetics, which are attributed to hypersensitivity of merely muscarinic receptors in the central nervous system. The underlying mechanism of the cholinergic hypersensitivity may be an increased number of postsynaptic receptors or an activation of the postsynaptic intracellular second-messenger systems via muscarinic mechanisms (Janowsky et al., 1994). Overstreet and coworkers developed a genetic animal model of depression based on rats selectively bred for their cholinergic hypersensitivity in order to obtain more insight in the cholinergic dysfunction in depressed patients (Overstreet, 1986; Overstreet et al., 1992). These rats show reduced motor activity and increased immobility during the forced swimming test. Indirect (peripheral) information about alterations in the cholinergic function in depression can be obtained by assessing spontaneous motor behavior and measuring the parasympathetic regulation of the cardiovascular system in depressed patients. The role of the cholinergic system in these neurobiological functions will be explained later on.

Interactions between neurotransmitter and neuroendocrine systems

It should be emphasised that although the above hypotheses focus on one specific neurotransmitter or neuroendocrine system, they recognise interactions between the described system and other neurotransmitter and endocrine systems. For instance, mood and behavioral effects of central acting cholinomimetics can be counteracted by (nor)adrenergic/dopaminergic activation and vice versa, and cholinomimetic agents have a stimulating effect on the CHR factor and thus elevate serum ACTH and cortisol levels (Janowsky et al., 1994; Janowsky and Overstreet, 1995). More recent studies also demonstrated that glucocorticoids regulate the neurotransmission by amines through controlling the gene expression of aminergic receptors (Holsboer et al, 1996; Holsboer, 2001).

3 Antidepressant treatment

One of the therapeutic strategies of major depressive disorder is the pharmacological treatment with antidepressants, which started in the 1950s after the unexpected

discovery of the antidepressive effect of the tricyclic antidepressants (TCAs) and the nonselective monoamine oxidase inhibitors (MAOIs). The conventional antidepressants are clinically effective, but they induce several and sometimes severe side effects and can be toxic when used in overdose. To illustrate, TCAs inhibit the reuptake of serotonin and noradrenaline (and to a lesser extent dopamine), but also antagonise acetylcholinergic muscarinic (M1), histaminergic (H1), and adrenergic (α1) receptors (Stahl, 1998; Berman et al., 1999). The anticholinergic side effects of TCAs are dry mouth, blurred vision, constipation, urinary retention, memory impairment, and altered cardiovascular regulation (e.g. tachycardia). In addition, the antihistaminergic properties of TCAs may cause sedation and weight gain and the anti-adrenergic properties postural hypotension. The novel antidepressants are considered to lack the troublesome side effects of the conventional antidepressants, because they have more selective acting pharmacological profiles. For instance selective serotonin reuptake inhibitors (SSRIs) retained the ability to block the serotonin (5HT) reuptake, but have no effect on M1, H1, and α1 receptors and no noradrenaline reuptake blocking properties. However, they induce other side effects because they agonise 5-HT_2 postsynaptic receptors, with as consequence agitation, motor restlessness, insomnia, and sexual dysfunction, as well as agonise 5-HT_3 postsynaptic receptors, leading to nausea, diarrhea and headache (Stahl, 1998).

TCAs and SSRIs belong to the first choice pharmacological treatments in depressed patients. The efficacy of TCAs and SSRIs in terms of absolute response rates is still unclear, because the reported response rates vary enormously. Partly, this is the consequence of methodological shortcomings of prior clinical trials in study design, sample size, treatment duration, and control of drug plasma levels. Anderson (2000) compared the therapeutic efficacy of TCAs and SSRIs in a meta-analysis (out- and inpatients, n = 10706; studies, n = 102) and concluded that SSRIs had an equivalent therapeutic efficacy in reducing depressive mood as the TCAs in general practice and outpatients. However, SSRIs were less effective than TCAs in hospitalised patients (23% less reduction of clinical rating scale scores for depression). The favourable effects of TCAs in comparison to SSRIs in depressed inpatients may be explained by more adequate treatment regimes due to the control of drug plasma levels (Bruijn et al., 1999; Bruijn, 2000). This would be especially true for TCAs, such as imipramine, amitriptyline and nortriptyline, with a proven therapeutic plasma level. Furthermore, it is possible that inpatients are more responsive to TCAs because of their severity of depression, the presence of melancholic and/or psychotic features, and their course of illness and treatment history. However, Anderson (2000) concluded that there was no relationship between the clinical superiority of TCAs and age, severity of depression and antidepressant

dose in the inpatients, and stated therefore that differences in pharmacological profiles played a role.

As discussed above, TCAs and SSRIs increase monoamine levels in the synaptic cleft immediately (within days), while the therapeutic response occurs after several weeks. One hypothesis is that the increase in monoamine levels reduces the fire rate of monoamine neurons over time by inhibition of presynaptic 5-HT_1 serotonergic and α_2 noradrenergic autoreceptors (Duman, 1999). Another possibility is the down regulation (decreased sensitivity) of 5-HT_2 serotonergic and β adrenergic postsynaptic receptors, and the up regulation (increased sensitivity) of 5-HT_1 serotonergic postsynaptic receptors. During the last few years it has been theorised that the elevation of monoamines stimulates the intracellular second messenger pathway by activating specific 5-HT serotonergic and β adrenergic postsynaptic receptors. The second messenger pathway regulates many cellular processes and the gene expression of proteins. As stated above, the improvement of the corticosteroid receptor function also seems to play a role in the efficacy of antidepressants (Holsboer, 2001).

Antidepressants may also have favourable effects on disturbances in neurobiological functions, such as psychomotor activity and autonomic cardiac functioning. These effects can be established directly by pharmacological actions or by the induced improvement of clinical state. However, it is often difficult and complex to unravel the underlying mechanisms, because at the same time some antidepressants have negative effects on these functions. The effects of TCAs and SSRIs on the daily pattern of motor activity and the autonomic regulation of the cardiovascular system will be discussed below.

4 Psychomotor dysfunction in major depressive disorder

The psychomotor dysfunction in depressed patients is characterised by psychomotor retardation and agitation. According to Widlöcher (Widlöcher, 1983; Dantchev and Widlöcher, 1998) psychomotor retardation is a central feature of depressive illness. Psychomotor retardation is reflected in the slowing down of motor activities. Retarded patients show for instance slowed speech, fixed facial expression, less spontaneous movements of the limbs and trunk, and impaired gait and stride. Psychic activity is also slowed down which is reflected amongst others in reduced fluency of speech, loss of interest, and impaired memory and concentration (Widlöcher, 1983). According to the SADS (Schedule for Affective Disorders and Schizophrenia) the most important manifestations of agitation are: unable to sit still, pacing,

handwringing, pulling or rubbing hair, skin, clothing, outbursts of complaining or shouting, talking on and on or unable to stop talking (Endicott and Spitzer, 1978). Parker et al. (1990, 1991, 1993) outlined that the fundamental construct of the psychomotor disturbance in depressed patients is a neurocognitive-based disturbance which is expressed in both retardation and agitation. They recognised 18 observer rated signs of psychomotor disturbance in depressed patients. Factor analyses distinguished signs that were present in the case of retardation, as well as of agitation, signs that were exclusive for retardation and signs exclusive for agitation. The psychomotor disturbance was suggested to be specific for the melancholic subtype of depression (Parker et al., 1990, 1993, 1999).

Sobin and Sackeim (1997) gave an overview of the involvement of dopaminergic dysfunctions in psychomotor disturbances in depressed patients. Originally, Van Praag and Korf (1971) proposed that disorders of central dopamine metabolism are related to motor states of depressed patients. In various studies evidence was found that disturbances in the basal ganglia and the ganglia/thalamo-cortical circuit play a role in the psychomotor dysfunction. More recently mesolimbic and mesocortical projections of the dopamine system were found to be directly involved in motor behavior through their regulation of purposeful behavior, motivation and the ability to experience pleasure, instead of decreased dopamine metabolism in the nigrostriatal dopamine system (see overview Verhoeven and Tuinier, 1999). However, the studies of Janowsky et al. (1972, 1994, 1995) and Overstreet (1986) indicated that also cholinergic mechanisms are involved in the psychomotor retardation, because cholinergic stimulation results in the reduction of explorative behavior and the inhibitory behavioral effects of this stimulation are exaggerated in depressed patients. These views are not contradictory because dopaminergic and cholinergic neurotransmitter systems are known to interact with motor functions (Janowsky et al., 1994).

4.1 Daily pattern of motor activity

The number of studies to the normal 24-hour profile of motor activity is limited. Renfrew et al. (1987) studied the diurnal patterns of motor activity in healthy males between 21-83 years, and Lieberman et al. (1989) in healthy males and females between 19-35 years and between 65-94 years. The diurnal patterns in both studies were characterised by a large increase in motor activity in the early morning and a decline in motor activity during the evening and night. Renfrew et al. (1987) found smooth diurnal patterns, whereas Lieberman et al. (1989) reported diurnal patterns that were characterised by one or two peaks dependent on age and gender. Figure 1

presents the 24-hour pattern of motor activity in a group of healthy persons between 30-65 years based on our own data (Volkers et al., 1997; Tulen et al., 2001).

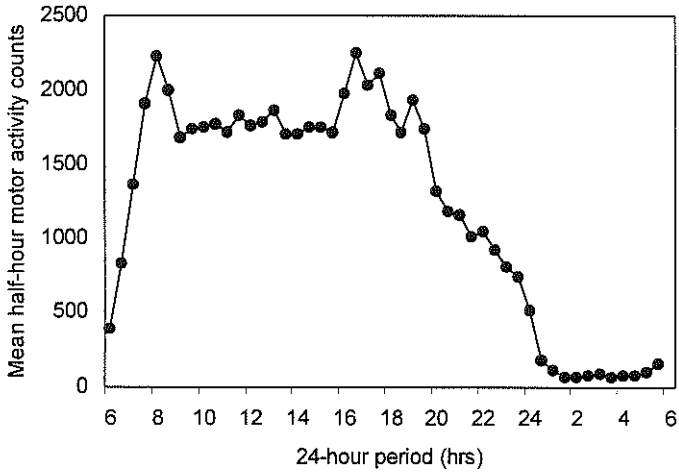

Figure 1 Daily pattern of motor activity in healthy persons (33 males and 31 females; mean age: 48.5 years, SD: 9.9) based on mean half-hour motor activity counts, averaged for three 24-hour periods (adapted from Volkers et al., 1997 and Tulen et al., 2001).

Among the methods of measuring the psychomotor dysfunction in depression, perhaps none is as intuitively apparent as the continuous monitoring of motor activity in a natural environment (Sobin and Sackeim, 1997). Tryon (1991) discussed the validity, reliability, and (clinical) applications of the available devices for ambulatory motor activity. The first activity monitors were in essential self-winding mechanical wrist-watches with a limited recording period (maximal several hours). Subsequently, wrist activity monitors were developed that detected by means of tilt sensors the frequency of tilt from the horizontal plane or from any plane in the case of a triaxial device. These tilt counters were telemetric, which means that each movement resulted in a FM signal transmission that was detected by a nearby receiver. Wrist-actigraphs are the most advanced and most frequently used ambulatory activity monitors. When measured from the non-dominant wrist, it is a valid and reliable method (Tryon, 1991; Patterson et al., 1993; Middelkoop et al., 1997a). These actigraphs contain a piezoelectric sensor that measures the number of movements above a certain acceleration threshold during a fixed time epoch. Wrist-actigraphy is an easy-to-use method for quantifying spontaneous motor activity

during a continuous period of several days in the habitual environment of subjects. Diurnal variations in motor activity provide insight in alterations in day- and nighttime motor activity levels, the distribution of motor activity over the day (e.g. fragmentation of motor activity, immobility, phase and daily peak(s) of the circadian activity-rhythm) and, in combination with sleep logs, the changes in the sleep-wake pattern.

4.2 Determinants of the 24-hour pattern of motor activity in depressed patients

Clinical state

Studies to the daily pattern of motor activity in depression have mainly focused on differences between unipolar and bipolar depressed patients, and suggest that the mean motor activity level in bipolar depressed patients is lower than in unipolar patients (Kupfer et al., 1974; Kuhs and Reschke, 1992; Wolff et al., 1985; Teicher, 1995). As a consequence, there is only a limited number of studies comparing the 24-hour motor activity patterns between unmedicated depressed patients and healthy control subjects. Unmedicated depressed patients demonstrated decreased motor activity levels and reduced fragmentation of motor activity during daytime, and an earlier timing or phase of the circadian rhythm of motor activity (Wehr et al., 1980; Wolff et al., 1985; Van Londen et al., 1998). Equivocal results were reported about changes in the motor activity during the sleep period. Thus, the clinical state may affect both motor activity levels and the distribution of motor activity over the day in depressed patients. Shortcomings of the referred studies were the small number of patients included in the studies and the fact that two studies were performed in patients with different subtypes of depression. Therefore, previous findings should be replicated in a larger group of depressed patients with one subtype of depression. To understand the origin of interindividual variations in the daily pattern of motor activity within unmedicated depressed patients, it is relevant to study additionally the relationship between 24-hour motor activity and specific clinical features. In depressed patients, motor activity levels were found to be positively associated with anxiety and hyperactivity rating scores (Kupfer et al., 1974; Joffe et al., 1987) and negatively with clinical ratings of retardation (Joffe et al., 1987; Royant-Parola et al., 1986; Raoux et al., 1994). Yet, psychotic features (delusions and hallucinations) have not been explicitly studied with respect to 24-hour motor activity.

Antidepressants

There are a few studies that have evaluated the effect of antidepressant treatment on the 24-hour motor activity pattern. Increased daytime motor activity levels were

observed after treatment with lithium (Kupfer et al., 1974), treatment with carbamazepine (Joffe et al., 1987) and a combined treatment with TCAs and benzodiazepines (Raoux et al., 1994; Royant-Parola et al., 1986; Benoit et al., 1985). After the latter treatment also less periods of immobility during day- and nighttime were found. In general, changes in motor activity levels have been attributed to improvement of depressive mood state (Teicher, 1995). However, studies in rats suggest that antidepressants may also have a pharmacological effect on overt motor behavior. Prolonged treatment with the TCAs imipramine and desipramine had a stimulating effect on overt motor behavior (Overstreet et al., 1995; West and Weiss, 1998). This was also found for the SSRI sertraline, but not for the SSRI fluoxetine. In humans, a single dose or dose administration for several days with TCAs, but not with SSRIs, impaired the psychomotor performance on laboratory psychomotor tasks (Fairweather et al., 1996; Hawley et al., 1997). In congruence with this finding, depressed patients treated with dothiepin (TCA) showed lower motor activity levels after 10 days of treatment than patients treated with fluoxetine (SSRI) (Stanley et al., 1999). The different effects between TCAs and SSRIs in healthy subjects and depressed patients were explained by the sedative side effects of TCAs. However, the sedative effects of antidepressants may disappear in depressed patients after one or two weeks of treatment due to the development of tolerance to these side effects (O'Hanlon and Freeman, 1995). More research is necessary to clarify the effect of TCAs and SSRIs on the 24-hour motor activity in depressed patients after several weeks of treatment, and to unravel the contribution of pharmacological effects and improvement of clinical state to changes in the daily pattern of motor activity after antidepressant treatment.

Personality, age and gender

The interpretation of data in depressed patients can benefit much from quantitative knowledge of the spontaneous motor activity patterns in healthy subjects. Normal data can be used as a reference for the clinical data, but also provide information about which factors are responsible for the diversity in spontaneous patterns of motor activity. There are several wrist-actigraphy studies in healthy adults addressing aspects of normal motor activity patterns in a natural environment. The influence of age and gender is most frequently studied with respect to interindividual variations, but the large discrepancies in findings do not allow us to make general statements about the effect of age and gender on day- and nighttime motor activity levels and the circadian rhythm of motor activity (Renfrew et al., 1987; Lieberman et al., 1989; Brown et al., 1990; Witting et al., 1990; Van Hilten et al., 1993). Personality is also of interest as determinant of overt motor activity. King (1986) theorised that overt

spontaneous motor activity was positively associated with extroversion and histrionic personality traits. The theorised relationship between histrionic traits and motor activity level was demonstrated in patients with a panic disorder, though no relationship was found between extroversion and motor activity level (King et al., 1988). Positive results were also found with children. More energy, less inhibition, more attention seeking, more dominance, more engagement in social play, greater assertiveness and less compliance were related to higher ambulatory measured levels of motor activity among 3 and 4 years old (Buss et al., 1980). Even in younger children (2.5 years), ratings of 'negative peer interaction' and 'excitability' were found to be positively correlated with motor activity levels, whereas ratings of 'seeking help with object blocks' were negatively correlated (Halverson and Waldrop, 1973). The outcome of studies to the effect of personality in healthy subjects may be supportive for our assumption that personality traits contribute to the altered daily pattern of motor activity in depressed patients.

5 Autonomic cardiac dysfunction in major depressive disorder

Over the years many clinical and epidemiological studies have reported an increased risk of cardiovascular morbidity and mortality in patients with a depressive disorder (Malzberg, 1937; Hayward, 1995; Glassman and Shapiro, 1998; Musselman et al., 1998). The risk may be enlarged in patients with a major depression in comparison to patients with a minor depressive disorder (Penninx et al., 2001). The autonomic cardiac dysfunction, as demonstrated by a decreased heart rate (HR) variability and reduced baroreflex, is one of the biological mechanisms that may underlie the increased risk of cardiovascular disease (Dalack and Roose, 1990; Yeragani, 1995; Musselman et al., 1998; Watkins et al., 1999; Gorman and Sloan, 2000). Decreased HR variability and a reduced baroreflex are observed in several cardiovascular diseases (Dalack and Roose, 1990; Huikuri, 1995; Huikuri et al., 1996; Parati et al., 2001). Furthermore, they increase the risk of arrhythmic events and sudden death after an acute myocard infarct (Hohnloser et al., 1994; Stys and Stys, 1998; La Rovere et al., 1998), and are suggested to be predictors for cardiovascular morbidity and mortality in community based studies (Tsuji et al., 1996; Singh et al., 1998; Kikuya et al., 2000).

5.1 Autonomic regulation of the cardiovascular system

The cardiovascular system is regulated by several complex control processes in order to supply blood to all body tissues and to maintain cardiovascular homeostasis

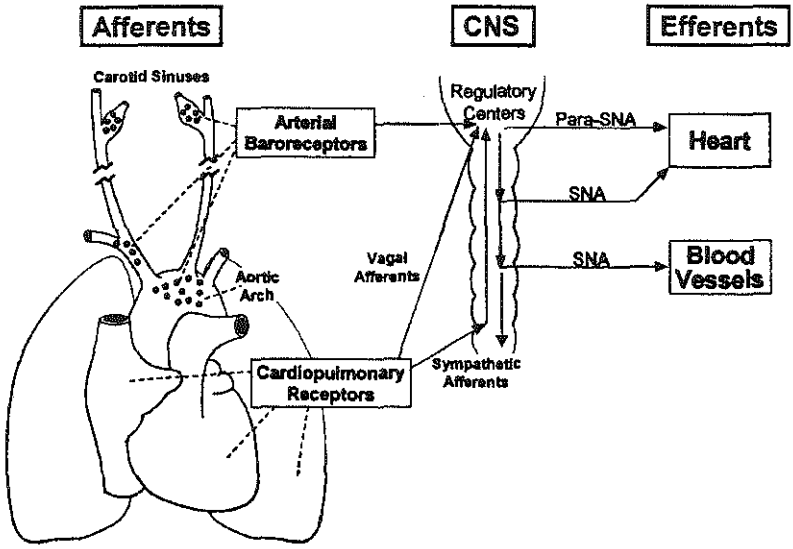

Figure 2 A schematic representation of the central and autonomic (sympathetic and parasympathetic) nervous system pathways involved in the regulation of the cardiovascular system. Afferent neurons transmit sensory output from the cardiovascular and respiratory systems to the central regulatory centers, whereas efferent neurons transmit signals to the heart and blood vessels (adapted from Chapleau and Abboud, 2001).

(Guyton, 1991; Malliani et al., 1991; Sved, 1999). The neural pathways involved in the short-term regulation of HR and blood pressure (BP) are illustrated in figure 2. The autonomic nervous system regulates the heart and circulation by their effect on the heart and blood vessels. Sympathetic activity to the heart leads to an increase in HR, whereas activation of the vagus nerves to the heart has an antagonising effect, thus a decrease of HR (Guyton, 1991; Sved, 1999). Sympathetic innervation of the blood vessels is directed primarily at the precapillary arterioles, which are the main source of vasoconstriction with subsequent increases in vascular resistance and central arterial blood pressure. The sympathetic and parasympathetic (vagal) outflow to the heart and blood vessels is determined by the cardiovascular control center in the caudal brain stem (medulla) (Guyton, 1991; Sved, 1999; Chapleau and Abboud, 2001). Principally, the vasomotor center in the rostra ventrolateral medulla (RVLM) transmits excitatory signals to sympathetic preganglionic neurons that innervate the heart and blood vessels. The cardiomotor center in the nucleus ambiguus (NA) and

the dorsal motor nucleus (DMN) of the vagus stimulates the vagal outflow to the heart. The RVLM and NA/DMN are innervated by neurons of the nucleus of the tractus solitarius (NTS), which is modulated by higher brain centers (e.g. hypothalamus and motor cortex) and is the endpoint of the reflex projections of the arterial baroreceptors and the venous cardiopulmonary baroreceptors (Guyton, 1991; Sved, 1999; Chapleau and Abboud, 2001).

The baroreflex is the best known and probably most important negative feedback mechanism to maintain the arterial pressure within a narrow normal range (Guyton, 1991; Parati, 2000). Baroreceptors in the aortic arch and carotid sinuses (figure 2) are stimulated by vascular stretch due to increases in arterial blood pressure. Increased baroreceptor afferent activity inhibits sympathetic activity and stimulates parasympathetic activity, which is rapidly followed by a decrease of the arterial pressure due to a decrease in vascular resistance and HR (Sved, 1999; Chapleau and Abboud, 2001). In contrast, when the arterial pressure decreases the baroreflex has an opposite effect and causes a rise in blood pressure. The relationship between alterations in arterial BP and changes in HR is indicative for the baroreflex function.

The short-term cardiovascular regulation is reflected in sinusoidal rhythmic oscillations with different frequencies. Figure 3 shows the variations in HR (presented as interbeat intervals (IBI) and systolic blood pressure (SBP) during a 5 minute period of supine rest. The baroreflex control induces spontaneous BP variations with a frequency around 0.10 Hz (Mayer waves) that may be the result of resonance in the vasomotor system (De Boer et al., 1985; 1987; Mulder, 1985; Wesseling and Settels, 1985; Mulder, 1988a; Guyton, 1991). The baroreflex response is also reflected in HR variations with a frequency around 0.10 Hz. These BP and HR variations are considered to be associated with changes in sympathetic activity (Tulen et al., 1994; Pagani and Malliani, 2000), although the HR variations around this frequency may also represent parasympathetic activity. Akselrod et al. (1981,1985) and Pomeranz et al. (1985) demonstrated in dogs and humans respectively that the blockade of parasympathetic activity to the heart by a peripheral muscarinic agent abolished the respiration-linked fluctuations in HR, but also diminishes HR fluctuations around the 0.10 Hz.

Variations in the HR related to the respiratory frequency (usually between 0.2-0.4 Hz) are called sinus respiratory arrhythmia (RSA) or high frequency (HF) variations (Porges and Byrne, 1992; Parati et al., 1995). In figure 3 the fast rhythm of the respiratory signal is illustrated and this rhythm is also visible in the IBI and SBP time series. This phenomenon is mainly caused by vagal activity to the heart due to the respiratory control center in the medulla which inhibits the vagal output to the heart during inspiration (Berntson et al., 1993; Grossman and Kollai, 1993; Guyton,

1991; Pagani and Malliani, 2000). The dominant role of parasympathetic activity in these HR variations is inferred from clinical and experimental observations of autonomic manoeuvres such as vagal stimulation, muscarinic blockade by drugs and the vagotomy (Malliani et al., 1991). It should be realised that respiration related BP variations do not represent vagal activity, but are caused by the mechanical effects of respiration on the pressure gradients, size, and functions of the heart and large thoracic vessels (Parati et al., 1995). HR variations around the frequency of 0.04 Hz are caused by various mechanisms involved in the vascular modulation including

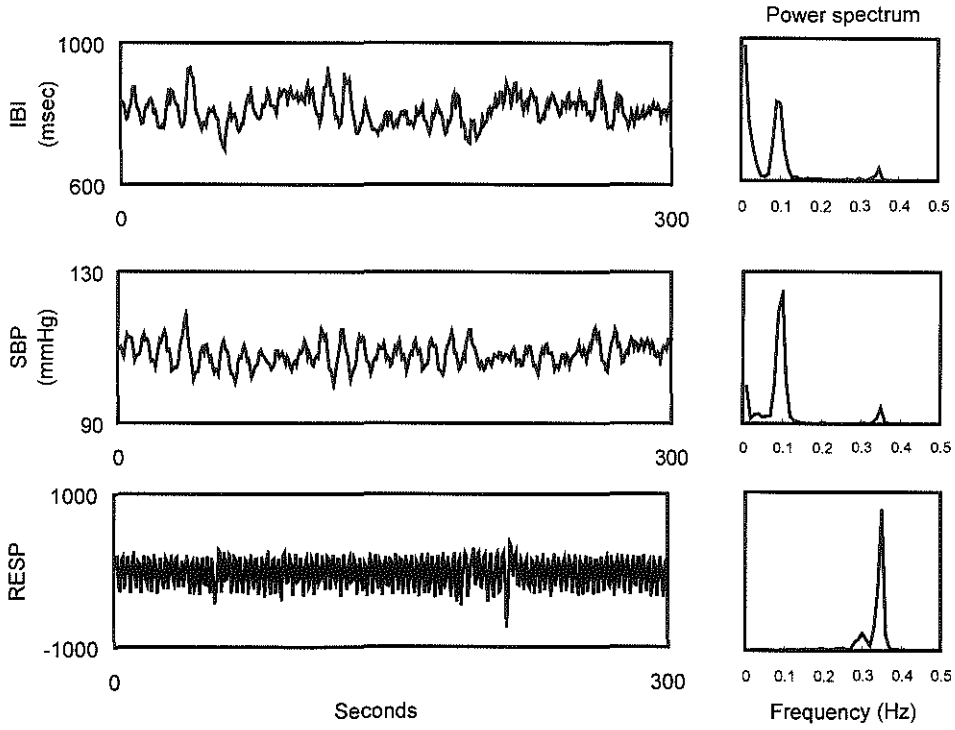

Figure 3 Examples of spontaneous variations in interbeat interval (IBI), systolic blood pressure (SBP) and respiration (RESP) during a 300 sec period of supine rest. The power spectra (presented on the right) of the time series show the variation per frequency point in the frequency range between 0.02-0.50 Hz. The spectral power was assessed by the squared modulation index (Van Dellen et al., 1985).

local influences of thermoregulation, renin-angiotensin system, and endothelial factors (Parati et al., 1995).

Spectral analysis is an adequate tool to unravel the sympathetic and parasympathetic processes involved in the short-term modulation of the cardiovascular system (Akselrod et al., 1985; Malliani et al., 1991; Montano et al., 1994; Parati et al., 2000). The variation or 'power' of HR and BP per frequency and frequency range can be quantified by spectral analysis (Parati et al., 1995). Figure 3 shows a power spectrum obtained in the frequency range between 0.01 to 0.50 Hz for the IBI and BP time series and the respiratory signal. The power spectra of the IBI and BP are characterised by a peak around 0.10 Hz and all spectra show a respiration related peak (with a frequency around 0.35 Hz). There is consensus that the HR power in the frequency range between 0.15-0.50 Hz is an index for parasympathetic activity and that the BP power in the frequency range around 0.10 Hz is an index for sympathetic activity (Parati et al., 1995; Task Force, 1996). As argued above the HR power around this frequency range is suggested to reflect both sympathetic and parasympathetic activity (Parati et al., 1995). Moreover, spectral analysis is appropriate to estimate the sensitivity of the spontaneous baroreflex in the different frequency ranges (Robbe et al., 1987; Saul, 1991; Parati et al., 2000). HR variability in the HF range may be a peripheral noninvasive indicator of the cholinergic dysfunction, because acethylcholine is an important neurotransmitter of the parasympathetic nervous system.

5.2 Determinants of autonomic cardiac functioning in depression

Clinical state

Dalack and Roose (Roose et al., 1989; Dalack and Roose, 1990) monitored the HR over a 24-hour period in 11 unmedicated patients with major depression and were the first who reported that high frequency variations in HR of depressed patients were diminished in comparison to healthy subjects. However, the majority of later studies comparing unmedicated depressed patients and healthy subjects provided less evidence for a decreased HR variability or reduced baroreflex sensitivity (BRS) (Yeragani et al., 1991; Rechlin et al., 1994a; Tulen et al., 1996a; Lehofer et al., 1997; Moser et al., 1998). Nevertheless, these studies reported increased HR levels and altered (increased or decreased) BP levels, indicating that alterations in the autonomic regulation in unmedicated depressed patients may be restricted to overall HR and BP levels. On the other hand it is plausible that the decrease in HR variability and BRS can not be detected on group level, because these cardiovascular parameters are only affected in subgroups of depressed patients with specific clinical features. Anxiety

and agitation in depressed patients may be accompanied by elevated HR levels (Stein et al., 1994) and more anxiety was reported to be associated with lower HR variability and less baroreflex control (Rechlin et al., 1994b; Tulen et al., 1996b; Watkins et al., 1999). Furthermore, cardiovascular control mechanisms may be influenced by psychotic features, because Parker et al. (1995) hypothesised that psychotic patients in comparison to nonpsychotic patients were more likely to demonstrate disturbances in vegetative functions. A relationship between psychomotor retardation, which is probably characterised by less overall physical activity, and autonomic cardiac functioning, in particular a decreased HR variability, was also suggested (Thayer et al., 1998; Watkins et al., 1999). It is surprising that so far this relationship has not been examined.

Antidepressant treatment

It is well known that treatment with conventional antidepressants induces various cardiovascular side effects. For instance, TCAs have the potency to cause tachycardia, orthostatic hypotension, conduction delays, and cardiac arrhythmias (Littman, 1993). TCAs also decrease the HR variability, indicating diminished vagal cardiac control due to the anticholinergic properties of TCAs (Yeragani et al., 1995; Tulen et al., 1996a). The novel antidepressants, such as the SSRIs, are developed to be free of cardiovascular side effects, but some influence on the autonomic cardiac function should not be excluded. For instance, Lederbogen et al. (2001) demonstrated recently in depressed patients that paroxetine treatment with a high dose (40 mg) resulted in decreased HR variability, probably due to the anticholinergic properties of paroxetine. In contrast, no changes in HR variability were reported after treatment with fluvoxamine in depressed patients (Rechlin et al., 1994b), although fluvoxamine treatment has the tendency to decrease the mean HR (Wakelin, 1986; Hewer et al., 1995; Laird et al. 1993; Rechlin et al., 1994b). The effects of SSRIs should be further clarified, especially on HR and BP variability and BRS. Balogh et al. (1993) stated that antidepressants, especially antidepressants without strong cardiovascular effects, may also have a beneficial effect on the cardiovascular system through their therapeutic effect on depressive mood.

Risk factors

More recently interest has grown in another type of determinants: the higher prevalence of cardiovascular risk factors in depressed patients. Cigarette smoking is the most salient lifestyle risk factor in depressed patients (Glassman et al., 1990; Glassman, 1993; Breslau et al., 1998). Hayward (1995) concluded in his review that the frequency of cigarette smoking in depressed patient is about 50%, while this

percentage ranges between 20-30% in the general population. Additionally, he stated that the frequency of smoking is particularly high in depressed inpatients. The relationship between depression and cholesterol is much more complex and confusing. Up until the 1980s it was assumed that there would be a positive relationship between depression and cholesterol (Oxenkrug et al., 1983; Wardle, 1995). Later on, studies appeared that found that depressive disorder and depressive symptoms were related to lower levels of total and HDL cholesterol (Morgan et al., 1993; Horsten et al., 1997; Maes et al., 1997; Chen et al., 2001). Furthermore, depression may be related to other risk factors such as physical inactivity and overweight (Ariyo, 2000), but research on this issue is scarce. Detailed insight in the effect of cardiovascular risk factors on autonomic regulation in healthy subjects may contribute to the understanding of the relevance of these factors for autonomic dysfunctions in depressive disorder.

Cigarette smoking is suggested to enhance HR and BP levels, increase BP variability, decrease HF variability of HR, and reduce BRS (Hayano et al., 1990; Niedermaier et al., 1993; Mancia et al., 1997; Gerhardt et al., 1999; Ragueneau et al., 1999). Higher total cholesterol and low density lipoprotein (LDL) cholesterol levels could be related to lower overall HR variability (Kupari et al., 1993; Christensen et al., 1999). Several studies have paid attention to the effects of other well known cardiovascular risk factors, including physical inactivity and an increased body mass index, on autonomic cardiac functioning, but equivocal results were reported (Kupari et al., 1993; Molgaard et al., 1994; Kageyama et al., 1997; Fagard et al., 1999; Kardos A et al., 2001). In healthy subjects the effect of smoking on cardiovascular variability and baroreflex sensitivity needs to be further investigated, and the effect of lipid levels, levels of physical activity and overweight on these parameters should be studied more in detail.

6 Aims of the studies and outline of this thesis

6.1 Aims of the studies

The studies of this thesis concern the spontaneous pattern of motor activity and autonomic cardiac functioning in major depressive disorder. The main purpose of the studies was to obtain insight in the psychomotor and autonomic cardiac dysfunction in depression by investigating the 24-hour pattern of motor activity and the autonomic (sympathetic and parasympathetic) regulation of the cardiovascular system in healthy subjects and depressed inpatients. The data of the patients were assessed during a psychotropic drug free period drug and after double blind treatment during

4 weeks with imipramine or fluvoxamine. It was hypothesised that clinical state and antidepressant treatment affect the 24-uur pattern of motor activity and autonomic regulation in depressed patients. Furthermore, personality traits were theorised to contribute to variation in the 24-uur pattern of motor activity, and risk factors to variation in cardiovascular variability and baroreflex sensitivity. In addition, measurements of the spontaneous motor behavior and parasympathetic regulation in depressed patients were explored for their usefulness to clarify the cholinergic dysfunction in major depressive disorder.

The specific aims of the studies were the following:

1) To extract the time trend in the daily pattern of motor activity in healthy subjects and to examine the effect of personality on this pattern.
2) To evaluate the effect of risk factors on autonomic cardiac functioning in healthy subjects.
3) To establish alterations in the 24-motor activity and autonomic cardiac functioning in medication free depressed patients, in comparison to healthy subjects, and to determine the relevance of specific clinical features for and the relationship between these functions.
4) To compare the effect of treatment with a conventional tricyclic antidepressant (TCA) and a modern selective serotonin reuptake inhibitor (SSRI) on the 24-hour pattern of motor activity in depressed patients and to explore the contribution of the improvement of clinical state to the changes after treatment.
5) To compare the effect of treatment with a TCA and a SSRI on autonomic cardiac functioning in depressed patients, and to unravel the effects of pharmacological actions and improved depressive mood on the alterations in autonomic regulation observed after treatment.

6.2 Outline of this thesis

In chapter 2, a study to the 24-hour pattern of motor activity in the natural environment of healthy subjects is presented. The shape of the daily pattern of motor activity was modelled by random regression analysis and we examined whether the temperament dimensions of the Tridimensional Personality Questionnaire (TPQ), age and gender were related to overall levels of motor activity and the shape of the diurnal pattern.

Chapter 3 deals with the influence of cardiovascular risk factors on the autonomic modulation of the cardiovascular system in healthy subjects. Cigarette smoking, lipid levels, body mass index, habitual physical activity, age and gender were

investigated as determinants of mean heart rate and blood pressure, cardiovascular variability and baroreflex sensitivity. To obtain large intraindividual variation, the cardiovascular measurements were performed during supine rest and head-up tilt.

The fourth chapter presents a detailed study to the psychomotor and autonomic cardiac dysfunction in major depressive disorder. Unmedicated severely depressed inpatients and healthy control subjects were compared regarding their 24-hour motor activity and autonomic regulation. Within the patient group the relevance of specific clinical features (anxiety, agitation, psychomotor retardation, and psychotic features) and the relationship between motor activity and cardiovascular parameters were explored.

In chapter 5 the effect of the tricyclic antidepressant imipramine and the selective serotonin reuptake inhibitor fluvoxamine on the 24-hour pattern of motor activity in major depressive disorder is described. Mean motor activity levels, fragmentation of motor activity, and immobility were studied during a psychotropic drugfree period and after a double blind treatment of 4 weeks under control of plasma levels. The contribution of changes in severity of depression, psychomotor retardation and agitation to alterations in the motor activity parameters were discussed.

Chapter 6 reports about the autonomic regulation of the cardiovascular system in depressed patients before and after treatment with imipramine or fluvoxamine. We investigated the effect of orthostatic challenge on cardiovascular parameters in each treatment group and tried to unravel the pharmacological effect and the influence of improved depressive mood on changes in cardiovascular parameters after treatment.

In the last chapter the main findings of the studies of this thesis are summarised, discussed, and integrated. A critical appraisal of the applied methodology is given, and suggestions for future research in this field are provided.

Chapter 2

Effect of personality dimensions on the diurnal pattern of motor activity

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1 Abstract

The effects of personality dimensions, age, and gender on 24-hour motor activity patterns were studied in 101 healthy subjects between 20–70 years. We measured motor activity by wrist-actigraphy and personality dimensions by the Tridimensional Personality Questionnaire (TPQ) of Cloninger. Random Regression Models were used to estimate the effects of personality dimensions, age, and gender on the diurnal pattern of motor activity. Harm Avoidance as well as Reward Dependence influenced the overall level of motor activity, independent of age and gender. Subjects high on Harm Avoidance showed lower activity levels than subjects low on Harm Avoidance, whereas subjects high on Reward Dependence had higher overall levels of motor activity than subjects low on Reward Dependence. Older subjects were found to be less active than younger subjects, but the activity level did not differ between males and females.

