Autonomic nervous system functioning in major depression and anxiety disorders

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1.

General Introduction

INTRODUCTION

In 2006, the Harvard University Gazette headed: "Depression is bad for your heart, and your bad heart is bad for your depression, how depressing is that!" which strikingly accentuates the indissoluble and enigmatic association between depression and cardiovascular diseases.

On the list of leading contributors to the global burden of disease, as measured by the Disability Adjusted Life-Years (DALYs, which includes the lost years of life, the prevalence of the disease and a weight factor for the seriousness of the disease[1]), depression and anxiety disorders hold positions two and four. In addition, cardiovascular diseases hold first (coronary artery diseases) and third place (stroke) on this rank[2], not only worldwide but also in the Netherlands (**Figure 1**).

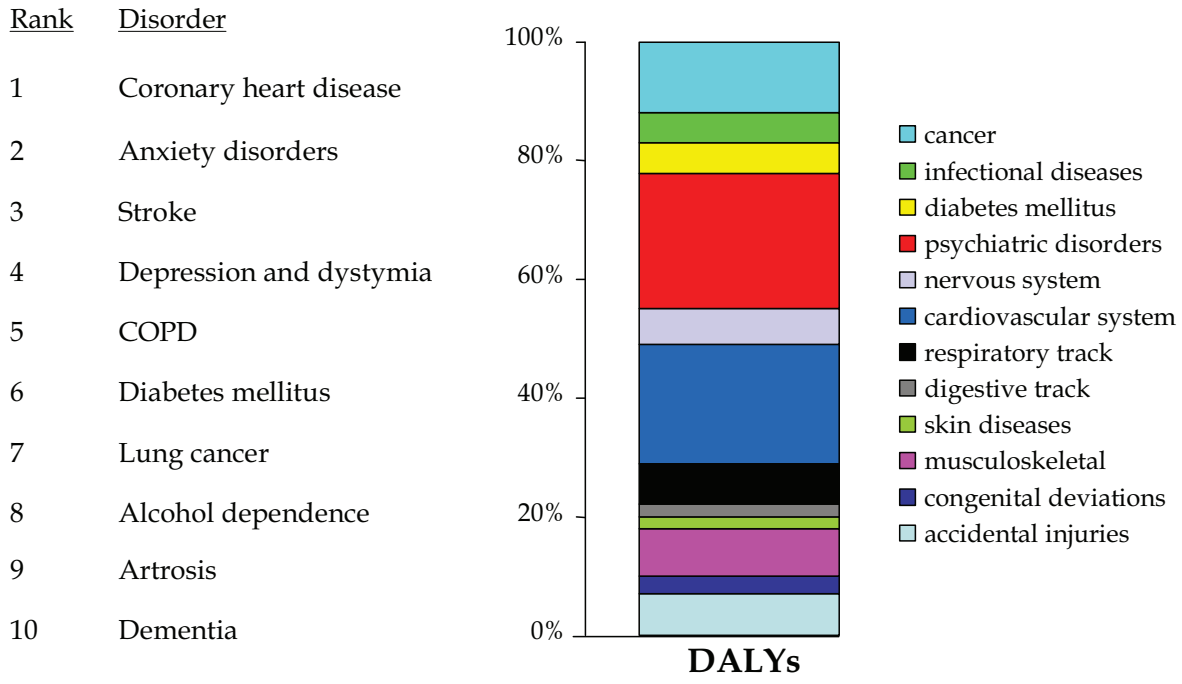


Figure 1. *Rank of disorders contributing most to the Dutch burden of disease and distribution of all burden of disease (based on data of the RIVM[2])*

This figure clearly illustrates that depression, anxiety and cardiac diseases are leading causes in daily disability and cause a serious reduction in quality of life. Because of this major impact on worldwide public health and the high co-occurrence of both depression and heart disease on the one hand and anxiety and

heart disease on the other hand, an extensive body of research focuses on the pathways involved in these relations, although exact mechanisms remain unclear. It is presumed that the autonomic nervous system plays an important role in this 'black box' since dysregulation of this system not only causes cardiac or coronary diseases[3-6], but also potentially associates with depression and anxiety disorders[7-10]. In the present thesis, the functioning of the autonomic nervous system in depressive and anxiety disorders was investigated to examine its possible role in the link between these disorders and cardiovascular diseases.

