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Heart Rate Variability in Stress-related Fatigue, Adolescent Anxiety and Depression and its Connection to Lifestyle

ERIK OLSSON

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Abstract
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Heart rate varies constantly as a consequence of activity in the sympathetic and parasympathetic autonomic nervous systems (SNS and PNS). In short-term recordings, heart rate variability (HRV) is mostly related to the inhibitory activity of the vagal nerves, which are part of the PNS. HRV is lower when under stress as well as in several illnesses and psychiatric conditions. Decreased HRV is also related to cardiac disease, which is the leading cause of death worldwide. Autonomic imbalance, measured as HRV, is suggested as a mediator between psychosocial distress and cardiovascular disease.

The aim of the present thesis was to investigate the connection between HRV and psychosocial distress, including psychiatric problems (studies I and II), and lifestyle factors (study III). In study I, additional physiological measures sensitive to autonomic activity and results from a continuous attention test were investigated in parallel with HRV. In studies II and III the participants were adolescents.

The results show that HRV is lower in women with stress-related fatigue and adolescent girls with a psychiatric diagnosis compared to healthy control groups. However, these groups did not exhibit an increase in physiological measures of SNS origin, which supports the assumption that the observed hyperarousal is related to decreased vagal activity rather than increased SNS activity. Women with stress-related fatigue made more impulsive errors and had a "risky" response style in the continuous attention test. There was a negative correlation between test performance and HRV. Decreased vagal activity is thus associated with deficient behavioural inhibition. In study III, HRV in a group of healthy adolescent boys and girls was positively associated with physical activity but not with other lifestyle measures.

Even at young age HRV is a sensitive marker of autonomic imbalance resulting from psychosocial stress. Future longitudinal research will show whether HRV can be used for early identification of people at risk of cardiovascular disease and whether such interventions will lower the risk of cardiac morbidity.

Keywords: heart rate variability, autonomic nervous system, vagal tone, allostatic load, stress, fatigue, anxiety, depression, continuous performance, attention, cardiovascular risk, lifestyle, physical activity

Erik Olsson, Department of Psychology, Box 1225, Uppsala University, SE-75142 Uppsala, Sweden

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…when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric [vagus] nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body.

Charles Darwin, The Expression of Emotion in Man and Animals, 1872

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Olsson, E. M. G., Roth, W. T. & Melin, L. (2010) Psychophysiological characteristics of women suffering from stress-related fatigue. *Stress and Health*, 26(2):113-126

II Henje Blom, E., Olsson, E. M., Serlachius, E., Ericson, M., & Ingvar M. (2010) Heart rate variability (HRV) in adolescent females with anxiety disorders and major depressive disorder. *Acta Pædiatrica,* 99(4):604-611

III Henje Blom, E., Olsson, E. M., Serlachius, E., Ericson, M., & Ingvar, M. (2009). Heart rate variability is related to self-reported physical activity in a healthy adolescent population. *Eur J Appl Physiol,* 106(6):877-883.

Contents

Introduction 11
The adaptiveness of physiology 11
Heart rate variability 14
The quantification of HRV 15
Stress, exhaustion and HRV 18
Depression, anxiety and HRV 19
Lifestyle and HRV 21
The influence of age, gender and genetics on HRV 21
Stress response measures other than HR and HRV 22
Cardiovascular risk factors 23
SSRIs and cardiovascular risk 24
Cognitive performance 24
Aims of the present thesis 25

The empirical studies 27
General method of measuring heart rate variability 27
Study I: Psychophysiological characteristics of women suffering from stress-related fatigue 28
Aims 28
Method 28
Results 31
Discussion 34
General method of studies II and III 38
Participants 38
Study II: Heart rate variability is related to anxiety and depression in adolescent girls 39
Aim 39
Method 39
Results 41
Discussion 44
Study III: Heart rate variability is related to self reported physical activity in a healthy adolescent population 45
Aim 45
Method 45
Results 45
Discussion 46