2 Introduction

Several biologically based personality theories have hypothesized relationships between personality characteristics and neurophysiological or neuroendocrine parameters (e.g. Eysenck, 1967; Zuckerman et al., 1980; Cloninger, 1987). These theories have so far neglected to put forward a direct association between personality dimensions and locomotor activity. However, King (1986) theorised that overt spontaneous motor activity and personality styles, like extroversion and histrionic personality traits, would interrelate. More specifically, it was predicted that individuals with histrionic or extroverted traits would show enhanced motor activity to incentives. The theorised relationship between histrionic traits and motor activity level was demonstrated in patients with a panic disorder, though no relationship was found between extroversion and motor activity level (King et al., 1988). Positive results also have been found with children. For example, more energy, less inhibition, more attention seeking, more dominance, more engagement in social play, greater assertiveness and less compliance were related to higher ambulatory measured levels of motor activity among 3- and 4-year-olds (Buss et al., 1980). Even in younger children (2.5 years), ratings of "negative peer interaction" and "excitability" were found to be positively correlated with motor activity levels, whereas ratings of "seeking help with object blocks" were negatively correlated (Halverson and Waldrop, 1973). These findings underline the potential relevance of personality dimensions and individual differences for levels of overt motor activity.

In this study, we examined in a large group of healthy subjects whether personality traits are related to the overall level of motor activity independent of the effects of age and gender. Cloninger's Tridimensional Personality Questionnaire (TPQ; 1987) was used to assess personality traits. Cloninger (1987) developed a neurobiological learning model with three genetically independent temperament dimensions: Novelty Seeking, Harm Avoidance, Reward Dependence. In contrast to other multidimensional personality models (e.g. Eysenck's), Cloninger's model assumes that the observed phenotypic structure of personality may differ from the underlying biogenetic structure because variations in behavior result from the interaction between environmental and genetic influences (Cloninger 1987, 1991, 1998, 1999). The TPQ was based on a synthesis of information derived from family studies, studies of longitudinal development, and psychometric studies of personality structure, as well as neuropharmacological and neuroanatomical studies of behavioral conditions and learning in men and animals. Subsequent research using the TPQ showed that one subscale (i.e. Persistence) of the Reward Dependence dimension was relatively independent of the three postulated temperament dimensions, and consequently was assumed to be an additional genetically independent temperament dimension (Cloninger, 1994; Stallings et al., 1996). Genetic analysis demonstrated that 54% to 61% of the stable variation of the four TPQ dimensions could be ascribed to heritability and that the dimensions had little or no genetic correlations with one other (Cloninger, 1994).

The TPQ dimensions have predictable patterns of interaction with specific classes of environmental stimuli (Cloninger, 1987). Novelty Seeking is the tendency toward excitement in response to novel stimuli or cues signalling potential rewards or relief from punishment. This tendency leads to frequent exploratory activity in pursuit of potential rewards, as well as active avoidance of monotony and potential punishment. Individuals high on Novelty Seeking are excitable, exploratory, curious, enthusiastic, and impulsive, whereas individuals low on Novelty Seeking are indifferent, uninquiring, unenthusiastic, stoical, and tolerant of monotony (Cloninger, 1987, 1994, 1998, 1999). Harm Avoidance is a tendency to respond intensely to signals of aversive stimuli. Presumably, individuals high in Harm Avoidance learn to inhibit behavior to avoid punishment, novelty, and nonreward; they tend to be cautious, fearful, tense, apprehensive, and passive, whereas individuals low on this dimension tend to be carefree, relaxed, daring, courageous, and composed. Reward Dependence is the tendency to respond intensely to signals of reward (particularly verbal signals of social approval and sentiment). Individuals high on Reward Dependence tend to maintain or resist extinction of behavior that has previously been associated with reward or relief from punishment. They are eager to help and

please others, tender-hearted, dedicated, warmly sympathetic, and sensitive to verbal signals of social reinforcement, whereas those low on Reward Dependence are practical, tough-minded, cold, and socially insensitive. Finally, Persistence is the tendency to persevere in behavior despite frustration and fatigue. High scorers on Persistence are industrious, hard-working, persistent, and stable, whereas low scorers are inactive, indolent, unreliable, and unstable.

If Cloninger's theory about specific relationships between temperament dimensions and the activation, inhibition, and maintenance of behavior is true, then we expect the TPQ dimensions to be related to individual differences in spontaneous patterns of motor activity. Because Novelty Seeking is postulated to be linked to exploratory activity and Harm Avoidance to the inhibition of behavior, we expected that high scorers on Novelty Seeking should exhibit higher levels of motor activity, whereas high scorers on Harm Avoidance should exhibit lower levels of motor activity. Additionally, low scorers on Persistence are thought to be inactive and indolent, suggesting that Persistence should be positively related to motor activity levels. There was no theoretical or rational ground to expect in advance an effect of Reward Dependence on motor activity level.

King et al. (1988) emphasized that in studies investigating the relationship between personality traits and behavior, behavior needs to be measured over multiple time points and in many situations because situationally and temporally limited measures of behavior often show low correlations with personality traits. Accordingly, in this study, wrist-actigraphy was used to monitor motor activity during three days and nights in a natural environment. Wrist-actigraphy is an unobtrusive, objective method for assessing 24-hour patterns of spontaneous motor activity and has been demonstrated to measure motor activity in a valid and reliable way (Patterson et al., 1993; Tryon, 1991; Middelkoop et al., 1997a). Because previous studies demonstrated an effect of age and gender on wrist-actigraphy data (Lieberman et al., 1987; Witting et al., 1989; Van Hilten et al., 1993; Brown et al., 1990), we also studied the effects of age and gender on the pattern of motor activity.

3 Method

3.1 Subjects

From November, 1995, through March, 1997, 101 subjects between 20–70 years of age participated in the study. The study population consisted of students (n=23), housewives (n=16), individuals who were employed (n=58), and subjects who were retired (n=4). Exclusion criteria were: a history of mental illness, sleep disorders,

current medical illness, medication use interfering with the activity pattern, recent circadian shifts, and working during evening hours and night-time. Recordings of two female participants were excluded from the data analysis because of illness during the recording period. The recordings of two other female participants were lost due to technical problems. The remaining study population consisted of 51 males (mean age: 40.1 years, range: 20–66) and 46 females (mean age: 40,9 years, range: 20–67). Recruitment was aimed at an equal division of men and women in three beforehand-defined age groups (between 20–35 years, between 36–50 years and between 51–70 years). The first age group comprised 39 subjects, the second 30, and the third 28. The Medical Ethics Committee of the University Hospital Rotterdam-Dijkzigt approved the study, and subjects were not paid for their participation.

3.2 Personality Questionnaire

Within one week after the recording period, the Dutch version of the Tridimensional Personality Questionnaire (TPQ) (Cloninger, 1987; Dutch version: Van Den Brink et al., 1993) was completed. Two subjects returned incomplete questionnaires (missing items > 2), therefore the data of these subjects were not used in the analysis. The TPQ is a 100-item, true/false questionnaire, including 34 items for Novelty Seeking, 34 items for Harm Avoidance, 31 items for Reward Dependence, 9 items for Persistence, and 2 items for general information about the manner in which the questionnaire was completed. As previously discussed, Persistence was originally a subscale of Reward Dependence, but empirical evidence indicated that separation from Reward Dependence was required (Cloninger, 1994; Stallings et al., 1996). Prior research demonstrated that the internal consistency estimates for the dimensions were moderate to good (α is between 0.65 and 0.85), and the test-retest reliability estimates moderately high (r is between 0.70 and 0.79) (Cloninger, 1994). The test-retest reliability was based on an interval of 6 months.

3.3 Wrist-actigraphy

To assess spontaneous 24-hour motor activity, subjects wore a wrist-actigraph continuously during 4 days and nights, either from Monday morning until Friday morning or from Tuesday morning until Saturday morning in their natural environment. The standard procedure was to measure motor activity from Monday morning until Friday morning, but for practical reasons 33% of the subjects wore the actigraph from Tuesday morning till Saturday morning. Day- and night-time motor activity was always measured on weekdays, but the motor activity on Friday night might have differed from other weekdays. However, post-hoc analyses revealed no systematic differences between the activity pattern of Friday night and the other

evenings.The nondominant wrist was chosen as the recording site, because recordings of the nondominant wrist are assumed to be more reflective of movements of the total trunk and less of movements involved in performing specific tasks such as writing (McPartland et al., 1975; Middelkoop et al., 1997a). The subjects maintained their habitual 24-hour pattern of activities at home and outside and were only allowed to take off the actigraph during bathing. The actigraph (Gaehwiler Electronic; size 51 x 36.5 x 21 mm) contained a monoaxial piezoelectric acceleration sensor and counted the number of suprathreshold movements of the wrist (> 0.1 g acceleration) per 30-s epochs. The analogue sensor signal was sampled at a frequency of 8 Hz and subsequently filtered by a band-pass filter of 0.25-3.0 Hz.

The first day and night of the recording period was used to acclimate subjects to wearing the actigraph. Therefore, wrist-actigraphy recordings of the last three days and nights were used for data analysis. According to Middelkoop and Sadeh (1997b), three days are necessary to obtain reliable motor activity data because of interday variations. A clock-time-based analysis was applied to compute, for each day, half-hour motor activity counts from 6 a.m. until 6.00 a.m the next morning. Thereafter, half-hour motor activity counts were averaged for the recording days, and subsequently, these mean half-hour activity counts were averaged for several periods of the day.

The 24-hour interval (from 6 a.m.–6 a.m.) was divided in eight periods, reckoning with findings of earlier studies and the assumed activity pattern of the study population. The first period, from 6 a.m. until 7 a.m., was chosen because in the studies of Lieberman et al. (1989) and Renfrew et al. (1987), older subjects were more active than younger subjects during this period. The second period, from 7 a.m. until 9 a.m., was assumed to reflect the period of getting up and travelling to work. The third period, from 9 a.m. until noon, represented the morning, and the fourth period, from noon until 4:30 p.m., the afternoon. The fifth period, from 4:30 p.m. until 6:30 p.m., was supposed to be the period during which subjects returned home. The sixth period, from 6:30 p.m. until 11 p.m., reflected the evening. Finally the seventh period, from 11 p.m. until 2:30 a.m., was assumed to represent for most subjects the period during which they went to bed and fell asleep; the last period, from 2:30 a.m. until 6 a.m., represented the late night.

3.4 Statistical Analysis

Pearson product-moment correlations were computed to investigate the relationships among the four personality dimensions, and between age and each personality dimension. To test differences between males and females on the personality dimensions, we used t-tests for independent samples.

To estimate the effects of personality, age and gender on the diurnal pattern of motor activity, Random Regression Models (RRMs) for continuous data were used. The analysis of motor activity data was performed with the program Proc Mixed of the statistical package, Statistical Analysis Systems (SAS for Windows, release 6.12). RRMs estimate individual effects instead of effects for the total study population (Bock, 1983; Gibbons et al., 1993). The random regression approach uses data from individuals augmented by information from the total study population to estimate for each subject the personal trend across time. RRMs are characterised by the following model equation: "$Y=\beta_0+\beta_1X_1+\ldots+\beta_kX_k+b_0+b_1Z_1+\ldots+b_mZ_m+\varepsilon_{ij}$", where $X_1, \ldots, X_k$ are group indicators and $Z_1, \ldots, Z_k$ are subject indicators. In RRMs, the intercept and time effects are allowed to differ for individuals, and therefore are called random terms. RRMs have advantages above the usually applied MANOVAs for repeated measurements. In RRMs, data are used efficiently, resulting in a more adequate estimation of the time trend. RRMs can cope with missing values because the estimation of an individual time trend is based on non-missing data for that individual. This implies that missing values are assumed to be missing at random (Rubin, 1987), and subjects may have data for different time points. In contrast to the classical ANOVA for repeated measurements, RRMs allow more general and realistic error structures. In this study we assumed an "unstructured" error structure, which allows both correlations between measurements and variances of measurements to differ (Gibbons et al., 1993; Verbeke and Molenberghs, 1997). In other words, variances and covariances may differ between repeated measurements. It should be noted that patterns of 24-hour motor activity have seldom been analysed by statistical models for repeated measurements and, as far as we know, never by Random Regression Models. Diurnal patterns in healthy subjects and patient groups have often been analysed per hour, per period of the day, per daytime and night-time, and per total day. The disadvantage of separate analyses is that the time trend itself cannot be identified.

The motor activity data were characterised by skewed distributions of mean half-hour motor activity counts, large differences between mean motor activity counts, and large variability within each mean motor activity count (mean, SD, range: period 1: 459, 888, 8-6457; period 2: 1840, 1109, 117-5569; period 3: 1752, 903, 226-5551; period 4: 1819, 921, 226-5747; period 5: 1093, 1093, 166-5572; period 6: 1597, 812, 193-3815; period 7: 550, 435, 14-1935; period 8: 101, 111, 11-715). Due to these characteristics, the model did not fit well (-2 REML Log Likelihood >> 5000). A $\log_{10}$ transformation was performed on the mean half-hour motor activity counts resulting in normality of data (mean, SD, range: period 1: 2.2, 0.36, 0.93-3.81; period 2: 3.1, 0.37, 2.1-3.8; period 3: 3.2, 0.23, 2.4-3.7; period 4: 3.2, 0.24, 2.4-3.8; period 5:

3.3, 0.27, 2.2-3.8; period 6: 3.1, 0.27, 2.3-3.6; period 7: 2.6, 0.46, 1.2-3.3; period 8: 1.8, 0.36, 1.05-2.85). The use of the transformed motor activity counts in the RRMs improved the model fit (-2 REML Log Likelihood < 600). The time variable was constructed by taking the middle of each predefined period of the day, which resulted in the following fixed time points for the data series: 1, 2.5, 5, 8.75, 12.00, 15.25, 17.25 and 20.75 hrs.

Analyses were conducted in two steps:

Step 1

The effect of time on the diurnal pattern of motor activity was studied. The model estimating the time trend was built by adding fixed time effects of increasing order one by one until they were nonsignificant, and by adding random time effects of increasing order one by one until their variance components were negative (Brown and Prescott, 1999).

Step 2

We evaluated the main effects of personality dimensions, age, and gender on the motor activity pattern. The main effect terms were added simultaneously to the RRM for the time trend. The effects of the personality dimensions were studied in separate analyses to simplify the description and to improve the understanding of the RRMs.

4 Results

4.1 Correlations Between Personality Dimensions, Age and Gender

Novelty Seeking showed significant, negative correlations with Harm Avoidance (r=-0.22, $p<0.05$) and Reward Dependence (r=-0.21; $p<0.05$). Other correlations between the personality dimensions were nonsignificant (all r's<0.14; p's>0.19). Females showed significantly higher scores than males on Harm Avoidance (mean=13.1, sd=5.6 and mean=10.5, sd=5.0 respectively, $p<0.01$) and Reward Dependence (mean=14.1, sd=3.8 and mean=11.4, sd=3.8 respectively, $p<0.05$), but no significant gender differences were found for Novelty Seeking or Persistence. Age was significantly negatively correlated with Novelty Seeking (r=-0.32, $p<0.05$) and with Persistence (r=-0.22, $p<0.01$), indicating that older subjects have lower scores on these personality dimensions than younger subjects.

4.2 Time trends in the motor activity data

Figure 1 shows an example of a 24-hour actigram. The diurnal pattern, based on mean half-hour motor activity counts for the whole study population, is presented in

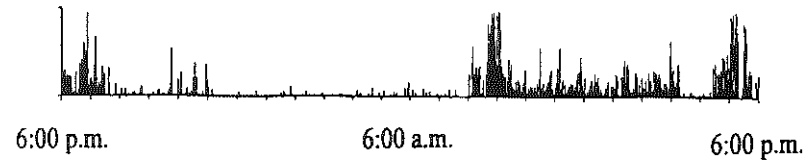

Figure 1 Raw data of a 24-hour motor activity recording of a 22-year-old male. The x-axis represents the clock time (beginning and ending at 6 p.m.) and the y-axis the number of counts per 30-sec epoch.

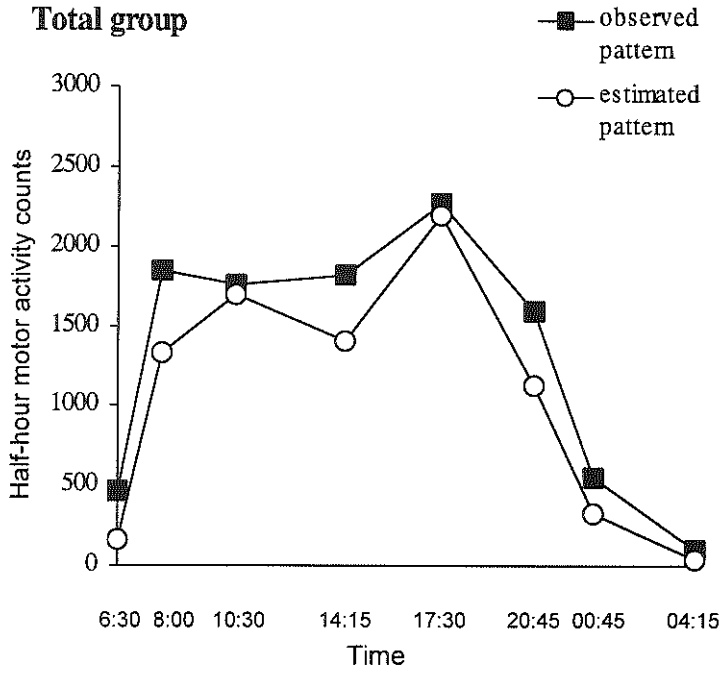

Figure 2 Observed and estimated diurnal pattern of motor activity for the whole study population. The diurnal pattern was estimated based on the following equation: mean half-hour motor activity counts = $0.83 + (1.8 \times time) + (-0.5 \times time^2) + (0.06 \times time^3) + (-0.004 \times time^4) + (1 \times 10^{-4} \times time^5) + (-1 \times 10^{-6} \times time^6)$.

figure 2. On visual inspection, the diurnal pattern is characterised by a large increase in motor activity level from the first period (6–7 a.m.) to the second period of the day (7–9 a.m.), followed by slightly decreased motor activity levels in the next two periods (9 a.m.– 4:30 p.m.), a peak of motor activity in the period from 4:30 p.m. until 6:30 p.m. and a gradual decline in motor activity during the evening and the night. We found that the 24-hour pattern of motor activity could be modelled by six fixed time effects (time, time^2, time^3, time^4, time^5 and time^6) and three random effects (intercept, time, time^2). Thus, the estimated pattern was characterised by a linear time trend, in addition to 5 points of inflexion (figure 2). Dependent on the strength of the higher order time effects, the points of inflexion were more or less pronounced in the estimated pattern. The RRM for the time trend was used as reference model in the analyses of the main effects of personality, age and gender.

Table 1 Significant effects of time, Harm Avoidance (HA), Reward Dependence (RD) and age on the motor activity pattern.

	RRM for the time effect			RRM for the effects of time, HA, age and gender			RRM for the effects of time, RD, age and gender		
variable	df	t	p	df	t	p	df	t	p
Intercept	96	7.1	<.001	92	8.6	<.001	91	5.7	<.001
Time	96	13.3	<.001	94	12.9	<.001	94	12.9	<.001
Time^2	96	-9.1	<.001	94	-8.9	<.001	94	-8.9	<.001
Time^3	96	6.5	<.001	94	6.3	<.001	94	6.3	<.001
Time^4	96	-4.6	<.001	94	-4.5	<.001	94	-4.5	<.001
Time^5	96	3.2	=.002	94	3.0	<.001	94	3.0	=.003
Time^6	96	-2.1	=.04	94	-2.0	=.05	94	-2.0	=.05
Harm Avoidance				469	-2.7	=.007			
Reward Dependence							469	3.5	<.001
Age				469	-3.8	<.001	469	-3.8	<.001
Gender				469	1.6	ns	469	-0.5	ns

RMM, Random Regression Model

4.3 Estimated Effects of Personality

Contrary to our prediction, the main effects of Novelty Seeking and Persistence were not significant, indicating that the overall level of motor activity was similar for

subjects with high scores and low scores on these personality dimensions. The main effect of Harm Avoidance on the motor activity pattern was significantly positive and that of Reward Dependence significantly negative (table 1). The effects were independent of age and gender. This finding indicates that overall levels of motor activity were low for individuals high on Harm Avoidance in comparison to individuals low on Harm Avoidance, and overall levels were high for individuals high on Reward Dependence in comparison to individuals low on Reward Dependence.

4.4 Estimated Effects of Age and Gender

A significant negative effect of age on the diurnal pattern of motor activity was found in all four RRMs (see also table 1), indicating that older subjects have lower overall levels of motor activity than younger subjects. In none of the RRMs did we find an effect of gender.

5 Discussion

In a healthy population of men and women between 20–70 years, we studied the effects of the TPQ personality dimensions: Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence, and the effects of age and gender on the diurnal pattern of motor activity. On visual inspection, the diurnal pattern was characterised by a large increase in motor activity level during the beginning of the day, a gradual decline in motor activity during the evening and the night, and a peak in motor activity between 4:30 p.m. and 6:30 p.m. Two of the four TPQ dimensions were significantly related to the overall level of motor activity. We found that subjects high on Harm Avoidance showed lower overall levels of motor activity than subjects low on Harm Avoidance, whereas subjects high on Reward Dependence showed higher overall levels than subjects low on this dimension. Cloninger (1987) hypothesized that Harm Avoidance is linked to the inhibition of behavior to avoid punishment, novelty, and nonreward. Therefore, we expected in advance that subjects high on Harm Avoidance would have lower levels of motor activity. In accordance with our study, Buss et al. (1980) found in children a negative relationship between "inhibition" and motor activity levels. Reward Dependence is theorised to reflect the tendency to respond intensively to signals of reward (particularly verbal signals of social approval and sentiment) and to maintain or resist extinction of behavior that has previously been associated with rewards or relief from punishment (Cloninger, 1987). In agreement with our findings, Buss et al. (1980) found that

children who were high on attention seeking and more engaged in social play also showed higher levels of motor activity.

Personality theories vary much in their description and naming of personality dimensions, which makes it difficult to compare the findings of our study with previous studies. For instance, Novelty Seeking only partly overlaps with Zuckerman's dimension of impulsive sensation seeking (r=0.68) and Eysenk's extraversion dimension (r=0.44) (Zuckerman and Cloninger, 1996). In patients with a panic disorder, no relationship was found between mean motor activity levels and impulsivity (King et al., 1988). Because impulsivity is a part of Cloninger's Novelty Seeking, this finding is in agreement with our observation that Novelty Seeking had no effect on the level of motor activity. In Cloninger's model, the TPQ dimensions are suggested to have predictable patterns of interaction with specific classes of environmental stimuli. In this study we examined overall relationships with spontaneous motor activity patterns without taking into account the interaction effects between TPQ dimensions and discrete environmental stimuli. It is possible that we did not obtain an effect for Novelty Seeking because specific situations involving excitement, novelty, and impulse provocation either did not arise or arose infrequently during routine daily activities.

Older subjects demonstrated lower overall levels of motor activity than younger subjects. Renfrew et al. (1987) also reported a decrease in the motor activity level due to aging, but Lieberman et al. (1989) found an increase and Witting et al. (1990), no change at all. Diurnal patterns of motor activity have not been studied in prospective longitudinal studies. Biological processes due to aging could be responsible for the changes in diurnal patterns, but these changes may also be ascribed to differences in the type of daily activities and the preference for leisure time activities. For instance, 57% of the oldest age group in this study were retired or housewives, which could have resulted in an alteration of the diurnal pattern of motor activity. In addition, Renfrew et al. (1987) found that older subjects watched television for most of the evening, while younger subjects were engaged in other activities. Although subjects did not keep an activity diary in this study, similar differences in activity type may explain our finding as well. Regardless of the origin of the differences between age groups, our data show that it is important to take age into account in studies of diurnal patterns of motor activity.

Little data are available on 24-hour profiles of motor activity in healthy subjects. Renfrew et al. (1987) presented diurnal patterns of motor activity in males between 21–83 years, and Lieberman et al. (1989) in males and females between 19–35 years and between 65–94 years. Although these studies differed from ours regarding the selected time points and monitoring devices, diurnal patterns in both

studies were also characterised by a large increase in motor activity in the early morning and a decline in motor activity during the evening and night. In the study of Renfrew et al. (1987), smooth diurnal patterns (without peaks) of motor activity were found, whereas in the Lieberman et al. (1989) study, diurnal patterns were characterised by one or two peaks dependent on age and gender. Possibly, interindividual variations in the pattern of motor activity are most pronounced during the morning and afternoon.

Several potential shortcomings of the present study should be acknowledged. We did not code season. Consequently, the potential influences of season on the motor activity pattern could not be evaluated. Furthermore, in future studies it may be relevant to take into account the modifying effects of specific situational requirements and triggers on the relationships between personality dimensions and 24-hour patterns of motor activity. Activity logs, in addition to wrist-actigraphy, may also be helpful for interpreting the observed patterns of motor activity.

6 Conclusions

The diurnal pattern of motor activity was characterised by a large increase in motor activity in the early morning, a gradual decline in motor activity during the evening and the night, and one peak of motor activity between 4:30 p.m. and 6:30 p.m.. Both Harm Avoidance and Reward Dependence influenced the overall level of motor activity: subjects high on Harm Avoidance showed lower activity levels than subjects low on this dimension, and high scorers on Reward Dependence showed higher activity levels than low scorers. Age had a negative effect on the motor activity level, indicating that older subjects were overall less active than younger subjects. Overall, this study showed that spontaneous patterns of motor activity are related to core dimensions of personality.

7 Acknowledgements

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Chapter 3

Age, gender and risk factors as determinants of interindividual variation in cardiovascular variability and baroreflex sensitivity

Submitted

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1 Abstract

Community studies showed that reduced cardiovascular variability may be a predictor of cardiovascular diseases. We studied in normotensive subjects the effects of age, gender and several risk factors on cardiovascular variability and baroreflex sensitivity and focused on the importance of these factors as determinants of interindividual variation. In 65 subjects (38.4 ± 11.2 years) we obtained coefficients of variation (CV) of heart rate (HR) and blood pressure (BP) during periods of rest and orthostatic challenge. In addition, log power values of HR and BP in the mid frequency (MF) band (0.07-0.14 Hz), log power values of HR in the high frequency (HF) band (0.15-0.50 Hz) and a baroreflex sensitivity (BRS) index were assessed by spectral analysis. Overall HR variability, MF and HF variability of HR and BRS were decreased by age. Mean HR values were positively related to total and high density lipoprotein (HDL) cholesterol plasma levels, and negatively to levels of physical activity. In addition, mean BP values were increased by a higher body mass index (BMI). Cardiovascular variability and BRS were not affected by risk factors, with the exception of overall HR variability which was decreased in smokers and subjects with a higher BMI. Thus, age turned out to be an important determinant of HR variability and BRS, but not of BP variability. Risk factors played a role in the modulation of the cardiovascular system, but mainly through their effects on mean HR and BP levels.

2 Introduction

Spectral analysis of heart rate HR and blood pressure BP variability has been applied to study in detail the autonomic modulation of cardiovascular control mechanisms (Akselrod et al., 1985; Malliani et al., 1991; Saul et al., 1991; Tulen et al., 1994; Tulen et al., 1996a; Task Force, 1996). HR variability in the HF domain (0.15-0.50 Hz) is related to respiratory variations (respiratory sinus arrhythmia) and reflects vagal (parasympathetic) modulation. BP variability in the frequency domain around 0.1 Hz reflects alterations in peripheral vasomotor resistance due to baroreflex-mediated sympathetic control. HR variability in this frequency domain represents changes in baroreflex response and similarly reflects sympathetic activity, although an influence of vagal activity has also been suggested (Pomeranz et al., 1985). Additional information about the autonomic control of the cardiovascular system can be obtained by studying the transfer functions between systolic blood pressure (SBP) and interbeat interval (IBI) time series to provide non-invasive indices of BRS (Saul et al., 1991; Parati et al., 2000).

Age has been reported to influence autonomic cardiac functioning. HR variability in the two described frequency domains and BRS were decreased by age (Lipsitz et al., 1990; Ryan et al., 1994; Laitinen et al., 1998; Kardos et al., 2001). Less is known about gender differences and their origin. Some studies suggested that healthy females have a lower BRS than males (e.g. Laitinen et al., 1998; Kardos et al., 2001).

Community based studies found that a reduced cardiovascular variability may be a predictor for cardiac events, cardiovascular mortality and the onset of hypertension (Tsuji et al., 1996; Kikuya et al., 2000; Singh et al., 1998). Therefore, it is relevant to obtain knowledge about the role of cardiovascular risk factors in cardiovascular variability and BRS. For instance, the acute effects of cigarette smoking were enhanced HR and BP levels (Niedermaier et al., 1993; Mancia et al., 1997; Gerhardt et al., 1999; Ragueneau et al., 1999), an increased BP variability (Mancia et al., 1997; Gerhardt et al., 1999), a decreased HF variability of HR (Niedermaier et al., 1993), and a decreased BRS (Mancia et al., 1997; Gerhardt et al., 1999). Measurements taken after smoking cessation probably provide information about the long-term effects of smoking on the autonomic cardiac modulation. After an overnight of smoking cessation, smokers demonstrated in comparison to non-smokers a decreased HR variability in the HF domain (Hayano et al., 1990), and an increased HR and BP variability in the lower frequency domain (Ragueneau et al., 1999). In addition, higher total cholesterol and low density lipoprotein (LDL) cholesterol levels were suggested to be related to lower overall HR variability (Kupari et al., 1993; Christensen et al., 1999). These relationships need to be further explored, especially because subjects with hypercholesterolaemia showed no differences in the autonomic neural regulation and BRS in comparison to healthy subjects (Koskinen et al., 1995). Furthermore, a decrease was found in HR variability in the HF domain in physically inactive subjects (Molgaard et al., 1994), and in subjects with a higher BMI (Kageyama et al., 1997). However, other studies reported the lack of a relationship (Kupari et al., 1993; Fagard et al., 1999). Only one study has focused on the relationship between risk factors and BRS (Kardos et al., 2001). The BRS was inversely related to smoking and BMI, but no relationship with physical activity was observed.

The objective of this study was to investigate in healthy normotensive subjects 1) the effects of age and gender and 2) the effects of several risk factors (smoking, lipid levels, BMI and habitual physical activity) on mean HR and BP level, HR and BP variability, and BRS. The importance of these factors as determinants of interindividual variation was evaluated. We were especially interested in determinants of BP variability and BRS, because they have been less frequently addressed than

determinants of HR variability. Cardiovascular measurements were performed during supine rest and head-up tilt to obtain data with a large intraindividual variation. These conditions were chosen because orthostatic challenge is characterised by an increase in sympathetic activity and a decrease in parasympathetic activity resulting in clear alterations in mean HR and SBP, HR and BP variability and BRS (Tulen et al., 1994; Tulen et al., 1996). The effect of orthostatic challenge was studied in advance of the effects of age, gender and risk factors.

3 Methods

3.1 Subjects

Sixty-five healthy normotensive subjects (32 males and 33 females) between 20-59 years of age (38.4 ± 11.2) participated in the study. Health status was evaluated on the basis of medical history information and present state of the physical and mental condition. Specific inclusion criteria were: no cardiovascular disease, no metabolic or respiratory pathologies, no current medical treatment, and medication-free for at least three months prior to the study. Normotensive status was evaluated during supine rest and defined as SBP < 140 mmHg and DBP < 90 mmHg. All participants gave written informed consent. The Medical Ethical Committee of the University Hospital Rotterdam Dijkzigt approved the study.

3.2 Protocol

Cardiovascular recordings were performed between 09.00-12.30 hours. On the morning of the cardiovascular recordings, subjects were allowed to have a light breakfast, but drinking coffee and smoking were not permitted. Blood sampling took place between 08.30-11.00 hours after an overnight fast on the experimental day itself or within one week after the experiment. The cardiovascular recording session consisted of 5 sequential experimental periods preceded by a stabilisation period of 15 minutes. This study presents data from the first two experimental periods: supine rest (10 min) and orthostatic challenge (10 min). Orthostatic challenge was performed by a passive 60° head-up tilting. During the experiment, subjects were requested to relax, to move as little as possible, not to speak, to breath regularly and to stay awake.

3.3 Recording and analysis of cardiovascular data

Electrocardiogram (ECG), BP and respiration were continuously on-line digitised at a sample frequency of 1024 Hz by a DI-200 data acquisition card (Dataq Instruments, Akron, Ohio, USA) and stored on a personal computer by Windows compatible data

Acquisition Software (WinDaq 1.38, Dataq Instruments) for this acquisition card. The ECG was derived from a precordial lead, amplified by a polygraph (Nihon Kohden, Tokyo, Japan). BP was recorded with a servoplethysmomanometer for continuous noninvasive measurements of finger arterial BP, by use of the "volume clamp" technique of Penaz (1976) (Finapres 2300 NIBP monitor; Ohmeda, Englewood, CO, USA). A cuff was fixed around the middle finger of the non-dominant hand, which was kept at the level of the heart throughout the entire experiment to optimise the correspondence with intrabrachial pressure changes (Parati et al., 1989). Thoracic and abdominal respiration were measured separately by means of impedance plethysmographs (Nihon Kohden). For the recording of thoracic and abdominal respiration, adhesive disposable Ag/AgCl electrodes (Red Dot; 3M Health Care, Borken, Germany) were placed on the lateral side of the chest at the level of the umbilicus and the nipples.

Subsequently, R-R intervals in the ECG were detected with an accuracy of 1 millisecond and transposed to HR series. SBP and DBP were defined per R-R interval of the ECG with an accuracy 0.1 mmHg. For prolonged BP recordings, the Finapres device has a built in "lock-adjust" procedure for the automatic adjustment of the finger cuff pressure by means of a servosystem, which is activated in parallel with blood flow changes. This self-adjusting procedure was used every 2 to 5 minutes during the experimental session to prevent slow drifts and therefore unreliable recordings. Blood pressure pulses missed due to this procedure (2 to 4 each time) were estimated by interpolation between two preceding and two succeeding pulses, and addition of a small amount of noise (0.25 x SD) to the interpolated value in order to prevent excessive reduction in variability (Mulder, 1988). The experimental periods of 10 min were split up in 2 segments of 5 minutes and corrected for technical and physiological artefacts in the IBI, SBP, DBP and respiration time series. Isolated extra-systolic contractions within a time segment were corrected by a linear interpolation procedure. If more than 5% of the total number of IBIs and 15% of the total number of BP pulses in a time segment needed correction, the period was excluded from further analyses.

The last 5 minute time segment of each experimental condition was further analysed by spectral analysis. HR and BP time series of the 5 minute time segments were subjected to a discrete Fourier transformation, based on nonequidistant sampling of the R-wave incidences (Carspan program) (Mulder et al., 1988; Van Steenis et al., 1994), to yield power spectra of the rhythmic oscillations over a frequency range of 0.02 to 0.50 Hz, with a resolution of 0.01 Hz. For each 5 minute time segment the following cardiovascular parameters were calculated: mean HR, mean SBP and mean DBP, variation coefficients of HR, SBP and DBP (CVI,

coefficient of variation of IBI; CVS, coefficient of variation of SBP; CVD, coefficient of variation of DBP), power of the MF band (0.07-0.14 Hz) of HR and SBP, and power of the HF band (0.15-0.50 Hz) of HR. The MF band in this study is similar to the low frequency domain of 0.04 –0.15 Hz as defined by the Task Force guideline (1996).

Spectral power for each selected frequency band was expressed in relative terms, that is as a fraction of the mean value of the considered signal (squared modulation index) (Van Dellen et al., 1985). If this measure is computed for the whole spectrum (0.01-0.50 Hz) it is directly comparable to the squared variation coefficient. The spectral power data were transformed to natural logarithmic values to obtain a normal distribution of data. Finally, per time segment the gain (or modulus) in the MF band between SBP and IBI time series was computed as an index of BRS (Saul et al., 1991; Parati et al., 2000), based on frequency points with a coherence $\geq$ 0.35 (Saul et al., 1991; Parati et al., 2000; Robbe et al., 1987).

In addition, per time segment samples of the respiratory signals were obtained at each incidence of the R-wave. Respiratory time series, mostly of the abdominal respiration signal, were subjected to spectral analysis in the same way as the HR and BP time series. The power spectra of the respiratory time series were evaluated primarily to assess whether interindividual variation in cardiovascular variability was related in some way to variation in the respiratory frequency. Per time segment the dominant respiratory frequency in the power spectrum was obtained.

3.4 Risk factors

Smoking, physical activity and body mass index

Thirty-six participants were non-smokers and 29 were smokers. Smokers were asked to estimate their daily use of cigarettes. Ten persons smoked less than 10 cigarettes per day, 11 persons smoked between 10 and 20 cigarettes per day, and 8 persons $\geq$20 cigarettes per day. In the statistical analysis we compared smokers (code=1) with non-smokers (code=0). The Baecke questionnaire (validated Dutch version) (Pols et al., 1995) was applied for the assessment of an index of habitual physical activity, which was based on activity related to work, sport and leisure time. Anthropometric measurements were done to obtain the weight and height for the calculation of the BMI (kg/m^2).