Depression and anxiety disorders

In The Netherlands, depression and anxiety are not only in the top five of disease burden but in the top ten of most expensive disorders as well. On a yearly basis, about 6% of the Dutch population suffers from a depression and about 11% from an anxiety disorder[11-14]. Females generally have a depression or anxiety disorder twice as often as men do[15].

Depression

Depression is defined as feeling down and gloomy or experiencing a severe loss of interest and pleasure in normally enjoyable activities most of the day and almost every day for at least two weeks. When these criteria are met and attended by at least three or four other symptoms (such as severe eating problems, major change in weight, insomnia, loss of energy, feelings of restlessness or inhibition, melancholy, feeling useless/worthless, feelings of guilt, and recurrent suicidal thoughts) a major depressive disorder (MDD) or unipolar disorder[16] may be present.

Anxiety disorders

Different anxiety disorders are characterized by different fears and physical symptoms. Panic disorder is characterized by sudden anxiety attacks attended with bodily symptoms like gasping for breath, cardiac palpitation, chest pain, nausea, dizziness, shivering, trembling, sweating, cold tremors or tinglings. Patients with panic disorder often have feelings of derealization (outer world is unreal) and depersonalization (living outside the body/mind or as in a dream) and sometimes avoid situations or places in which they had attacks before or that seem arousing/provocating (this avoidance is also known as agoraphobia). Agoraphobia also exists without panic disorder; persons only exhibit a fear of getting panic-like

symptoms and avoid situations with many people or from which one cannot escape (e.g. in public transport, crowded shops, or church, or being in a queue, driving through tunnels or on the highway) without actually experiencing a panic attack. Generalized anxiety disorder is depicted by the continuous pondering about daily worries such as work, finance, health, and shelter without any concrete immediate cause. Amongst the bodily symptoms are fatigue, concentration problems, irritability, dry mouth, cardiac palpitations, aching muscles, sweating, swallow-complaints, diarrhoea, and faint view. The fear of eating, writing, and speaking in public or being in the middle of attention in general, is called social phobia and often is accompanied by panic-like bodily symptoms[16].

A high comorbidity is seen between depression and anxiety disorders: About 60% of persons with depression or anxiety disorders has a second diagnosis of depression or anxiety as well[17-21]. Anxiety disorders often precede depression diagnoses; however, this does not necessarily imply a causal relation[22,23]. The prognosis for persons with comorbid depressive and anxiety disorders is poorer than for patients who have a depressive or anxiety disorder alone. Patients with comorbidity have increased severity of symptoms, increased risk of suicidality, a more chronic course, and more somatic complaints. In addition, comorbidity is more difficult to treat, it takes more time to remission and higher doses of medication are needed[22,24-26].

Cardiovascular disease in depressive and anxiety disorder

Besides the high comorbidity between depression and anxiety, many somatic diseases are seen in patients with a depressive or anxiety disorder as well. For instance, Diabetes Mellitus[27-29], Parkinson's disease[30,31] and cardiovascular diseases[32-34] are more likely to be present in persons with depression or anxiety than in persons without these psychiatric diagnoses. Especially, the comorbidity between depression and anxiety disorders and cardiovascular diseases (CVD) has received much attention in the research field, possibly because of the high mortality and disease burden of CVD[1]. Persons with depression and anxiety have a higher prevalence, incidence, and risk of CVD and concurrently, patients with CVD have a higher risk of getting depressed or anxious[32,34-40]. Among the possible mechanisms that have been hypothesized to explain the relationship between depressive/anxiety disorders and CVD are unhealthy lifestyle factors and dysregulation of metabolic processes, of the hypothalamic-pituitary-adrenal-axis, of inflammatory processes, and of autonomic nervous system functioning.

Depressed and anxious persons tend to exhibit an unhealthier lifestyle than persons without these diagnoses. They generally smoke and drink more (often), engage less in physical activity, have unhealthy food patterns, and a higher body mass index. All of these factors separately, but especially their combination, have been associated with increased risk for CVD[41,42]. A lot of research has been performed on the relationship between depressive and anxiety disorders and metabolic dysregulation and the metabolic syndrome. The metabolic syndrome is characterized by three or more of the following metabolic dysregulations:

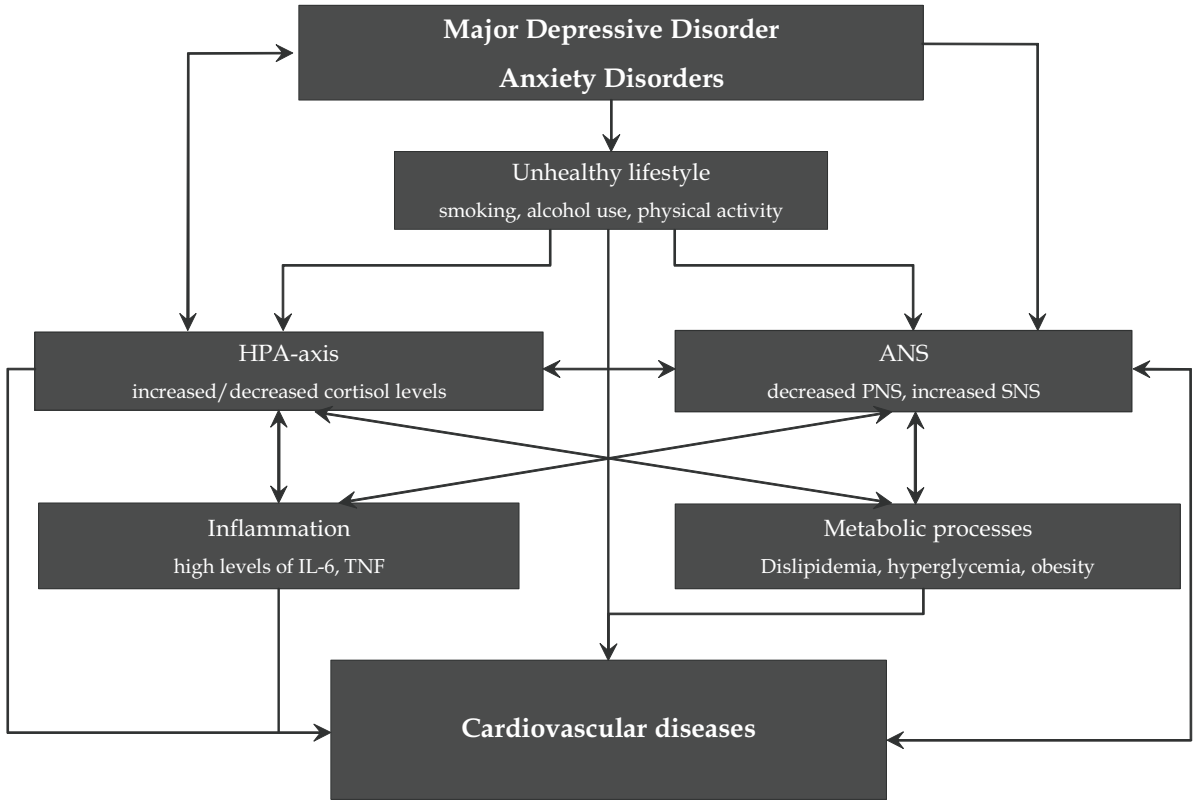


Figure 2. *Schematic representation of possible connections between systems involved in the occurrence of cardiovascular disease*

dyslipidemia, systolic hypertension, hyperglycaemia, and excessive waist circumference. Research provided evidence for causality in both ways, indicating that depression results in metabolic abnormalities, but also that metabolic abnormalities (irrespective of their origin) result in depression and anxiety[43-46]. A closely related process is that of inflammation. It is hypothesized that depression and anxiety coincide with increased production of specific inflammatory markers,

which might lead to arterial inflammation processes related to CVD[47-51]. High cortisol levels that were found in depression and anxiety, caused by increased HPA-axis activity, are associated with increased risk for CVD as well[52, 53].

Dysregulation of the autonomic nervous system, leading to for instance increased heart rate, has proven to be associated with depression and anxiety and with increased risk of CVD. Therefore, it has been hypothesized to play an important role in the relationship between depression, anxiety and CVD[3,6,9,54-58]. Probably, all above-mentioned processes are highly intertwined on a neuronal, chemical, and metabolic level[46,47,49,59-63] and therefore, underlying mechanisms are complex (**Figure 2**).

The autonomic nervous system

The autonomic nervous system (ANS) controls bodily functions that are engaged in homeostasis (the balancing of biophysiological processes in response to changes in the internal and external environment to achieve a physiological steady state). The ANS mainly regulates automatic processes in the body such as sweating, heart rate frequency, pupil reflexes, energy regulation, digestion, and renal function. Specifically, the ANS is involved in the human stress response. The ANS has two divisions or branches: the sympathetic nervous system (SNS), which prepares the human body for action in times of danger and stress and is therefore defined with the term "fright, flight and fight" and the parasympathetic nervous system (PNS) which regulates the resting state of the body and is therefore known as the "rest and digest" branch.