General discussion 48
Limitations 51
Future research 52

Acknowledgements 53

References 54

Abbreviations

AD	Anxiety Disorder
ANOVA	Analysis of Variance
ANS	Autonomic Nervous System
AUC	Area Under the Curve
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMI	Body Mass Index
CFS	Chronic Fatigue Syndrome
CNS	Central Nervous System
DBP	Diastolic Blood Pressure
DAWBA	Development and Wellbeing Assessment Diagnosis
DSM-IV	The Diagnostic and Statistical Manual of Mental Disorders 4th ed.
ECG	Electrocardiogram
GAS	General Adaptation Syndrome
HF	High Frequency power
HPA	Hypothalamic Pituitary Adrenocortical
HR	Heart Rate
HRV	Heart Rate Variability
IBI	Inter-Beat Interval
ICD-10	International Classification of Diseases 10th rev.
LF	Low Frequency power
MADRS	Montgomery Asberg Depression Rating Scale
MDD	Major Depressive Disorder
PD	Panic Disorder
PNS	Parasympathetic Nervous System
PTSD	Post Traumatic Stress Disorder
RR	Respiration Rate
RSA	Respiratory Sinus Arrhythmia
SBP	Systolic Blood Pressure
SCL	Skin Conductance Level
SDNN	Standard Deviation of Inter-Beat Intervals
SDQ	Strengths and Difficulties Questionnaire
SNS	Sympathetic Nervous System
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Subjective Units of Distress
VE	Vital Exhaustion

Introduction

The adaptiveness of physiology

Heart rate (HR) constantly fluctuates in a seemingly random fashion. Of course, an organ as vital as the heart does not beat randomly. Can we give meaning to these apparently meaningless fluctuations? Is it just noise or is it music? This question was raised in an article in 1989 where the authors stated that these fluctuations "have traditionally been ignored or, at best, treated as noise to be averaged out" (Appel, Berger, Saul, Smith, & Cohen, 1989). We will come back to this question. Let us first consider a bigger picture; it is not only our HR that varies.

Our bodies are constantly responding to everything we experience. Among other things, muscle tension, breathing rate and sweating continuously change. These changes are important in the support of fundamental behaviour, such as eating and reproduction, and in order to maintain an inner stability, known as homeostasis. When we face an external threat or challenge, the physiological response is called the "stress response". Walter Cannon (1915) coined the term "fight or flight response" to describe this response, since the pattern facilitates the behaviours fight and flight, which are believed to be the most relevant to survival in these situations. The stress response involves many physiological systems, for example, the heart beats faster, the breathing rate increases and muscles tense up. Central to Cannon's research was the importance of homeostasis. Our human bodies are capable of autonomically maintaining, for example, a stable core temperature, blood pH, blood glucose and oxygen supply to the brain and the heart. Our ability to maintain homeostasis has developed during evolution and is not as autonomic in, for example, reptiles and lower vertebrates. Cannon writes "homeostasis has released for the exercise of their peculiar services, the higher functions of the brain" (Cannon, 1941). Cannon lived and worked during both World Wars and could draw parallels between mobilization of a person's physiological resources and the priorities of a society. A time of peace and harmony may involve the provision of infrastructure and building facilities, while emergency and acute problems require resources (Cannon, 1941). In parallel, the body needs a balance between resource spending (catabolic) responses and saving (anabolic) states to maintain physiological equilibrium and health. This brings us to the concept *allostasis*, which has evolved from *homeostasis* to include the more slow and quantitatively larger changes that

still make up an adaptive balance (McEwen, 1998). The human stress response will help us to adapt to the dangers and threats in our environment, with spending of resources during stress and saving during safety, when the stress response is no longer needed. If the activated, consuming processes are; overworked, fail to shut off after stressful events or respond inadequately to the initial challenge, it may lead to reduced adaptiveness and disease. These states are called allostatic load or overload (McEwen, 1998).