Lipid levels

A blood sample (10 ml) was obtained by a venipuncture after an overnight fast. Serum total cholesterol concentration was determined enzymatically by the

Boehringer Mannheim method. The serum high density lipoprotein (HDL) cholesterol concentration was also determined enzymatically by a colorimetric test following the same protocol as the determination of total cholesterol concentration. Before performing the colorimetric test, HDL cholesterol was separated by precipitating apoprotein B-containing lipoproteins from serum. Serum low density lipoprotein (LDL) cholesterol was precipitated by adding polyvinyl sulphate and subsequently the LDL cholesterol concentration was calculated from the difference between total cholesterol concentration and the cholesterol concentration in the supernatant after centrifugation. Finally, serum triglyceride concentration was determined by the enzymatic hydrolysis of triglycerides with subsequent determination of the liberated glycerol by colorimetry. The assay of plasma lipid and lipoproteins took place at the Clinical Chemical Laboratory of the University Hospital Rotterdam Dijkzigt.

3.5 Statistical analysis

Before analysing the effects of orthostatic challenge, age, gender, and risk factors on autonomic cardiac functioning, we evaluated whether there was multicollinearity of the risk factors. Multicollinearity refers to the situation in which determinants of a multiple regression analysis are too strongly intercorrelated, which may result in an incorrect estimation of regression coefficients and/or incorrect corresponding standard errors (Gunst and Mason, 1980). Each risk factor was estimated by the other risk factors by multiple regression analyses. From the formula of VIF[1], it can be derived that multiple regression correlation coefficients are not allowed to exceed the value of 0.87 to avoid the risk of multicollinearity. In the case of multiple correlation coefficients higher than 0.87 one or more risk factors were left out of further statistical analyses. P values < 0.05 were regarded as significant. The analyses were performed by the statistical package of SPSS (release 9.0). The effects of orthostatic challenge, age, gender, and risk factors on the cardiovascular parameters and respiratory frequency were studied by random regression models (RRMs). In RRMs individual effects are estimated instead of effects for the total study population (Bock, 1983; Gibbons et al., 1993). The random regression approach uses data from individuals augmented by information of the total study population to estimate for

[1] Gunst and Mason (1980) stated that there is a high risk for multicollinearity when variance inflation factors (VIF) in multiple regression analyses exeed the value of 4. The formula of VIF ($1/(1 - \sqrt{R_i^2})$) indicates that a value of 4 is accompanied by $\sqrt{R_i^2} = 0.75$ (R is the correlation between the observed value of a determinant and the value estimated on the basis of the other determinants). Therefore the correlation between observed values and estimated values may not exceed the value of 0.87 ($\sqrt{R_i^2} = \sqrt{0.75} = 0.87$).

each subject the personal trend across time. Because in RRMs the intercept and the slope due to time are allowed to differ for individuals they are random terms. In this study the intercept was used as a random term in order to obtain optimal model fits. In comparison to the usually applied MANOVAs, in RRMs data are used efficiently resulting in a more adequate estimation of effects. RRMs can cope with missing values because the estimation of an individual time trend is based on non-missing data for a given individual. This implies that missing values are assumed to be missing at random (Rubin et al., 1987) and subjects may have data for different time points. Furthermore, RRMs allow more general and realistic error structures than the classical ANOVA for repeated measurements. In this study the type of error structure was 'unstructured', which implies that correlations between measurements may vary and variances of measurements are allowed to differ (Gibbons et al., 1993; Verbeke and Molenberghs, 1997). In other words, (co)variances may differ between repeated measurements.

The procedure was as follows:
Step 1) The main effect of orthostatic challenge was studied.
Step 2) The RRMs of step 1 were extended by entering simultaneously the main effects of age and gender.
Step 3) The RRMs in step 2 were extended by entering simultaneously the main effects of all risk factors.
The model fit of RRMs of step 2 were compared with these of step 1, and the model fit of RRMs of step 3 with these of step 2. A statistical improvement of the model fit implies that the data are significantly better estimated by the determinants. The improvement of the model fit was tested with chi square statistics by comparing the -2 Log Likelihood values of the models, accounting for the difference in degrees of freedom. Effects in the RRMs were reported as unstandardised β's and p values < 0.05 (two-tailed) were regarded as significant. For the RRMs the program Proc Mixed of the statistical package Statistical Analysis Systems (SAS for Windows, release 6.12) was applied.

4 Results

4.1 Effect of orthostatic challenge (step 1)

Table 1 shows the cardiovascular parameters and respiratory frequency during supine rest and passive head-up tilt. The RMMs for the effect of orthostatic challenge (table 2) demonstrated a significant increase in mean HR ($\beta = 16.5$, $P < 0.001$), SBP ($\beta =$

3.5, $p < 0.01$), DBP ($\beta = 11.6$, $p < 0.001$) (see also figures 2 and 3), CVS ($\beta = 0.5$, $p < 0.05$) and MF power of SBP ($\beta = 0.9$, $p < 0.001$). Significant decreases were observed in the HF power of HR ($\beta = -1.1$, $p < 0.001$) and the BRS index ($\beta = -5.1$, $p < 0.001$). The alteration in the HF power of HR was not accompanied by a significant change in the CVI. There was no significant difference in respiratory frequency between supine rest and orthostatic challenge.

Table 1 Characteristics of cardiovascular parameters and respiratory frequency[a]

	Supine rest	Head-up tilt
HR (beats/min)	64.8 ± 7.8	81.3 ± 11.5
CVI (%)	5.2 ± 2.4	5.1 ± 1.9
MF log power HR	6.2 ± 1.0	6.3 ± 1.0
HF log power HR	6.3 ± 1.1	5.3 ± 1.3
SBP (mmHg)	116.2 ± 14.0	120.1 ± 13.8
CVS (%)	4.5 ± 1.7	5.0 ± 1.6
MF log power SBP	5.4 ± 0.8	6.2 ± 0.7
DBP (mmHg)	60.4 ± 9.1	72.1 ± 8.9
CVD (%)	4.6 ± 1.6	4.8 ± 1.2
BRS (ms/mmHg)	11.4 ± 5.3	6.7 ± 3.9
Resp. Freq. (Hz)	0.23 ± 0.07	0.23 ± 0.08

[a] Data represent mean ± SD. HR, heart rate; CVI, coefficient of variation of interbeat intervals; MF, mid frequency band (0.07-0.14 Hz); HF, high frequency band (0.15-0.50 Hz); SBP, systolic blood pressure; CVS, coefficient of variation of SBP; DBP, diastolic blood pressure; CVD, coefficient of variation of DBP; BRS, baroreflex sensitivity; Resp. Freq., respiratory frequency.

4.2 Effect of age and gender (step 2)

The RRMs for the effect of orthostatic challenge were extended with the effect of age and gender (table 2). Age and gender were entered simultaneously. The effect of orthostatic challenge remained the same after adjusting for age and gender effects. The model fit of the RRMs for BP variability got worse, indicating that age and gender were no proper determinants in the applied models. The model fit of all other RRMs improved, although not always significantly. Age and gender turned out to have no effect on mean HR and BP level, but older subjects showed in comparison to younger subjects a decreased CVI ($\beta = -0.07$, $p < 0.001$), MF power of HR ($\beta =$

-0.03, $p < 0.01$), and HF power of HR ($\beta = -0.06$, $p < 0.01$). The effect of age on the power spectrum is illustrated in figure 1. The BRS index was also decreased by age ($\beta = -0.2$, $p < 0.001$). Respiratory frequency turned out to be higher in women than in men ($\beta = 0.04$, $p < 0.05$).

Table 2 Random regression analyses of the effect of orthostatic challenge, age and gender on cardiovascular parameters and respiratory frequency[a]

	RRMs step 1 effect of	RRMs step 2 effect of		Improvement Model Fit[b]
	OC	Age	Gender	(χ^2, df=2)
HR (beats/min)	16.5***	-0.06	3.3	3.2
CVI (%)	-0.2	-0.07***	-0.2	7.2*
MF log power HR	0.1	-0.03**	-0.4	4.4
HF log power HR	-1.1***	-0.06***	0.3	16.9***
SBP (mmHg)	3.5**	0.10	1.4	2.9
CVS (%)	0.5*			
MF log power SBP	0.9***			
DBP (mmHg)	11.6***	0.1	1.5	2.5
CVD (%)	0.2			
BRS (ms/mmHg)	-5.1***	-0.2***	0.06	11.7**
Resp. Freq. (Hz)	$8*10^4$	$7*10^4$	0.04*	12.0**

[a] Effects presented as unstandardised β's. [b] RRMs step 1 versus step 2 (only RRMs with an improved model fit are presented). *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.01$. HR, heart rate; CVI, coefficient of variation of interbeat intervals; MF, mid frequency band (0.07-0.14 Hz); HF, high frequency band (0.15-0.50 Hz); SBP, systolic blood pressure; CVS, coefficient of variation of SBP; DBP, diastolic blood pressure; CVD, coefficient of variation of DBP; BRS, baroreflex sensitivity; Resp. Freq., respiratory frequency. OC, orthostatic challenge. Gender code: men=0, women=1.

4.3. Effect of risk factors (step 3)

The characteristics of the risk factors of the healthy subjects are given in table 3. We observed high multiple correlation coefficients for total, HDL and LDL cholesterol levels ($r = 0.98$, $p < 0.001$, $r = 0.85$, $p < 0.001$ and $r = 0.98$, $p < 0.001$ respectively). This indicates that each of these factors could almost be predicted in total by the other risk factors. To control for multicollinearity, LDL cholesterol was not used in the random regression models.

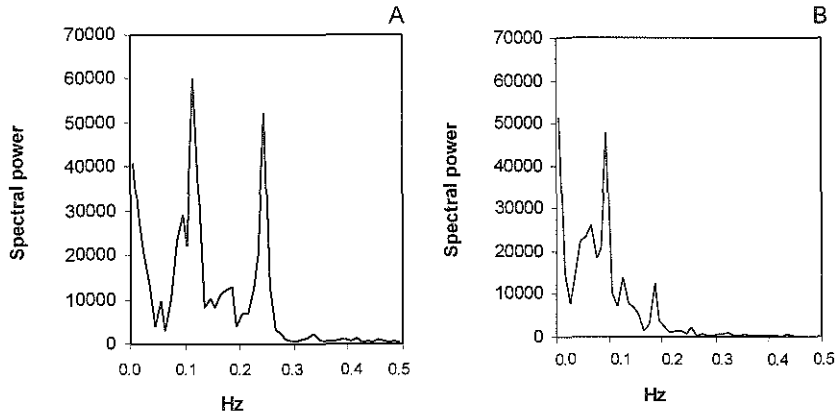

Figure 1 Example of the power spectrum of interbeat intervals (IBI) of a young subject (28 years) (a) and a older subject (50 years) (b) during supine rest. It is apparent that the HR variability in the older subject was lower than the HR variability in the younger subject, especially the variability of the HF band (0.15-0.50 Hz). The spectral power was assessed by the squared modulation index (Van Dellen et al., 1985).

The RRMs of step 2 were extended by entering simultaneously the effects of smoking, lipid levels, BMI and habitual physical activity (table 4). The inclusion of risk factors in the statistical models resulted in a highly significant improvement of the model fit for HR, SBP and DBP. There was no substantial alteration of the effect of orthostatic challenge, age and gender on the cardiovascular parameters. Total and HDL cholesterol levels had a positive effect on mean HR (β = 2.6, $p < 0.05$ and β = 6.4, $p < 0.05$ respectively), whereas the index for habitual physical activity (Baecke questionnaire) affected the mean HR negatively (β = -2.6, $p < 0.05$) (see figure 2). Furthermore, both SBP and DBP were increased in subjects with a higher BMI (β = 1.7, $p < 0.01$ and β = 1.2, $p < 0.01$ respectively) (figure 3).

The RRMs for CVI, BRS and respiratory frequency showed a nonsignificant improvement of their model fit. In these models the effect of orthostatic challenge, age and gender was similar to the effect observed in step 2. There was a significant effect of smoking and BMI on CVI; smokers showed a decreased CVI (β = -1.1, $p < 0.05$) in comparison to non-smokers, and subjects with a higher BMI a decreased CVI in comparison to subjects with a lower BMI (β = -0.2, $p < 0.05$). These findings were restricted to overall HR variability and were not valid for HR variability in the MF and HF band. The model fit of the RRMs for BP variability parameters was

deteriorated, indicating that similar to age and gender the risk factors were no proper determinants of interindividual variation.

Table 3 Characteristics of the risk factors

	Mean ± SD	Range
Smoking (cigarettes per day)	5.8 ± 8.8	0-40
Total cholesterol (mmol/l)	5.2 ± 1.1	3.5-8.3
HDL cholesterol (mmol/l)	1.4 ± 0.4	0.4-2.5
LDL cholesterol (mmol/l)	3.4 ± 1.0	1.6-6.4
Triglyceride (mmol/l)	1.2 ± 0.6	0.4-3.1
BMI (kg/m^2)	23.9 ± 3.3	17.5-31.3
Baecke score	8.1 ± 1.0	6.0-11.2

LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; BMI, body mass index; Baecke score, index habitual physical activity.

5 Discussion

This study showed that all HR variability parameters and the BRS index were decreased by age, but not affected by gender. In contrast, age and gender were no proper determinants of BP variability. A positive relationship was observed between mean HR, and total and HDL cholesterol, and a negative relationship between mean HR and habitual physical activity. In addition, BMI had a positive effect on mean SBP and DBP. The risk factors were no relevant determinants of interindividual variation in cardiovascular variability parameters or BRS. However, a lower CVI was found in smokers and subjects with a higher BMI.

The observed effect of orthostatic challenge on autonomic cardiac functioning is in line with earlier findings (Tulen et al., 1994; Tulen et al., 1996a). In healthy subjects the MF power of the SBP was increased during orthostatic challenge due to the augmentation of sympathetic activity, and the HF power of the HR was decreased due to diminished vagal activity. The lack of an alteration in MF power of the HR in this study supports the suggestion that HR variability in this frequency band represents both sympathetic and vagal activity.

Table 4 Random regression analyses testing the effect of risk factors on cardiovascular parameters and respiratory frequency, adjusted for the effect of orthostatic challenge, age and gender[a]

	RRMs step 3 for the effect of						Improvement
	Smoking (yest/no)	Total Cholesterol	HDL Cholesterol	Trigliceride	BMI	Baecke score	Model fit (χ^2, df=6)
HR (beats/min)	-2.7	2.6*	6.4*	-0.5	0.5	-2.6*	33.0***
CVI (%)	-1.1*	0.08	-0.5	0.6	-0.2*	0.2	7.2
MF log power HR							
HF log power HR							
SBP (mmHg)	-3.0	1.0	-2.1	-2.0	1.7**	-2.7	34.1***
CVS (%)							
MF log power SBP							
DBP (mmHg)	-2.7	0.3	2.6	-1.7	1.2	-1.9	31.3***
CVD (%)							
BRS (ms/mmHg)	-1.3	-0.5	-1.2	1.3	-0.1	0.6	11.5
Resp. Freq. (Hz)	$-5*10^3$	0.01	-0.02	-0.02	$2*10^3$	$7*10^3$	38.7***

[a] Effects presented as unstandardised β's, [b] RRMs step 2 versus RRMs step 3 (only RRMs with an improved model fit are presented). *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.01$. HR, heart rate; CVI, coefficient of variation of interbeat intervals; MF, mid frequency band (0.07-0.14 Hz); HF, high frequency band (0.15-0.50 Hz); SBP, systolic blood pressure; CVS, coefficient of variation of SBP; DBP, diastolic blood pressure; CVD, coefficient of variation of DBP; BRS, baroreflex sensitivity; Resp. Freq., respiratory frequency. OC, orthostatic

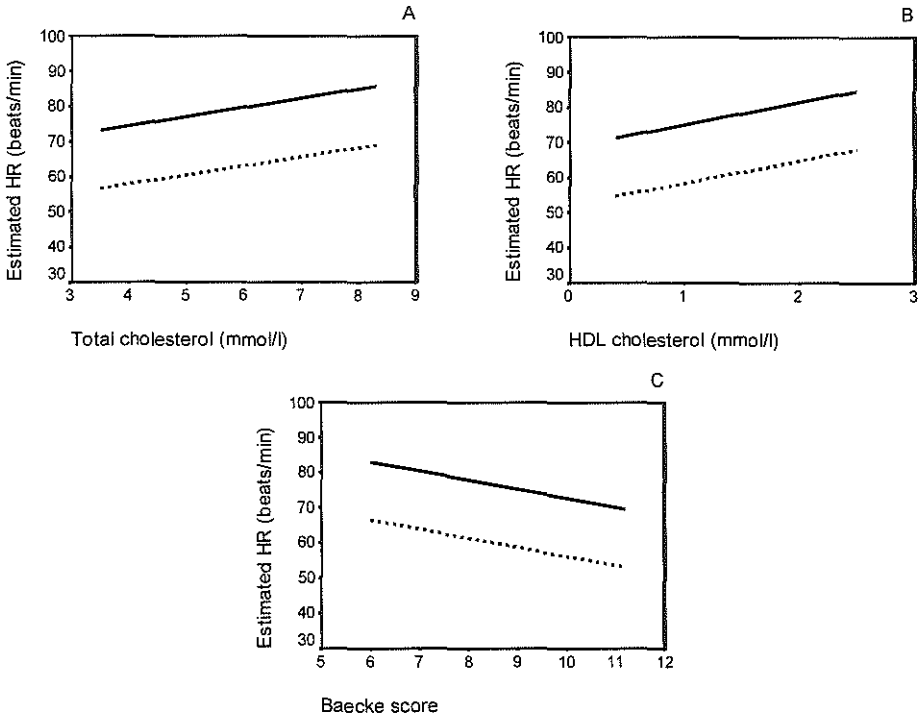

Figure 2 Estimated effects of total cholesterol (a), HDL cholesterol (b), and physical activity (c) on mean HR levels. _ _ _ _ , supine rest; _____ , head-up tilt; HR, heart rate; HDL, high density lipoprotein. The HR was estimated by the following regression equation: estimated HR = 59.6 + (16.5*condition) + (2.6*total cholesterol) + (6.4*HDL cholesterol) – (2.6*Beacke index). Regression lines were calculated per experimental condition (supine rest=0, orthostatic challenge=1). Per risk factor the regression lines were calculated by filling in the minimum and maximum value of that specific risk factor and the mean values of the other two risk factors in the equation.

Prior research also showed that HR variability in both frequency domains decreases by age (Lipsitz et al., 1990; Ryan et al., 1994; Laitinen et al., 1998; Kardos et al., 2001), probably due to changes in autonomic functioning and/or to reduced compliance of the arterial walls resulting in less sensitivity of the baroreceptors. It was surprising that the addition of age and gender effects to the RRMs for BP variability parameters resulted in deteriorated model fits revealing that age and gender were not proper determinants of BP variability, at least not in the linear models we

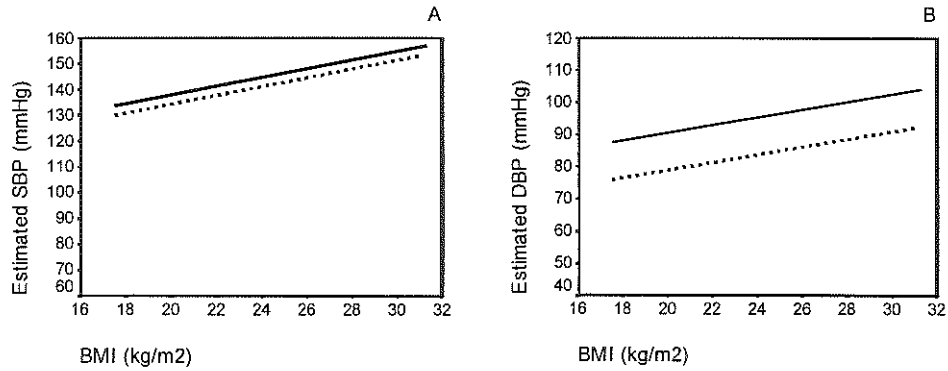

Figure 3. Estimated effects of BMI on mean SBP level (a), and mean DBP level (b). _ _ _ _ , supine rest; _____ , head-up tilt; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure. The SBP and DBP were estimated by the following regression equations: estimated SBP= 96.8 + (3.5*test) + (1.7*BMI) and estimated DBP = 43.3 + (11.6*test) + (1.2*BMI). Regression lines were calculated per experimental condition (supine rest = 0, orthostatic challenge = 1) and by filling in the minimum and maximum BMI value.

applied. We could not confirm the finding that females would demonstrate a lower BRS than males (Laitinen et al., 1998; Kardos et al., 2001).

The inclusion of risk factors in the RMMs for the effect of orthostatic challenge, age and gender resulted in a highly significantly improved model fit for HR, SBP and DBP, and clear effects of one or more risk factors. Both smoking and BMI had a significant negative effect on CVI, but the risk factors did not contribute to interindividual variation in BP variability or BRS. Similar to our findings, Gerhardt et al. (1999) found unchanged mean HR, SBP and DBP values in heavy smokers after an overnight deprivation of smoking. We could not confirm the decreased HR variability in the HF band reported by Hayano et al. (1990). The effect of smoking was controlled in the RRMs for the effect of age, gender and the other risk factors, but a minor point of this study was the limited number of heavy smokers. However, community studies (Kageyama et al., 1997; Fagard et al., 1999) also reported small or no differences in autonomic control mechanisms between smokers and non-smokers.

Fagard et al. (1999) found in men, but not in women, that HR was inversely related to leisure-time physical activity, and HF power of HR positively to occupational activity. We also observed that higher level of habitual physical activity resulted in a decrement of the mean HR, but we could not detect an effect on HR or SBP variability. Physical training has been postulated to increase cardiac vagal

modulation and reduce HR levels, which may also result to a certain extent from decreased cardiac sympathetic activity. Thus, the influence of habitual physical activity on HR level may originate from a combination of sympathetic and parasympathetic, but this was not supported by our findings of HR variability in the MF and HF band.

Both total and HDL cholesterol had a positive effect on mean HR values. Previous studies in healthy subjects have reported positive relationships between total cholesterol and LDL cholesterol, and HR (Kupari et al., 1993; Christensen et al., 1999), but no or an inverse relationship between HDL cholesterol and HR was expected because HDL cholesterol is the 'healthy' cholesterol and protects against coronary heart disease. The positive relationship between triglyceride and HR reported by Christensen et al. (1999) was not confirmed by our findings. In addition, previous studies suggested that total and LDL cholesterol were related to a suppression of overall HR variability (Kupari et al., 1993; Christensen et al., 1999), but none of the lipid levels in this study turned out to be an important determinant of cardiovascular variability or BRS, On the other hand, the absence of an effect of lipid levels on BRS was in line with the study of Koskinen et al. (1995) in which the BRS of subjects with hypercholesterolaemia was compared with that of healthy subjects.

Finally, BMI was found to be related to higher mean SBP and DBP levels, and a decreased CVI. The relationship between obesity and BP frequently has been documented, but no biological model for this relationship has been established (Kaufman et al., 1997). A higher BMI was also related to a decreased overall HR variability, but there was no effect of BMI on the HF power of HR. The latter result was in contrast to the study of Kageyama et al. (1997), but in line with other community studies (Kupari et al., 1993; Fagard et al., 1999).

It is striking that so many equivocal findings have been reported about whether and which risk factors are responsible for interindividual differences in cardiovascular variability and BRS. An explanation could be the differences in methodology between studies and the use of less adequate statistical analysis techniques. We optimised our statistical analysis by applying random regression models instead of classical MANOVAs, controlling the effect of each risk factor for the effect of age, gender and the other risk factors, taking into account the risk of multicollinearity, and testing the improvement of model fits. This was all done to obtain a valid estimation of regression coefficients and to estimate properly the corresponding standard errors.

6 Conclusions

In healthy normotensive subjects interindividual variation in HR variability and BRS decreased by age, but gender did not influence HR variability or BRS. Both age and gender were not proper determinants of BP variability. Mean HR levels were positively related to total and HDL cholesterol, and negatively to levels of physical activity. Mean BP levels were positively related to BMI. Furthermore, overall HR variability was decreased in smokers and subjects with a higher BMI, but risk factors had no significant effect on BRS. The interindividual variation in BP variability could not properly been determined by the risk factors. The fact that HR and BP levels were differentially affected by one or more risk factors reveals that risk factors do play a complex role in the modulation of the cardiovascular system.

7 Acknowledgements

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Chapter 4

Motor activity and autonomic cardiac functioning in major depressive disorder

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1 Abstract

The daily pattern of motor activity and the autonomic cardiovascular regulation were studied in major depression to quantify changes in psychomotor function and autonomic cardiac functioning. Additionally, relationships between motor activity parameters, cardiovascular measures and specific clinical features were examined. Wrist-actigraphy was used to monitor 24-hour motor activity for 67 unmedicated (unipolar) depressed inpatients and 64 control subjects. During supine rest, spectral analysis was applied to assess HR and SBP variability, a baroreflex sensitivity (BRS) index and the respiratory frequency, in addition to mean heart rate (HR) and blood pressure (BP) levels for the patient group and a second control group (N=51). The patients showed a lower motor activity level and a reduced fragmentation of motor activity during wake, and a higher motor activity level and a decreased immobility during sleep. The mean HR and DBP level and the respiratory frequency were higher in the patient group than in the control group, but no differences in HR and SBP variability or BRS were found. Furthermore, motor activity parameters and cardiovascular measures of the patients were related to agitation and retardation and overall, patients with lower motor activity levels demonstrated lower SBP levels. This study confirms that the 24-hour pattern of motor activity is altered in unmedicated depressed inpatients, but limited evidence was found for an autonomic cardiac dysfunction. Within the patient group there were relationships between motor activity parameters, cardiovascular measures, and clinical features, but the underlying neurobiological pathways need to be further explored.

2 Introduction

Neurobiological processes in depressed patients are evaluated to obtain insight in the etiology of depression, to find biological predictors for successful treatment outcome and to examine (side) effects of treatments. Dysfunctions of these neurobiological processes are, amongst others, reflected in changes in psychomotor function and autonomic cardiac functioning (Joyce and Paykel, 1989). Parker (2000) classified depressive disorders on the basis of three clinical features: mood state features (e.g. anxiety), observable psychomotor disturbance, and psychotic disturbance. These clinical features were hypothesised to be generated by different neurobiological processes, which may explain treatment specificity of clinical subtypes of depressed patients. Parker's model implies that psychomotor function and autonomic cardiac functioning are probably related to the presence of specific clinical features. In

addition, Thayer et al. (1998) speculated that disturbances in both functions are also related with one another.

One part of the psychomotor dysfunction is retardation that has been recognised as the central feature of depression (Widlocher, 1983). In retarded patients, motor and psychic activities are slowed down. Alterations in motor activity are, for instance, slowed speech, fixed facial expression, less spontaneous movements of the limbs and trunk, an impaired gait and stride. Reduced fluency of speech, loss of interest, and impaired memory and concentration are examples of changes in psychic activity. Disturbances in cholinergic mechanisms may play a role in retardation, because cholinergic stimulation results in the reduction of explorative behavior and the inhibitory behavioral effects of this stimulation are exaggerated in depressed patients (Janowsky et al., 1994). Also dopaminergic dysfunctions are assumed to be responsible for the psychomotor dysfunction (Sobin and Sackeim, 1997), although this is not contradictory because these neurotransmitter systems are known to interact with motor functions (Janowsky et al., 1994). It is still debated whether agitation is also a symptom of the psychomotor dysfunction or mainly the result of anxiety (Dantchev and Widlocher, 1998).

Prior research in which overt motor behavior was quantified by means of wrist-actigraphy (a method to monitor diurnal patterns of motor activity) demonstrated that depressive disorder may be related to decreased daytime motor activity levels and to alterations in the distribution of motor activity (Teicher, 1995). In depressed patients, motor activity levels were found to be positively associated with anxiety and hyperactivity rating scores (Kupfer et al., 1974; Joffe et al., 1987), and negatively with clinical ratings of retardation (Joffe et al., 1987; Royant-Parola et al., 1986; Raoux et al., 1994). Schatzberg and Rothschild (1992) concluded on the basis of several biological studies that the dopaminergic system is more active in psychotic depression than in nonpsychotic depression. Surprisingly, the relationship between psychotic features (delusions and hallucinations) and for instance motor activity levels has not been explored.

Autonomic dysfunctions in depressive disorder, particularly the reduction of parasympathetic (vagal) activity, result in sleep disturbances, altered appetite, dry mouth, constipation and cardiac complaints. Cardiovascular variability has been studied to obtain more insight in the origin of cardiac complaints in depressed patients (e.g., Akselrod et al., 1981; Malliani et al., 1991; Tulen et al., 1994, 1996a). The sympathetic nervous system regulates the cardiovascular system through the baroreflex control of peripheral vascular resistance, inducing spontaneous BP variations with a frequency of about 0.10 Hz (Mayer waves) and compensatory variations in the (HR) with the same frequency. Variations in the HR signal with

higher frequencies follow the variations in respiration (respiratory sinusarrythmia), and result from centrally mediated cardiac vagal (parasympathetic) activity. During the last years interest has grown in HR variability in depressive disorder, because clinical studies demonstrated that depressed patients had decreased HR variability, probably due to a reduced parasympathetic activity (Dalack and Roose, 1990; Rechlin et al., 1994b; Lehofer et al., 1997). The latter may explain the increased risk of cardiovascular disease observed in this patient group (Glassman, 1998).

Within depressed patients, elevated HR levels may accompany agitation or comorbid anxiety (Stein et al., 1994). In addition, more anxiety was associated with lower HR variability (Rechlin et al., 1994b; Dalack and Roose, 1990; Tulen et al., 1996a) and reduced baroreflex control (Watkins et al., 1999). Parker et al. (1995) hypothesised that psychotic patients in comparison to nonpsychotic patients were more likely to demonstrate disturbances in vegetative functions. Therefore, it seems plausible that cardiovascular control mechanisms are in some way related to psychotic features. In depressed patients the relationship between psychomotor function and autonomic cardiac functioning has not been studied. If there is a relationship between disturbances in psychomotor function and the autonomic modulation of the cardiovascular system, this would provide evidence for common neurobiological mechanisms, for instance cholinergic mechanisms, since they play a role in both dysfunctions.

In unmedicated depressed patients, the number of detailed studies to disturbances in motor activity and cardiovascular control mechanisms is limited, and only small sample sizes have been examined. In this study, a large number of unmedicated, severely depressed (unipolar) inpatients were compared with healthy controls, regarding their pattern of motor activity and autonomic cardiac functioning. We used wrist-actigraphy to obtain patterns of motor activity. Information about autonomic cardiac functioning was derived from HR, BP and respiratory recordings during supine rest. Spectral analysis was applied to analyse HR and BP variability and to assess BRS. We also examined whether interindividual variations in the patient group were associated with different clinical features (anxiety, agitation, retardation, psychotic features) and explored the relationship between the motor activity parameters and cardiovascular measures in depressed patients.

3 Methods

3.1 Subjects

Sixty-seven patients between 32 and 65 years of age, who met the DSM-IV criteria (APA, 1994) for a major depressive disorder (subtype unipolar) participated in the study. The diagnosis was based on the depression items of the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978). Patients were admitted to the Depression Unit of the Department of Psychiatry of the University Hospital Rotterdam – Dijkzigt and were measured after a psychotropic drug free period of at least seven days. On the day of the cardiovascular measurement the patients were on average 12 days medication free. Included were patients with an initial score of at least 13 on the 17 item Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1967). The patient group had a mean HRSD score of 27.2 (SD = 4.6).

This article reports motor activity data of in total 58 patients (18 males, 40 females; mean age = 52.1, SD = 8.9) and cardiovascular data of in total 54 patients (19 males, 35 females; mean age = 52.1, SD = 8.5). Motor activity data of 9 patients were unsuitable for data analysis because of treatment with a dopaminergicum (1 patient), technical failure (2 patients), shortened measurement period (4 patients) and an incomplete daily sleep-wake log (2 patients). Cardiovascular data of 13 patients were not included in the data analysis, because of cardiovascular diseases and/or diabetes mellitus (12 patients) and too many artefacts (1 patient).

Motor activity data of the patients were compared with data of 64 healthy subjects (33 males, 31 females; mean age = 48.5, SD = 9.9) (control group 1). The control subjects were recruited by means of advertisements. Health status of the control subjects was determined on the basis of medical history information, and present state of the physical and mental condition (based on an intake interview and a questionnaire). Specific exclusion criteria were: a personal history of mental illness, sleep disorders, current medical illness, diseases and drugs interfering with the activity pattern, and recent circadian shift and working during evening hours and night-time. Cardiovascular data of the patients were compared with data from another healthy group (25 males, 26 females; mean age = 45.7, SD = 8.0) (control group 2). The subjects were recruited and screened in the same way as control group 1. The assessment of health status was also similar as in control group 1. Specific exclusion criteria for this group were: no personal history of mental illness, no current medical illness, and no medication use during the three months prior to the measurements.

All participants gave written informed consent after the study protocol was fully explained. The Medical Ethical Committee of the University Hospital Rotterdam-Dijkzigt approved the study.

3.2 Measures

Clinical subgroups

The patient group was divided in eight overlapping subgroups in the following way: 1) patients with high and low anxiety, 2) agitated and nonagitated patients, 3) retarded and nonretarded patients, and 4) patients with and without psychotic features. The research diagnostic criteria (RDC) (Spitzer et al., 1978) as measured by the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) were used to subdivide the patients, with the exception of the division in high and low anxiety patients. We calculated for each patient a total anxiety score that was based on SADS items (in total 13) that refer to anxiety, agitation and sleep complaints. Patients with a score above the median were classified as high anxiety patients, and patients with a score below the median as low anxiety patients.

Motor activity monitoring

Wrist-actigraphy has been demonstrated to measure motor activity in a valid and reliable way (Patterson et al., 1993; Tryon, 1991; Middelkoop et al., 1997). Subjects wore an actigraph on their non-dominant wrist for three consecutive weekdays and nights, except during bathing. Patients were instructed to maintain their normal activity pattern on the ward, and controls their normal pattern at home and outside. The actigraph (Gaehwiler Electronic) contained a monoaxial piezoelectric acceleration sensor and counted the number of suprathreshold movements of the wrist (> 0.1 g acceleration) for every 30-sec epoch. Subjects also recorded in a daily log the instances of actigraphy removal, the estimated time of sleep onset and estimated time of final awakening in the morning. The following motor activity parameters were obtained and averaged for the three recording days: 1) motor activity level (average number of counts per epoch, as percentage of the maximum number of counts possible) during wake and sleep, 2) fragmentation index of motor activity (number of groups of consecutive zero count epochs divided by the total number of zero count epochs) during wake and sleep, and 3) immobility index (proportion of zero count epochs, relative to the total number of epochs) during sleep. The fragmentation index expresses the extent to which rest periods are interrupted by activity, whereas the immobility index expresses the relative amount of rest.

Cardiovascular and respiratory measurements

On the morning of the cardiovascular measurements, subjects were not allowed to drink coffee or smoke. After a stabilisation period of 15 minutes, the electrocardiogram (ECG) (precordial lead), BP (noninvasive, Finapres), and the respiration (impedance plethysmographs) were measured continuously during 10 minute supine rest. ECG, BP and respiration were on-line digitised at a sample frequency of 1024 Hz and processed according to procedures described by Tulen et al. (1996a, 1996b). The last five minutes of the 10 minutes of supine rest were used for further analysis, with the restriction that no more than 5% of the total number of heartbeats and 15% of the total number of BP pulses needed correction.

Spectral analysis was applied (Carspan program) to yield power spectra of the rhythmic oscillations over a frequency range of 0.02 to 0.50 Hz (Mulder et al., 1988b; Van Steenis et al., 1994). In addition to mean HR, SBP and DBP, the power of the MF band (0.07-0.14 Hz) of HR and SBP, and the power of the HF band (0.15-0.50 Hz) of HR were calculated. Spectral power for each selected frequency band was expressed in relative terms (squared modulation index) (Mulder et al., 1988). A natural logarithmic transformation was performed to the spectral power data to obtain normal distributed data. As an index of BRS, the gain (or modulus) between SBP and interbeat interval (IBI) time series in the MF frequency range was calculated (Robbe et al., 1987; Parati et al., 2000).

Per time segment also the dominant respiratory frequency in the power spectrum was determined. To ensure that in this study HR and SBP variability in the MF band were not influenced by respiratory linked variations, the HR and SBP variability measures and the BRS index of subjects with a dominant respiratory frequency < 0.15 Hz were not included in the statistical analysis. In total, 2 patients and 8 controls had a respiratory frequency < 0.15 Hz.

3.3 Statistical analysis

Multivariate linear regression analyses were applied to compare motor activity data and cardiovascular data between patients and controls. The effect of study group was evaluated, while controlling for the effects of age and gender. Within the patient group the effects of the clinical features on motor activity and cardiovascular data were studied simultaneously by multivariate linear regression models, while adjusting for age and gender. Subsequently, these regression models were extended in one step with the effects of the motor activity parameters, in order to study the relationship between motor activity data and cardiovascular data. To prevent multicollinearity (the situation in which determinants of a multiple regression analysis are too strongly intercorrelated), immobility was left out as determinant in the models (Gunst and

Mason, 1980). Effects in the regression analyses were reported as unstandardised β's and P values of ≤ 0.10 (two-tailed) were regarded as significant. The statistical analyses were performed with SPSS for Windows (release 9.0).

4 Results

Unmedicated Depressed Patients versus Healthy Controls

Depressed patients were less active during the day, but more active during the night than the controls (table 1). During wake the patient group also had a lower fragmentation index, and during sleep a lower immobility index than the control group. During supine rest, depression resulted in higher mean HR and DBP levels, and a higher respiratory frequency, but no alterations were observed for HR and SBP variability in the MF band, for HR variability in the HF band, or for the BRS index (table 2).