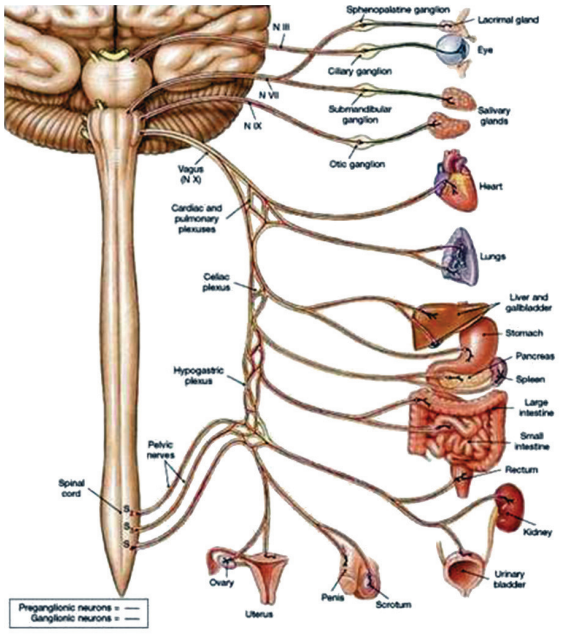
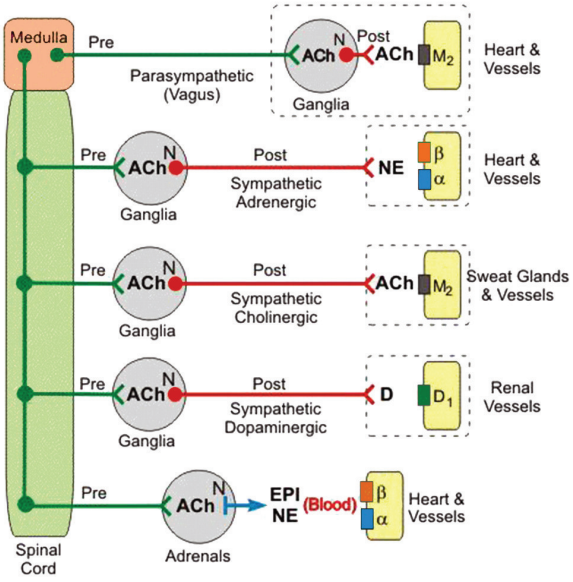


Figure 3. *Distribution of parasympathetic innervation of the organs by cranial and sacral nerves (adapted from Fundamentals of Anatomy & Physiology[64])*

The parasympathetic nervous system

The parasympathetic nervous system or craniosacral division controls the organs via afferent fibres (the preganglionic fibres) of the oculomotor (III), facial (VII), glossopharyngeal (IX) and vagal (X) cranial nerves and the second, third and fourth sacral spinal



CNS = central nervous system; Pre = preganglionic; Post = postganglionic; ACh = acetylcholine; N = nicotinic receptor; NE = norepinephrine; EPI = epinephrine; D = dopamine; M_2 = muscarinic receptor; β = β-adrenoceptor; α = α-adrenoceptor; D_1 = dopaminergic receptor

Figure 4. *Neurotransmitters and receptors in the innervation of the parasympathetic and sympathetic branch (adapted from Cardiovascular Pharmacology Concepts*[65]

nerves (**Figure 3**). These preganglionic fibres innervate the postganglionic neurons in the ganglia, which are (in case of the parasympathetic nervous system) located close to the organs. The neurotransmitter acetylcholine (ACh) is enforced which binds to the nicotine receptors on the postganglionic neurons (**Figure 4**). The postganglionic fibres also use ACh to innervate the organs, although the receptors on the organs are muscarinic. Target organs of the parasympathetic nervous system include salivary glands, the heart, lungs, liver and gall bladder, intestines and reproductive organs. The nervus vagus is the principal nerve of the PNS and the sole parasympathetic nerve to innervate the heart. Vagal fibres end on cardiac plexi on the sinoatrial node (SA node or pacemaker cells) and the atrioventricular node (AV node or electric relay station). Stimulation of the vagal nerve generally causes a decrease in pacemaker rate, thereby causing a decrease in heart rate and a parallel increase in heart rate variability (variation in heart rate frequency).