Activation in a typical fight or flight pattern is not the only stress response. The "freeze-response" is characterized by immobilization and sometimes appears in life-threatening situations and when facing blood or injuries. If neither fight nor flight are available choices, or if an individual is seriously hurt, to "freeze" may be an adaptive behaviour.

It is mainly through our autonomic nervous system (ANS) that signals from the brain reach the target organs which make up the stress responses. The ANS consists of two branches; the sympathetic and the parasympathetic nervous system (SNS and PNS). Roughly speaking, one can say that while the SNS is mainly catabolic, raising activity and spending recourses, PNS is anabolic, lowering activity and saving recourses. While the SNS is characterized by "fight and flight", the PNS is characterized by "rest and digest". One example is that activity in the SNS increases HR while activity in the PNS lowers it. These two branches of the ANS do not necessarily work in an anticipatory manner. They can also interact or operate in a completely unrelated way (Berntson, Cacioppo, & Quigley, 1991; Hugdahl, 1996). Often overlooked is the fact that the vagus nerve, which is an important part of the PNS, contains both myelinated and unmyelinated nerve fibres that descend from slightly different places in the medulla in the central nervous system (CNS). In the Polyvagal theory, Stephen Porges described the two vagal systems and argued for their importance in behaviour (Porges, 2001). Myelinated nerve fibres descend from the nucleus ambiguus while unmyelinated nerve fibres descend from dorsal motor nucleus. These two types of neuron have developed at different times in evolution. The unmyelinated vagus is older. Reptiles have unmyeliniated vagal nerves but only mammals have myelinated ones. Mammals' uniqueness means that we, in the early stages of evolution, could regulate activation and energy consumption by inhibition only. It is comparable to regulating a car's speed with only a brake, which is manageable but not very sophisticated. It is through this branch of the ANS that the so-called freeze response, mentioned above, operates. This response can, at worst, be lethal since it can make the heart stop. Phylogenetically, the myelinated vagus is the latest, even later than the SNS. The myelinated nerve fibres are involved in our preparation for dealing with the most complex of human environments, namely the social. This involves controlling facial muscles, our prosody in speech and muscles in the ear that allow us to focus our listening on either human voices or lower frequencies (elephant herds approaching) depending on the situation (Porges, 2007). All these as-

pects are important for social interaction. An increasingly intelligent physiology has evolved and we have become more sophisticated in our adaptation to the environments we may find ourselves in. The ANS is not as non-cognitive and separate from cortical structures in the CNS as pedagogical models might indicate. Instead much research suggests that the CNS and the ANS are intimately related (Hugdahl, 1996). With special focus on the PNS, Julian Thayer and colleagues have proposed a theory called the Neurovisceral integration model, where the inhibitory action originating in the prefrontal cortex, via the vagus nerve, is of importance for affective and attentional regulation in anxiety and depression (Thayer & Lane, 2000). In support of this theory, correlations between regional cerebral blood flow and HRV have been found (Åhs, Sollers, Furmark, Fredrikson, & Thayer, 2009). The Neurovisceral integration model has also been the basis of research, indicating that vagal activity may influence glucose regulation, hypothalamic pituitary adrenocortical (HPA) system functioning and inflammatory processes (Thayer & Sternberg, 2006).

ANS is not the only system by which the body is becoming physiologically prepared. The HPA-system, mentioned in passing above, with its secretion of cortisol, is an important system involved in the human stress response. We will touch on this subject below even though focus in the following will be on the ANS and especially on HR.