Table 1 Motor activity in depressed patients and controls

	Patient group			Control group 1			Effect of depression[a]		
	N	Mean	SD	N	Mean	SD	B	df	p
Motor activity level during wake	58	6.9	3.4	64	11.6	5.4	-4.8	3	<0.001
Fragmentation of activity during wake	58	0.4	0.2	64	0.5	0.1	-0.06	3	<0.01
Motor activity level during sleep	57	0.8	0.6	64	0.5	0.3	0.3	3	<0.001
Fragmentation of activity during sleep	57	0.05	0.02	64	0.05	0.03	0.005	3	n.s.
Immobility during sleep	57	0.91	0.06	64	0.93	0.03	-0.03	3	<0.01

[a]Multivariate linear regression analysis to test the effect of study group (patient group=1, control group=0), while controlling for the effects of age and gender (see section 3.2 for explanation of parameters).

Division in clinical subgroups

From the 58 patients included in the analysis of the motor activity data, 22 patients showed high anxiety, 14 patients agitation, 37 patients retardation and 14 patients psychotic features. In addition, from the 54 patients included in the cardiovascular data analysis, 20 patients demonstrated high anxiety, 12 patients agitation, 32 patients retardation, and 16 patients psychotic features.

Table 2 Cardiovascular parameters in depressed patients and controls

	Patient group			Control group 2			Effect of depression[a]		
	N	Mean	SD	N	Mean	SD	B	df	p
Heart rate (beats/min)	54	76.8	12.0	51	65.5	7.9	11.8	3	<0.001
Log power MF band HR	47	5.7	1.1	43	6.0	0.9	-0.02	3	n.s.
Log Power HF band HR	47	5.6	1.4	43	6.0	1.0	-0.2	3	n.s.
Systolic blood pressure (mmHg)	53	131.9	21.8	51	123.2	19.9	5.3	3	n.s.
Log power MF band SBP	46	5.5	0.9	43	5.4	0.8	0.1	3	n.s.
Diastolic blood pressure (mmHg)	53	70.9	10.8	51	64.9	13.2	4.3	3	≤0.09
BRS index (ms/mmHg)	45	7.4	4.8	42	9.7	4.5	-0.9	3	n.s.
Respiratory frequency (Hz)	53	0.26	0.07	51	0.23	0.07	0.03	3	<0.05

[a]Multivariate linear regression analysis to test the effect of study group (patient group=1, control group=0), while controlling for the effects of age and gender (see section 3.2 for explanation of parameters).

Differences in Relation to Clinical Features

Agitation had a significantly positive effect on the motor activity level during wake (table 3a), in contrast to retardation, which had a significantly negative effect on motor activity level both during wake and sleep (table 3b). Thus, agitated patients showed increased motor activity levels only during wake, while retarded patients demonstrated decreased motor activity levels throughout the whole day. Furthermore, retarded patients showed less fragmentation of motor activity during wake. The presence of high anxiety and psychotic features did not contribute significantly to variations in the motor activity pattern between patients.

Table 3a Differences in motor activity between depressed patients related to clinical features[a]

	Anxious				Agitated			
	high (N=22)		low (N=36)		yes (N=14)		no (N=44)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Motor activity level during wake	7.7	3.7	6.4	3.1	8.4 [b]	3.5	6.4	3.2
Fragmentation of activity during wake	0.41	0.10	0.37	0.14	0.40	0.09	0.38	0.14
Motor activity level during sleep	0.93	0.57	0.65	0.62	0.95	0.59	0.69	0.62
Fragmentation of activity during sleep	0.06	0.03	0.05	0.03	0.05	0.03	0.05	0.03
Immobility during sleep	0.89	0.08	0.92	0.05	0.89	0.08	0.91	0.06

[a] The effects of the clinical features (presence=1, absence=0) were tested simultanously by multivariate linear regression analyses, while controlling for the effects of age and gender (see section 3.2 for explanation of parameters).

[b] Significant main effect of agitaton (β=3.5, df=6, $p<0.05$).

Table 3b Differences in motor activity between depressed patients related to clinical features[a]

	Retarded				Psychotic Features			
	yes (N=37)		no (N=21)		yes (N=14)		no (N=44)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Motor activity level during wake	5.6 [b]	2.3	8.8	3.5	6.3	2.3	6.9	3.4
Fragmentation of activity during wake	0.35 [c]	0.12	0.45	0.11	0.36	0.11	0.39	0.13
Motor activity level during sleep	0.59 [d]	0.42	1.05	0.80	0.63	0.35	0.79	0.67
Fragmentation of activity during sleep	0.05	0.03	0.06	0.03	0.05	0.04	0.05	0.03
Immobility during sleep	0.92	0.06	0.89	0.06	0.92	0.06	0.91	0.06

[a] The effects of the clinical features (presence=1, absence=0) were tested simultanously by multivariate linear regression analyses, while controlling for the effects of age and gender (see section 3.2 for explanation of parameters).

[b] Significant main effect of retardation (β=-4.0, df=6, $p<0.001$).

[c] Significant main effect of retardation (β=-0.10, df=6, $p<0.01$).

[d] Significant main effect of retardation (β=-0.44, df=6, $p<0.05$).

Table 4a Differences in cardiovascular parameters between depressed patients in relation to clinical features[a]

	Anxious				Agitated			
	high (N=20)		low (N=34)		yes (N=12)		no (N=42)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Heart rate (beats/min)	78.8	14.4	75.6	10.4	83.2[b]	13.8	74.9	11.0
Log power MF band HR	5.9	0.9	5.6	1.2	6.0	0.9	5.6	1.1
Log power HF band HR	5.8	1.3	5.5	1.5	5.7	1.2	5.5	1.5
Systolic blood pressure (mmHg)	134.7	24.0	130.3	20.8	139.4[c]	27.8	129.7	19.6
Log power MF band SBP	5.3	0.7	5.6	1.1	5.3	0.8	5.5	1.0
Diastolic blood pressure (mmHg)	72.0	10.1	70.2	11.1	72.9	10.4	70.2	10.9
BRS index (ms/mmHg)	9.3	6.0	6.5	3.8	8.3	5.0	7.2	4.8
Respiratory frequency (Hz)	0.27	0.07	0.27	0.06	0.27	0.08	0.27	0.06

[a] The effects of the clinical features (presence=1, absence=0) were tested simultanously by multivariate linear regression analyses, while controlling for the effects of age and gender (see section 3.2 for explanation of parameters).

[b] Significant main effect of agitation (β=11.0, df=6, p=0.06). [c] Significant main effect of agitation (β=19.7, df=6, p=0.05).

Table 4b Differences in cardiovascular parameters between depressed patients in relation to clinical features[a]

	Retarded				Psychotic Features			
	yes (N=32)		no (N=22)		yes (N=16)		no (N=38)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Heart rate (beats/min)	77.9	12.7	75.2	11.1	78.3	10.6	76.1	12.7
Log power MF band HR	5.6	1.2	5.9	0.9	5.5	1.3	5.8	1.0
Log power HF band HR	5.4	1.5	5.8	1.3	5.1	1.5	5.8	1.4
Systolic blood pressure (mmHg)	127.9[b]	20.0	137.6	23.4	133.7	21.6	131.1	22.2
Log power MF band SBP	5.4	0.9	5.6	1.1	5.5	1.1	5.5	0.9
Diastolic blood pressure (mmHg)	68.5[c]	10.9	74.2	9.8	70.9	11.1	70.8	10.8
BRS index (ms/mmHg)	7.4	4.7	7.5	5.0	6.6	4.0	7.7	5.0
Respiratory frequency (Hz)	0.27	0.07	0.26	0.06	0.30	0.09	0.26	0.05

[a] The effects of the clinical features (presence=1, absence=0) were tested simultanously by multivariate linear regression analyses, while controlling for the effects of age and gender (see section 3.2 for explanation of parameters).

[b] Significant main effect of retardation (β=-13.9, df=6, p<0.05). [c] Significant main effect of retardation (β=-6.9, df=6, p<0.05).

Regarding autonomic cardiac functioning during supine rest, agitation had a significantly positive effect on mean HR and SBP level (table 4a), whereas retardation had a significantly negative effect on both mean SBP and DBP level (table 4b). These findings indicate that agitated patients had higher HR and SBP levels than nonagitated patients, and retarded patients had lower SBP and DBP levels than nonretarded patients. No differences were found for any cardiovascular measure or for respiratory frequency between patients with high and low anxiety and patients with and without psychotic features. The effects of agitation and retardation were controlled for the presence of the other clinical features and for age and gender.

Relationship Motor Activity Measures and Cardiovascular Parameters in Patients
In the patient group, variation in the mean SBP level was significantly explained by the motor activity level during wake (β=2.5, df=10, $p \leq 0.08$), revealing that higher SBP levels during supine rest were observed in patients who were more active during the wake period.

5 Discussion

This study reports differences in motor activity levels, and fragmentation and immobility indices during the wake and sleep period between unmedicated, severely depressed inpatients and healthy control subjects. The patient group also showed higher mean HR and DBP levels, and a higher respiratory frequency in comparison to the control group. However, no significant differences were observed in HR and SBP variability and the BRS index. In the patient group, the clinical features agitation and retardation were related to motor activity and autonomic cardiac functioning. The alterations in mean HR and BP levels in agitated and retarded patients were not accompanied by differences in HR and SBP variability, or in the BRS index. None of the cardiovascular measures were related to the presence of high anxiety or psychotic features. Finally, less active patients were found to have lower SBP levels during supine rest.

Although previous studies have examined motor activity patterns in unmedicated depressed patients (Wehr et al., 1980; Wolff et al., 1985; Van Londen et al., 1998), this is the first study in a large sample of unipolar depressed patients (n=58). In contrast, Wehr et al. (1980) studied 10 bipolar depressed patients, Wolff et al. (1985) a mixed group of 25 bipolar and 5 unipolar depressed patients, and Van Londen et al. (1998) 9 bipolar, 2 psychotic, and 37 unipolar depressed patients. In congruence with our findings, in these studies decreased motor activity levels and

reduced fragmentation of motor activity during daytime were observed. Van Londen et al. (1998) also found that depressed patients showed higher motor activity levels during the sleep period than the control group. A potential confounding factor in this study was the difference in study environment (hospital setting versus home environment) and as a consequence the difference in type of daily activities. Based on the fact that Van Londen et al. (1998) found nearly the same results in a patient group comprising mainly outpatients, we assumed that study environment played a minor role.

Retardation had the largest influence on the motor activity pattern in our unmedicated patient group. Ten of the 37 retarded patients of whom motor activity data were collected were also classified as agitated, but despite the common occurrence in a number of patients retardation and agitation had clear effects independent of one another. This study confirms the lack of a relationship between the motor activity pattern and anxiety in unmedicated depressed patients observed in previous studies (Kupfer et al., 1974; Raoux et al., 1994). No relationship was also observed with the presence of psychotic features. Twelve (86%) of the 14 patients with psychotic features were retarded (57%) or retarded and agitated at the same time (29%), whereas 29 (66%) of the 44 patients without psychotic features showed retardation (43%), agitation (9%) or a combination of these features (14%). Parker et al. (1999) reported that agitation, but not retardation was more likely to be present in psychotic depression than in nonpsychotic depression, but that psychomotor disturbances were more severe in psychotic than nonpsychotic depression. Possibly retardation and agitation obscured the effects of the psychotic features themselves.

Rechlin et al. (1994b) observed in 16 unmedicated depressed patients increased HR levels and less HR variability in the HF range. In this study severe depression was accompanied by higher HR levels, but no evidence was found for differences in HR variability. Similar findings were reported by Lehofer et al. (1997) and Moser et al. (1998) in 23, respectively 26 unmedicated depressed patients. Lehofer et al. (1997) postulated that the elevated HR level in depressed patients possibly derives from an increased 'autonomous' HR (=the HR present when there is no control of the autonomic nervous system at all) instead of a reduced parasympathetic activity. Additional support for the lack of disturbances in cardiovascular variability in unmedicated depressed patients was found in the studies of Tulen et al. (1996a) and Yeragani (1991). It should be emphasised that all discussed studies controlled for the effects of age and gender, and examined patients after a medication free period of at least 7 days. On average our patients had a higher respiratory frequency than the controls, which may have influenced both MF and HF variability. Because we controlled for the possible effects of slow breathing on MF

variability, it is unlikely that differences in respiratory frequency are responsible for the lack of an effect of depressive disorder on HR and SBP variability. Before clear statements can be made about whether or not depression is related to alterations in HR and SBP variability, the influence of other factors such as duration of depressive disorder, history of treatment with antidepressants, and relationships with specific clinical features need to be explored.

Epidemiological studies demonstrated that anxiety may be related to an increase in the risk of cardiovascular disease, and clinical studies suggest that anxiety disorders are related to reduced HR variability (Gorman and Sloan, 2000). Therefore, the presence of anxiety in depressed patients possibly plays a role in the increased mortality and morbidity of cardiovascular disease in depression (Watkins et al., 1999). Prior research demonstrated that in unmedicated depressed patients anxiety was related to lower HR variability in the HF range (Tulen et al., 1996b) and an impaired baroreflex control of the heart (Watkins et al., 1999). In this study the role of anxiety in the higher risk of cardiovascular disease in depression could not be confirmed. Although Parker et al. (1995) found vegetative dysfunctions in psychotic depression, in this study none of the cardiovascular measures differed between patients with and without psychotic features. In contrast, agitated patients showed higher mean HR and SBP levels than nonagitated patients, and retarded patients demonstrated lower mean SBP and DBP levels than nonretarded patients. The fact that motor activity and autonomic cardiac functioning, especially reduced HR variability, may be related to one another, has been suggested before (Thayer et al., 1998; Watkins et al., 1999), but this is the first study that presents data on this issue. In line with the finding that agitation and retardation are related to motor activity levels and mean BP levels, we found for the whole depressed group that lower levels of motor activity were associated with lower mean SBP levels. At present it is too early to speculate about the existence of common neurobiological pathways underlying both functions, since both sets of parameters reflect peripheral as well as central neurobiological processes in depression.

6. Summary

Unmedicated depressed inpatients showed an altered diurnal pattern of motor activity and increased mean HR and DBP levels, but no changes in cardiovascular variability or BRS. In the patient group motor activity parameters and cardiovascular measures were related to the presence of retardation and agitation and overall, patients with lower motor activity levels during wake demonstrated lower BP levels during supine

rest. Our results may contribute to further understanding of the neurobiological processes involved in (subtypes of) depression, and additionally may enlarge our knowledge of treatment specificity of these clinical subtypes.

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Chapter 5

24-Hour motor activity after treatment with imipramine or fluvoxamine in major depressive disorder

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1 Abstract

The psychomotor dysfunction in depression is related to alterations in the diurnal pattern of motor activity. After antidepressant treatment the motor activity level may be changed due to the improvement of depressive mood or pharmacological actions. The purpose of this study was to evaluate in 52 depressed inpatients the effects of imipramine (tricyclic antidepressant - TCA) and fluvoxamine (selective serotonin reuptake inhibitor - SSRI) on the 24-hour motor activity pattern. Motor activity was monitored by wrist-actigraphy during a medication free period and after 4 weeks of treatment. Clinical improvement was not different after imipramine or fluvoxamine treatment: the Hamilton depression score decreased significantly in patients treated with imipramine, as well as in patients treated with fluvoxamine; the clinical retardation score also reduced significantly in both treatment groups. However, after treatment patients treated with imipramine showed significantly higher motor activity levels during the wake period in comparison to the medication free period, and more fragmentation of motor activity during sleep. Treatment with fluvoxamine did not result in alterations in the 24-hour pattern of motor activity. The improvement of depressive mood and retardation seems to play a minor role in the change of the pattern of motor activity after imipramine.

2 Introduction

Psychomotor dysfunction is an important clinical feature of major depressive disorder, which may be reflected in alterations of the spontaneous 24-hour pattern of motor activity (Dantchev and Widlocher, 1998). Unmedicated depressed patients showed, in comparison to healthy controls, decreased motor activity levels and less fragmentation of motor activity during daytime and, in addition, less immobility during nighttime (Wehr et al., 1980; Wolff et al., 1985; Van London et al., 1998; Volkers et al., 2000). Only a limited number of studies have evaluated the effects of antidepressant treatment on the pattern of motor activity. After a combined treatment with TCAs and benzodiazepines, depressed patients demonstrated higher daytime motor activity levels (Raoux et al., 1994), and less periods of immobility during day- and nighttime (Raoux et al., 1994; Royant-Parola et al., 1986; Benoit et al., 1985). In general, changes in the motor activity pattern after antidepressant treatment have been assumed to be caused by the improvement of depressive mood (Raoux et al., 1994; Royant-Parola et al., 1986; Kupfer et al., 1974; Joffe et al., 1987).

On the basis of studies in rats we expected that antidepressants may also have pharmacological effects on overt motor behavior. Janowsky and colleagues (Janowsky and Risch, 1987; Janowsky et al., 1994; Overstreet et al., 1995) have investigated the role of cholinergic mechanisms in affective disorders. Depressed patients showed exaggerated (behavioral, physiological and sleep) responses to cholinergic agents in comparison to control subjects, therefore rats were bred with increased cholinergic sensitivity. Important characteristics of these rats were their reduced activity and increased immobility during the forced swimming test. Overstreet et al. (1995) mentioned that the exaggerated immobility was counteracted by the chronic treatment of imipramine, desipramine (TCA), and sertraline (SSRI). West and Weiss (1998) found an increase in struggling behavior in rats developed for low activity in the forced swimming test after prolonged administration of imipramine and desipramine, but not after fluoxetine (SSRI). The studies in rats suggested that the TCAs imipramine and desipramine may have a stimulating effect on overt motor behavior. The effects of the SSRIs sertraline and fluoxetine were conflicting.

In humans, the effects of TCAs and SSRIs on psychomotor functioning were compared mainly in healthy subjects after a single dose or after dose administration of several days, and have focused on the performance on laboratory psychomotor tasks (Fairweather et al., 1996; Hawley et al., 1997). TCAs, but not SSRIs, resulted in an impairment of the psychomotor performance (e.g. slower reaction times). There is one clinical study (Stanley et al., 1999) that examined differences in spontaneous 24-hour motor activity between unipolar depressed outpatients treated with a TCA or a SSRI. After 10 days, depressed patients treated with fluoxetine (SSRI) showed higher motor activity levels than patients treated with dothiepin (TCA). This was explained by the sedative side effects of TCAs. The effects of antidepressant treatment on motor activity in depressed patients seems to be different from the effects in rats, but the rats received antidepressants for a longer period. It is assumed that over time tolerance develops to the sedative effects of antidepressants (O'Hanlon and Freeman, 1995).

In this study, we examined the changes in clinical state and the motor activity pattern in 52 severely depressed inpatients after a double blind, randomised treatment with either imipramine or fluvoxamine (SSRI). The motor activity pattern was monitored by wrist-actigraphy during a psychotropic drug free period and after 4 weeks of treatment at therapeutic plasma levels of the drugs. Based on the findings in rats (Janowsky et al., 1994; Overstreet et al., 1995; West and Weiss, 1998), we expected that the motor activity increased after imipramine, but there was not enough theoretical ground to have expectations about the effect of fluvoxamine. In

addition, the change in clinical state was evaluated in the two treatment groups, in order to determine the importance of clinical improvement to changes in the 24-hour motor activity pattern.

3 Experimental procedures

3.1 Subjects

Participants were 52 depressed patients (20 males, 32 females; mean age 52.5 ± 8.7 years), who were admitted to the Depression Unit of the Department of Psychiatry of the University Hospital Rotterdam Dijkzigt and participated in a clinical study to the effectiveness of imipramine versus fluvoxamine. Inclusion criteria were a major depressive disorder (unipolar subtype) according to the DSM-IV criteria, accompanied by an initial score of at least >13 on the 17-item Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1967). The diagnosis was based on clinical observation and the depression items of the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978). Specific exclusion criteria were: 1) the presence of a contraindication for imipramine or fluvoxamine, 2) a history of an adequate treatment (therapeutic plasma levels) during 4 weeks with amitriptyline, desipramine, nortriptyline, imipramine, or clomipramine, or the presence of an acute indication for electroconvulsive therapy (ECT), and 3) a response of more than 50% on the initial HRSD score to placebo medication. The placebo medication was administered to all patients during 4 days before onset of treatment. The study was approved by the Medical Ethical Committee of the University Hospital Rotterdam Dijkzigt. All patients gave written informed consent before the start of the study after the study protocol was fully explained.

3.2 Design and procedure

After admission all psychotropic drugs were discontinued. In total 45 patients used antidepressants of which 12 patients (23.1%) TCAs, 14 patients (26.9%) SSRIs, 3 patients (5.8%) lithium, 2 patients (3.8%) monoamine oxidase inhibitors (MAOIs), and 5 patients (9.6%) other antidepressants. Antipsychotics were taken by 6 patients (11.5%) and benzodiazepines by 31 patients (59.6%). After a psychotropic drug free period of at least 7 days, the patients were randomly assigned to a double blind treatment with either imipramine or fluvoxamine. The dose was adjusted each week on the basis of plasma levels in order to obtain optimal doses that corresponded to therapeutic plasma levels for imipramine (imipramine + desipramine) of 200-300 μg/l and for fluvoxamine of 150-200 μg/l. After four weeks of treatment with

optimal doses, the treatment effectiveness was determined by the HRSD and the Clinical Global Improvement Scale (CGIS) (Guy, 1976). During the treatment period no psychopharmaca were allowed besides the study medication.

During the psychotropic drug free period and after 4 weeks of treatment at adequate plasma levels, the motor activity pattern was monitored by wrist-actigraphy during four consecutive weekdays and nights. At the start of the baseline measurement the duration of the medication free period was on average 10.8 days. The first day and night of the recording period were used to acclimatise the patients to wearing the actigraph. The patients were instructed to maintain their normal activity pattern on the ward and to take off the actigraph only during bathing. Furthermore, the instances of actigraph removal, the estimated time of sleep onset and estimated time of final awakening in the morning were recorded in a daily log. Preferably the patients completed the daily log themselves, but if necessary they were assisted by the researcher or nursing staff.

3.3 Clinical ratings

Besides the HRSD, the validated Dutch version of the Salpêtrière Retardation Rating Scale (SRRS) (Widlocher, 1983; Weme et al., 1996) was filled in to measure psychomotor retardation during the medication free period and after 4 weeks of treatment at therapeutic plasma levels. The SRRS comprises 14 items that are related to motility (3 items), speech (3 items), objective cognitive activity (2 items), and subjective appreciation of cognitive activity (6 items). The score on the HRSD item for agitation was used as indicator for agitation. The two senior psychiatrists of the ward filled in all clinical scales.

3.4 Motor activity monitoring

Wrist-actigraphy is a reliable and valid method to monitor 24-hour motor activity patterns (Patterson et al., 1993; Tryon, 1991; Middelkoop et al., 1997a). The actigraph (Gaehwiler Electronics) (size 51 x 36.5 x 21 mm) contained a monoaxial piezoelectric acceleration sensor and counted the number of suprathreshold movements of the wrist (>0.1 g acceleration) for every 30-sec epoch. The analogue sensor signal was sampled at a frequency of 8 Hz and subsequently filtered by a band-pass filter of 0.25-3.0 Hz. The non-dominant hand was chosen as recording site, because it reflects movements of the total trunk and less movements involved in specific tasks such as writing (McPartland et al., 1975; Middelkoop et al, 1997a). Because the first day and night of the recording period were used to acclimatise patients to wearing the actigraph, the data of this day were not used for analysis. Three recording days are

required to obtain reliable motor activity data, because of interday variations in motor activity within subjects (Middelkoop and Sadeh, 1997b).

A clock-time based analysis was applied to compute, for each day, half-hour motor activity counts from 6.00 hrs in the morning until 6.00 hrs the next morning. The half-hour motor activity counts were averaged for the recording days. In addition, the following global motor activity parameters were assessed and averaged for the recording days: 1) motor activity level (average number of counts per epoch, as percentage of the maximum number of counts possible (= 253)) during wake and sleep, 2) fragmentation index of motor activity (number of groups of consecutive zero count epochs divided by the total number of zero count epochs) during wake and sleep, and 3) immobility index (proportion of zero count epochs divided by the total number of epochs) during sleep. The wake period was defined as the time between final awakening in the morning and sleep onset in the evening minus the duration of daytime napping, and the sleep period as the time between sleep onset in the evening and final awakening in the morning.

3.5 Statistical analysis

General regression analyses were applied for the comparison of clinical scores and global motor activity parameters between the two treatment groups during the medication free period. We controlled for possible age and gender differences between the treatment groups. Random regression models (RRMs) for continuous data were applied to study changes in clinical scores and the pattern of motor activity after treatment with imipramine and fluvoxamine. Analyses were performed separately for the two treatment groups and the treatment effects were controlled for the effects of age and gender. RRMs estimate individual effects instead of effects for the total study population (Bock, 1983; Gibbons et al., 1993). The random regression approach uses data from individuals augmented by information from the total study population to estimate for each subject the personal trend across time. In RRMs, the intercept and time effects are allowed to differ for individuals, and are therefore called random terms. In this study the intercept was a random term. The advantage of this analysis technique above the usually applied MANOVAs for repeated measurements is an efficiently use of data, because RRMs can cope with missing values. The estimation of an individual time trend is based on non-missing data for that individual. This implies that missing values are assumed to be missing at random (Verbeke and Molenberghs, 1987), and subjects may have data for different time points. RRMs allow more general and realistic error structures. In this study we assumed an 'unstructured' error structure, which allows both correlations between measurements and variances of measurements to differ (Bock, 1983; Verbeke and

Molenberghs, 1987). In other words, variances and covariances may differ between repeated measurements.

The effects of the regression analyses were reported as unstandardised β's and p values < 0.05 (two-tailed) were assumed to be significant. The statistical analysis was performed with the program Proc Mixed of the statistical package Statistical Analysis Systems (SAS for Windows, release 6.12). Our study population was a subsample of the total patient group that participated in the drug trial. As the trial was still going on at the time of the data analysis, the data were presented as mean ± SD and no information was provided that could be related to individual subjects. Data were analysed independently of the psychiatrists involved in the drug trial.

4 Results

4.1 Clinical improvement

Twenty-five patients received imipramine and 27 patients fluvoxamine. The mean (± SD) dose for imipramine was 220.7 (± 93.4) mg and for fluvoxamine 201.0 (± 86.5) mg. In addition, the mean (± SD) plasma level for patients treated with imipramine

Table 1 Clinical characteristics of patients treated with imipramine or fluvoxamine[a]

	imipramine (n=25)	fluvoxamine (n=27)
Hamilton depression scale score		
Untreated	27.7 ± 5.1	27.0 ± 5.4
After treatment	15.5 ± 8.0[b]	19.4 ± 9.7[c]
SRRS score		
Untreated	24.7 ± 10.2	25.6 ± 8.4
After treatment	13.6 ± 9.1[b]	17.4 ± 11.6[b]
Hamilton agitation item score		
Untreated	0.67 ± 0.82	0.81 ± 0.92
After treatment	0.39 ± 0.72	0.48 ± 0.85

[a] Values given are mean ± SD. [b] $p < 0.001$, [c] $p < 0.01$, random regression analyses for the comparison of clinical scores before and after antidepressant treatment, while controlling for age and gender effects. SRRS, Salpêtrière Retardation Rating Scale.

(imipramine + desipramine) was 275.4 (± 80.0) µg/l and for patients treated with fluvoxamine 182.4 (± 41.8) µg/l. In total 2 patients dropped out the study during treatment. As expected in view of the randomised design of the study, none of the clinical scores during the medication free period was significantly different between the treatment groups. After 4 weeks of treatment at therapeutic plasma levels, the patients treated with imipramine, as well as the patients treated with fluvoxamine, demonstrated a significant decrease of the HRSD score (β = -12.1, $p < 0.001$ and β = -7.6, $p < 0.001$ respectively) (table 1). Similar findings were observed for the SRRS scores; both after imipramine and fluvoxamine there was a reduction of the retardation score (β = -11.1, $p < 0.001$ and β = -8.2, $p < 0.01$ respectively). The reduction of the agitation score was not significant in both treatment groups.

4.2 Changes in motor activity pattern

Figure 1 and 2 present the pattern of motor activity before and after imipramine or fluvoxamine treatment. There were no significant differences between patients treated with imipramine and fluvoxamine concerning the global motor activity parameters during the medication free period (table 2). Patient treated with imipramine showed a significant increase in the mean motor activity level during wake (β = 1.8, $p < 0.001$). The mean motor activity level during sleep was not significantly changed by the antidepressant treatments. Both treatment groups

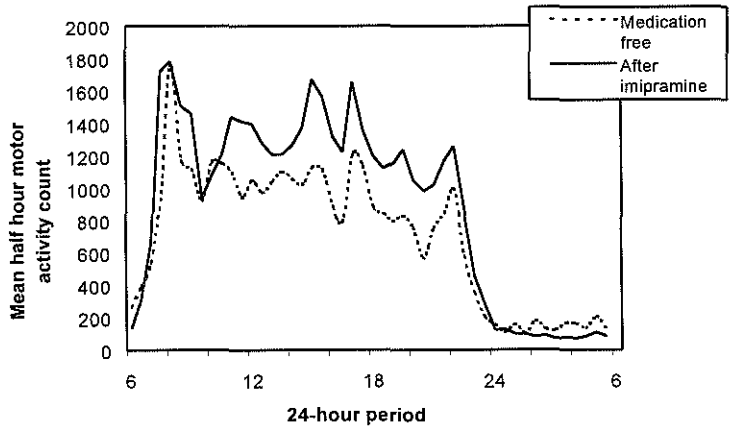

Figure 1 Mean half hour motor activity counts for the 24-hour period (from 6.00 hrs – 6.00 hrs) of depressed patients before and after treatment with imipramine.

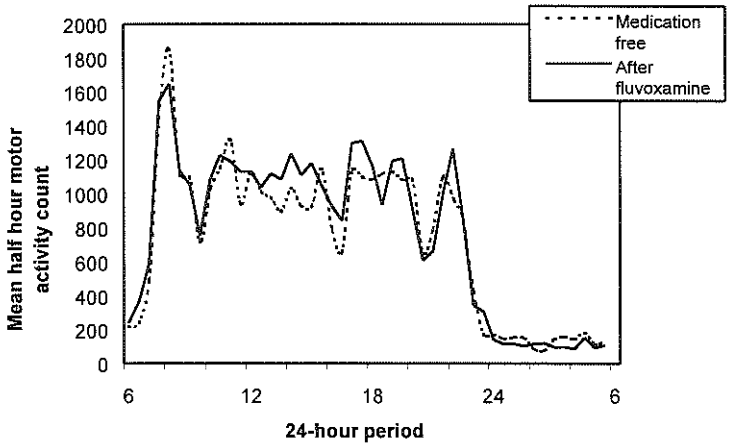

Figure 2 Mean half hour motor activity counts for the 24-hour period (from 6.00 hrs – 6.00 hrs) of depressed patients before and after treatment with fluvoxamine.

showed no alteration in the fragmentation index during the wake period, but during the sleep period patients treated with imipramine showed a higher fragmentation index ($\beta = 0.02$, $p < 0.05$) in comparison to the medication free period. A higher fragmentation index indicates that periods without any motor activity were more often interrupted by activity. The immobility index during sleep was not altered by the two antidepressant treatments, indicating that there was no alteration in the relative amount of periods without motor activity.

5 Discussion

This study showed that, on average, there was a clinical improvement of depressive mood in the depressed inpatients after treatment at adequate plasma levels with imipramine as well as with fluvoxamine. Furthermore, based on clinical evaluations a reduction in retardation, but not in agitation, was observed in the two treatment groups. There were clear alterations in the motor activity pattern in patients treated with imipramine, but not in patients treated with fluvoxamine, at least not after the treatment period we evaluated. After imipramine there was an increase in the mean motor activity level during wake and more fragmented motor activity during sleep.

The treatment with imipramine (during 26 or 60 days) had a stimulating effect on reduced overt motor behavior in rats (Overstreet et al., 1995; West and

Table 2 Global motor activity parameters of patients treated with imipramine or fluvoxamine[a]

	imipramine (n=25)	fluvoxamine (n=27)
Motor activity during wake[d]		
Untreated	6.7 ± 3.2	7.3 ± 3.5
After treatment	8.6 ± 3.5[b]	7.4 ± 3.7
Motor activity during sleep[d]		
Untreated	0.68 ± 0.59	0.83 ± 0.68
After treatment	0.54 ± 0.25	0.68 ± 0.42
Fragmentation index during wake[e]		
Untreated	0.38 ± 0.13	0.43 ± 0.11
After treatment	0.40 ± 0.13	0.38 ± 0.12
Fragmentation index during sleep[e]		
Untreated	0.047 ± 0.018	0.057 ± 0.037
After treatment	0.067 ± 0.033[c]	0.071 ± 0.043
Immobility index during sleep[f]		
Untreated	0.92 ± 0.04	0.90 ± 0.06
After treatment	0.91 ± 0.04	0.91 ± 0.06

[a]Values given are mean ± SD. [b]$p < 0.001$, [c]$p < 0.05$, random regression analyses for the comparison of the 24-hour pattern of motor activity before and after antidepressant treatment, while controlling for age and gender effects. [d]Average number of counts per epoch, as percentage of the maximum number of counts possible. [e]Number of groups of consecutive zero count epochs divided by the total number of zero count epochs. [f]Proportion of zero count epochs divided by the total number of epochs.

Weiss, 1998), therefore we expected an increase in motor activity in depressed patients after imipramine. The higher daytime motor activity in patients treated with imipramine was in agreement with our expectation. The lack of a change in motor activity levels after fluvoxamine was consistent with the finding that the treatment of fluoxetine during 26 days did not result in alterations in reduced motor activity in rats (West and Weiss, 1998). The higher motor activity levels during daytime after imipramine were supported by the clinical study of Raoux et al. (1994). They found in 26 depressed inpatients (5 bipolar and 21 unipolar) that the daytime motor activity was increased after a combined treatment of a TCA (clomipramine, maprotiline, or trimipramine) and benzodiazepines. They ascribed the change in the motor activity pattern to the clinical improvement of the patients. Our results are in conflict with the results of Stanley et al. (1999). They compared in 14 unipolar depressed

outpatients the effect on motor activity of a TCA (dothiepin) or a SSRI (fluoxetine). Patients who received fluoxetine were overall more active during daytime after 10 days of treatment than patients that received dothiepin, especially between 6.00 and 8.00 hrs. The lower motor activity levels in patients treated with dothiepin were suggested to originate from sedative side effects. In our opinion the treatment period in our study was long enough (on average 5 weeks when measurements were performed) to develop tolerance to sedation. Furthermore, their number of patients was limited and no pre-treatment measurements were taken into account. In contrast, we studied a large group of depressed patients, each patient was treated with clinically optimal doses due to the control of plasma levels, and the observed effects in our study were not obscured by comedication of other psychotropic drugs. A limitation of the evaluation after 4 weeks of adequate treatment was that a direct comparison between our findings and those of Stanley et al. (1999) could not be made. SSRIs are known to induce infrequently movement disorders such as agitation and akathisia (a form of motor restlessness) (Leo, 1996; Stahl, 1998). On group level we found no support for the presence of these phenomena after fluvoxamine, however we can not rule out that these phenomena occurred at the beginning of treatment.

After imipramine also the motor activity during sleep was more fragmented, which was not accompanied by alterations in the motor activity level or the immobility index. The higher fragmentation index could refer to more nocturnal awakenings and/or arousals during sleep. However, Thase (1998) stated that only the TCAs clomipramine, desipramine and protriptyline may have disruptive effects on sleep maintenance. Although SSRIs induce insomnia and can increase the number of nocturnal awakenings (Thase, 1998; Stahl, 1998), the motor activity level, fragmentation of motor activity and the immobility during sleep were not changed after fluvoxamine.

TCAs inhibit the reuptake of serotonin (5-HT) and norepinephrine, and in addition block the acethylcholinergic, $\alpha 1$ adrenergic, and histaminergic receptors. SSRIs are known to block the reuptake pump of serotonin. Although there are several differences between the pharmacological profiles of imiprimanine and fluvoxamine, one explanation for the effect of imipramine might be its anticholinergic and (nor)adrenergic properties. Future research should investigate the 24-hour motor activity pattern in depressed patients after treatment with other TCAs and SSRIs, and with newer antidepressants such as the selective noradrenaline reuptake inhibitors (SNRIs). In the first place, to obtain more insight in the neurobiological mechanisms underlying the increase of motor activity after antidepressant treatment. Secondly, to find out whether the effects of imipramine and

fluvoxamine on the 24-hour motor activity were drug specific or can be generalised to other TCAs and SSRIs.

In both treatment groups there was a significant reduction in the severity of depression and retardation, indicating that the clinical effectiveness of both antidepressants was not different in this study. Although patients received antidepressant treatment during 4 weeks with optimal doses, there was a low percentage 29% of patients (in total 15) that showed a therapeutic response. Patients with an improvement of >50% of the initial HRSD score, or a moderate or markedly clinical improvement as measured by the CGIS were defined as responders. The percentage responders did not significantly differ between the treatment groups. Unfortunately, the number of responders in the treatment groups was too small to study the effects of imipramine and fluvoxamine in responders and nonresponders separately. Thus, a contribution of the improvement of clinical state to the increase in daytime motor activity can not be ruled out, but it appears to play a minor role. This statement is supported by a previous study that showed no significant correlations between global motor activity parameters and the severity of depression in 66 unmedicated depressed patients including the patients of this study (Volkers et al., 2000). However, in these patients retardation was related to lower motor activity levels throughout the entire day, and agitation to higher motor activity levels during wake (Volkers et al., 2002a). Post-hoc general regression analyses of the presently used patient group showed that after treatment the HRSD scores in both treatment groups were not related to global motor activity parameters while controlling for age and gender effects, but interestingly this was also the case for the retardation and agitation scores. Furthermore, post-hoc random regression analyses indicated that the increase in motor activity after imipramine was not modified by changes in the HRSD, retardation or agitation scores. For this reason, the clinical relevance of our findings needs to be further explored, especially in relation to psychomotor retardation. Even after the treatment with imipramine the daytime motor activity levels in depressed patients were still lower than in healthy control subjects. To illustrate, the mean (± SD) motor activity during wake was 8.6 ± 3.5 in depressed patients treated with imipramine and 11.6 (± 5.4) in healthy subjects (Volkers et al., 2002b). For this reason, patients should be followed during the entire hospital stay and after discharge to find out whether the effects of imipramine and fluvoxamine on motor activity are more pronounced after a longer treatment period and/or in their natural environment.