The sympathetic nervous system

Sympathetic afferents leave the spinal cord at thoracic and lumbar levels to innervate the target organs of the sympathetic branch (or thoracolumbar division, **Figure 5**).

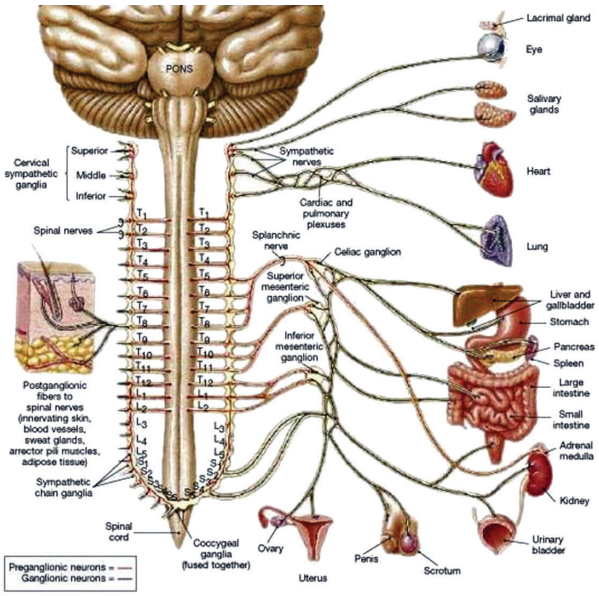


Figure 5. *Distribution of sympathetic innervation of the organs by thoracic and lumbar nerves (adapted from Fundamentals of Anatomy and Physiology*[64]

These preganglionic fibres innervate the postganglionic nerves in the ganglia, which are located close to the spinal cord (in case of the sympathetic nervous system), by ACh. The postganglionic fibres on the other hand, administer several different neurotransmitters. ACh is employed to innervate sweat glands through muscarinic receptors, dopamine acts on dopamine receptors and innervates renal vessels, and norepinephrine (NE) is used as neurotransmitter to innervate the heart and blood vessels. NE acts on α-adrenergic receptors (in e.g. arterioles) and on β-adrenergic receptors (on e.g. the heart, Figure 4). The cardiac sympathetic plexi lie on the ventricles and atria near the SA and VA node. Innervation of α- adrenergic receptors has vasoconstrictive properties and in this way increases blood pressure. Innervation of β-adrenoceptors increases the SA-rate thereby increasing heart rate. In addition, it increases contractility by direct stimulation of the muscles of the atria and ventricles.

Measures of autonomic nervous system activity

In general, there are two ways to measure the autonomic nervous system: (1) the actual sympathetic or parasympathetic activity (autonomic drive) by, for example, measuring action potentials in the nerves or by NE spillover and (2) the effect of autonomic activity on the organs (autonomic control), for example by measuring skin conductance or heart rate. Measuring autonomic drive has a high validity but is also invasive and less feasible. Measuring autonomic control is non-invasive and has a high feasibility, but can introduce within- or between subject variations because of differences in receptor density or efficacy. However, since the autonomic effect on the organs (rather than the autonomic drive in the nerves) mostly determines the vulnerability for and development of diseases, this is a very suitable manner to study ANS functioning in disease-related research. In addition, it enables ANS measurements in large samples.

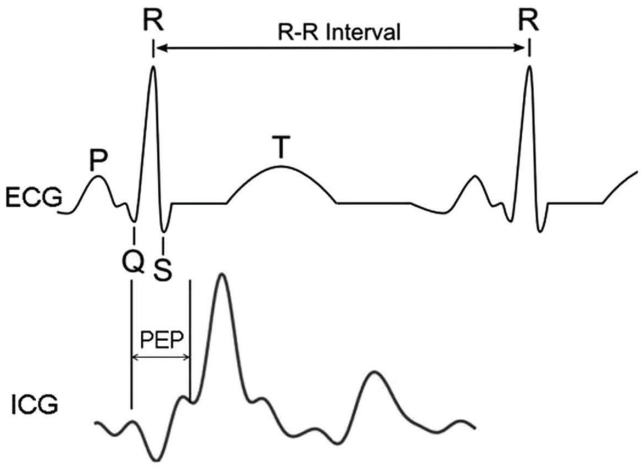


Figure 6. *Timing relationship between ECG and ICG signals, with two successive R tops to illustrate an R-R interval*