In addition to a general congenital preparedness to respond physiologically, these reactions can be learned. This allows us to adapt to our specific environment. For example, we can learn to react with arousal in environments where we have experienced danger. This coupling of a specific relevant but idiosyncratic environment and a physiological response is accomplished by classical, or Pavlovian, conditioning. Conditioning experiments have frequently been carried out on both humans and animals. There was, for example, a tradition in the Soviet Union following Pavlov. Instrumental, or operant, conditioning, on the other hand, is applicable first of all to overt behaviours that involve voluntary muscles. Most famous are B. F. Skinner's experiments with his operant conditioning chamber, also known as the "Skinner box", where laboratory animal behaviours, such as pressing a lever, were reinforced in a variety of schedules. Signals to voluntary muscles are mainly distributed through the somatic nervous system and not the ANS. It has been debated whether the ANS could be instrumentally conditioned. In the 1960s, Neal Miller conducted some famous experiments in which he used Curare to paralyse the muscles of rats. He then tried to instrumentally reinforce HR increases and decreases (DiCara & Miller, 1968; Miller & Banuazizi, 1968). This was done in several experiments with seemingly clear effects on ANS behaviours through the principles of instrumental conditioning. If this was true, we would be able to learn to control physiological responses, which were thought of as autonomic, in the same manner as we learn how to play tennis or to cycle. Miller's findings were the basis and

starting point for biofeedback as a therapeutic method. Biofeedback has since been found to be effective for a variety of problems, such as headache and hypertension (Yucha & Montgomery, 2008). Even though this principle seems to work in clinical practice, Neal Miller's experiments, and the conclusions made, have been questioned. The experiments could not be replicated, and the method using curare to paralyse muscles turned out to be more complicated and less clear-cut than he had thought (Dworkin & Miller, 1986). It has also been questioned whether it is evolutionarily beneficial to us if the ANS can be instrumentally conditioned (Peters, 1974). Several experiments were conducted before 1974. Thereafter this issue has been more or less dead. Barry Dworkin, a former student of Miller's, promises in an article of 1995 to return to this subject (Dworkin & Dworkin, 1995). To date, nothing convincing is to my knowledge published, by him or anyone else.

In conclusion, it is clear that our physiology has the capacity to be highly adaptive to a variety of situations. Now the perspective will be narrowed to the focus of the present thesis, namely the HR. We will return to the question raised by Appel et al., quoted above (1989) – Are the fluctuations in HR noise or music?

Heart rate variability

Since 1989 when Appel et al. put their question to press, the body of research about heart rate variability (HRV) has grown. Several statistical methods have been applied, and meaning has been gathered from this signal.

We know that HR is very responsive to behaviour. As the metabolic demands increase, for example when running, the heart beats faster, but also when comfortably seated in an armchair, psychological stimulus, such as frightening pictures, arithmetic tasks, loud noise, being observed by others etc, will raise HR. As already mentioned, HR is regulated through both branches of the ANS. The PNS is faster in its response and accounts for more variability than the SNS, at least in shorter time spans. The PNS acts upon HR through the vagal nerves. Beside physical activity and emotions, breathing causes a large proportion of the variability in HR. This works mainly by central respiratory reflexes affecting the vagus nerve, partially blocking it during inhalation, which raises HR, and then when vagus is in full inhibitory effect during exhalation, the HR decelerates. This variability is called Respiratory sinus arrhythmia (RSA). RSA has therefore been used as an indicator of vagal activity and is frequently employed in functional tests of the ANS. While breathing is considered a source of high frequency HRV, body temperature regulation is a source of very slow HRV of which other sources are to a large extent still unknown (Berntson et al., 1997).

As mentioned above, we can find two types of vagal nerve fibre which have evolved at different phylogenetic time points, descending from differ-

ent places in the medulla. While the older vagus is unmyelinated, the newer is myelinated. To some extent, these two types of nerve fibre work in a similar fashion and both have an inhibitory effect on HR. However, there are situations when they are in conflict with each other. In fetal distress during delivery, activity in the unmyelinated vagus can cause bradycardia which can be lethal. Activity in the myelinated vagus in newborns is, on the other hand, a sign of health and is protective (Porges, 2007). This inconsistency of the vagal nerve function is called the "vagal paradox". Activity in the myelinated vagus can be observed in the RSA during normal breathing while the unmyelinated vagus is slower in its response.