6 Summary

In depressed inpatients the treatment with imipramine resulted in an increase in motor activity during daytime and more fragmentation of motor activity during sleep. Patients treated with fluvoxamine demonstrated no alterations in the 24-hour pattern of motor activity. The clinical improvement in depressive mood and retardation seems to play a minor role in this finding. Future studies should explore the possible contribution of anticholinergic and (nor)adrenergic properties of imipramine to the change in motor activity level.

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Chapter 6

Effects of imipramine, fluvoxamine and depressive mood on autonomic cardiac functioning in major depressive disorder

Submitted

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1 Abstract

Diminished HR variability is considered to play a role in the relationship between depression and the increased risk of cardiovascular disease. The pharmacological effects of antidepressants and depressive mood itself may contribute to alterations in the autonomic cardiac functioning, but so far only a limited amount of data are available. Therefore, we studied the effects of two different types of antidepressant treatments (imipramine and fluvoxamine), in addition to the effect of depressive mood, on the cardiovascular system in depressed patients. Depressed inpatients were studied during a drug free period and after 4 weeks of adequate treatment of imipramine (n=17) or fluvoxamine (n=24). Heart rate (HR) variability, blood pressure (BP) variability, and a baroreflex sensitivity (BRS) index during supine rest and orthostatic challenge were analysed by means of spectral techniques to obtain non-invasive parameters of sympathetic and parasympathetic activity. Both imipramine and fluvoxamine reduced sympathetic and parasympathetic activity, although the effects of fluvoxamine were much less pronounced. Severity of depression was positively related to mean heart rate in the imipramine group, and to mean blood pressure in the fluvoxamine group. However, in both treatment groups, changes in the cardiovascular parameters after treatment were not influenced by changes in depressive mood. Our findings suggest that alterations in cardiovascular variability and baroreflex sensitivity in depressed patients after antidepressant treatment should be attributed to the pharmacological actions of antidepressants rather than to changes in depressive mood.

2 Introduction

Diminished HR variability is considered to be one of the biological mechanisms that play a role in the relationship between depression and the increased risk of morbidity and mortality of cardiovascular disease (Musselman et al., 1998). Cardiovascular variability is frequently analysed to provide estimates of sympathetic and parasympathetic regulation of the cardiovascular system (Akselrod et al., 1985; Malliani et al., 1991; Parati et al., 1989, 2000). HR variability that is related to respiratory variations usually between 0.20-0.35 Hz (respiratory sinus arrhythmia) results from centrally mediated cardiac vagal (parasympathetic) activity. BP variability in the frequency domain around 0.10 Hz (Mayer waves) reflects alterations in peripheral vasomotor resistance due to baroreflex-mediated sympathetic control. HR variability in this frequency domain represents changes in the baroreflex response and

similarly reflects sympathetic activity, although an influence of vagal activity has also been suggested.

Tricyclic antidepressants (TCAs) are known for their cardiovascular side effects such as tachycardia, orthostatic hypotension, conduction delays, and cardiac arrhythmias (Littman et al., 1993). TCAs also induce decreased HR variability, indicating diminished vagal cardiac control due to the anticholinergic properties of TCAs (Yeragani et al., 1995; Tulen et al., 1996a). Selective serotonin reuptake inhibitors (SSRIs) are considered to be devoid of strong pharmacological actions on the cardiovascular system, but their cardiovascular effects should not be overlooked. To illustrate, Lederbogen et al. (2001) found in depressed patients that paroxetine treatment with a high dose (40 mg) resulted in decreased HR variability, probably due to the mild anticholinergic properties of paroxetine. In addition, fluvoxamine treatment has the tendency to decrease the mean HR in depressed patients (Wakelin, 1986; Hewer et al., 1995; Laird et al. 1993; Rechlin, 1994c). However, no effect on HR variability was found (Rechlin, 1994c). These findings should be clarified by studying the effect of fluvoxamine treatment both on HR and BP variability and on BRS by means of spectral analysis. Shores et al. (2001) found recently a suppression of sympathetic activity in healthy controls after a short-term treatment of sertraline. Therefore, the mean HR after fluvoxamine treatment could be decreased due to reduced cardiac sympathetic activity.

The majority of studies in unmedicated depressed patients reported no alterations in cardiovascular variability or BRS (Yeragani et al., 1991; Rechlin, 1994c; Tulen et al., 1996a; Lehofer et al., 1997; Moser et al., 1998). Nevertheless, in two studies (Lehofer et al., 1997; Moser et al., 1998) and in a previous study of our own (Volkers et al., 2002a) increased HR levels were observed in unmedicated depressed patients, implying the relevance of research on the influence of depressive mood on autonomic regulation. Besides their pharmacological effects, antidepressants may also affect the cardiovascular system through their therapeutic effect on mood state. Balogh et al. (1993) observed that the improvement of depressive mood due to antidepressant treatment had a beneficial effect on the autonomic modulation by increasing HR variability. This was especially the case after treatment with the SSRI fluoxetine and the dopamine/noradrenaline reuptake inhibitor bupropion; both antidepressants that were assumed to have no strong cardiovascular effects.

To obtain more insight in the contribution of antidepressant treatment to alterations in autonomic cardiac functioning in depressed patients, we studied the effects of a double blind treatment with imipramine or fluvoxamine on the autonomic regulation of the cardiovascular system in 52 depressed inpatients. During a medication free period and after 4 weeks of treatment at adequate plasma levels

cardiovascular measurements were performed during supine rest (SR) and orthostatic challenge (OC). HR and BP variability and BRS were assessed by means of spectral analysis. In each treatment group, also the overall effect of depressive mood on cardiovascular parameters was evaluated and the influence of the alteration in depressive mood state on the change of the cardiovascular parameters after treatment.

3 Methods and Materials

3.1 Patients

Fifty-two depressed inpatients (20 men and 32 women; mean age 52.5 years, range 32-65 years) with a major depressive disorder (unipolar subtype) according to DSM-IV criteria participated in a clinical trial to the effectiveness of imipramine versus fluvoxamine. The Medical Ethical Committee of the hospital approved the study and all patients gave written informed consent. Inclusion criteria were an initial score of >13 on the 17 item Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1967). The diagnosis was based on clinical observation and the depression items of the Schedule for Affective Disorders and Schizophrenia (SADS) (Endicott et al., 1978). As exclusion criteria served: a history of an adequate treatment (therapeutic plasma levels) during 4 weeks with a TCA and a response of more than 50% on the initial HRSD score to placebo medication 4 days prior to active treatment.

3.2 Design and Procedure

After a psychotropic drug free period of at least 7 days (average duration 10.6 days), the patients were randomly assigned to a double blind treatment of imipramine or fluvoxamine and were treated during 4 weeks with optimal doses that corresponded to therapeutic plasma levels for imipramine (imipramine + desipramine) of 200-300 μg/l and for fluvoxamine of 150-200 μg/l. No other psychotropic drugs were allowed. Two patients dropped out the study during treatment due to suicide and severe hypotension. Patients with cardiovascular disease and/or diabetes mellitus (n = 11) were excluded afterwards from data analysis. Consequently, this study reports data of 41 patients (imipramine n = 17, fluvoxamine n = 24), of whom 35 patients used psychotropic drugs before participating in the study; TCAs (9), SSRIs (11), lithium (1), monoamine oxidase inhibitors (MAOIs) (2), other antidepressants (5), antipsychotics (6) and benzodiazepines (25). The mean (± SD) dose of imipramine was 221.7 (± 109.7) mg and the mean (± SD) plasma level 281.8 (± 96.8)

μg/l. The mean (± SD) dose of fluvoxamine was 194.3 (± 84.8) mg and the mean (± SD) plasma level 182.0 (± 42.5) μg/l.

Each week the HRSD was scored to ascertain severity of depression. The HRSD score of the medication free period and that assessed after 4 weeks of treatment at adequate plasma levels were used to evaluate changes in depressive symptomatology. The cardiovascular measurement was performed in the morning, after an overnight fast of smoking and coffee drinking, similarly during the medication free period and after treatment.

3.3 Cardiovascular Measurement

Electrocardiogram (ECG), BP and respiration were continuously sampled with 1024 Hz during 10 min SR and 10 min OC (60° head-up tilting). The ECG was derived from a precordial lead, BP was recorded by a noninvasive measurement of finger arterial BP (Finapres) (Penaz, 1976), and respiration was measured by means of an impedance plethysmograph. R-R intervals in the ECG were detected with an accuracy of 1 millisecond and transposed to interbeat interval (IBI) time series. Systolic and diastolic blood pressure (SBP and DBP) were defined per IBI with an accuracy 0.1 mmHg. In addition, at each incidence of the R-wave the value of the respiratory signal was obtained. The IBI, SBP, DBP and respiratory time series of the last 5 minutes of SR and OC were used for spectral analysis.

The time series were subjected to a discrete Fourier transformation, based on nonequidistant sampling of the R-wave incidences (Carspan program) (Mulder et al., 1988b; Van Steenis et al., 1994), to yield power spectra of the rhythmic oscillations over a frequency range of 0.02 to 0.50 Hz. Per time segment we calculated the mean HR, SBP and DBP, variation coefficients of HR and SBP (CVI, coefficient of variation of IBI; CVS, coefficient of variation of SBP), mid frequency (MF, 0.07-0.14 Hz) power of HR and SBP, high frequency (HF, 0.15-0.50 Hz) power of HR, and the dominant respiratory frequency. Spectral power for each selected frequency band was expressed in relative terms, that is as a fraction of the mean value of the considered signal (squared modulation index) (Van Dellen et al., 1985). If this measure is computed for the whole spectrum (0.01-0.50 Hz) it is directly comparable to the squared variation coefficient. The spectral power data were transformed to natural logarithmic values to obtain a normal distribution of data. The MF band used in this study is comparable with the low frequency domain of 0.04 –0.15 Hz as defined by the Task Force guidelines (Task Force, 1996). Finally, per time segment the gain (or modulus) in the MF band between SBP and IBI time series was computed as an index of BRS (Saul et al., 1991; Parati et al., 2000; Robbe et al., 1987).

3.4 Statistical analysis

Random regression models (RRMs)[1] for continuous measurements were applied to study the effect of posture (SR=1, OC=2) on the cardiovascular parameters before and after treatment, and the effect of antidepressant treatment (medication free=1, treatment=2) on the HRSD score and on the cardiovascular parameters during SR, as well as during OC. Subsequently, the HRSD score was included in the original RRMs to test the overall effect of severity of depression on the cardiovascular variables (cardiovascular data were combined for the drug free period and the period after treatment) during SR and OC. If both antidepressant treatment and the HRSD score had a significant effect on a specific cardiovascular parameter, the interaction term of these two determinants was entered in the extended RRMs to study the modifying effect of severity of depression on the effect of antidepressant treatment. The plausibility of extended RRMs was determined by comparing their model fit with the model fit of the original RRMs. The improvement of model fit was tested with chi-square statistics by comparing –2 Log Likelihood values of the restricted and extended RRMs, accounting for differences in degrees of freedom.

All analyses were performed separately for the two treatment groups. In the RRMs the effects of the determinants were always tested simultaneously and they were controlled for age and gender. Effects were reported as unstandardised β's and p values < 0.05 (two-tailed) were regarded to be significant. The statistical analysis was performed with the program Prox Mixed of the statistical package Statistical Analysis Systems (SAS for Windows, release 6.12).

[1] Random regression models for continuous data estimate individual effects instead of effects for the total study population (Bock, 1983; Gibbons et al., 1993). The random regression approach uses data from individuals augmented by information from the total study population to estimate for each subject the personal trend across time. In RRMs, the intercept and time effects are allowed to differ for individuals, and are therefore called random terms. In this study the intercept was a random term. The advantage of this analysis technique above the usually applied MANOVAs for repeated measurements is an efficiently use of data, because RRMs can cope with missing values. The estimation of an individual time trend is based on non-missing data for that individual. This implies that missing values are assumed to be missing at random (Verbeke and Molenberghs, 1987), and subjects may have data for different time points. RRMs allow more general and realistic error structures. In this study we assumed an 'unstructured' error structure, which allows both correlations between measurements and variances of measurements to differ (Gibbons et al., 1993; Verbeke and Molenberghs, 1987). In other words, variances and covariances may differ between repeated measurements.

4 Results

4.1 Clinical state

A significant reduction of severity of depression was found in patients treated with imipramine and fluvoxamine after 4 weeks of treatment at adequate plasma levels. The HRSD score in the imipramine group decreased from 26.7 (± 4.9) to 13.2 (± 9.8) (β=-13.4, $p<0.001$) and in the fluvoxamine group from 26.2 (± 5.2) to 19.6 (± 9.3) (β=-6.7, $p<0.001$).

4.2 Cardiovascular data

4.2.1 Drug free period, effect of orthostatic challenge

Before treatment orthostatic challenge resulted in both treatment groups in a significantly higher mean HR, mean DBP, MF power of SBP, and a significantly lower CVI, HF power of HR, and BRS (tables 1 and 2). Patients in the fluvoxamine group also showed a significantly lower MF power of HR in response to orthostatic challenge, and patients in the imipramine group a significantly increased respiratory frequency. Orthostatic hypotension was defined as a SBP reduction of >15 mmHg in response to orthostatic challenge. During the drug free period orthostatic hypotension was observed in none of the patients in the imipramine group and in 3 patients in the fluvoxamine group.

4.2.2 Imipramine

Cardiovascular effects

Patients showed significantly higher mean HR levels during SR and OC after imipramine treatment in comparison to the medication free period (table 1). In addition, there was a significant decrease during SR and OC in the CVI, MF and HF power of HR, and MF power of SBP. The reduction of the BRS index was only significant during OC. After treatment, OC resulted in the same significant changes of the cardiovascular parameters as before treatment, except that the decrease in MF power of HR became significant after treatment and the significance of the increased respiratory frequency disappeared. Imipramine treatment induced orthostatic hypotension in one patient.

Effect of depressive mood, in addition to cardiovascular effects

The extended RRMs for HR had an improved model fit and showed that the HRSD score had overall a significant positive effect on mean HR (table 3). This implies that

Table 1 Cardiovascular parameters of patients treated with imipramine (n=17)[a]

	Supine rest	Head-up tilt	Effect of head-up tilt (β)
HR (beats/min)			
Untreated	72.3 (± 12.0)	92.3 (± 12.9)	20.0 (p<0.001)
After treatment	86.6 (± 7.8)	106.1 (± 11.9)	19.4 (p<0.001)
Effect of treatment (β)	15.2 (p<0.001)	14.8 (p<0.001)	
CVI (%)			
Untreated	4.8 (± 2.0)	3.5 (± 1.4)	-1.3 (p<0.01)
After treatment	2.3 (± 1.1)	1.7 (± 0.6)	-0.6 (p<0.05)
Effect of treatment (β)	-2.5 (p<0.001)	-1.8 (p<0.001)	
MF log power HR			
Untreated	5.8 (± 1.0)	5.6 (± 1.2)	-0.3 (p=ns)
After treatment	4.4 (± 1.0)	3.0 (± 1.2)	-1.4 (p<0.001)
Effect of treatment (β)	-1.5 (p<0.001)	-2.5 (p<0.001)	
HF log power HR			
Untreated	5.9 (± 1.5)	4.7 (± 1.5)	-1.2 (p<0.01)
After treatment	4.2 (± 1.3)	3.0 (± 1.4)	-1.2 (p<0.05)
Effect of treatment (β)	-1.7 (p<0.001)	-1.6 (p<0.001)	
SBP (mmHg)			
Untreated	122.8 (± 16.0)	127.3 (± 20.0)	2.4 (p=ns)
After treatment	124.3 (± 14.4)	128.1 (± 19.7)	3.8 (p=ns)
Effect of treatment (β)	-0.9 (p=ns)	1.6 (p=ns)	
CVS (%)			
Untreated	4.5 (± 1.6)	5.8 (± 2.0)	1.3 (p=ns)
After treatment	3.5 (± 2.1)	4.7 (± 1.2)	1.1 (p<0.05)
Effect of treatment (β)	-1.2 (p=ns)	-1.0 (p=ns)	
MF log power SBP			
Untreated	5.1 (± 0.7)	6.3 (± 0.8)	1.1 (p<0.05)
After treatment	3.4 (± 1.1)	4.4 (± 0.7)	0.9 (p<0.5)
Effect of treatment (β)	-1.8 (p<0.001)	-1.9 (p<0.001)	
DBP (mmHg)			
Untreated	68.3 (± 8.9)	80.5 (± 11.7)	11.5 (p<0.001)
After treatment	68.0 (± 10.2)	79.2 (± 12.9)	11.2 (p<0.01)
Effect of treatment (β)	-1.0 (p=ns)	-0.5 (p=ns)	
BRS (ms/mmHg)			
Untreated	10.3 (± 5.6)	3.5 (± 2.2)	-6.7 (p<0.001)
After treatment	8.4 (± 4.1)	2.2 (± 1.6)	-6.2 (p<0.001)
Effect of treatment (β)	-2.3 (ns)	-1.7 (p<0.05)	
Resp. Freq. (Hz)			
Untreated	0.25 (± 0.04)	0.28 (0.07)	0.03 (p<0.01)
After treatment	0.27 (± 0.04)	0.25 (0.09)	0.02 (p=ns)
Effect of treatment (β)	0.02 (p=ns)	-0.03 (p=ns)	

[a]Values given are mean ± SD. The effect of treatment and orthostatic challenge were studied by RRMs, while controlling for age and gender. HR, heart rate; CV, variation coefficient; MF, mid-frequency; HF, high-frequency; SBPand DBP, systolic and diastolic blood pressure; BRS, baroreflex sensitivity; Resp. Freq., respiratory frequency.

Table 2 Cardiovascular parameters of patients treated with fluvoxamine (n=24)[a]

	Supine rest	Head-up tilt	Effect of head-up tilt (β)
HR (beats/min)			
Untreated	78.0 (± 10.1)	96.9 (± 14.0)	19.0 (p<0.001)
After treatment	75.7 (± 10.8)	91.7 (± 14.7)	16.0 (p<0.001)
Effect of treatment (β)	-2.2 (p=ns)	-5.4 (p=ns)	
CVI (%)			
Untreated	4.8 (± 2.3)	3.6 (± 1.6)	-1.3 (p<0.05)
After treatment	3.4 (± 1.2)	3.0 (± 1.3)	-0.4 (p=ns)
Effect of treatment (β)	-1.1 (p<0.05)	-0.6 (p<ns)	
MF log power HR			
Untreated	5.8 (± 1.2)	5.1 (± 1.4)	-0.7 (p<0.01)
After treatment	5.3 (± 1.0)	4.7 (± 1.1)	-0.6 (p<0.01)
Effect of treatment (β)	-0.5 (p<0.05)	-0.4 (ns)	
HF log power HR			
Untreated	5.6 (± 1.3)	4.0 (± 1.2)	-1.6 (p<0.001)
After treatment	4.9 (± 1.0)	4.1 (± 1.0)	-0.8 (p<0.01)
Effect of treatment (β)	-0.7 (p<0.01)	0.6 (p=ns)	
SBP (mmHg)			
Untreated	137.5 (± 25.8)	133.8 (± 20.6)	2.1 (p=ns)
After treatment	136.0 (± 23.7)	136.9 (± 21.0)	1.6 (p=ns)
Effect of treatment (β)	-0.8 (p=ns)	0.5 (p=ns)	
CVS (%)			
Untreated	4.9 (± 1.5)	5.4 (± 1.4)	0.6 (p=ns)
After treatment	4.8 (± 2.4)	4.2 (± 1.1)	-0.6 (p=ns)
Effect of treatment (β)	-0.3 (p=ns)	-1.2 (p<0.001)	
MF log power SBP			
Untreated	5.5 (± 0.8)	6.1 (± 0.9)	0.6 (p<0.01)
After treatment	5.3 (± 1.0)	5.8 (± 0.9)	0.4 (p<0.05)
Effect of treatment (β)	-0.3 (p≤0.05)	-0.4 (p<0.04)	
DBP (mmHg)			
Untreated	72.7 (± 13.0)	81.4 (± 10.9)	11.9 (p<0.001)
After treatment	70.2 (± 10.1)	80.6 (± 9.7)	10.9 (p<0.001)
Effect of treatment (β)	-1.7 (p=ns)	-1.3 (p=ns)	
BRS (ms/mmHg)			
Untreated	6.8 (± 3.9)	2.6 (± 1.6)	-4.1 (p<0.001)
After treatment	5.6 (± 3.5)	3.0 (± 2.0)	-2.9 (p<0.001)
Effect of treatment (β)	-0.8 (p=ns)	0.04 (p=ns)	
Resp. Freq. (Hz)			
Untreated	0.26 (± 0.08)	0.28 (± 0.07)	0.02 (p=ns)
After treatment	0.27 (± 0.07)	0.29 (± 0.08)	0.02 (p=ns)
Effect of treatment (β)	0.009 (p=ns)	0.01 (p=ns)	

[a]Values given are mean ± SD. The effect of treatment and orthostatic challenge were studied by RRMs, while controlling for age and gender. HR, heart rate; CV, variation coefficient; MF, mid-frequency; HF, high-frequency; SBPand DBP, systolic and diastolic blood pressure; BRS, baroreflex sensitivity; Resp. Freq., respiratory frequency.

severity of depression was positively related to a higher mean HR in the imipramine treatment group during SR and OC, when data were combined for the medication free period and the period after treatment. After entering the effect of the HRSD score, the effect of imipramine on mean HR became larger. The inclusion of the interaction term 'treatment effect and effect of HRSD score' in the RRM for HR resulted in improved model fits (SR, χ^2=197.8-193.3=4.5, df=1, $p<0.05$ and OC, χ^2=206.4-202.6=3.8, df=1, $p<0.05$). However, the interaction term itself was not significant, indicating that increases in HR were not influenced by the alteration in severity of depression. The model fit of the extended RRMs for mean SBP and of the extended RRM for mean DBP during OC also improved, but the effect of the HRSD score was nonsignificant. The model fit of the extended RRMs for mean DBP during SR, HR and SBP variability parameters and BRS deteriorated. Thus, severity of depression was no proper determinant of these parameters.

4.2.3 Fluvoxamine

Cardiovascular effects

There was no significant effect of fluvoxamine treatment on mean HR, SBP and DBP (table 2). However, during SR the patients demonstrated a significant decrease in CVI, MF and HF power of HR, and MF power of SBP and during OC there was a significant decrease in CVS and MF power of SBP. After treatment, the same cardiovascular parameters showed a significant response to OC. Only the decrease in CVI was no longer significant. Orthostatic hypotension remained present in 1 patient after fluvoxamine treatment, but disappeared in the two other patients.

Effect of depressive mood, in addition to cardiovascular effects

Only the RRMs for mean SBP and DBP showed an improved model fit after including the HRSD score (table 3). The HRSD score had a positive effect on mean SBP during OC and on mean DBP during both SR and OC. This reveals that, overall, more severely depressed patients showed higher BP levels (data were combined for the medication free period and the period after treatment). The effect of fluvoxamine treatment on mean SBP and DBP remained nonsignificant. The model fit of the RRMs for mean HR, cardiovascular variability and BRS became worse after entering the HRSD score, implying that variation in these parameters could not be adequately explained by severity of depression.

Table 3 The effect of the HRSD score on the cardiovascular variables in patients treated with imipramine (n=17) and fluvoxamine (n=24)[a]

	imipramine		fluvoxamine	
	Supine rest	Head-up tilt	Supine rest	Head-up tilt
HR (beats/min)				
Effect of treatment (β)	22.7 ($p<0.001$) [b]	23.6 ($p<0.001$) [c]		
Effect of HRSD (β)	0.6 ($p<0.05$)	0.7 ($p<0.05$)		
SBP (mmHg)				
Effect of treatment (β)	-5.4 (p=ns)	6.3 (p=ns)	3.5 (p=ns)	6.2 (p=ns) [d]
Effect of HRSD (β)	-0.4 (p=ns)	0.4 (p=ns)	0.6 (p=ns)	0.8 ($p<0.05$)
DBP (mmHg)				
Effect of treatment (β)		4.5 (p=ns)	1.2 (p=ns) [e]	2.4 (p=ns) [f]
Effect of HRSD (β)		0.4 (p=ns)	0.4 ($p<0.05$)	0.5 ($p<0.01$)

[a] The effects of RRMs with a significantly or nonsignificantly improved model fit were presented. All effects were controlled for age and gender. Significantly improved model fits: [b] χ^2=203.3-197.8=5.5, df=1, $p<0.05$, [c] χ^2=211.5-206.4=5.1, df=1, $p<0.05$, [d] χ^2=338.7-333.9=4.8, df=1, $p<0.05$, [e] χ^2=324.5-319.7=4.8, df=1, $p<0.05$, and [f] χ^2= 283.0-275.3=7.7, df=1, $p<0.01$. HR, heart rate; SBP and DBP, systolic and diastolic blood pressure.

5 Discussion

The increase in mean HR level after imipramine treatment is in line with previous studies in patients with major depression, panic disorders and generalised anxiety disorder (McLeod et al., 1992; Yeragani et al., 1992; Tulen et al., 1996a). Because there was no significant difference between respiratory frequency before and after treatment, we attributed the increase in mean HR and decrease in HR variability of the HF band to diminished parasympathetic (vagal) activity, due to the anticholinergic properties (blockade of muscarine$_1$ receptors) of imipramine. After imipramine treatment, the SBP variability in the MF band was also decreased; indicating reduced sympathetic tone, although there were no clear alterations of mean SBP and DBP levels. This phenomenon was also observed in the only previous study to the effect of imipramine treatment on BP variability in depressed patients (Tulen et al., 1996a). This suppression may be explained by the potency of TCAs to block the noradrenaline reuptake in the central and sympathetic nervous system (Veith et al., 1994). The lower HR variability in the MF band probably reflected both the inhibition of sympathetic activity and parasympathetic activity. The effect of imipramine on parasympathetic processes was supported by the decreased BRS. Orthostatic challenge resulted in similar significant changes in the cardiovascular

parameters during the medication free period and after treatment, with the exception of the changes in the MF variability of HR and the respiratory frequency. Although orthostatic hypotension is assumed to be the major side-effect of TCAs, just one depressed patient developed orthostatic hypotension.

The decrease in mean HR after fluvoxamine treatment was not significant, but during orthostatic challenge there was a tendency for the decrease to reach significance ($p<0.08$). This finding is in agreement with that of other studies performed in depressed patients (Wakelin, 1986; Hewer et al., 1995; Laird et al. 1993; Rechlin, 1994c). It was striking that fluvoxamine treatment resulted in lower overall HR variability, MF and HF variability of HR, and MF variability of SBP during SR, and in lower overall SBP variability and MF variability of SBP during OC. This is the first study demonstrating an inhibition of sympathetic and parasympathetic activity after fluvoxamine treatment in depressed patients, although the inhibition of parasympathetic activity was only present during SR and all effects were much less pronounced than the effects of imipramine. The inhibition of sympathetic activity may explain the nonsignificantly reduced mean HR levels. Furthermore, the same cardiovascular parameters showed a significant response to orthostatic challenge before and after treatment, only the decrease in CVI was no longer significant. Fluvoxamine treatment had a beneficial effect on orthostatic hypotension in 2 patients, because their orthostatic hypotension was no longer present after treatment. In contrast to the present study, Rechlin (1994c) found after 14 days in a smaller group of depressed patients ($n = 8$) no effect of fluvoxamine on time domain measures of HR variability. However, we treated patients for several weeks under control of plasma levels, we applied the technique of spectral analysis, and we took the influence of respiratory frequency into account. In addition, random regression models were applied to optimise the statistical analysis. We expected a decreased cardiac sympathetic activity after fluvoxamine treatment, because Shores et al. (2001) found in healthy controls that the plasma noradrenaline appearance rate was decreased after a short-term (3 days) treatment with the SSRI sertraline, reflecting suppression of sympathetic activity. They suggested that the agonist action of sertraline on 5-HT_{1a} receptors was involved in this suppression. However, Szabo et al. (1992) assumed that a 'non-specific' noradrenaline reuptake mechanism was responsible for the reduction in renal nerve sympathetic activity, mean heart rate, and clearance of plasma noradrenaline after the administration of high doses of fluvoxamine in anaesthetised rabbits. The assumption was based on the observation that the serotonin reuptake was already maximally blocked at lower doses of fluvoxamine.

The patients in the present study were all severely depressed. On group level, both antidepressants induced a significant reduction of depressive mood. Severity of depression had a positive overall effect on mean HR in the imipramine group, but the increase in mean HR due to imipramine treatment was not mediated by changes in depressive mood. In the fluvoxamine group severity of depression had a positive overall effect on mean SBP during orthostatic challenge, and mean DBP during both supine rest and orthostatic challenge. Interestingly, severity of depression was no proper determinant of any of the variability parameters or BRS, at least not in the linear regression models we applied. The discrepancy between the effect of severity of depression on mean HR and on HR variability is to a certain extent supportive for the statement of Lehofer et al. (1997) that depression is related to an elevated intrinsic HR level (=the HR present when there is no control of the autonomic nervous system at all) rather than to alterations in the autonomic cardiac modulation. We could not confirm the finding of Balogh et al. (1993) that improvement of depressive mood contributes to changes in cardiovascular parameters after antidepressant treatment.

6 Conclusions

Sympathetic and parasympathetic activity is reduced in depressed patients after imipramine and fluvoxamine treatment, although the effects of fluvoxamine were much less pronounced. In the imipramine group severity of depression was overall, positively related to mean HR levels and in the fluvoxamine group to mean BP levels. Depressive mood had no influence on changes in the cardiovascular parameters due to antidepressant treatment. The effect of fluvoxamine on autonomic cardiac activity needs to be further clarified and its clinical relevance should be studied, especially in relation to the risk of cardiovascular disease in depression. Our findings suggests that in depressed patients alterations in cardiovascular variability and BRS after antidepressant treatment should be attributed to the pharmacological effects of the antidepressants rather than to changes in depressive mood itself.

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Chapter 7

Discussion

1 Introduction

This thesis addresses the spontaneous pattern of motor activity and autonomic cardiac functioning in healthy subjects and patients with a major depressive disorder. The general aim of the presented studies was to obtain insight in the psychomotor and autonomic cardiac dysfunction in major depression, and to establish the potential determinants. In addition, the relevance of the parameters of spontaneous motor behavior and parasympathetic activation as indirect (peripheral) indicators of the cholinergic dysfunction in depressed patients was explored. The patients were studied during a psychotropic drug free period and after double blind treatment with either the tricyclic antidepressant (TCA) imipramine or the selective serotonin reuptake inhibitor (SSRI) fluvoxamine. Wrist-actigraphy was used to assess the 24-hour pattern of motor activity and spectral analysis was applied to obtain information about the autonomic (sympathetic and parasympathetic) regulation of the cardiovascular system. In this chapter the findings of the studies are summarised, discussed and integrated, the methods of the studies are critically reviewed and recommendations for future research are done.

2 Motor activity in major depression

2.1 Profile of the 24-hour pattern of motor activity

In the second chapter of this thesis the shape or (in statistical terms) the time trend of the daily pattern of motor activity was specified in 99 healthy control subjects between 20-70 years. The daily pattern was assessed by monitoring the 24-hour motor activity with a wrist-actigraph for 3 consecutive days and nights. On visual inspection, the pattern was characterised by a large increase of motor activity in the early morning, a peak of motor activity in the late afternoon, and a gradual decline during the evening and night. Random regression analyses demonstrated that the shape of the diurnal pattern could be modelled by a complex function of six time effects, indicating that the estimated pattern was characterised by a linear time trend and 5 points of inflexion. The increase in motor activity in the early morning and a decline in motor activity during the evening and night are in line with previous studies to the profile of the 24-hour motor activity in healthy subjects (Renfrew et al., 1987; Lieberman et al., 1989). Support for a complex time trend was found in a study of Brown et al. (1990), who observed in 23 healthy subjects between 22 and 54 years, on the basis of cosinor analyses, that the waveform of the circadian rhythm of motor activity is not quite sinusoidal.

In chapter 4 the 24-hour pattern of motor activity was compared between healthy subjects and unmedicated depressed patients with a focus on alterations in mean motor activity levels, fragmentation of motor activity and immobility in patients. However, on visual inspection of figure 1 in chapter 2 and figures 1 and 2 in chapter 5 it is clear that there is an essential difference in the 24-hour profile between healthy subjects and unmedicated depressed patients (see also Tulen et al., 2001). In contrast to the healthy subjects, the diurnal pattern of the unmedicated depressed patients was not characterised by a motor activity peak in the late afternoon. This difference in the 24-hour profile was confirmed by explorative statistical analyses that indicated that the time trend in unmedicated depressed patients may be less complex than in healthy subjects and that it can be estimated by a linear trend and 2 points of inflection.

The patients were hospitalised and many patients attended the closed ward during the medication free period. They followed a structured day schedule with fixed hours for eating, therapy, visiting, and in bed- and out-bed times. Thus, the 24-hour motor activity of the patients was measured in a rather controlled environment. In contrast, healthy subjects followed their normal activity regime at home, work and college. However, occupational activities were always performed during office hours. The difference in the profile of the daily pattern supports the assumption that the motor activity peak in the afternoon was related to returning home from work or college.

2.2 Differences between healthy subjects and unmedicated depressed patients

In chapter 4 we compared the 24-hour pattern of motor activity between 64 healthy subjects (33 males and 31 females; mean age = 48.5) (control group 1) and 58 unmedicated patients (18 males and 35 females; mean age = 52.1) with a major depressive disorder (subtype: unipolar). The mean (SD) score on the 17 item version of the Hamilton Rating Scale of Depression (HRSD) (Hamilton, 1967) was 27.2 (4.6), which indicates that the patients were severely depressed. We optimised the study design by measuring a large sample of patients, all suffering from one subtype of depression, by measuring the motor activity during three consecutive days and nights, by controlling for age and gender differences, and by restricting the measurements as far as possible to weekdays to rule out a weekend effect. In comparison to the healthy subjects, the patients had lower motor activity levels during the wake period and higher activity levels during the sleep period. In addition, during the wake period the patient group showed a reduced fragmentation of motor activity and during sleep a decreased immobility. The reduced motor activity level and fragmentation of motor activity during daytime are consistent with the findings in unmedicated depressed

patients reported by Wehr et al. (1980), Wolff et al. (1985) and Van Londen et al. (1998).

As discussed before, there was a difference in study environment between patients and healthy subjects (hospital setting versus home environment). However, we questioned whether the depressed patients at the time of the baseline measurement would have been more active in their home environment than at the ward, in view of their severe depression. It is more likely that it is the other way around; the patients were more active at the ward than they would have been in their home environment, because from the first day of admission they were stimulated by the nursing staff to perform all kind of activities. Beacke et al. (1982) considered that occupational activities, sport, and other physical activities during leisure time are the three components that determine habitual physical activity. In healthy subjects occupational activities may have had an important influence on the morning and evening motor activity, but according to the Baecke questionnaire all subjects had daily occupations with low activity levels (e.g. clerical work, teaching, studying, housework, medical practise, and occupations with a university education). Van Londen et al. (1998) found nearly the same patient data in a group of mainly depressed out-patients. This supports the assumption that major depressive disorder affects the 24-hour motor activity and indicates that the influence of study environment may play a minor role.

Prior research in patients without antidepressant treatment (Royant-Parola et al., 1986; Raoux et al., 1994) and a previous study of our own using motor activity data of an unmedicated group depressed patients, including the patients examined in chapter 4 (Volkers et al., 2000), demonstrated that objective ratings of severity of depression is no determinant of the interindividual variation in motor activity parameters assessed by wrist-actigraphy. In chapter 4 the unmedicated depressed patient group was divided in subgroups with specific clinical features according to the research diagnostic criteria (RDC) (Spitzer et al., 1978) as measured by the Schedule for Affective Disorder and Schizophrenia (SADS) (Endicott and Spitzer, 1978). The presence of high anxiety and psychotic features was not related to the motor activity parameters, but agitation and retardation were independent determinants of the mean motor activity level and fragmentation of motor activity. Agitation was positively related to motor activity levels during wake, whereas retardation negatively to motor activity levels during both wake and sleep. Furthermore, retardation was related to less fragmentation of motor activity during wake. The latter results confirm the negative relationship between clinical ratings of retardation (Salpêtrière Retardation Rating Scale (SRRS) of Widlocher (1983) and daytime activity levels in depressed patients free of antidepressants reported by Van Londen et al. (1998). Raoux et al.

(1994) also found this relationship but only in patients who later on showed a therapeutic response to antidepressant treatment and not in nonresponders. In contrast, the relationship between retardation and lower motor activity levels was not replicated by Royant-Parola et al. (1986). The relationship between clinical ratings and motor activity parameters in unmedicated depressed patients is not well documented. Only Joffe et al. (1982) studied the 24-hour motor activity in relation to hyperactivity scores in depressed patients, but this was restricted to the period during antidepressant treatment and not before. They found a positive relationship between hyperactivity scores and daytime motor activity counts.

Summarising, motor activity levels in unmedicated depressed patients are lower during wake and higher during sleep than in healthy subjects. The patients also showed a reduced fragmentation index during wake and a decreased immobility during sleep. Within the patient group agitation was positively related to levels of motor activity and retardation negatively. The motor activity parameters were not associated with the presence of high anxiety or psychotic features.