There are various laboratory and ambulatory devices designed to measure cardiac autonomic control by recording the electrocardiogram (ECG) and the impedance cardiogram (ICG). Some distinct advantages of ambulatory ECG/ICG devices are that the measurements are not bound to a fixed experimental location, are less obtrusive than laboratory recordings, and yield recordings that are more naturalistic. Heart rate that is controlled by both PNS and SNS activity is derived from the interval between R-R waves in the ECG (**Figure 6**). Heart rate is 60000 divided by the time between two R-R waves (or inter-beat-interval, IBI). For instance, a mean IBI of 882 milliseconds equals a mean heart rate of 68 beats a minute. Time domain indices of heart rate variability include the standard deviation of normal-to-normal interval (SDNN, mainly PNS activity but also SNS[66]), the root mean square of successive differences (RMSSD, pure measure of cardiac vagal control[67]), and respiratory sinus arrhythmia (RSA, pure measure of cardiac vagal control[68-70]). From the ICG the pre-ejection period (PEP) can be derived. Under conditions of unchanged preload and afterload[71] the PEP is a pure measure of cardiac sympathetic control on the contractility of the heart[72,73], with a high PEP signalling low SNS activity.

Cardiac autonomic control in depression and anxiety disorders

As the ANS acutely reacts to threatening and stressful situations, it is hypothesized that the chronic or recurrent stress induced by depressive and anxiety disorders is associated with chronic increases in SNS and decreases in PNS activity. Studies that review or meta-analyze cardiac vagal control report small differences between healthy persons and depressed[74] and anxious persons[58,75]. To date, no reviews have been reported on cardiac sympathetic control, but several - quite small – studies measuring NE spillover or muscle sympathetic nerve activation suggest that persons with anxiety and depression indeed exhibit increased SNS activity[76-78]. However, a major problem with the reported findings is that they failed to take into account potential effects of antidepressant use on SNS and PNS activity. For instance, Van Zyl *et al*. (2008[79]) in a review of the effects of antidepressants on measures of heart rate variability concluded that heart rate variability is reduced by tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs) and that TCAs increased heart rate. In addition, Koschke *et al*. (2009[80]) showed that serotonergic and noradrenergic antidepressants (SNRIs) show the same associations. A paper by Barton *et al*. (2008[81]) further suggests that SSRIs have an SNS decreasing effect. In short, the widespread

antidepressant use among mood disorder patients may have confounded the previously reported relationship between ANS activity and depression and anxiety.

The Netherlands Study of Depression and Anxiety (NESDA)

To study the epidemiology of autonomic nervous system functioning in depressive and anxiety disorders, the present thesis is based on a large depression and anxiety cohort: the Netherlands Study of Depression and Anxiety (NESDA). NESDA is a prospective cohort study that started with 2981 participants, 18-65 years of age, with and without depressive and anxiety disorders. Participants were recruited from 65 general practices (n=1610), from two population studies (ARIADNE[82] and NEMESIS[83], n=564) and through mental health care institutions (n=807). In this way, persons with a variety in severity of psychopathological symptoms were included. The mean age of the study sample was 41.9 years (standard deviation [SD] =13.0) and 66.4% was female. All respondents were invited to one of the 17 field locations to participate in the NESDA study.

The NESDA interviews were performed by ca. 40 trained interviewers and taped to monitor data-quality and interviewer performance. The baseline interview was conducted between 2004 and 2007, took about three and a half hours, and consisted of a blood draw, administering several psychiatric questionnaires, a medical examination (e.g. measurement of length, weight, blood pressure and grip strength), and a computer task. For a detailed description of the rationales, objectives and methods of NESDA we refer to Penninx *et al*. (2008)[84]. A face-to-face follow-up was performed after two years and 87.0% of the participants responded (n=2596). Similar assessment composition as used at baseline was conducted to create comparable interviews.

Psychiatric diagnoses

The Composite Interview Diagnostic Instrument (CIDI) – lifetime version 2.1 – based on the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) - was used as the main diagnostic instrument. The CIDI determines the presence or absence of depressive and anxiety disorders. In total, 1688 persons met a current MDD or anxiety diagnosis, 632 had a MDD or anxiety disorder in remission, and 652 were defined as healthy controls. Of the persons with a current diagnosis, 22.7% had a current MDD diagnosis, 33.9% had a current

anxiety disorder diagnosis and 43.4% had a comorbid (current MDD and a current anxiety disorder) diagnosis.