Much effort has been put into explaining the origin of HRV and its relationship to different clinical conditions, while its function (what is it good for?) has been treated more sparsely. Oxygen supply and temperature regulation, for example, are mentioned above. The function of RSA is especially puzzling. One study aimed at examining the function of RSA found that pulmonary gas exchange is much more effective if inhalation and exhalation are matched to heart rate acceleration and deceleration, respectively, compared to a regular HR or the opposite pattern (Hayano, Yasuma, Okada, Mukai, & Fujinami, 1996).

HRV has become an important measure in health research. It has been demonstrated to be an independent predictor of mortality and also of hypertension (Bigger, Fleiss, Rolnitzky, & Steinman, 1993; Singh et al., 1998). A decreased HRV has been found to be related to an increased risk of death and to have a predictive value for life expectancy and health (Tsuji et al., 1996). The causality between decreased HRV and illness is still not clear. It may be that the presence of a dysregulated ANS shown in decreased HRV causes less adaptive responses to the strains of life, resulting in accumulating physiological strain, or that decreased HRV is an early symptom of a failing cardiovascular system.

The quantification of HRV

Heart rate variability is exactly what it says, namely the variability in HR. However simple this may sound, there has been considerable effort put into quantifying it. The measures used can be put into one of two categories of statistics; time domain or frequency domain. Time domain measures are based on the inter-beat interval (IBI), i.e. the distance in milliseconds (ms) between normal heart beats, most often measured as R-R intervals in an electrocardiogram (ECG; see *Figure 1*). The measure most often used in this category is the standard deviation of the IBIs (SDNN). Another example is the count of every consecutive IBI that differs from the next by more than 50 ms, called NN50. There are several further indices more or less related to the SDNN and NN50 that represent different aspects of variability, some of

which are more general while others are more specific, and some are robust while others are sensitive. In frequency domain measures, methods like the Fourier transformation or Fast Fourier transformation applied on the R-R tachogram are used to explore variability in IBIs as a function of frequency (see *Figure 2*). With these methods, the complexity of the variation is separated into different frequency components. Much the same methodology can be applied to music. The complex waveform of the sound of a chord consists of the specific and characteristic frequency components of the included notes which can be separated and identified with Fourier transformation. In the same way, different frequency components are separated from the complex variability of a beating heart which can be made visible in a periodogram (see *Figure 3*). Slower variability, parallel to bass notes in music, can have several causes, while fast variability, high pitch notes, must be vagal. In a periodogram from a 24 hour HR recording, four different peaks are often observable. Based on these peaks, four frequency bands are commonly used. The slowest is called ultra low frequency power (0.0001 – 0.003 Hz). Here we can find influences of circadian and diurnal rhythms that can be related to, for example, activity cycles or temperature regulation. Very low frequency power (0.003 – 0.04 Hz) can be caused by, for example, movements and stress. In the band of low frequency power (LF; 0.04 – 0.15 Hz), a typical peak called Mayer waves is usually observable. This variability is believed to be the result of oscillations in the baroreceptor and chemoreceptor reflexes. Some variability caused by very slow breathing and stress is also possible in this frequency band. Activity in the unmyelinated (older) vagus can be observed in this frequency band. The fourth band is called high frequency power (HF; 0.15 – 0.4 Hz) and its main influence is normal breathing. Therefore HF is often used synonymously with RSA. The myelinated (newer) vagus operates in this frequency band. Sometimes the ratio of LF to HF is used as an indication of sympatho-vagal balance. The rationale behind this index is that, compared to HF, LF is more influenced by the SNS. HRV measures in the different frequency domain indices are generally correlated, and they all have a connection to health (Task Force, 1996).