2.3 Effect of imipramine and fluvoxamine on the 24-hour motor activity

In chapter 5 the 24-hour motor activity was investigated in 52 depressed patients during a psychotropic free period and after 4 weeks of adequate double blind treatment with either the TCA imipramine (n=25) or the SSRI fluvoxamine (n=27). At the start of the baseline measurement the average duration of the medication free period was 11 days. In patients treated with imipramine, as well as fluvoxamine there was a significant decrease in severity of depression (HRSD score) and psychomotor retardation (SRRS score), but a nonsignificant decrease in agitation (score on the agitation item of the HRSD). In addition, the patients treated with imipramine showed an increased motor activity level during wake and a higher fragmentation index during sleep. The treatment with fluvoxamine did not result in alterations in the 24-hour motor activity. Post-hoc analyses demonstrated that the increase in motor activity after imipramine was not modified by either changes in severity of depression or in retardation and agitation scores.

So far, few studies have quantified the effects of antidepressants on the 24-hour motor activity in depressed patients (Teicher, 1995). There are several older studies to the effect of lithium and amitriptyline treatment (Kupfer et al., 1974; Weiss et al., 1974; Kupfer et al., 1975; Heninger and Kirstein, 1977) that showed that these antidepressant attenuated the increased motor activity levels of predominantly agitated depressed patients and elevated the motor activity levels of predominantly retarded depressed patients. Later studies demonstrated that depressed patients showed higher motor activity levels after a combined treatment with TCAs and

benzodiazepines (Raoux et al., 1994), and less periods of immobility during day- and nighttime (Raoux et al., 1994; Royant-Parola et al., 1986; Benoit et al., 1985). Moreover, the study of Joffe et al. (1987) reported that the treatment with carbamazepine in 19 depressed patients (15 bipolar, 3 unipolar, and 1 schizoaffective) tended to increase the total 24-hour motor activity level in responders, but not in nonresponders. Yet, there is one previous study that compared patients treated with a TCA with patients treated with a SSRI. Stanley et al (1999) reported that after 10 days patients treated with dothiepin (TCA) had lower motor activity levels than patients treated with fluoxetine (SSRI). The lower levels after dothiepin were explained by the sedative side effects of dothiepin. A shortcoming of this study was that no medication free baseline period was incorporated and that 10 days are relatively short to evaluate the effect of antidepressant treatment because after several weeks patients may develop tolerance to sedative side effects.

Changes in the motor activity pattern have been considered to be related to the improvement of depressive mood (Kupfer et al., 1974; Raoux et al., 1994; Royant-Parola et al., 1986; Joffe et al., 1987; Benoit et al., 1985). This is not in line with our findings that clinical ratings of depressive mood, retardation and agitation were no determinants of the increase in motor activity after imipramine. Previously, Joffe et al. (1987) also found no correlation between changes in the level of motor activity and alterations in the clinical ratings of motor hyperactivity, motor retardation, anxiety, excitement, and tension in therapeutic responders and nonresponders. Because the improvement of clinical state due to imipramine and fluvoxamine was not related to changes in the motor activity parameters, we proposed that the 24-hour motor activity was mainly influenced by the pharmacological action of the antidepressants. In rats prolonged treatment with antidepressants, especially with TCAs, was found to have a stimulating effect on overt motor behavior (Overstreet et al., 1995; West and Weiss, 1998). It was emphasised that imipramine has cholinergic and (nor)adrenergic properties, but fluvoxamine not. The relevance of anticholinergic actions of antidepressants for the stimulation of decreased overt behavior is further discussed in section 4.

2.4 Role of Harm Avoidance and Reward Dependence

In chapter 2 we studied the effect of the temperament dimensions of the Tridimensional Personality Questionnaire (TPQ) of Cloninger (1987, 1993, 1994) on the diurnal pattern of motor activity in healthy subjects. Harm Avoidance and Reward Dependence influenced the overall level of motor activity, but did not affect the shape of the 24-hour pattern. Individuals with high scores on Harm Avoidance (the tendency to be fearful, tense, apprehensive, and passive) demonstrated lower

motor activity levels than individuals with low scores on this temperament trait. Individuals with high scores on Reward Dependence (the tendency to be eager and please others, tenderhearted, dedicated, warmly, dependent and sociable) had higher overall motor activity levels than subjects with low scores on Reward Dependence. Novelty Seeking and Persistence had no significant effect on the 24-hour motor activity.

This is the first study that investigated in healthy adult subjects the relationship between personality and the spontaneous pattern of motor activity. Biological based personality theories have put forward relationships between neurophysiological and neuroendocrine parameters (Eysenck, 1967; Zuckerman et al., 1980; Cloninger, 1987), but not with overt motor behavior. Because Harm Avoidance is hypothesised to be linked to the inhibition of behavior in order to avoid punishment, novelty and frustrative nonreward (Cloninger, 1987), higher scores on Harm Avoidance were expected in advance to be related to lower overall levels of motor activity. Cloninger (1994) stated that Reward Dependence is related to social behavior, such as seeking social contact and communicating with other people. The relationship between social behavior and higher motor activity levels was previously found by Buss et al. (1980) in young children. In this perspective, it is interesting to mention that prolonged SSRI treatment may have an effect on social behavior: paroxetine administration enhanced behavioral indices of affiliation behavior in healthy subjects (Knutson et al., 1998). However, this was not found after fluoxetine (Gelfin et al., 1998). Theoretically, fluvoxamine could have increased the motor activity level in the study of chapter 5 by improving social behavior, but the unchanged motor activity levels provided no support for this argumentation.

The data of the healthy subjects are relevant for the interpretation of reduced daytime motor activity in depressed patients. Many studies demonstrated that Harm Avoidance scores are lower in depressed patients than in healthy subjects (Brown et al., 1992; Joffe et al., 1993; Hansenne et al., 1999; Marijnissen et al., 2001). In depressed patients there is no evidence that depressive mood is related to lower scores on Reward Dependence, but a recent study in healthy students showed that self-ratings of depression were negatively correlated with scores on Reward Dependence (Naito et al., 2000). Unfortunately, the personality data of the depressed patients of our study still need to be analysed. During the medication free period the motor activity levels in the patients were lower than in healthy subjects, but remarkably after imipramine and fluvoxamine treatment the levels remained reduced. Although the lowered motor activity levels after treatment may be explained by the incomplete improvement of clinical state of 71% of the patients and the hospital environment, it seems reasonable to hypothesise that higher scores of Harm

Avoidance may contribute to lower basal motor activity in major depressive disorder. To obtain insight in this issue, it is recommended to follow depressed patient more frequently during their hospital stay and after discharge in their home environment.

2.5 Definition of agitation and its relationship with retardation

One reason for the lack of studies to the relationship between clinical ratings of agitation and objective measures of 24-hour motor activity in depressed patients is the absence of a clear definition of the phenomenon of agitation in major depressive disorder (Sobin and Sackeim, 1997; Lemke and Hesse, 1998; Lemke et al., 1999). Consequently, there are no rating scales available that specifically measures agitation, apart from the 18-item CORE questionnaire of Parker and Hadzi-Pavlovic (1996) for the psychomotor disturbance in depression which comprises an agitation subscale of 5 items (facial apprehension, facial agitation, motor agitation, verbal stereotype, and stereotyped movements). As a result, global items of commonly used clinical scales such as the Hamilton Rating Scale of Depression (HRSD) are frequently applied to obtain an impression of agitation in depressed patients. Psychomotor agitation is characterised by several observable behavioral manifestations, but it is unknown which of these manifestations are reflected in a positive score on one single item (Sobin and Sackeim, 1997).

Lemke et al. (1999) stated that retardation and agitation are not mutually exclusive phenomena and that they need to be measured as independently varying phenomena. Dantchev and Widlocher (1998) emphasised that mania instead of agitation is the opposite of retardation, and that retardation and agitation are two manifestations of a broader psychomotor dysfunction. The increase in activity, flight of ideas and distractibility observed in mania would be more the reverse of retardation than agitation, while agitation was postulated to be more the result of other causes, mainly anxiety. Our data support the idea that retardation and agitation are two distinct manifestations, because 10 of the 58 unmedicated depressed patients presented retardation and agitation simultaneously. Additionally, we found opposite effects of retardation and agitation on motor activity level during wake that were independent of each other. Furthermore, our results support the suggested relationship between agitation and anxiety because all patients with agitation (n=14) demonstrated high anxiety. Parker and Hadzi-Pavlovic (1996) have a contradictory hypothesis about the relationship between agitation and retardation. Factor analyses showed that the scores on the retardation and agitation subscales of the CORE questionnaire were not related, but they concluded that this does not necessarily mean that agitation occurs independently of retardation in the clinical context. Based on clinical observation, it was suggested that agitation is probably superimposed on

retardation (dependent relationship). In our sample of unmedicated depressed patients participating in the study of chapter 4 this seems not the case, because 4 of the 14 agitated patients were not classified as retarded.

2.6 Method of wrist-actigraphy

The wrist-actigraph is a valid and reliable method to monitor the spontaneous pattern of motor activity in a natural environment when motor activity is monitored for at least three consecutive day and nights (Tryon, 1991; Patterson et al., 1993; Middelkoop et al., 1997a; Middelkoop and Sadeh, 1997b). To increase the validity of the data in the presented studies the total measurement period was extended to four days, of which the first day was used to acclimatise subjects to wearing the actigraph. Although the actigraphs were calibrated to produce the same output, in practise variation occurred in the measured motor activity counts between different devices. To minimise this difference we standardised the positioning protocol, used the same actigraph for repeated measurements within patients, and took care that all actigraphs were used with the same frequency. The wrist-actigraph that was used in our studies was comfortable to wear as wristwatch, and only a small number of patients and a few healthy subjects experienced wearing the wrist-actigraph as stressful and unpleasant. Some patients were paranoid about the real function of the actigraph; e.g. they thought they were spied on or reported that they felt electric stimuli that were induced by the actigraph. There are now advanced wrist-actigraphs (e.g. Actiwatch of Cambridge Neurotechnology) available that have a more compact size, weight less, have an increased internal memory capacity and are waterproof or water resistant. For practical and ethical reasons we measured the 24-hour motor activity in the depressed patients two times, before and after treatment, but the features of the new devices may offer the opportunity to monitor the 24-hour motor activity for a period of several weeks in these patients.

Future studies to the spontaneous pattern in motor activity in depressed patients may also benefit of the optimised bandpass filters of the new devices; for instance the Actiwrist has a bandpass filter of 3.0-11.0 Hz. Van Someren et al. (1996) recommended that motor activity data will gain validity when the highpass filter of single axis wrist-actigraphs, like the one we used, is increased from 0.25 to 0.5 Hz and the lowpass filter from 3.0 to 11.0 Hz. A highpass filter > 0.05 was suggested to reduce the contribution of the gravitation force and prevent a positive bias for motor activity levels in subjects with a low frequency of movement accelerations. Furthermore, Van Someren et al. (1996) found that accelerations of wrist-movements are not limited to very low frequencies, but range between the 0.25 to 11.0 Hz.

3 Autonomic cardiac functioning in major depression

3.1 Differences between healthy subjects and unmedicated depressed patients

In chapter 4, we also compared the autonomic regulation of the cardiovascular system during supine rest between 51 healthy subjects (25 males and 26 females; mean age 45.7) (control group 2) and 54 unmedicated depressed patients (19 males and 35 females; mean age = 52.1). The technique of spectral analysis was applied to unravel sympathetic and parasympathetic processes of the cardiovascular regulation. On the day of the cardiovascular measurement, patients were on average medication free for 12 days. The patients demonstrated an increased mean heart rate (HR) and diastolic blood pressure (DBP), but no alterations were found with respect to HR power in the mid-frequency band (MF: 0.07-0.14 Hz) and high-frequency band (HF: 0.15-0.50 Hz), systolic blood pressure (SBP) power in the MF band and baroreflex sensitivity (modulus). This study supported the suggestion that major depressive disorder is related to alterations in the cardiovascular system, but the parameters for cardiovascular variability and baroreflex sensitivity were not different indicating no alterations in sympathetic and parasympathetic processes.

In the late 1980s and early 1990s Dalack and Roose (Roose et al., 1989; Dalack and Roose, 1990; Roose and Dalack, 1992;) proposed that HR variability in the HF range was decreased in depressed patients probably due to a reduced parasympathetic activity. A decreased HR variability may explain in part the increased risk of cardiovascular morbidity and mortality in major depressive disorder (Glassman and Shapiro, 1998; Musselman et al., 1998). However, the majority of studies in unmedicated depressed patients have reported less evidence for alterations in HR and BP variability or baroreflex sensitivity (Rechlin et al., 1994b; Lehofer et al., 1997; Moser et al., 1998; Tulen et al., 1996a; Yeragani, 1991). Similar to our results, these studies did report an increase in mean HR in depressed patients. Lehofer et al. (1997) suggested that the elevated mean HR levels might derive from an increased setpoint (a higher intrinsic HR), rather than from reduced parasympathetic activity.

Cigarette smoking was found to be associated with increased mean HR and BP levels and BP variability, and decreased HF variability of HR and baroreflex sensitivity (Niedermaier et al., 1993; Mancia et al., 1997; Gerhardt et al., 1999; Ragueneau et al., 1999; Hayano et al., 1990). To avoid an acute effect of smoking, all participants were instructed not to smoke on the morning of the cardiovascular measurement. The nursing staff took care that the patients did not forget this instruction or secretly smoked a cigarette. We do not expect a large bias of smoking status on the cardiovascular data of the patients, because the number of smokers among the depressed patients (42%) was nearly equal to that of the healthy control

group (about 45%) (see chapter 3). However, a confounding effect of smoking status can not be ruled out completely, because the percentage of subjects who smoked ≥ 20 cigarettes differed between patients (27%) and controls (12%). This difference was caused by the difficulty to recruit heavy smokers for the healthy control group, especially in the age category > 45 years.

Although there were no differences between healthy subjects and unmedicated depressed patients in cardiovascular variability or baroreflex sensitivity on group level, within the patient group the presence of agitation was related to higher mean levels of HR and SBP and the presence of retardation to lower mean levels of SBP and DBP. Both agitation and retardation did not influence the HR and SBP power data or the baroreflex sensitivity index. The presence of high anxiety and psychotic symptoms was not related to any of the cardiovascular parameters. Previously, Thayer et al. (1998) and Watkins et al. (1999) suggested that psychomotor retardation, through decreased physical activity, may result in altered autonomic cardiac functioning, especially decreased HR variability. The relationship between retardation and reduced HR variability was not confirmed in our study. Stein et al. (1994) concluded in their review that, in general, the mean HR is elevated in subgroups of depressed patients with symptoms of agitation or comorbid anxiety disorders, but not in retarded patients. They argued that the increased HR may originate from increased sympathetic activity and/or decreased parasympathetic activity. However, we did not find that the increase in mean HR in the agitated patients was accompanied by changes in cardiovascular variability or altered baroreflex sensitivity, neither was high anxiety during the current episode of depression related to higher mean HR or changes in one of the other cardiovascular parameters.

Further exploration of the data of this study by linear regression analyses indicated that also the score on the tension/anxiety scale of the shortened Profile of Mood State (POMS) (Shacham, 1983; Wald and Mellenbergh, 1990) was not related to the cardiovascular parameters. The absence of a relationship between anxiety and cardiovascular parameters is in contrast with the study of Tulen et al. (1996b), who demonstrated in unmedicated depressed patients that high scores on trait anxiety were related to an increased HR and a decreased HF power of HR. Like our results, Watkins et al. (1999) and Moser et al. (1998) found no relationship between state and trait anxiety and HF variability of HR in unmedicated depressed patients, but on the other hand Watkins et al. (1999) observed a negative correlation between state anxiety scores and baroreflex sensitivity. It seems that the observed relationship between anxiety disorders, for example panic disorder, and increased MF variability of HR and decreased HR variability (Yeragani, 1995; Gorman and Sloan, 2000) may

not be simply generalised to a relationship between high anxiety (state and trait) scores and enhanced sympathetic activity and reduced parasympathetic activity in major depressive disorder.

3.2 Effect of antidepressant treatment and depressive mood on autonomic regulation. In chapter 6 the effect of imipramine, fluvoxamine, and depressive mood on the autonomic regulation of the cardiovascular system was examined in 52 depressed patients (20 males and 32 females; mean age = 52.5 years) during a medication free period and after 4 weeks of double blind treatment at therapeutic plasma levels. Cardiovascular parameters were obtained during supine rest and orthostatic challenge (60% head-up tilt). After imipramine, patients showed higher mean HR levels and decreased overall HR variability (variation coefficient), MF and HF power of HR, MF power of SBP and baroreflex sensitivity. In the imipramine group, severity of depression was positively related to the mean HR (data were combined for the baseline and post-treatment period), but improvement of depressive mood was not related to changes in mean HR after treatment. There was no effect of fluvoxamine on mean HR, SBP and DBP. However, after fluvoxamine, patients did demonstrate a decreased overall HR and SBP variability, MF and HF power of HR, and MF power of SBP. In this treatment group severity of depression was positively related to mean BP levels.

The increase in mean HR and decrease in HF variability of HR after TCAs are considered to be caused by the anticholinergic properties of this type of antidepressant (Jakobsen et al., 1984; Yeragani et al., 1992; Rechlin et al., 1994a; Rechlin et al., 1994b; Tulen et al., 1996a). There were no significant changes in the mean SBP and DBP, but the decreased MF power of SBP suggested that imipramine also reduced sympathetic activity. This decrease of SBP power was also reported in the only previous study to the effect of imipramine on BP variability (Tulen et al., 1994). Veith et al. (1983) found in depressed patients after long-term treatment with several TCAs (imipramine, doxepin, and amitriptyline) increased plasma noradrenaline levels pointing to an activation of the sympathetic nervous system. However, in a later study it was found that desipramine, given for 2 days, resulted in a reduction of plasma noradrenaline levels in healthy subjects and depressed patients (Veith et al., 1994). This was assumed to be compatible with a short-term inhibition of sympathetic activity. However, the initial inhibition was reversed in the patients after several weeks of treatment with an associated rise in plasma adrenaline, which was not caused by increased extravascular and vascular rates of noradrenaline, but attributed to a reduction of plasma clearance. In this view, it should be stressed that indices of sympathetic activity (for instance catecholamine levels, muscle sympathetic

nerve activity, and BP variability in the MF band) are not just mutually exclusive but need to be regarded as complementary (Tulen et al., 1994; Pagani and Malliani, 2000). Even cardiovascular parameters of sympathetic activity such as the MF variability of SBP and the Pre-ejection Period (PEP) provide distinct, but additional information about sympathetic activity. Recently, Schachinger et al. (2001) found evidence that SBP variability around the frequency of 0.10 Hz is a marker of central sympathetic activity and PEP of peripheral sympathetic activity.

Based on the available studies, Roose et al. (1998) concluded that SSRIs slightly decrease the HR, do not routinely slow intracardiac conduction, do not affect supine or standing BP levels or induce orthostatic hypotension. However, our study showed that fluvoxamine treatment diminished HR and SBP variability indicating a suppression of sympathetic and parasympathetic activity similar to imipramine, although the effects of fluvoxamine were much less pronounced. This is in contrast with the study of Rechlin (1994c) who reported after 14 days fluvoxamine treatment in a smaller group of depressed patients (n=8) no effect at all on HR variability. Similar to our results, a decreased HR variability was recently reported in depressed patients and in patients with a panic disorder after treatment with the SSRI paroxetine (Yeragani et al., 1999; Lederbogen et al., 2001). However, the pharmacological profiles of fluvoxamine and paroxetine are not quite similar, since paroxetine is known to have cholinergic properties. Future studies should explore the effect of fluvoxamine on autonomic cardiac functioning in patients after several months or even years, because the cardiovascular effects of fluvoxamine may become more prominent over time.

After 4 weeks of antidepressant treatment, improvement of depressive mood had no favourable effect on the cardiovascular parameters. This is in contrast with the statement of Balogh et al. (1993) that antidepressants, especially antidepressants without strong cardiovascular effects, have a beneficial effect on the cardiovascular system through their efficacy on depressive mood. The HRSD score decreased significantly in both treatment groups, but as discussed in chapter 6 only about 30% of the patients showed a therapeutic response. It is possible that the number of responders in our study was too small to detect a relationship between improvement of depressive mood and alterations in autonomic regulation.

3.3 Role of risk factors

A higher prevalence of one or more risk factors in depressed patients may contribute to alterations in the autonomic regulation, in addition to clinical state and antidepressant treatment. Research on the role of risk factors in the autonomic regulation of healthy subjects may provide more insight in the relevance of these

factor for autonomic cardiac dysfunctions in major depressive disorder. In chapter 3 the effect of age, gender and risk factors on the autonomic modulation was studied in 65 healthy subjects between 20-59 years of age. Mean HR, SBP and DBP, HR and SBP variability, and baroreflex sensitivity were measured during supine rest and orthostatic challenge (60% head-up tilt). Older subjects showed reduced overall HR variability, MF and HF power of HR as well as baroreflex sensitivity. Higher total and high density lipid (HDL) cholesterol levels and lower levels of habitual physical activity were related to a higher mean HR. Furthermore, the body mass index was positively related to mean SBP and DBP, and negatively to the overall HR variability. Smoking was also negatively related to overall HR variability.

The decrease in HR variability and baroreflex sensitivity by age has been reported in previous studies (Lipsitz et al., 1990; Ryan et al., 1994; Laitinen et al., 1998), but it was striking that model fit analyses indicated that age and gender were no suitable determinants of the overall SBP variability and the MF power of SBP. From a physiological point of view, it is difficult to explain why age is related to HR variability, but not to BP variability, while all these parameters play a role in the modulation of the cardiovascular system. One possibility is that the relationship between age and BP variability should be estimated by a more complex function, instead of the applied linear function. The risk factors influenced mean HR and BP levels, but they had only minor effects on cardiovascular variability and baroreflex sensitivity. Yet, there have been too many equivocal findings reported to make final statements about whether and which risk factors are related to cardiovascular variability and baroreflex sensitivity.

The study of chapter 3 was performed based on the hypothesis that depression is related to an increased prevalence of cardiovascular risk factors, which may contribute to the increased risk of cardiovascular disease in major depression (Glassman and Shapiro, 1998; Musselman et al., 1998). Smoking is the most important risk factor for cardiovascular disease in major depressive disorder (Breslau et al., 1998; Glassman and Shapiro, 1998). There exist several theories regarding the role of smoking in major depression. The psychoactive effect of nicotine may elevate mood and the sense of well-being. Therefore depressed patients would self-medicate with cigarettes (Hayward, 1995; Breslau et al., 1998). Smoking may increase the vulnerability to major depression by influencing neurotransmitter systems involved in the development of depression. Furthermore, genetic factors may predispose to both conditions (Kendler et al., 1993).

Depression may also be related to disturbances in the lipid metabolism (Wardle, 1995; Morgan et al., 1993; Horsten et al., 1997; Maes et al., 1997; Chen et al., 2001). Information on the relationship between depression and alterations in the

body mass index and habitual physical activity is limited. However, Ariyo et al. (2000) found recently in a large community study that physical activity was inversely related to depression scores and that a higher body mass index was related to higher depression scores.

Additional analyses revealed that the patient group studied in chapter 4 consisted of 38 nonsmokers and 28 smokers (the smoking status of 1 patient was unknown). Four patients smoked less than 10 cigarettes per day, 6 patients between 10 and 20 cigarettes per day and 18 patients ≥ 20 cigarettes per day. The smoking rate of 42% was somewhat lower than the 50% suggested by Hayward (1995), but higher than the 20-30% observed in the general population. In our patient group, the mean values of total cholesterol (5.1 mmol/l), HDL cholesterol (1.4 mmol/l), low density cholesterol (LDL) (3.4 mmol/l), and triclyceride (1.3 mmol/l) were in the normal range and showed much similarity with the mean values of healthy subjects included in the study of chapter 3. The mean value of the body mass index in our patient groups was 27.5 kg/m^2, which is above the criterium of ≥ 0.25 kg/m^2 for moderate overweight (WHO, 1995), while that of the healthy subjects was 23.9 (kg/m^2). In contrast, we found in a pilot study that the habitual physical activity of the last year did not differ between depressed patients and healthy subjects.

To conclude, risk factors influence mean HR and BP levels in healthy subjects, but their effect on HR and BP variability and baroreflex sensitivity is limited. Preliminary data suggest that the smoking rate and body mass index were increased in the depressed patient group of our studies.

3.4 Respiration

HR and SBP power data were obtained during spontaneous breathing, although the subjects were asked to breathe regularly and not to speak. The unmedicated depressed patients showed, on average, a significantly higher respiratory frequency than the healthy subjects. Higher respiratory frequencies and smaller tidal volume (depth of breathing) were found to reduce the HF power of HR (Brown et al., 1993). This finding resulted in the recommendation to control the breathing frequency, for instance by a metronome, in order to improve the interpretation of spectral data obtained in experimental settings.

In our earlier studies, depressed patients experienced controlled breathing as difficult and uncomfortable leading to increase mean HR and BP levels. Furthermore, controlled breathing in this patient group is hampered by the presence of a hyperventilation-like pattern in some of the patients. Recently, Bloomfield et al. (2001) wrote a critical note on the study of Brown et al. (1993). They demonstrated that metronome-guided breathing in comparison to spontaneous breathing induced

only a small decrease in HF power of HR. This decrease appeared to be extremely small in comparison to the large difference in HF power of HR they found between healthy subjects and cardiac patients. Furthermore, within these groups HF power was relatively constant across the range of typical breathing frequencies. Therefore, Bloomfield et al. (2001) argued the need of controlled breathing, because it also introduces other biases in the cardiovascular measurement.

Time-frequency analysis of cardiovascular variability may elucidate the relationship between respiration and HR variations (Van Steenis and Tulen, 1996; Novak and Novak, 1993a, 1993b). This analysis presents the power of a signal in time and frequency simultaneously (Cohen, 1995). An advantage of this type of analysis above the spectral analysis is that it does not assume stationary signals and that is can describe transient and sustained changes in frequency and amplitude over time. Recently, Van Steenis et al. (submitted) developed a new technique that provides simultaneously the instantaneous amplitude and frequency of a signal in time within a narrow frequency band, for instance the HF band. This technique may be used to make a comparison between the time-frequency data of the respiratory and HR signal, and may allow us to make statements about the extent to which changes in the respiratory frequency and depth are followed by alterations in frequency and amplitude of the HR signal.

4 Cholinergic dysfunction in depressed patients

Since Janowsky and colleagues proposed the cholinergic hypothesis of depression (Janowsky et al., 1972), considerable evidence has accumulated supporting a role of the cholinergic system in the etiology of depression (Janowsky et al., 1994; Janowsky and Overstreet, 1995). Increased central cholinergic activity and/or cholinergic hypersensitivity through an increased number of postsynaptic receptors or activation of the intracellular second-messenger system may be responsible for depressed mood, behavioral inhibition (e.g. reduced spontaneous motor activity) and changes in the REM sleep observed in depressed patients. As a consequence of the very rapid metabolism of acetylcholine and the absence of traceable metabolites, it is difficult to measure central cholinergic functions directly. Central cholinergic agents have an effect on many physiological variables, including polysomnographic, psychomotor, cardiovascular, papillary, neuroendocrine, neurohormonal, thermoregulatory, salivary and sweat parameters (Dilsaver, 1986; Akselrod et al., 1985; Janowsky et al., 1994; Janowsky and Overstreet, 1995). Because of their sensitivity to cholinergic

manipulations, these parameters may be appropriate (peripheral) markers of the central cholinergic function.

In humans, the reduction of motor behavior induced by central cholinergic agonists and cholinesterase inhibitors is very similar to psychomotor retardation in depressed patients (Janowsky et al., 1994). In this respect, the reduced level of spontaneous motor activity during daytime in unmedicated depressed patients as described in chapter 4 may reflect a cholinergic dysfunction. Yet, it is unknown which parts of the brain are involved in the cholinergic dysfunction in depressed patients. Alterations in psychomotor activity in major depression can originate from various central cholinergic systems. In fact, the cholinergic neurons in the neostratum are interneurons that control normal motor function in interaction with nigrostriatal dopamine and striatal GABAergic neurons (Hyman and Nestler, 1993; Chau et al., 2001). In addition, cholinergic neurons in the basal forebrain have projections to limbic structures such as the hippocampus and amygdala, which are amongst others important for motivation (Hyman and Nestler, 1993; Chau et al., 2001). Finally, the reticular activating system has a distinct cholinergic component that is involved in behavioral arousal (Dilsaver, 1986).

In chapter 5 we suggested that the anticholinergic and/or (nor)adrenergic properties of imipramine were responsible for the increase in daytime motor activity after treatment. A large number of studies demonstrated that acute and chronic administration of anticholinergic drugs can cause behavioral activation in rats (Janowsky et al., 1972; Overstreet et al., 1995; Daws and Overstreet, 1999). As far as we know the effects of central anticholinergic agents on spontaneous motor behavior in humans have not been evaluated. It is also plausible that imipramine increases motor activity in depressed patients through a direct or indirect effect on other neurotransmitter systems. To illustrate, behavioral inhibition by the cholinergic agonist physostigmine was found to be rapidly reversed by stimulation of the central noradrenergic and dopaminergic system (Janowsky et al., 1994). The fact that exaggerated immobility in cholinergic hypersensitive rats could be reduced by both the TCAs imipramine and desipramine, and the SSRI sertraline points to the possibility of an interaction between muscarinic and aminergic post-receptors in the G protein function or in other aspects of the cellular second pathway (Daws and Overstreet, 1999). If this would be the underlying mechanism of increased motor activity after antidepressant treatment, the treatment period with fluvoxamine may have been too short to establish an effect. To elucidate these mechanisms the measurement of the 24-hour pattern of motor activity in depressed patients before, during and after prolonged administration of a central anticholinergic, a TCA, a SSRI,

a selective noradrenaline reuptake inhibitor (SNRI) and placebo should be performed.

Acetylcholine is an important neurotransmitter of the parasympathetic system (Powley, 1999). Blockade of the parasympathetic activity to the sinus node of the heart by acute challenges of muscarinic antagonists and vagotomy resulted in the abolishment of the HF variation of the HR (Akselrod et al., 1981,1985; Pomeranz et al., 1985; Malliani et al., 1991). Therefore, HR power in the high frequency band (0.15-0.50 Hz) is considered to be an index of parasympathetic activity (Parati et al., 1995; Task Force, 1996), but may also be an indirect marker of cholinergic activity in major depression. The study of chapter 4 showed that the HR power in the HF band was not different between unmedicated depressed patients and healthy subjects. If HF power is a marker for cholinergic activity indeed, this finding is not supportive for a cholinergic dysfunction in major depression. However, the role of the cholinergic system in parasympathetic cardiac control is complex, because an increased HF power of HR was found after low-doses of cholinergic antagonists probably due to central activation (Montano et al., 1998). For this reason, HR variability in the HF band cannot be considered to be a simple indicator of cholinergic activity.

In chapter 6 we reported that after treatment with imipramine, a reduction in HF power of HR occurred in the depressed patient group. Anticholinergic effects of imipramine were considered to be responsible for this effect. Fluvoxamine is assumed to be free of cholinergic actions, but nevertheless the patients demonstrated a decreased HF power of HR after fluvoxamine. Future studied should focus on the origin of this effect.

Dilsaver (1986) emphasised that combining peripheral markers of central cholinergic mechanisms would provide more insight in the cholinergic dysfunction in major depression. Some evidence was found in chapter 4 for a relationship between the psychomotor function and autonomic cardiac functioning in depressed patients. Overall, the unmedicated depressed patients with lower motor activity levels demonstrated higher SBP levels. Based on this finding no statements could be made about the existence of common neurobiological pathways. Challenge studies in healthy subjects investigating simultaneously the effect of cholinergic agents on the 24-hour motor activity and autonomic cardiac functioning may further clarify the relationship between motor activity and cardiovascular parameters in depression. They may also provide additional information about how central and peripheral cholinergic processes influence these parameters.

5 Conclusions

Based on the studies of this thesis, the following conclusions were drawn:

1) The 24-hour pattern of motor activity in healthy subjects is characterised by a complex time trend. The overall level of motor activity is related to Harm Avoidance and Reward Dependence, but the time trend is not affected by these personality traits.

2) Risk factors have an effect on mean heart rate and blood pressure during supine rest and orthostatic challenge in healthy subjects. The influence of these factors on heart rate and blood pressure variability and baroreflex sensitivity is restricted to a decreased overall heart rate variability in smokers and subjects with a higher body mass index.

3) There are differences in the 24-hour pattern of motor activity and the autonomic regulation of the cardiovascular system between unmedicated depressed patients and healthy subjects. Agitation is related to increased heart rate and blood pressure levels and retardation to decreased blood pressure levels in these patients. There is also a positive relationship between motor activity and blood pressure.

4) Imipramine treatment in depressed patients results in higher motor activity levels during wake and more fragmentation of motor activity during sleep. Fluvoxamine treatment does not affect the 24-hour motor activity level. The effect of imipramine may be caused by its pharmacological action, rather than by clinical improvement.

5) Sympathetic and parasympathetic activity is reduced in depressed patients after imipramine and fluvoxamine treatment, although the reduction after fluvoxamine is much less pronounced. Heart rate and blood pressure levels are positively related to severity of depression, but improvement of depressive mood does not modify changes in these cardiovascular parameters after antidepressant treatment.

References

Akselrod S, Gordon D, Ubel FA, Shannon DC, Berger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213(4504):220-222.

Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. Am J Physiol 1985;249(4 pt 2):H867-H875.

American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 4th edition. Washington, DC, USA: APA, 1994.

Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord 2000;58(1):19-36.

Angst J. Course and prognosis of mood disorders. In: Gelder MG, López-Ibor JJ Jr, Andreasen NC (eds). New oxford textbook of psychiatry. New York, USA: Oxford University Press, Inc., 2000;Vol 1:719-724.

Ariyo AA, Haan M, Tangen CM, Rutledge JC, Cushman M, Dobs A, Furberg CD. Depressive symptoms and risks of coronary heart disease and mortality in elderly Americans. Cardiovascular Health Study Collaborative Research Group. Circulation 2000;102(15):1773-1779.

Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. Am J Clin Nutr 1982;36(5):936-942.

Balogh S, Fitzpatrick DF, Hendricks SE, Paige SR. Increases in heart rate variability with successful treatment in patients with major depressive disorder. Psychopharmacol Bull 1993;29(2):201-206.

Benoit O, Royant-Parola S, Borbely AA, Tobler I, Widlocher D. Circadian aspects of motor activity in depressed patients. Acta Psychiatr Belg 1985;85(5):582-592.

Berman RM, Belanoff JK, Charney DS, Schatzberg AF. Principles of harmacotherapy of depression. In: Charney DS, Nestler EJ, Bunney BS (eds). Neurobiology of mental illness. New York: Oxford University Press, 1999:419-432.

Berntson GG, Cacioppo JT, Quigley KS. Respiratory sinus arrhythmia: autonomic origins, physiological mechanisms, and psychophysiological implications. Psychophysiology 1993;30(2):183-196.

Bijl RV, Van Zessen G, Ravelli A. Psychiatrische morbiditeit onder volwassenen in Nederland: het NEMESIS-onderzoek. II. Prevalentie van psychiatrische stoornissen. Ned Tijdschr Geneeskd 1997;141(50):2453-2460.

Bloomfield DM, Magnano A, Bigger JT Jr, Rivadeneira H, Parides M, Steinman RC. Comparison of spontaneous vs. metronome-guided breathing on assessment of vagal modulation using RR variability. Am J Physiol Heart Circ Physiol 2001;280(3):H1145-H1150.

Board F, Persky H, Hamburg DA. Psychological stress and endocrine functions. Psychsom Med 1956;18(4):324-333.

Bock R. Within-subject experimentation in psychiatric research. In: Gibbons R, Dyskens M (eds). Statistical and Methodological Advances in Psychiatric Research. New York: Spectrum Books, 1983:59-90.

Breslau N, Peterson EL, Schultz LR, Chilcoat HD, Andreski P. Major depression and stages of smoking. A longitudinal investigation. Arch Gen Psychiatry 1998; 55(2):161-166.

Brown AC, Smolensky MH, D'Alonzo GE, Redman DP. Actigraphy: a means of assessing circadian patterns in human activity. Chronobiol Int 1990;7(2):125-133.

Brown SL, Svrakic DM, Przybeck TR, Cloninger CR. The relationship of personality to mood and anxiety states: a dimensional approach. J Psychiatr Res 1992; 26(3):197-211.

Brown TE, Beightol LA, Koh J, Eckberg DL. Important influence of respiration on human R-R interval power spectra is largely ignored. J Appl Physiol 1993; 75(5):2310-2317.

Brown H, Prescott R (eds). Applied mixed models in medicine. New York: Wiley, 1999.

Bruijn JA, Moleman P, Mulder PG, Van Den Broek WW. Depressed in-patients respond differently to imipramine and mirtazapine. Pharmacopsychiatry 1999;32(3):87-92.

Bruijn JA. New better than old? Detection of differences in efficacy between treatments of depression under optimal conditions. Rotterdam, The Netherlands: Erasmus University, 2000. (thesis)

Bunney WE Jr, Davis JM. Norepinephrine in depressive reactions. A review. Arch Gen Psychiatry 1965;13(6):483-494.

Buss DM, Block JH, Block J. Preschool activity level: personality correlates and developmental implications. Child Development 1980;51:401-408.

Chapleau MW, Abboud FM. Neuro-cardiovascular regulation: from molecules to man. Introduction. Ann N Y Acad Sci 2001;940:xiii-xxii.

Chau DT, Rada P, Kosloff RA, Taylor JL, Hoebel BG. Nucleus accumbens muscarinic receptors in the control of behavioral depression: antidepressant-llike effects of local M1 antagonist in the Porsolt swim test. Neuroscience 2001;104(3):791-798.