Autonomic nervous system measurements in NESDA: VU-AMS

In NESDA, ANS activity was measured using the VU University Ambulatory Monitoring Device (VU-AMS), which was developed at the Department of Biological Psychology of the VU University (www.psy.vu.nl/vu-ams)[85,86]. The VU-AMS is an ambulatory device that participants were wearing during the NESDA interview and was attached to the belt or put in a pocket. In this way, participants had full freedom of movement and a semi-natural setup was created. The VU-AMS measures ECG and ICG by six electrodes placed on the chest and back (**Figure 7**). The device was attached on average one and a half hour after the start of the interview (right before the blood pressure measurement). An 'event button' could be used to mark a specific time point in the signal to register changes in assessment or posture. A built-in vertical accelerometer enabled us to distinguish between sitting and standing/walking and to excise the latter non-stationary parts from the final data used in the analyses. At baseline, VU-AMS data was present for 2861 persons, in 118 participants measurements failed due to attachment and signal problems of the electrodes (e.g. caused by excessive sweating, breast hair or severe obesity) and other technical difficulties or poor signal quality (e.g. artefacts or undefinable noise). After excluding irregular or non-stationary parts (on average 19.5 minutes), an average registration of 98 minutes (SD=24.5) was obtained in the final VU-AMS sample. The mean heart rate in this sample during these 98 minutes was 72.0 beats a minute (SD=9.6).

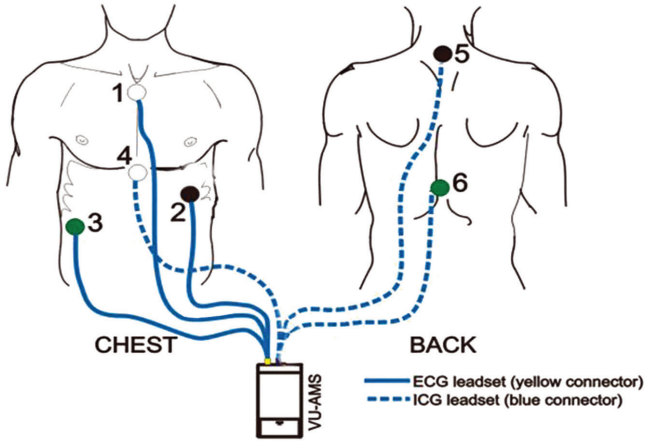


Figure 7. *VU-AMS and lead electrode placement*

Other (mental) health and lifestyle factors

To profile symptoms of depression and anxiety the 30-item Inventory of Depressive Symptomatology (IDS) self-report version[87] and the 21-item Beck Anxiety Inventory (BAI[88]) were used. The IDS and BAI measure different

symptoms distinctive for depression (e.g. insomnia) and anxiety (e.g. dizziness) but also provide total scores, which can be used as indicators of severity.

Respondents were asked to bring along the containers of medication they used in the past month. Medication names (brands and active component), dose, and advised frequency of intake were copied by the interviewer. In addition, information about duration of use, current use, and side effects was obtained. Brand and substance names corresponding the Anatomical Therapeutic Chemical (ATC) Classification codes of the World Health Organization Collaborating Centre for Drug Statistics Methodology[89] were used to classify medication. Of specific interest in this thesis were cardiac medication (ATC code C, e.g. antihypertensives), metabolic related medication (different ATC codes, e.g. nicotinic acid) and psychopharmaca (ATC code N). Three types of psychopharmaca were distinguished: antidepressants (N06A), benzodiazepines (N03AE, N05BA, N05CD, and N05CF), non-depression related psychoactive medication (N01, anaesthetic drugs; N02, analgesic drugs; N03, anti-epileptic drugs; N04, anti-Parkinson disease drugs; N05, psycholeptic drugs; N06B, psychostimulants; N06D, antidementia drugs, and N07, other nervous system drugs). Antidepressants were further classified as selective serotonin re-uptake inhibitors (SSRIs, N06AB), tricyclic antidepressants (TCAs, N06AA), and serotonergic and noradrenergic working antidepressants (SNRIs, including mirtazapine and venlafaxine).

Information on lifestyle habits such as smoking, alcohol use, and physical activity was obtained. In addition, the presence of chronic diseases such as cardiovascular diseases, thyroid diseases, ulcers, cancer, and diabetes was determined.