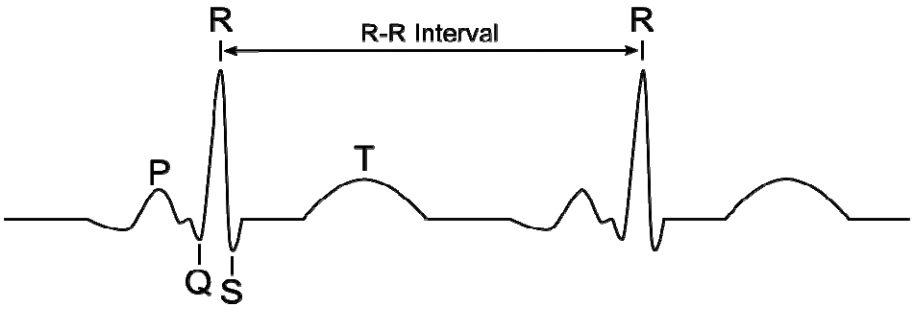

Figure 1. Electrocardiogram (ECG) showing the R-R interval (inter-beat interval).

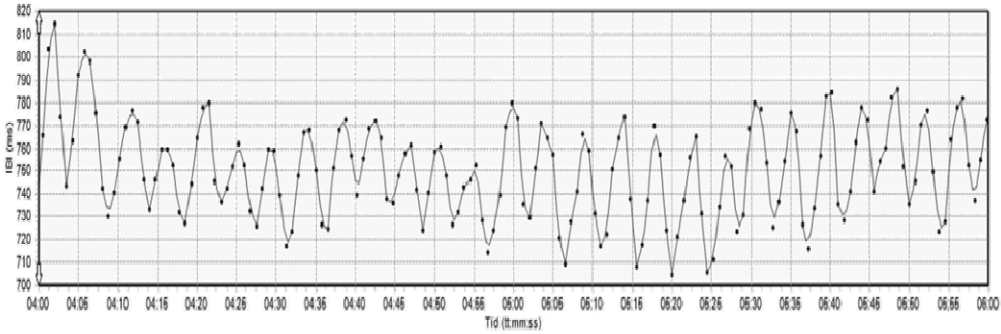

Figure 2. R-R tachogram illustrating the R-R intervals (IBIs) on a 2 minute time axis.

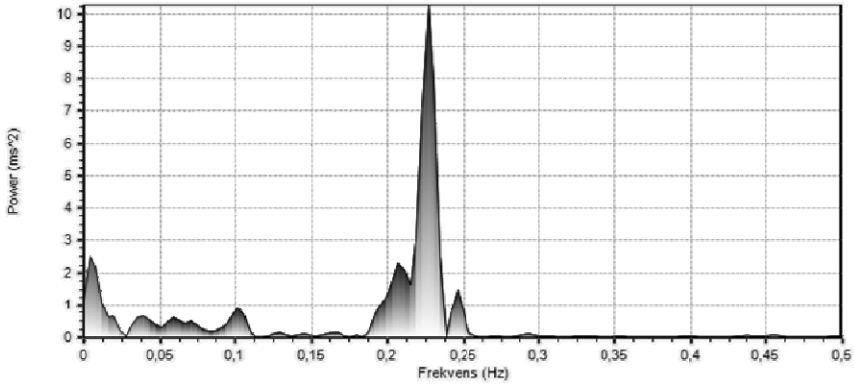

Figure 3. The R-R interval variability in Figure 2 as a function of frequency.

Stress, exhaustion and HRV

A connection between HRV and acute stress has been established. For example, when there are high stress levels during computer work, HRV is lower (Hjortskov et al., 2004), and exposure to stressors and daily worrying are both related to decreased HRV the same day and even during the subsequent night (Brosschot, Van Dijk, & Thayer, 2007). It has also been found that workers under high levels of strain have lower HRV than workers under low levels of strain (Kang et al., 2004).