Chen CC, Lu FH, Wu JS, Chang CJ. Correlation between serum lipid concentrations and psychological distress. Psychiatry Res 2001;102(2):153-162.

Christensen JH, Toft E, Christensen MS, Schmidt EB. Heart rate variability and plasma lipids in men with and without ischaemic heart disease. Atherosclerosis 1999;145:181-186.

Cloninger CR. A systematic method for clinical description and classification of personality variants. A proposal. Arch Gen Psychiatry 1987;44(6):573-588.

Cloninger CR, Przybeck TR, Svrakic DM. The tridimensional personality questionnaire: US normative data. Psychol Rep 1991;69:1047–1057.

Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Arch Gen Psychiatry 1993;50(12):975-990.

Cloninger CR, Przybeck TR, Svrakic DM, Wetzel RD. Applications to mood disorders. In: The temperament and character inventory (TCI): a guide to its development and use. St. Louis, Missouri: Washington University, 1994:111-116.

Cloninger CR. The genetics and psychobiology of the seven-factor model of personality. In: Silk KR (ed). Biology of Personality Disorders, 1998:63–92.

Cloninger CR (ed). Personality and psychopathology. Washington: American Psychiatric Press, Inc., 1999.

Cohen L. Time-frequency analysis. Englewood Cliffs, NJ: Prentice Hall Inc, 1995.

Dalack GW, Roose SP. Perspectives on the relationship between cardiovascular disease and affective disorder. J Clin Psychiatry 1990;51(Suppl 4-9).

Dantchev N, Widlocher DJ. The measurement of retardation in depression. J Clin Psychiatry 1998;59(Suppl 14):19-25.

Daws LC, Overstreet DH. Ontogeny of muscarinic cholinergic supersensitivity in the Flinders Sensitive Line rat. Pharmacol Biochem Behav 1999;62(2):367-380.

De Boer RW, Karemaker JM, Strackee J. Description of heart-rate variability data in accordance with a physiological model for the genesis of heartbeats. Psychophysiology 1985;22(2):147-155.

De Boer RW, Karemaker JM, Strackee J. Hemodynamic fluctuations and baroreflex sensitivity in humans: a beat-to-beat model. Am J Physiol 1987;253(3 Pt 2): H680-H689.

De Kloet ER, Rots NY, Cools AR. Brain-corticosteroid hormone dialogue: slow and persistent. Cell Mol Neurobiol 1996;16(3):345-356.

De Weme RJ, Hoeksema T, Goekoop JG. De Widlocher remmingsschaal, een nederlandse schaal voor het meten van psychomotorische remming. Acta Neuropsychiatrica 1996;8:56-63.

Dilsaver SC. Cholinergic mechanisms in affective disorders. Future directions for investigation. Acta Psychiatr Scand 1986;74(4):312-334.

Dunam, RS. The neurochemistry of mood disorders: preclinical studies. In: Charney DS, Nestler EJ, Bunney BS (eds). Neurobiology of mental illness. New York: Oxford University Press, 1999:333-347.

Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. Arch Gen Psychiatry 1978;35:837-844.

Eysenck HJ (ed). The biological basis of personality. Springfield, IL.: Charles C. Thomas, 1967.

Fagard RH, Pardaens K, Staessen JA. Influence of demographic, anthropometric and lifestyle characteristics on heart rate and its variability in the population. J Hypertens 1999;17:1589-1599.

Fairweather DB, Ashford J, Hindmarch I. Effects of fluvoxamine and dothiepin on psychomotor abilities in healthy volunteers. Pharmacol Biochem Behav 1996;53(2):265-269.

Gelfin Y, Gorfine M, Lerer B. Effect of clinical doses of fluoxetine on psychological variables in healthy volunteers. Am J Psychiatry 1998;155(2):290-292.

Gerhardt U, Vorneweg M, Riedash M, Hohage H. Acute and persistence effects of smoking on the baroreceptor function. J Auton Pharmacol 1999;18:105-108.

Gibbons JL. Cortisol secretion rate in depressive illness. Arch Gen Psychiatry 1964;10:572-575.

Gibbons RD, Hedeker D, Elkin I, Waternaux C, Kraemer HC, Greenhouse JB, Shea MT, Imber SD, Sotsky SM, Watkins JT. Some conceptual and statistical issues in analysis of longitudinal psychiatric data. Arch Gen Psychiatry 50, 739–750. Arch Gen Psychiatry 1993;50(9):739-750.

Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, Johnson J. Smoking, smoking cessation, and major depression. JAMA 1990;264(12): 1546-1549.

Glassman AH. Cigarette smoking: implications for psychiatric illness. Am J Psychiatry 1993;150(4):546-553.

Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. Am J Psychiatry 1998;155(1):4-11.

Gorman JM, Sloan RP. Heart rate variability in depressive and anxiety disorders. Am Heart J 2000;140(Suppl 4):77-83.

Grossman P, Kollai M. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: within- and between-individual relations. Psychophysiology 1993;30(5):486-495.

Gunst R, Mason R. Regression analyses and its applications; data oriented approach. New York; Dekker, 1980.

Guy W. Assessment manual for psychopharmacology. U.S. Department of Healthy Education and Welfare, Rochville 2170222, 1976.

Guyton AC. Nervous regulation of the circulation, and rapid control of arterial pressure. In: Guyton AC (ed). Textbook of medical physiology. USA: W.B. Saunders Company 1991:194-202.

Halverson CF, Waldrop MF. The relations of mechanically recorded activity level to varieties of preschool play behavior. Child Development 1973;44:678-681.

Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6(4):278-296.

Hansenne M, Reggers J, Pinto E, Kjiri K, Ajamier A, Ansseau M. Temperament and character inventory (TCI) and depression. J Psychiatr Res 1999;33(1):31-36.

Hawley CJ, McPhee S, Quick SJ, Smith VR. A review of the psychomotor effects of paroxetine. Int Clin Psychopharmacol 1997;12(1):13-18.

Hayano J, Yamada M, Sakakibara Y, Fujinami T, Yokoyama K, Watanabe Y, Takata K. Short- and long-term effects of cigarette smoking on heart rate variability. Am J Cardiol 1990;65:84-88.

Hayward C. Psychiatric illness and cardiovascular disease risk. Epidemiol Rev 1995; 17(1):129-138.

Heninger GR, Kirstein L. Effects of lithium carbonate on motor activity in mania and depression. J Nerv Ment Dis 1977;164(3):168-175.

Hewer W, Rost W, Gattaz WF. Cardiovascular effects of fluvoxamine and maprotiline in depressed patients. Eur Arch Psychiatry Clin Neurosci 1995;246(1):1-6.

Hirschfeld RM. History and evolution of the monoamine hypothesis of depression. J Clin Psychiatry 2000;61(Suppl 6):4-6.

Hohnloser SH, Klingenheben T, Van De Loo A, Hablawetz E, Just H, Schwartz PJ. Reflex versus tonic vagal activity as a prognostic parameter in patients with sustained ventricular tachycardia or ventricular fibrillation. Circulation 1994;89(3):1068-1073.

Holsboer F, Barden N. Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev 1996;17(2):187-205.

Holsboer F. Stress, hypercortisolism and corticosteroid receptors in depression: implications for therapy. J Affect Disord 2001;62(1-2):77-91.

Horsten M, Wamala SP, Vingerhoets A, Orth-Gomer K. Depressive symptoms, social support, and lipid profile in healthy middle-aged women. Psychosom Med 1997;59(5):521-528.

Huikuri HV. Heart rate variability in coronary artery disease. J Intern Med 1995; 237(4):349-357.

Huikuri HV, Ylitalo A, Pikkujamsa SM, Ikaheimo MJ, Airaksinen KE, Rantala AO, Lilja M, Kesaniemi YA. Heart rate variability in systemic hypertension. Am J Cardiol 1996;77(12):1073-1077.

Hyman SE, Nestler EJ. Overview of synaptic neurotransmission. In: Hyman SE, Nestler EJ (eds). The molecular foundations of psychiatry. Wahington, DC: American Psychiatric Press, 1993:55-93.

Jakobsen J, Hauksson P, Vestergaard P. Heart rate variation in patients treated with antidepressants. An index of anticholinergic effects? Psychopharmacology (Berl) 1984;84(4):544-548.

Janowsky DS, El-Yousef MK, Davis JM, Sekerke HJ. A cholinergic-adrenergic hypothesis of mania and depression. Lancet 1972;23;2(7778):632-635.

Janowsky DS, Risch SC. Role of acetylcholine mechanisms in the affective disorders. In: Meltzer HY (ed). Psychopharmacology. The third generation of progress. New York: Raven Press, 1987:527-533.

Janowsky DS, Overstreet DH, Nurnberger JI Jr. Is cholinergic sensitivity a genetic marker for the affective disorders? Am J Med Genet 1994;54(4):335-344.

Janowsky DS, Overstreet DH. The role of acetylcholine mechanisms in mood disorders. In: Bloom FE, Kupfer DJ (eds). Psychopharmacology. The fourth generation of progress. New York: Raven Press, 1995:945-956.

Joffe RT, Uhde TW, Post RM, Minichiello MD. Motor activity in depressed patients treated with carbamazepine. Biol Psychiatry 1987;22(8):941-946.

Joffe RT, Bagby RM, Levitt AJ, Regan JJ, Parker JD. The Tridimensional Personality Questionnaire in major depression. Am J Psychiatry 1993;150(6):959-960.

Joyce PR, Paykel ES. Predictors of drug response in depression. Arch Gen Psychiatry 1989;46(1):89-99.

Kageyama T, Nishikido N, Honda Y, Kurokawa Y, Imai H, Kobayashi T, Kaneko T, Kabuto M. Effects of obesity, current smoking status, and alcohol consumption on heart rate variability in male white-collar workers. Int Arch Occup Environ Health 1997;69(6):447-454.

Kardos A, Watterich G, de Menezes R, Csanady M, Casadei B, Rudas L. Determinants of spontaneous baroreflex sensitivity in a healthy working population. Hypertension 2001;37(3):911-916.

Kaufman JS, Asuzu MC, Mufunda J, Forrester T, Wilks R, Luke A, Long AE, Cooper RS. Relationship between blood pressure and body mass index in lean populations. Hypertension 1997;30(6):1511-1516.

Kendler KS, Neale MC, MacLean CJ, Heath AC, Eaves LJ, Kessler RC. Smoking and major depression. A causal analysis. Arch Gen Psychiatry 1993;50(1):36-43.

Kikuya M, Hozawa A, Ohokubo T, Tsuji I, Michimata M, Matsubara M, Ota M, Nagai K, Araki T, Satoh H, Ito S, Hisamichi S, Imai Y. Prognostic significance of blood pressure and heart rate variabilities: the Ohasama study. Hypertension 2000;36(5):901-906.

King R. Motivational diversity and mesolimbic dopamine: a hypothesis concerning temperament. In: Plutchik R, Kellerman H (eds). Emotion: Theory, Research and Experience. Biological foundations of Emotions. Orlando, Fl.: Academic Press, 1986:Vol 3.

King RJ, Bayon EP, Clark DB, Taylor CB. Tonic arousal and activity: relationships to personality and personality disorder traits in panic patients. Psychiatry Res 1988;25(1):65-72.

Kline NS. Clinial experience with iproniazid (Marsilid). J Clin Exp Psychopathol 1961;19(Suppl 1):72-78.

Knutson B, Wolkowitz OM, Cole SW, Chan T, Moore EA, Johnson RC, Terpstra J, Turner RA, Reus VI. Selective alteration of personality and social behavior by serotonergic intervention. Am J Psychiatry 1998;155(3):373-379.

Koskinen P, Kupari M, Virolainen J, Stjernvall J, Jolkkonen J, Tuomilehto J, Tikkanen MJ. Heart rate and blood pressure variability and baroreflex sensitivity in hypercholesterolaemia. Clin Physiol 1995;15(5):483-489.

Kuhn R. The treatment of depressive states with G22355 (imipramine hydrochloride). Am J Psychiatry 1958;115:459-464.

Kuhs H, Reschke D. Psychomotor activity in unipolar and bipolar depressive patients. Psychopathology 1992;25(2):109-116.

Kupari M, Virolainen J, Koskinen P, Tikkanen M. Short-term heart rate variability and factors modifying the risk of coronary artery disease in a population sample. Am J Cardiol 1993;72(18):897-903.

Kupfer DJ, Weiss BL, Foster G, Detre TP, McPartland R. Psychomotor activity in affective states. Arch Gen Psychiatry 1974;30(6):765-768.

Kupfer DJ, Foster FG, Detre TP, Himmelhoch J. Sleep EEG and motor activity as indicators in affective states. Neuropsychobiology 1975;1(5):296-303.

La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Baroreflex sensitivity and heart-rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 1998;351(9101):478-484.

Laird LK, Lydiard RB, Morton WA, Steele TE, Kellner C, Thompson NM, Ballenger JC. Cardiovascular effects of imipramine, fluvoxamine, and placebo in depressed outpatients. J Clin Psychiatry 1993;54(6):224-228.

Laitinen T, Hartikainen J, Vanninen E, Niskanen L, Geelen G, Lansimies E. Age and gender dependency of baroreflex sensitivity in healthy subjects. Appl Physiol 1998;84(2):576-583.

Lederbogen F, Gernoth C, Weber B, Colla M, Kniest A, Heuser I, Deuschle M. Antidepressive treatment with amitriptyline and paroxetine: comparable effects on heart rate variability. J Clin Psychopharmacol 2001;21(2):238-239.

Lehofer M, Moser M, Hoehn-Saric R, McLeod D, Liebmann P, Drnovsek B, Egner S, Hildebrandt G, Zapotoczky HG. Major depression and cardiac autonomic control. Biol Psychiatry 1997;42(10):914-919.

Lemke MR, Hesse AC. Psychomotor symptoms in depression. Am J Psychiatry 1998;155(5):709-710.

Lemke MR, Puhl P, Broderick A. Motor activity and perception of sleep in depressed patients. J Psychiatr Res 1999;33(3):215-224.

Leo RJ. Movement disorders associated with the serotonin selective reuptake inhibitors. J Clin Psychiatry 1996;57(10):449-454.

Leonard BE. Evidence for a biochemical lesion in depression. J Clin Psychiatry 2000; 61(Suppl 6):12-17.

Lieberman HR, Wurtman JJ, Teicher MH. Circadian rhythms of activity in healthy young and elderly humans. Neurobiol Aging 1989;10(3):259-265.

Lipsitz LA, Mietus J, Moody GB, Goldberger AL. Spectral characteristics of heart rate variability before and during postural tilt. Relations to aging and risk of syncope. Circulation 1990;81(6):1803-1810.

Littman AB. Review of psychosomatic aspects of cardiovascular disease. Psychother Psychosom 1993;60(3-4):148-167.

Maes M, Smith R, Christophe A, Vandoolaeghe E, Van Gastel A, Neels H, Demedts P, Wauters A, Meltzer HY. Lower serum high-density lipoprotein cholesterol (HDL-C) in major depression and in depressed men with serious suicidal attempts: relationship with immune-inflammatory markers. Acta Psychiatr Scand 1997;95(3):212-221.

Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. Circulation 1991;84(2):482-492.

Malzberg B. Mortality among patients with involuation melancholia. Am J Psychiatry 1937;93:1231-1238.

Mancia G, Groppelli A, Di Rienzo M, Castiglioni P, Parati G. Smoking impairs baroreflex sensitivity in humans. Am J Physiol 1997;273(3 Pt 2):H1555-H1560.

Marijnissen G, Tuinier S, Sijben AES, Verhoeven WMA. The temperament and character inventory in major depression. J Affect Disord, 2001.

McAllister-Williams RH, Ferrier IN, Young AH. Mood and neuropsychological function in depression: the role of corticosteroids and serotonin. Psychol Med 1998;28(3):573-584.

McLeod DR, Hoehn-Saric R, Porges SW, Zimmerli WD. Effects of alprazolam and imipramine on parasympathetic cardiac control in patients with generalized anxiety disorder. Psychopharmacology 1992; 107(4): 535-540

McQuade R, Young AH. Mc Future therapeutic targets in mood disorders: the glucocorticoid receptor. Br J Psychiatry 2000;177:390-395.

McPartland RJ, Kupfer DJ, Foster FG, Reisler KL, Matthews G. Objective measurement of human motor activity. Biotelemetry 175;2(6):317–323.

Middelkoop HA, Van Dam EM, Smilde-Van Den Doel DA, Van Dijk G. 45-hour continuous quintuple-site actimetry: relations between trunk and limb movements and effects of circadian sleep-wake rhythmicity. Psychophysiology 1997a;34(2):199-203.

Middelkoop HAM, Sadeh A. De rol en waarde van actimetrie bij de evaluatie van slaap-waak en gerelateerde stoornissen. Tijdschrift voor Psychiatrie 1997b;39:256–262.

Molgaard H, Hermansen K, Bjerregaard P. Spectral components of short-term RR interval variability in healthy subjects and effects of risk factors. Eur Heart J 1994;15:1174-1183.

Montano N, Ruscone TG, Porta A, Lombardi F, Pagani M, Malliani A. Power spectrum analysis of heart rate variability to assess the changes in sympathovagal balance during graded orthostatic tilt. Circulation 1994;90(4):1826-1831.

Morgan RE, Palinkas LA, Barrett-Connor EL, Wingard DL. Plasma cholesterol and depressive symptoms in older men. Lancet 1993;341(8837):75-79.

Moser M, Lehofer M, Hoehn-Saric R, McLeod DR, Hildebrandt G, Steinbrenner B, Voica M, Liebmann P, Zapotoczky HG. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? J Affect Disord 1998; 48(2-3):115-124.

Mulder G. Attention, effort, and sinusarrhythmia: How far are we? In: Orlebeke JF, Mulder G, Van Doornen LPJ (eds). The psychophysiology of cardiovascular control. New York: Plenum Press, 1985:407-423.

Mulder LJM. Assessment of cardiovascular reactivity by means of spectral analysis. Groningen, The Netherlands: University of Groningen, 1988a. (thesis)

Mulder LJM, Van Dellen HJ, Van Der Meulen P, Opheikens B. CARSPAN: a spectral analysis program for cardiovascular time series. In: Maarse FJ, Mulder LJM, Sjouw W, Akkerman A (eds). Computers in Psychology:

Methods, Instrumentation and Psychodiagnostica. Lisse, The Netherlands: Swets and Zeitlinger, 1988b:30-38.

Muller JC, Pryor WW, Gibbons JE, Orgain ES, Durham NC. Depression and anxiety occuring during rauwolfia therapy. JAMA 1955;159:836-839.

Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997a;349(9063):1436-1442.

Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: global burden of disease study. Lancet 1997b;349(9064):1498-1504.

Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry 1998;55(7):580-592.

Naito M, Kijima N, Kitamura T. Temperament and Character Inventory (TCI) as predictors of depression among Japanese college students. J Clin Psychol 2000;56(12):1579-1585.

Niedermaier ON, Smith ML, Beightol LA, Zukowska-Grojec Z, Goldstein DS, Eckberg DL. Influence of cigarette smoking on human autonomic function. Circulation 1993;88:562-571.

Novak P, Novak V. Time/frequency mapping of the heart rate, blood pressure and respiratory signals. Med Biol Eng Comput 1993a;31(2):103-110.

Novak V, Novak P, De Champlain J, Le Blanc AR, Martin R, Nadeau R. Influence of respiration on heart rate and blood pressure fluctuations. J Appl Physiol 1993b;74(2):617-26.

O'Hanlon JF, Freeman H. Categorising the behavioural toxicities of antidepressants. Proposals and requirements. Br J Psychiatry 1995;166(4):421-423.

Ormel J, Oldehinkel T, Brilman E, Van Den Brink W. Outcome of depression and anxiety in primary care. A three-wave 3 1/2-year study of psychopathology and disability. Arch Gen Psychiatry 1993;50(10):759-766.

Ormel J, Sytema S. Epidemiologische aspecten van stemmingsstoornissen. In: Den Boer JA, Ormel J, Van Praag HM, Westenberg HGM, D'Haenen H (eds). Handboek stemmingsstoornissen. Maarssen, The Netherlands: Elsevier/De Tijdstroom, 1999:50-71.

Overstreet DH. Selective breeding for increased cholinergic function: development of a new animal model of depression. Biol Psychiatry 1986;21(1):49-58.

Overstreet DH, Russell RW, Hay DA, Crocker AD. Selective breeding for increased cholinergic function: biometrical genetic analysis of muscarinic responses. Neuropsychopharmacology 1992;7(3):197-204.

Overstreet DH, Pucilowski O, Rezvani AH, Janowsky DS. Administration of antidepressants, diazepam and psychomotor stimulants further confirms the utility of Flinders Sensitive Line rats as an animal model of depression. Psychopharmacology (Berl) 1995;121(1):27-37.

Oxenkrug GF, Branconnier RJ, Harto-Truax N, Cole JO. Is serum cholesterol a biological marker for major depressive disorder? Am J Psychiatry 1983; 140(7):920-921.

Pagani M, Malliani A. Interpreting oscillations of muscle sympathetic nerve activity and heart rate variability. J Hypertens 2000;18(12):1709-1719.

Parati G, Casadei R, Gropelli A, Di Rienzo M, Mancia G. Comparison of finger and intra-arterial blood pressure monitoring at rest and during laboratory testing. Hypertension 1989;13(6 Pt 1):647-655.

Parati G, Saul JP, Di Rienzo M, Mancia G. Spectral analysis of blood pressure and heart rate variability in evaluating cardiovascular regulation. A critical appraisal. Hypertension 1995;25(6):1276-1286.

Parati G, Di Rienzo M, Mancia G. How to measure baroreflex sensitivity: from the cardiovascular laboratory to daily life. J Hypertens 2000;18(1):7-19.

Parati G, Di Rienzo M, Mancia G. Dynamic modulation of baroreflex sensitivity in health and disease. Ann N Y Acad Sci 2001;940:469-487.

Pariante CM, Miller AH. Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biol Psychiatry 2001;49(5):391-404.

Parker G, Hadzi-Pavlovic D, Boyce P, Wilhelm K, Brodaty H, Mitchell P, Hickie I, Eyers K. Classifying depression by mental state signs. Br J Psychiatry 1990; 157:55-65.

Parker G, Hadzi-Pavlovic D, Brodaty H, Boyce P, Mitchell P, Wilhelm K, Hickie I, Eyers K. Psychomotor disturbance in depression: defining the constructs. J Affect Disord 1993;27(4):255-265.

Parker G, Hadzi-Pavlovic D, Hickie I, Brodaty H, Boyce P, Mitchell P, Wilhelm K. Sub-typing depression, III. Development of a clinical algorithm for melancholia and comparison with other diagnostic measures. Psychol Med 1995;25(4):833-840.

Parker G, Hadzi-Pavlovic D. Development and structure of the CORE system. In: Melancholia. A disorder of movement and mood. Parker G, Hadzi-Pavlovic D (eds). New York, USA: Cambridge University Press, 1996;82-129.

Parker G, Wilhelm K, Mitchell P, Roy K, Hadzi-Pavlovic D. Subtyping depression: testing algorithms and identification of a tiered model. J Nerv Ment Dis 1999;187(10):610-617.

Parker G. Classifying depression: should paradigms lost be regained? Am J Psychiatry 2000;157(8):1195-1203.

Patterson SM, Krantz DS, Montgomery LC, Deuster PA, Hedges SM, Nebel LE. Automated physical activity monitoring: validation and comparison with physiological and self-report measures. Psychophysiology 1993;30(3):296-305.

Penaz J. Beitrag zur Fortlaufenden indirekten blutdruckmessung. Z Inn Med 1976; 31:1030-1033.

Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, Van Eijk JT, Van Tilburg W. Depression and cardiac mortality: results from a community-based longitudinal study. Arch Gen Psychiatry 2001;58(3):221-227.

Pols MA, Peeters PH, Bueno-De-Mesquita HB, Ocke MC, Wentink CA, Kemper HC, Collette HJ. Validity and repeatability of a modified Baecke questionnaire on physical activity. Int J Epidemiol 1995;24(2):381-387.

Pomeranz B, Macaulay RJ, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985;248 (1 Pt 2):H151-H153.

Porges SW, Byrne EA. Research methods for measurement of heart rate and respiration. Biol Psychol 1992;34(2-3):93-130.

Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149(8):999-1010.

Powley TL. Central control of autonomic functions. In: Zigmond MJ, Bloom FE, Landis SC, Roberts JL, Squire LR (eds). Fundamental Neuroscience. San Diego, USA: Academic Press, 1999:1027-1050.

Ragueneau I, Michaud P, Demolis JL, Moryusef A, Jaillon P, Funck-Brentano C. Effects of cigarette smoking on short-term variability of blood pressure in smoking and non smoking healthy volunteers. Fundam Clin Pharmacol 1999;13(4):501-507.

Raoux N, Benoit O, Dantchev N, Denise P, Franc B, Allilaire JF, Widlocher D. Circadian pattern of motor activity in major depressed patients undergoing antidepressant therapy: relationship between actigraphic measures and clinical course. Psychiatry Res 1994;52(1):85-98.

Rechlin T, Weis M, Claus D. Heart rate variability in depressed patients and differential effects of paroxetine and amitriptyline on cardiovascular autonomic functions. Pharmacopsychiatry 1994a;27(3):124-128.

Rechlin T, Weis M, Spitzer A, Kaschka WP. Are affective disorders associated with alterations of heart rate variability? J Affect Disord 1994b;32(4):271-275.

Rechlin T. The effect of amitriptyline, doxepin, fluvoxamine, and paroxetine treatment on heart rate variability. J Clin Psychopharmacol 1994c;14(6): 392-395

Reid IC, Stewart CA. How antidepressants work: new perspectives on the pathophysiology of depressive disorder. Br J Psychiatry 2001;178:299-303.

Renfrew JW, Pettigrew KD, Rapoport SI. Motor activity and sleep duration as a function of age in healthy men. Physiol Behav 1987;41(6):627-634.

Robbe HW, Mulder LJ, Ruddel H, Langewitz WA, Veldman JB, Mulder G. Assessment of baroreceptor reflex sensitivity by means of spectral analysis. Hypertension 1987;10(5):538-543.

Roose SP, Glassman AH, Dalack GW. Depression, heart disease, and tricyclic antidepressants. J Clin Psychiatry 1989;50(Suppl 12-6).

Roose SP, Dalack GW. Treating the depressed patient with cardiovascular problems. J Clin Psychiatry 1992;53(Suppl):25-31.

Roose SP, Glassman AH, Attia E, Woodring S, Giardina EG, Bigger JT Jr. Cardiovascular effects of fluoxetine in depressed patients with heart disease. Am J Psychiatry 1998;155(5):660-665.

Royant-Parola S, Borbely AA, Tobler I, Benoit O, Widlocher D. Monitoring of long-term motor activity in depressed patients. Br J Psychiatry 1986;149:288-293.

Rubin DB (ed). Multiple imputation for nonresponse in surveys. New York: Wiley, 1987.

Ryan SM, Goldberger AL, Pincus SM, Mietus J, Lipsitz LA. Gender- and age-related differences in heart rate dynamics: are women more complex than men? J Am Coll Cardiol 1994;24(7):1700-1707.

Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. Am J Physiol 1991;261(4 Pt 2):H1231-H1245.

Shacham S. A shortened version of the Profile of Mood States. J Pers Assess 1983;47(3):305-306.

Schachinger H, Weinbacher M, Kiss A, Ritz R, Langewitz W. Cardiovascular indices Of peripheral and central sympathetic activation. Psychosom Med 2001; 63(5):788-796.

Schatzberg AF, Rothschild AJ. Psychotic (delusional) major depression: should it be included as a distinct syndrome in DSM-IV? Am J Psychiatry 1992;149(6); 733-745.

Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry 1965;122(5):509-522.

Shore PA, Silver SL, Brodie BB. Interaction of reserpine, serotonin, and lysergic acid diethylamide in brain. Science 1955;122:284-285.

Shores MM, Pascualy M, Lewis NL, Flatness D, Veith RC. Short-term sertraline treatment suppresses sympathetic nervous system activity in healthy human subjects. Psychoneuroendocrinology 2001;26(4):433-439.

Singh JP, Larson MG, Tsuji H, Evans JC, O'Donnell CJ, Levy D. Reduced heart rate variability and new-onset hypertension: insights into pathogenesis of hypertension: the Framingham Heart Study. Hypertension 1998;32(2):293-297.

Sobin C, Sackeim HA. Psychomotor symptoms of depression. Am J Psychiatry 1997; 154(1):4-17.

Souery D, Blairy S, Mendlewicz J. Genetic and social aetiology of mood disorders. In: Gelder MG, López-Ibor JJ Jr, Andreasen, NC (eds). New oxford textbook of psychiatry. New York: Oxford University Press, Inc., 2000;Vol 1:701-711.

Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. Arch Gen Psychiatry 1978;35(6):773-782.

Stahl SM (ed). Psychopharmacology of antidepressants. London: Martin Dunitz, 1998.

Stallings MC, Hewitt JK, Cloninger CR, Heath AC, Eaves LJ. Genetic and environmental structure of the Tridimensional Personality Questionnaire: three or four temperament dimensions?. J Pers Soc Psychol 1996;70:127–140.

Stanley N, Fairweather DB, Hindmarch I. Effects of fluoxetine and dothiepin on 24-hour activity in depressed patients. Neuropsychobiology 1999;39(1):44-48.

Stein MB, Wilson KG, Uhde TW. The psychophysiology of depression and anxiety. In: Den Boer JA, Sitsen JM (eds). Handbook of Depression and Anxiety. New York: Dekker, 1994:159-190.

Street H, Sheeran P, Orbell S. Exploring the relationship between different psychosocial determinants of depression: a multidimensional scaling analysis. J Affect Disord 2001;64(1):53-67.

Stys A, Stys T. Current clinical applications of heart rate variability. Clin Cardiol 1998; 21(10):719-724.

Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157(10):1552-1562.

Sved AF. Cardiovascular System. In: Zigmond MJ, Bloom FE, Landis SC, Roberts JL, Squire LR (eds). Fundamental Neuroscience. San Diego, USA: Academic Press, 1999:1051-1062.

Szabo B, Karsch V, Starke K. Effects of inhibitors of neuronal uptake of 5-HT on sympathetic cardiovascular regulation. J Cardiovasc Pharmacol 1992; 20(1): 99-107

Task Force guidelines, heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996;17(3):354-381.

Teicher MH. Actigraphy and motion analysis: new tools for psychiatry. Harv Rev Psychiatry 1995;3(1):18-35.

Thase ME. Depression, sleep, and antidepressants. J Clin Psychiatry 1998;59(Suppl 4):55-65.

Thayer JF, Smith M, Rossy LA, Sollers JJ, Friedman BH. Heart period variability and depressive symptoms: gender differences. Biol Psychiatry 1998;44(4):304-306.

Tryon WW (ed). Activity measurement in psychology and medicine. New York: Plenum Press, 1991.

Tsuji H, Larson MG, Venditti FJ Jr, Manders ES, Evans JC, Feldman CL, Levy D. Impact of reduced heart rate variability on risk for cardiac events. The Framingham Heart Study. Circulation 1996;94(11):2850-2855.

Tuinier S, Verhoeven WMA. Dimensional classification and behavioral pharmacology of personality disorders; a review and hypothesis. Eur Neuropsychopharmacol 1995;5(2):135-146.

Tulen JH, Man in 't Veld AJ, Van Roon AM, Moleman P, Van Steenis HG, Blankestijn PJ, Boomsma F. Spectral analysis of hemodynamics during infusions of epinephrine and norepinephrine in men. J Appl Physiol 1994;76(5):1914-1921.

Tulen JH, Bruijn JA, De Man KJ, Pepplinkhuizen L, van den Meiracker AH, Man in 't Veld AJ. Cardiovascular variability in major depressive disorder and effects of imipramine or mirtazapine (Org 3770). J Clin Psychopharmacol 1996a; 16(2):135-145.

Tulen JHM, Bruijn JA, De Man KJ, Van Der Velden E, Pepplinkhuizen L, Man in 't Veld AJ. Anxiety and autonomic regulation in major depressive disorder: an exploratory study. J Affect Disord 1996b;40(1-2):61-71.

Tulen JHM, Volkers AC, Stronks D, Cavelaars M, Groeneveld W. Accelerometry in clinical psychophysiology. In: Fahrenberg J, Myrtek M (eds). Progress in ambulatory assessment. Seattle, USA: Hogrefe & Huber Publishers, 2001: 207-231.

Van Dellen HJ, Aasman J, Mulder LJM, Mulder G. Time domain versus frequency domain measures of heart rate variability. In: Orlebeke JF, Mulder G, Van Doornen LPJ (eds). The psychophysiology of cardiovascular control. New York: Plenum Press, 1985:353-374.

Van Den Brink W, Hargens C, Verheul R. Dutch version of the TPQ. Amsterdam, The Netherlands: Amsterdam Institute for Addiction Research, 1993.

Van Hilten JJ, Braat EA, Van Der Velde EA, Middelkoop HA, Kerkhof GA, Kamphuisen HA. Ambulatory activity monitoring during sleep: an evaluation of internight and intrasubject variability in healthy persons aged 50-98 years. Sleep 1993;16(2):146-150.

Van Londen L, Kerkhof GA, Van Den Berg F, Goekoop JG, Zwinderman KH, Frankhuijzen-Sierevogel AC, Wiegant VM, De Wied D. Plasma arginine vasopressin and motor activity in major depression. Biol Psychiatry 1998; 43(3):196-204.

Van Praag HM, Korf J, Puite J. 5-Hydroxyindoleacetic acid levels in the cerebrospinal fluid of depressive patients treated with probenecid. Nature 1970;225(239): 1259-1260.

Van Praag HM, Korf J. Retarded depression and the dopamine metabolism. Psychopharmacologia 1971;19(2):199-203.

Van Someren EJ, Lazeron RH, Vonk BF, Mirmiran M, Swaab DF. Gravitational Artefact in frequency spectra of movement acceleration: implications for actigraphy in young and elderly subjects. J Neurosci Methods 1996;65(1): 55-62.

Van Steenis HG, Tulen JHM, Mulder LJM. Heart rate variability spectra based on non-equidistant sampling: the spectrum of counts and the instantaneous heart rate frequency. Med Eng Phys 1994;16:355-362.

Van Steenis HG, Tulen JH. The exponential distribution applied to nonequidistantly sampled cardiovascular time series. Comput Biomed Res 1996;29(3):174-193.

Van Steenis HG, Martens WLJ, Tulen JHM. Quantification of the dynamic behavior over time of narrow-band components present in heart rate variability by means of the instantaneous amplitude and frequency. IEEE Transactions on Biomedical Engineering. (submitted, under editorial revision).

Veith RC, Raskind MA, Barnes RF, Gumbrecht G, Ritchie JL, Halter JB. Tricyclic antidepressants and supine, standing, and exercise plasma norepinephrine levels. Clin Pharmacol Ther 1983;33(6):763-769.

Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, et al. Sympathetic nervous system activity in major depression. Basal and desipramine-induced alterations in plasma norepinephrine kinetics. Arch Gen Psychiatry 1994;51(5):411-422.

Verbeke S, Molenberghs S. Linear mixed models in practise; a SAS-oriented approach. New York: Springer, 1997.

Verhoeven WMA, Tuinier S. Neurotransmitters, hormonen en depressies. Theorieën over de pathogenese. In: Den Boer, JA, Ormel J, Van Praag, HM, Westenberg HGM, D'Haenen H (eds). Handboek stemmingsstoornissen. Maarssen, The Netherlands: Elsevier/De Tijdstroom, 1999:172-178.

Verhoeven WM, Tuinier S. Two steps forward, one step back; paradigmatic changes in psychiatry. J Neural Transm 2001;108(6):617-627.

Volkers AC, Tulen JHM, Gieteling M, Wegewijs-De Jong M, Van Den Broek WW. Sleep quality and diurnal motor activity pattern in healthy adults, effects of age and gender. In: Beersma DGM, Arends JBAM, Van Bemmel AL, Hofman WF, Ruigt GSF. Sleep-wake research in the Netherlands. Utrecht, The Netherlands: Elinkwijk, 1997;Vol 8:119-124.

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. Severity of depression in relation to motor activity and self-reported sleep characteristics. In: Van Bemmel AL, Beersma DGM, Folgering H, Hofman WF, Ruigt GSF. Sleep-wake research in the Netherlands, 2000;Vol 11:140-144.

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. Motor activity and autonomic cardiac functioning in major depressive disorder. J Affect Disord, 2002a. (in press)

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. Effect of personality dimensions on the diurnal pattern of motor activity. J Personality 2002b;70(2):233-248.

Wakelin JS. Fluvoxamine in the treatment of the older depressed patient; double-blind, placebo-controlled data. Int Clin Psychopharmacol 1986;1(3):221-230.

Wald FDM, Mellenbergh GJ. De verkorte versie van de Nederlandse vertaling van de Profile of Mood States. Ned Tijdschrift Psychology 1990;45:86-90.

Wardle J. Cholesterol and psychological well-being. J Psychosom Res 1995;39(5): 549-562.

Watkins LL, Grossman P, Krishnan R, Blumenthal JA. Anxiety reduces baroreflex cardiac control in older adults with major depression. Psychosom Med 1999; 61(3):334-340.

Wehr TA, Muscettola G, Goodwin FK. Urinary 3-methoxy-4-hydroxyphenylglycol circadian rhythm. Early timing (phase-advance) in manic-depressives compared with normal subjects. Arch Gen Psychiatry 1980;37(3):257-263.

Weiss BL, Foster FG, Reynolds CF 3rd, Kupfer DJ. Psychomotor activity in mania. Arch Gen Psychiatry 1974;31(3):379-83.