During medical assessment weight, height, and waist circumference were measured. In addition six blood pressure measurements were performed, four times on the arm (two Doppler measurements and two with the OMRON M4 IntelliSense [HEM-752A, Omron Healthcare, Inc., Bannockburn, Illinois, USA]) and two times on the ankle (Omron). Blood was drawn in which, amongst others, glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, and inflammatory factor levels were determined.

General aim of this thesis

The main aim of this thesis is to examine parasympathetic and sympathetic activity in depression and anxiety disorders in a large cohort taking the effects of

antidepressants into account. An additional aim is to examine a specific part of the – highly intertwined – network of the biological systems that underlies the risk for

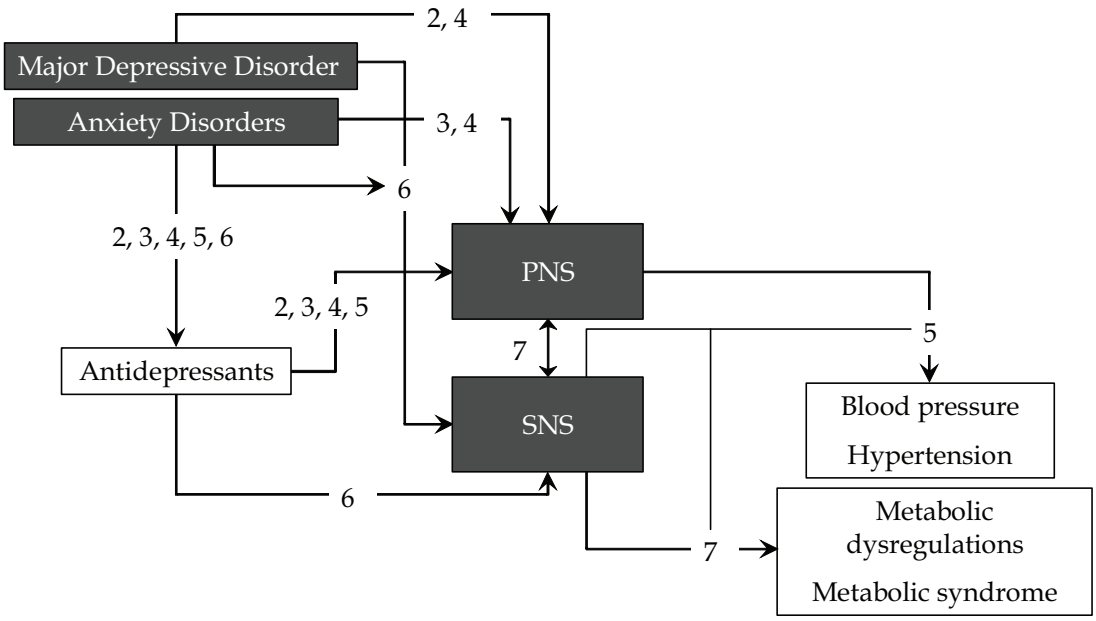


Figure 8. *Graphical representation of the outlines of the present thesis. Chapter numbers that address specific relations are given next to the arrows*

CVD: the relationship between ANS and metabolic abnormalities. The outline of this thesis is summarized in **Figure 8**.

Outline of this thesis

This thesis first addresses ANS activity in MDD and anxiety disorders using cross-sectional analyses. Subsequently, longitudinal data is analyzed to study causality of several previously found results. Finally, the relationship between two stress systems and the metabolic syndrome is examined.

As depicted in Figure 8, Chapter 2 covers the association between cardiac vagal control and MDD. Chapter 3 describes the relation between cardiac vagal control and anxiety disorders. Longitudinal results presented in Chapter 4 addresses the question whether antidepressant use affects cardiac vagal control and is causally related to cardiac changes. Whether effects of antidepressants on vagal control result in an increase in blood pressure is investigated in Chapter 5. The association between cardiac sympathetic control and anxiety/MDD is examined in Chapter 6, by comparing the PEP between healthy controls, antidepressant-naïve depressed and anxious persons, and persons with a depression or anxiety disorder using different antidepressants. Finally, the relationship between ANS activity and HPA-axis activity with metabolic

dysregulations and the metabolic syndrome is described in Chapter 7. Results of Chapter 2 through 7 are summarized and discussed in Chapter 8.

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