Wesseling KH, Settels JJ. Baromodulation explains short-term blood pressure variability. In: Orlebeke JF, Mulder G, Van Doornen LPJ (eds). The psychophysiology of cardiovascular control. New York: Plenum Press, 1985:69-97.

West CH, Weiss JM. Effects of antidepressant drugs on rats bred for low activity in the swim test. Pharmacol Biochem Behav 1998;61(1):67-79.

WHO Expert Committee Report. Physical status: the use and interpretation of World Health Organ Tech Rep Ser 1995;854:1-452.

Widlocher DJ. Psychomotor retardation: clinical, theoretical, and psychometric aspects. Psychiatr Clin North Am 1983;6(1):27-40.

Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. Biol Psychiatry 1990;27(6):563-572.

Wolff EA, Putnam FW, Post RM. Motor activity and affective illness. The relationship of amplitude and temporal distribution to changes in affective state. Arch Gen Psychiatry 1985;42(3):288-294.

Yeragani VK, Pohl R, Balon R, Ramesh C, Glitz D, Jung I, Sherwood P. Heart rate variability in patients with major depression. Psychiatry Res 1991;37(1):35-46.

Yeragani VK, Pohl R, Balon R, Ramesh C, Glitz D, Weinberg P, et al. Effect of imipramine treatment on heart rate variability measures. Neuropsychobiology 1992;26(1-2):27-32

Yeragani VK, Balon R, Pohl R, Ramesh C. Depression and heart rate variability. Biol Psychiatry 1995;38(11):768-770.

Yeragani VK, Jampala VC, Sobelewski E, Kay J, Igel G. Effects of paroxetine on Heart period variability in patients with panic disorder: a study of holter ECG records. Neuropsychobiology 1999;40(3):124-128.

Zuckerman M, Buchsbaum MS, Murphy D.L. Sensation Seeking and its biological correlates. Psychol Bull 1980;88(1):187–214.

Zuckerman M, Cloninger CR. Relationships between Cloninger's, Zuckerman's and Eysenck's dimensions of personality. Person Individ Diff 1996;21(2): 283–285.

Summary

Samenvatting

24-HOUR MOTOR ACTIVITY AND AUTONOMIC CARDIAC FUNCTIONING IN MAJOR DEPRESSIVE DISORDER

Major depressive disorder is an affective disorder and its life time prevalence in the Dutch population is about 15 %. It is a psychiatric disorder with a large disease burden. There are three important factors that are considered to contribute, alone or by interaction, to the development of this psychiatric disorder: genetic factors, psychosocial, and neurobiological factors. The major hypotheses about the neurobiological basis of major depression are the original monoamine hypothesis and the more recent hypothalamic-pituitary-adrenal (HPA) axis hyperactivity hypothesis. Depression is also proposed to be a manifestation of hypersensitivity of the cholinergic system, but the cholinergic dysfunction in depressed patients has not been extensively studied. Depressed patients can be treated effectively by antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). TCAs and SSRIs have a different pharmacological profile and their efficacy is suggested to be different in hospitalised patients.

One important feature of major depressive disorder is the psychomotor dysfunction, which is characterised by psychomotor retardation and/or agitation. Retardation is reflected in the slowing down of physical and psychic activity and manifestations of agitation are for instance being unable to sit still, pacing, and handwringing. Dysfunctions in the central dopaminergic system are involved in psychomotor disturbances in depressed patients, but cholinergic hypersensitivity may also be one of the underlying factors. The psychomotor disturbance is likely to be reflected in the spontaneous pattern of motor activity. Previous studies reported that depressed patients were less active during the day than healthy persons and that they had an altered distribution of motor activity throughout the day. Personality, age, and gender may be determinants of the diurnal pattern of motor activity in the general population, whereas in depressed patients the clinical state and antidepressant treatment are two additional factors that may influence 24-hour motor activity. Furthermore, a relationship between major depression and abnormalities in the autonomic regulation of the cardiovascular system has been suggested. The autonomic cardiac dysfunction, in particular diminished parasympathetic activity resulting in decreased heart rate (HR) variability, has been hypothesised to be one of the biological factors involved in the increased risk of cardiovascular disease in depressed patients. Alterations in the autonomic regulation in major depression may be related to clinical state, antidepressant treatment and the higher prevalence of risk factors.

The general aim of the studies of this thesis was to obtain insight in the psychomotor and autonomic cardiac dysfunctions in major depressive disorder and to evaluate the potential determinants of these dysfunctions. The 24-hour pattern of motor activity and the autonomic regulation of the cardiovascular system were evaluated in healthy subjects and unipolar depressed inpatients of the depression ward of the University Hospital Rotterdam - Dijkzigt. All patients participated in a clinical trial to the efficacy of antidepressant treatment and electroconvulsive therapy (ECT) in therapy-resistant depression. In this thesis, we used the patient data obtained during the psychotropic drug free period and after treatment with either the TCA imipramine or the SSRI fluvoxamine. The 24-hour pattern of motor activity was assessed by wrist-actigraphy, and spectral analysis of cardiovascular variability was applied to obtain information about the autonomic (sympathetic and parasympathetic) regulation of the cardiovascular system.

In **chapter 2** the effect of personality, age and gender on the overall level of motor activity and the shape of the diurnal pattern was studied in 99 healthy subjects between 20-70 years of age. The Tridimensional Personality Questionnaire (TPQ) of Cloninger was applied to assess four temperament traits (Novelty Seeking, Harm Avoidance, Reward Dependence and Persistence). On visual inspection, the 24-hour pattern of motor activity of healthy subjects was characterised by an increase in motor activity in the early morning, a peak of motor activity in the late afternoon, and a gradual decline of motor activity during the evening and night. The shape of the diurnal pattern or, in statistical terms, the time trend was estimated by six time terms. The overall level of motor activity was found to decrease by age, indicating that older subjects were overall less active than younger subjects, but age had no effect on the shape of the diurnal pattern. The 24-hour pattern of motor activity did not differ between males and females. Furthermore, Harm Avoidance was negatively related to overall levels of motor activity, and Reward Dependence positively. Similar to age, Harm Avoidance and Reward Dependence did not modify the time trend.

Summarising: This study showed that the diurnal pattern of motor activity has a complex time trend in healthy subjects. Dimensions of temperament and age were determinants of the overall level of motor activity in healthy subjects, but the shape of the diurnal pattern of motor activity was not influenced by these factors.

In **chapter 3** the role of age, gender and risk factors (smoking, plasma lipid levels, body mass index and habitual physical activity) in the autonomic regulation was investigated in 65 healthy subjects between 20-59 years of age. Mean HR, mean systolic and diastolic blood pressure (SBP and DBP), HR and SBP variability, and

baroreflex sensitivity were measured during supine rest and orthostatic challenge (60% head-up tilt). The baroreflex is a negative feedback mechanism to maintain the arterial blood pressure in a normal range. Orthostatic challenge induced an increase in mean HR and DBP, mid-frequency band (MF: 0.07-0.14 Hz) power of SBP, and a decrease in high-frequency band (HF: 0.15-0.50 Hz) power of HR and baroreflex sensitivity. The overall HR variability (variation coefficient), MF and HF variability of HR, and the baroreflex sensitivity were decreased by age. Furthermore, a higher mean HR was related to higher total and high density lipid (HDL) cholesterol levels and to lower levels of habitual physical activity. Mean SBP and DBP were positively related to the body mass index and the overall HR variability was negatively related to both smoking and the body mass index.

Concluding, this study demonstrated, in agreement with the literature, that orthostatic challenge is characterised by an augmentation of sympathetic activity and a reduction of parasympathetic (vagal) activity. Subjects with a higher age showed lower HF power of HR and decreased baroreflex sensitivity, suggesting that older subjects have a reduced parasympathetic activity. In healthy subjects the effect of risk factors on cardiovascular variability and baroreflex sensitivity may be limited. However, the fact that HR and BP levels were differentially affected by one or more risk factors reveals that these factors do play a complex role in the modulation of the cardiovascular system.

In **chapter 4** the spontaneous pattern of motor activity and the autonomic cardiac functioning during supine rest was studied in 67 unmedicated severely depressed inpatients between 35 and 65 years of age. The data of the patients were compared with data of two healthy control groups. Within the patient group, the relevance of specific clinical features (high levels of anxiety, agitation, retardation and psychotic features) was explored in relation to 24-hour motor activity and autonomic regulation, and the mutual relationship between motor activity parameters and cardiovascular parameters was evaluated.

In comparison to healthy subjects, the patients demonstrated a lower motor activity level during wake and a higher motor activity level during sleep. During the wake period, the patients also had a lower fragmentation of motor activity, indicating that rest periods were less frequently interrupted by motor activity. During sleep they showed a reduced immobility, which suggests a decrease in the relative amount of rest. Within the patient group, the presence of agitation was positively related to motor activity during wake, and the presence of retardation negatively to motor activity throughout the entire day and to fragmentation of motor activity during wake. Furthermore, depression was related to higher mean HR and DBP levels, but

not to HR and SBP variability or baroreflex sensitivity. Agitated depressed patients showed higher mean HR and SBP levels than nonagitated patients, whereas retarded patients demonstrated lower mean SBP and DBP levels than nonretarded patients. The motor activity level during wake was another determinant of the mean SBP.

These findings contribute to our understanding of the neurobiological basis of (subtypes of) depression. However, the relationship between disturbances in psychomotor activity and autonomic regulation, and the underlying pathway need to be further clarified. Major depressive disorder is related to changes in the 24-hour motor activity and the autonomic regulation of the cardiovascular system, but the latter changes were restricted to mean HR and BP levels. Within the patient group, both motor activity and cardiovascular parameters were influenced by the presence of agitation and retardation. Furthermore, we found an association between motor activity during wake and the mean SBP.

Chapter 5 describes how we investigated the effect of antidepressant treatment on the diurnal pattern of motor activity in 52 depressed patients (20 males, 32 females; mean age = 52.5 years). Patients were studied during a psychotropic drug free period of at least 7 days and after 4 weeks of treatment with either imipramine or fluvoxamine at therapeutic plasma levels of the drugs. On average, there was a clinical improvement of depressive mood and retardation in patients treated with imipramine, as well as in patients treated with fluvoxamine. After imipramine, the mean motor activity during wake and the fragmentation of motor activity during sleep were increased. Fluvoxamine treatment did not affect any of the wrist-actigraphy parameters. Post-hoc statistical analyses showed that the increase in motor activity after imipramine was not modified by changes in severity of depression or clinical scores of retardation and agitation. It was remarkable that in the imipramine group the motor activity levels during wake were still much lower after treatment than the activity levels of the healthy subjects described in chapter 2. One explanation for this finding may be the clinical setting in which the patients were measured.

To summarise, adequate treatment with imipramine, but not with fluvoxamine, resulted in an increased daytime motor activity. Improvement of the clinical state was not related to this change in motor activity, therefore differences in the pharmacological profile between imipramine and fluvoxamine could be responsible for this effect. Imipramine has anticholinergic and (nor)adrenergic properties, whereas fluvoxamine has not. The clinical relevance for the effect of imipramine on motor activity should be investigated in future studies, especially in relation to psychomotor retardation.

In **chapter 6** we evaluated the effect of antidepressant treatment on autonomic cardiac functioning during supine rest and orthostatic challenge in 52 depressed patients (20 males, 32 females; mean age = 52.5 years). Cardiovascular measurements were done during a psychotropic drug free period (average duration 11 days) and after 4 weeks of treatment with either imipramine or fluvoxamine at therapeutic plasma levels of both compounds. After imipramine, patients showed an elevated mean HR level and a diminished overall HR variability (variation coefficient), MF and HF power of HR, MF power of SBP and a reduced baroreflex sensitivity. In contrast, patients treated with fluvoxamine demonstrated no significant alterations in mean HR or BP. However, after fluvoxamine all HR variability parameters and MF variability of SBP were decreased during supine rest. During orthostatic challenge the overall as well as MF variability of SBP was decreased. On group level, the response pattern to orthostatic challenge only showed minor changes in each group after treatment. However, in the imipramine group 1 patient developed orthostatic hypotension during treatment, while in the fluvoxamine group orthostatic hypotension disappeared in 2 patients. Finally, in the imipramine group severity of depression was positively related to mean HR (when data of the baseline and post-treatment period were combined), but improvement of depressive mood did not modify the change in mean HR level after treatment. In the fluvoxamine group severity of depression was positively related to mean SBP and DBP.

The conclusion of this study was that both imipramine and fluvoxamine reduced sympathetic and parasympathetic activity in depressed patients, although the effects of fluvoxamine were much less pronounced. Depressive mood was positively related to mean HR and BP, but not to any of the parameters of cardiovascular variability or baroreflex sensitivity. The alterations in the autonomic regulation after treatment could be attributed to the pharmacological actions of the drugs and were not explained by improvement of depressive mood.

Chapter 7 presents the final conclusions of this thesis. Major depressive disorder is related to alterations in the spontaneous pattern of motor activity and in autonomic cardiac functioning, although the last one was restricted to mean HR and BP. Clinical state in depressed patients affects the 24-hour motor activity and autonomic regulation. However, pharmacological effects rather than improvement of clinical state were responsible for changes in the motor activity and cardiovascular parameters after treatment with imipramine or fluvoxamine. In healthy subjects a relationship was found between personality traits and overall levels of motor activity. This may be relevant for the interpretation of the motor activity data of depressed patients, because these patients probably have a lower Harm Avoidance score than

the general population. Some risk factors (higher lipid levels, less habitual physical activity and a higher body mass index) had clear effects on mean HR and BP, but we observed minor effects of risk factors on HR and SBP variability and baroreflex sensitivity in healthy subjects. The contribution of risk factors to autonomic cardiac functioning in depressed patients needs to be further investigated, especially because of the higher prevalence of risk factors in this patient group.

24-UURS MOTORISCHE ACTIVITEIT EN AUTONOME CARDIALE FUNCTIE IN DEPRESSIEVE STOORNISSEN

Depressie is een stemmingsstoornis waarvan de 'life-time' prevalentie in Nederland ongeveer 15% bedraagt, hetgeen betekent dat ongeveer 1 op de 7 mensen op een bepaald tijdstip in het leven lijdt aan een depressieve stoornis. Drie belangrijke factoren worden verondersteld, alleen of in samenwerking met elkaar, bij te dragen aan het ontstaan van deze psychiatrische ziekte. Dit zijn genetische factoren, psychosociale factoren en neurobiologische factoren. De twee meest gangbare hypothesen over de neurobiologische basis van depressieve stoornissen zijn de oorspronkelijke monoaminen hypothese en de ten opzichte hiervan meer recente hypothese over de hyperactiviteit van de hypothalamus-hypofyse-bijnier (HPA)-as. Depressie wordt daarnaast verondersteld het resultaat te kunnen zijn van een overgevoeligheid van het cholinerge zenuwstelsel (met acetylcholine als één van de belangrijkste neurotransmitters), maar de cholinerge disfunctie in depressieve patiënten is niet uitvoerig onderzocht. Depressieve patiënten kunnen succesvol behandeld worden met antidepressiva zoals de tricyclische antidepressiva (TCAs) en de selectieve serotonine heropname remmers (SSRIs). TCAs en SSRIs hebben verschillende farmacologische eigenschappen en de effectiviteit van beide antidepressiva is mogelijk verschillend bij patienten die zijn opgenomen in de kliniek.

Een belangrijk kenmerk van depressieve stoornissen is de psychomotorische disfunctie, waarbij een onderscheid gemaakt kan worden tussen psychomotorische retardatie (vertraging) en agitatie (motorische onrust). Retardatie heeft betrekking op de vertraging van zowel lichamelijke als geestelijke activiteiten, terwijl agitatie zich bijvoorbeeld uit in niet stil kunnen zitten, op en neer lopen, en handen wringen. Aangenomen wordt dat disfuncties van het centrale dopaminerge zenuwstelsel een rol spelen bij de veranderingen in de psychomotoriek van depressieve patiënten, maar de eerder genoemde overgevoeligheid van het cholinerge zenuwstelsel is mogelijk ook één van de onderliggende factoren. De verstoring in de psychomotoriek komt ook naar voren in het 24-uurs patroon van motorische activiteit; depressieve patiënten zijn minder actief overdag en hebben een veranderde verdeling van motorische activiteit over de dag heen. Een mogelijke determinant (bepalende factor) van het spontane motorisch activiteiten patroon bij gezonde personen is persoonlijkheid. Bij depressieve patiënten zijn het klinisch toestandsbeeld (b.v. ernst van de depressie) en de behandeling met antidepressiva twee aanvullende factoren die de 24-uurs motorische activiteit mogelijk beïnvloeden. Het is bekend dat depressieve stoornissen mogelijk ook samenhangen met verstoringen in de autonome regulatie van het cardiovasculaire systeem, of met andere woorden, de controle over het hart-

en vaatstelsel door het autonome zenuwstelsel, dat kan onderverdeeld worden in een sympathisch en parasympathisch gedeelte. De autonome cardiale disfunctie is één van de biologische factoren die verondersteld worden verantwoordelijk te zijn voor het verhoogde risico op hart- en vaatziekten bij depressieve patiënten. In het bijzonder zou het gaan om een verminderde activiteit van het parasympathische zenuwstelsel resulterend in een verlaagde hartslagvariabiliteit (variabiliteit van de tijdsintervallen tussen opeenvolgende hartslagen). Veranderingen in de autonome regulatie van het cardiovasculaire systeem bij depressieve patiënten hangen mogelijk samen met het klinisch toestandsbeeld of met het vaker voorkomen van risicofactoren voor hart- en vaatziekten (zoals roken) in deze patiëntengroep.

Het algemene doel van de onderzoeken beschreven in dit proefschrift was om meer inzicht te krijgen in de psychomotorische en autonome cardiale disfuncties bij depressieve patiënten en de mogelijke determinanten van deze disfuncties. Daartoe werd het 24-uurs patroon van motorische activiteit en de autonome regulatie van het cardiovasculaire systeem onderzocht bij gezonde personen en bij patiënten met een unipolaire depressieve stoornis. De patiënten waren opgenomen op de afdeling Psychiatrie van het Erasmus Medisch Centrum Rotterdam - Dijkzigt. Alle patiënten waren deelnemers aan een klinische studie naar de effectiviteit van de behandeling met antidepressiva en electroconvulsieve therapie (ECT) bij therapieresistente depressies. In dit proefschrift hebben we gebruik gemaakt van patiëntgegevens die werden verzameld tijdens een medicatie vrije periode (voor aanvang van de behandeling) en na dubbelblinde behandeling met de antidepressiva imipramine (een TCA) of fluvoxamine (een SSRI). Met behulp van een pols-actometer (een soort polshorloge met een versnellingssensor) werd gedurende drie dagen en nachten het spontane patroon van motorische activiteit geregistreerd. Hartslag, bloeddruk en ademhaling werden gemeten in het psychofysiologisch laboratorium van de afdeling Psychiatrie en vervolgens werd de techniek van spectraalanalyse toegepast om informatie te verkrijgen over de autonome regulatie van het cardiovasculaire systeem.

In **hoofdstuk 2** werd bij 99 gezonde personen tussen de 20 en 70 jaar het globale niveau van motorische activiteit en het beloop van het 24-uurs patroon bepaald. We bestudeerden het effect van persoonlijkheid, leeftijd en geslacht een effect op dit patroon. De gegevens van de gezonde personen dienden als normgegevens waarmee de gegevens van de patienten vergeleken konden worden. De Tridimensional Personality Questionnaire (TPQ) van Cloninger werd afgenomen om vier dimensies van temperament te bepalen (Novelty Seeking, Harm Avoidance, Reward Dependence, en Persistence). De motorische activiteit van de gezonde personen

uitgezet tegen de tijd laat zien dat er een toename van motorische activiteit aanwezig was in de vroege ochtend, een piek in de motorische activiteit aan het einde van de middag, en een geleidelijke daling van het motorische activiteiten niveau tijdens de avond en nacht. Het beloop over de 24-uurs periode bleek geschat te kunnen worden met zes verschillende tijdsfuncties. We vonden dat het globale niveau van motorische activiteit afnam bij een hogere leeftijd; oudere personen waren over het algemeen minder actief dan jongere personen, maar leeftijd had geen effect op het beloop van het dagelijkse patroon. Het 24-uurs patroon van motorische activiteit verschilde niet tussen mannen en vrouwen. Daarnaast bleek er een positieve relatie te bestaan tussen de Harm Avoidance score en het globale niveau van motorische activiteit en een negatieve relatie tussen de Reward Dependence score en dit niveau. Net als leeftijd, hadden Harm Avoidance en Reward Dependence geen effect op het beloop van het 24-uurs patroon.

Samenvattend: Het dagelijks patroon van motorische activiteit van gezonde personen kan beschreven worden met behulp van een complexe tijdsfunctie. Persoonlijkheidsdimensies en leeftijd bepaalden het globale niveau van motorische activiteit, maar zij waren geen determinanten van het beloop over de dag.

Hoofdstuk 3 beschrijft het onderzoek bij 65 gezonde personen tussen de 20 en 59 jaar naar de rol van leeftijd, geslacht en risicofactoren (roken, cholesterol, overgewicht, en dagelijkse hoeveelheid lichamelijke activiteit) bij de autonome regulatie van het cardiovasculaire systeem. De gemiddelde hartslag, systolische en diastolische bloeddruk, de hartslag- en systolische bloeddrukvariabiliteit, en de baroreflex gevoeligheid werden bepaald tijdens rust (in lighouding) en een orthostase test (60% passief rechtopstaand). De orthostase test leidde tot een toename van de gemiddelde hartslag en diastolische bloeddruk, een toename van de systolische bloeddrukvariatie in de midden frequentie band (MF: 0.07-0.14 Hz), en een afname van de hartslagvariatie in the hoge frequentie band (HF: 0.15-0.50 Hz). De globale hartslagvariabiliteit (variatie coëfficiënt), de MF en HF hartslagvariabiliteit en de baroreflex gevoeligheidsindex waren lager bij personen met een hogere leeftijd. Behalve een effect van leeftijd, ontdekten we dat de gemiddelde hartslag hoger was bij personen met hogere totaal en HDL (high density lipide) cholesterol waarden en bij personen met een geringere hoeveelheid dagelijkse lichamelijke activiteit. Ook kwam naar voren dat hogere systolische en diastolische bloeddruk waarden gerelateerd waren aan een hogere body mass index (een maat voor overgewicht), en dat verlaagde globale hartslagvariabiliteit zowel samenhing met roken als met een hogere body mass index.

De conclusie van bovenstaand onderzoek was dat de orthostase test resulteerde in een toegenomen sympathische activiteit en verminderde parasympathische (vagale) activiteit. Dit is in overeenkoms met de bestaande literatuur. Oudere personen vertoonden een lagere HF hartslagvariabiliteit en een verminderde baroreflex gevoeligheid. Dit suggereert dat ouder worden gepaard gaat met een afname van parasympathische activiteit. Bij gezonde personen is het effect van risico factoren op cardiovasculaire variabiliteit en baroreflex gevoeligheid mogelijk beperkt. Het feit dat enkele van de risicofactoren een (verschillend) effect hadden op de gemiddelde hartslag en bloeddruk, maakt duidelijk dat deze factoren een complexe rol spelen bij de regulatie van het cardiovasculaire systeem.

In **hoofdstuk 4** werden het spontane patroon van motorische activiteit en de autonome cardiale functie tijdens rust (in lighouding) onderzocht bij 67 medicatie vrije patiënten met een ernstige depressieve stoornis tussen de 35 en 65 jaar. De gegevens van de patiënten werden vergeleken met de gegevens afkomstig van twee gezonde controlegroepen. Binnen de patiëntengroep werd het belang van specifieke klinische kenmerken (hoog angstniveau, agitatie, retardatie en psychotische kenmerken) voor de 24-uurs motorische activiteit en de autonome regulatie onderzocht. Eveneens werd de onderlinge relatie tussen de parameters voor motorische activiteit en de cardiovasculaire variabelen vastgesteld. In vergelijking tot gezonde personen vertoonden de patiënten een lager niveau van motorisch activiteit tijdens wakker-zijn en een hoger niveau van motorische activiteit tijdens de slaap. Tijdens de waakperiode was ook de fragmentatie van de motorische activiteit verminderd, wat inhoudt dat rustperiodes minder vaak werden afgewisseld met motorische activiteit, terwijl er tijdens de slaap minder immobiliteit was, hetgeen betekent dat hier mogelijk sprake was van een afname van de relatieve hoeveelheid rust. Binnen de groep patiënten was de aanwezigheid van agitatie gerelateerd aan meer motorische activiteit tijdens de waakperiode, en de aanwezigheid van retardatie aan minder motorische activiteit gedurende de gehele dag en aan minder fragmentatie van motorische activiteit overdag.

De depressieve stoornis werd gekenmerkt door een hogere gemiddelde hartslag en diastolische bloeddruk, maar niet door veranderingen in hartslag- en systolische bloeddrukvariabiliteit of in baroreflex gevoeligheid. Geagiteerde depressieve patiënten hadden gemiddeld een hogere hartslag en systolische bloeddruk dan niet geagiteerde patiënten, terwijl patiënten met retardatie gemiddeld een lagere systolische en diastolische bloeddruk hadden dan patiënten zonder retardatie. Daarnaast bleek bij de patiënten het niveau van motorische activiteit tijdens de waakperiode positief gerelateerd te zijn aan de gemiddelde systolische bloeddruk.

Bovenstaande bevindingen dragen bij tot het begrip van de neurobiologische basis van (subtypen van) depressieve stoornissen. We vonden enig bewijs voor een verband tussen de verstoringen in de psychomotorische activiteit en de autonome regulatie, maar het onderliggende mechanisme moet nog verder verhelderd worden. Depressieve stoornissen hangen samen met veranderingen in de 24-uurs motorische activiteit en de autonome regulatie van het cardiovasculaire systeem, maar deze veranderingen komen alleen naar voren in de gemiddelde hartslag en bloeddruk niveaus. De aanwezigheid van agitatie en retardatie bepalen zowel de parameters voor motorische activiteit als de cardiovasculaire variabelen. Eveneens bestond er een verband tussen motorische activiteit tijdens de waakperiode en de gemiddelde systolische bloeddruk.

Hoofdstuk 5 beschrijft hoe het effect van de behandeling met antidepressiva op het dagelijkse patroon van motorische activiteit is nagegaan bij 52 depressieve patiënten (20 mannen, 32 vrouwen; gemiddelde leeftijd = 52,5 jaar). De patiënten werden in eerste instantie onderzocht tijdens een periode van tenminste 7 dagen waarin zij geen psychofarmaca gebruikten en een tweede keer na een behandeling van 4 weken met imipramine of fluvoxamine terwijl zij therapeutisch effectieve doseringen gebruikten van de desbetreffende antidepressiva. Op groepsniveau was er een klinische verbetering van de depressieve stemming en van de mate van retardatie zowel bij de patiënten die behandeld waren met imipramine als met fluvoxamine. Na imipramine was het globale motorische activiteiten niveau tijdens de waakperiode toegenomen evenals de fragmentatie van motorische activiteit tijdens de slaap. Na fluvoxamine werd geen enkele verandering waargenomen in de parameters voor motorische activiteit. Aanvullende statistische analyses toonden aan dat de toename van motorische activiteit na imipramine niet afhing van de verbeterde depressieve stemming of van veranderingen in de klinische scores voor agitatie en retardatie. Het was opvallend dat na behandeling met imipramine overdag het motorische activiteiten niveau nog steeds veel lager was dan dat van gezonde personen (zie hoofdstuk 2). Dit zou te maken kunnen hebben met de klinische setting waarin de patiënten verbleven.

Samenvattend: een adequate behandeling met imipramine, maar niet met fluvoxamine resulteerde in een toename van de motorische activiteit overdag. Aangezien verbeteringen in het klinisch toestandsbeeld niet gerelateerd waren aan de verandering in motorische activiteit, zouden farmacologische verschillen tussen imipramine en fluvoxamine verantwoordelijk kunnen zijn voor dit effect. Imipramine heeft bijvoorbeeld anticholinerge en (nor)adrenerge eigenschappen, terwijl fluvoxamine deze niet heeft. De klinische relevantie van het effect van imipramine op

de motorische activiteit bij depressieve patiënten met psychomotorische retardatie is een onderwerp voor toekomstig onderzoek.

In **hoofdstuk 6** bestudeerden we het effect van de behandeling met antidepressiva op de autonome regulatie tijdens rust (in lighouding) en tijdens een orthostase test bij dezelfde groep depressieve patiënten als in hoofdstuk 5. Cardiovasculaire metingen werden verricht tijdens een periode waarin geen psychofarmaca werden gebruikt (gemiddelde duur van deze periode was 11 dagen) en na een adequate behandeling van 4 weken met imipramine of fluvoxamine. Na behandeling met imipramine werd bij de patiënten een verhoogde gemiddelde hartslag gevonden, en een afname van de globale hartslagvariabiliteit, de hartslagvariatie in de MF en HF band, de bloeddrukvariatie in de MF band en de baroreflex gevoeligheid. Na behandeling met fluvoxamine werden geen significante veranderingen in de gemiddelde hartslag en bloeddruk aangetoond. Wij vonden echter wel een verlaging van alle parameters voor hartslagvariabiliteit en van de MF bloeddrukvariabiliteit tijdens rust en van de globale en MF bloeddrukvariabiliteit tijdens de orthostase test. Op groepsniveau namen we na beide behandelingen slechts kleine veranderingen waar bij het reactiepatroon op orthostatische inspanning. In de imipramine-groep ontwikkelde 1 patiënt orthostatische hypotensie gedurende de behandeling, terwijl in de fluvoxamine-groep orthostatische hypotensie bij 2 patiënten niet langer aanwezig was na behandeling. Tenslotte werd in de imipramine-groep een positief verband gevonden tussen de ernst van de depressie en de gemiddelde hartslag (wanneer de data van de baseline periode werden gecombineerd met de data verzameld na behandeling). Er was geen verband tussen de verbetering van de depressieve stemming en veranderingen in de cardiovasculaire variabelen.

De conclusie van dit onderzoek was dat zowel imipramine als fluvoxamine de sympathische en parasympathische activiteit verminderden bij depressieve patiënten, hoewel het effect van fluvoxamine veel minder duidelijk was dan het effect van imipramine. Patiënten die meer depressief waren hadden een hogere hartslag en bloeddruk, maar de parameters voor cardiovasculaire variabiliteit en de baroreflex gevoeligheid waren niet gerelateerd aan de mate van depressiviteit. Veranderingen in de autonome regulatie bij het gebruik van antidepressiva kunnen worden toegeschreven aan farmacologische effecten, en niet zozeer aan verbeteringen van de depressieve stemming

In **hoofdstuk 7** komen de eindconclusies van dit proefschrift aan bod. Een depressieve stoornis hangt samen met veranderingen in het spontane patroon van motorische activiteit en de autonome cardiale functie, waarbij de autonome disfunctie

beperkt is tot veranderingen in de gemiddelde hartslag en bloeddruk. Het klinisch toestandsbeeld heeft een effect op de 24-uurs motorische activiteit en de autonome regulatie, maar farmacologische effecten en niet de verbetering van het klinische toestandsbeeld lijken verantwoordelijk te zijn voor veranderingen bij depressieve patiënten na behandeling met imipramine en fluvoxamine. Bij gezonde personen bepaalden Harm Avoidance en Reward Dependence, beide dimensies van temperament, mede het globale niveau van de 24-uurs motorische activiteit. Deze bevinding zou van belang kunnen zijn bij de interpretatie van de gegevens over motorische activiteit van de patiënten, aangezien depressieve patiënten een lagere Harm Avoidance score hebben dan niet depressieve personen. Enkele risicofactoren (hogere cholesterol waarden, minder dagelijkse lichamelijke activiteit en een hogere body mass index) hingen samen met een hogere gemiddelde hartslag en bloeddruk bij gezonde personen, maar de effecten op cardiovasculaire variabiliteit en baroreflex gevoeligheid waren gering. Het is belangrijk dat in toekomstig onderzoek de rol van risicofactoren in de autonome cardiale functie bij depressieve patiënten nader wordt onderzocht, met name omdat risicofactoren meer voorkomen in deze patiëntengroep.

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Curriculum Vitae

Publicaties

Curriculum Vitae

Anita Christina Volkers werd geboren in Alkmaar op 14 januari 1970. In deze plaats doorliep zij de lagere school en later de middelbare school. In 1988 behaalde zij haar VWO diploma aan de Rijksscholengemeenschap Noord-Kennermerland. Aansluitend begon zij aan de opleiding Bewegingswetenschappen aan de Vrije Universiteit (VU) in Amsterdam. Zij studeerde precies 6 jaar na aanvang van deze opleiding af (op 31 augustus 1994) in de hoofdrichtingen Gezondheidkunde en Psychologie en de nevenrichting Docentenopleiding FBW. Tussen 1994 en 1996 was zij werkzaam als onderzoeksmedewerker bij de Docentenopleiding van de Faculteit der Bewegingswetenschappen van de VU en bij de Longitudinal Aging Study Amsterdam (LASA) van het EMGO instituut van deze universiteit. Daarnaast had zij een aanstelling als docent Psychologie en Sociologie bij de opleiding tot A-verpleegkundige van het Westfries Gasthuis in Hoorn. In 1996 volgde zij de Postdoctorale Opleiding Epidemiologie van het EMGO instituut (VU). In het kader van deze opleiding werkte zij als onderzoeksmedewerker bij de epidemiologische studie CALEUR (Calcium Europa) gecoördineerd door TNO. Vanaf september 1996 is zij als assistent in opleiding werkzaam bij de afdeling Psychiatrie van het Academisch Ziekenhuis Rotterdam – Dijkzigt en de afdeling Medische Psychologie & Psychotherapie van de Erasmus Universiteit in Rotterdam. In deze functie verrichtte zij het promotie onderzoek dat in dit proefschrift is besproken en verzorgde zij attitude en gespreksvaardigheden onderwijs aan studenten geneeskunde van de Erasmus Universiteit. In april 2002 begint zij aan haar nieuwe baan bij het Nivel in Utrecht. Bij dit instituut zal zij een epidemiologisch onderzoek uitvoeren naar de diagnostiek en behandeling van depressie bij ouderen in de huisartspraktijk.

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Publicaties

Gieteling M, Volkers AC, Tulen JHM, Van Den Broek WW. Motor activity before and after clinically effective biological treatment in depressed inpatients. In: Sleep-wake Research in the Netherlands. Beersma DGM, Arends JBAM, Van Bemmel AL, Hofman WF, Ruigt GSF (eds). Utrecht, The Netherlands: Elinkwijk BV, 1997;Vol 8: 47-50.

Volkers AC, Tulen JHM, Gieteling M, Wegewijs-De Jong M, Van Den Broek WW. Sleep quality and diurnal motor activity pattern in healthy adult: effects of age and gender. In: Sleep-wake Research in the Netherlands. Beersma DGM, Arends JBAM, Van Bemmel AL, Hofman WF, Ruigt GSF (eds). Utrecht, The Netherlands: Elinkwijk BV, 1997;Vol 8: 119-124.

Volkers AC, Tulen JHM, Van Den Broek WW. Relationships between sleep quality and diurnal variations in mood in healthy subjects. In: Sleep-wake Research in the Netherlands. Beersma DGM, Van Bemmel AL, Folgering H, Hofman WF, Ruigt GSF (eds). Utrecht, The Netherlands: Elinkwijk BV, 1998;Vol 9: 133-137.

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. Severity of depression in relation to motor activity and self-reported sleep characteristics. In: Sleep-wake Research in the Netherlands. Van Bemmel AL, Beersma DGM, Folgering H, Hofman WF, Ruigt GSF (eds), 2000;Vol 11:140-144.

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. Evaluation of motor behavior and sleep/wake pattern in depressed patients with wrist-actigraphy. In: Noldus LP (ed). Measuring Behavior 2000. Proceedings of the 3nd International Conferences on Methods and Techniques in Behavioral Research. Wageningen, The Netherlands: Noldus Information Technology b.v., 2000:341-342.

Tulen JH, Volkers AC, Stronks D, Cavelaars M, Groeneveld W. Accelerometry in clinical psychophysiology. In: Fahrenberg J, Myrtek M (eds). Progress in ambulatory assessment. Seattle WA, USA: Hogrefe & Huber Publishers, 2001, pp 207-231.

Volkers AC, Tulen JHM, Van Den Broek WW, Passchier J, Bruijn JA. Effects of antidepressant treatment on subjective sleep characteristics of depressed patients. In: Sleep-wake Research in the Netherlands. Van Bemmel AL, Beersma DGM, Hofman WF, Ruigt GSF, Vos PJE (eds), 2002;Vol 12:138-141.

Volkers AC, Tulen JHM, Duivenvoorden JH, Gieteling MJ, Wegewijs-De Jong M, Van Den Broek WW, Passchier J, Pepplinkhuizen L. Effect of personality dimensions on the diurnal pattern of motor activity. J Personality 2002; 70(2):233-248.

Volkers AC, Tulen JHM, Van Den Broek WW, Duivenvoorden JH, Passchier J, Pepplinkhuizen L. Age, gender, and risk factors as determinants of interindividual variation in cardiovascular variability and baroreflex sensitivity. (submitted)

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. Motor activity and autonomic cardiac functioning in major depressive disorder. J Affect Disord, 2002. (in press)

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. 24-Hour motor activity after treatment with imipramine or fluvoxoamine in major depressive disorder. E Neuropsychopharmacol, 2002. (in press)

Volkers AC, Tulen JHM, Van Den Broek WW, Bruijn JA, Passchier J, Pepplinkhuizen L. Efects of imipramine, fluvoxamine and depressive mood on autonomic cardiac functioning in major depressive disorder. (submitted)

Koetsier GC, Volkers AC, Tulen JHM, Passchier J, Van Den Broek, Bruijn JA. Attentional performance in major depressive disorder before and after treatment with imipramine or fluvoxamine. (submitted)