Prolonged stress can lead to exhaustion. This connection between stress and energy loss has been investigated under several names. Hans Selye has been one of the most influential researchers in this field. He proposed a model called the General adaptation syndrome (GAS; 1951). This model describes three consecutive stages for adaptation to prolonged stress. Selye writes "Anything that causes stress endangers life unless it is met by adequate adaptive responses; conversely, anything that endangers life causes stress and adaptive responses. Adaptability and resistance to stress are fundamental prerequisites for life and every vital organ and function participates in them" (1951). During the first phase, *the alarm reaction*, the threat overwhelms the physiology and balance is disturbed. Thereafter, during *the stage of adaptation*, resources are gathered and balance restored. The manifestations of the last phase, *stage of exhaustion*, resemble the alarm reaction and Selye states that "'the adaptation energy' is a finite quantity" (1951). The theory of GAS has been very influential and has often been applied to stress-related disease. Burnout syndrome may be the most well known example that also involves fatigue (Maslach, Schaufeli, & Leiter, 2001).

Related to this model is the already mentioned concept *allostasis*, which means adaptability through change and allostatic load, or even overload, which is defined as "the wear and tear on the body and brain resulting from chronic overactivity or inactivity of physiological systems that are normally involved in adaptation to environmental challenge" (McEwen, 1998). Much of what in Selye's GAS theory is somewhat blunt, unspecific and even contradicting later research has been dealt with in the literature about allostasis (McEwen, 2005). Decreased HRV has been linked to several measures of allostatic load and to poor recovery from stress. The possible importance of vagal activity to regulate allostatic systems other than cardiovascular has been proposed (Thayer & Sternberg, 2006; Weber et al., 2010).

Stress-related fatigue has been frequently linked to reduced HRV. For example, in fatigue due to overtraining, sleep deprivation, long working hours and extended simulated car driving, HR tends to be less variable (Baumert et al., 2006; Jiao, Li, Chen, Wang, & Qi, 2004; Mourot et al., 2004; Park et al., 2001; Sasaki, Iwasaki, Oka, & Hisanaga, 1999; Takase et al., 2004). HRV is also lower in patients with chronic fatigue syndrome (CFS) even though the link to stress in this condition is not clear (Boneva et al., 2007; de Becker et

al., 1998; Freeman & Komaroff, 1997; Yamamoto, LaManca, & Natelson, 2003). The relationship between stress-related fatigue and HRV is certainly of importance since psychosocial stress and stress-related fatigue have been found to be predictive of future cardiac events (Appels & Mulder, 1988; Appels & Schouten, 1991; Rozanski, Blumenthal, & Kaplan, 1999; Schatzkin et al., 1984).

In conclusion, reduced HRV can be observed both in stress and in fatigue believed to be a consequence of stress and is therefore an indication of allostatic load. There is a link from these conditions to cardiovascular disease. Whether HRV can be used to reduce this risk in stress conditions by, for example, identification of persons at risk is still unknown.

Depression, anxiety and HRV

The relationship between anxiety and depression and how they should be diagnosed has been discussed, and the standard way to diagnose them as separate phenomena has not gone unchallenged. Factor analytic studies have found a common feature of a negative affect in both syndromes, but with the difference that hyperarousal is specific to anxiety while anhedonia is specific to depression (Clark & Watson, 1991). In line with this, one large Dutch cohort study (more than 2000 subjects) found that patients with an AD had reduced HRV compared to healthy controls (Licht, de Geus, van Dyck, & Penninx, 2009). In that study there was no difference between different ADs. Evidence for an association between decreased HRV and panic disorder (PD) has been found in several studies (Friedman & Thayer, 1998; McCraty, Atkinson, Tomasino, & Stuppy, 2001; Yeragani et al., 1990; Yeragani et al., 1993). But not all the evidence is in agreement. For example, no HRV differences in PD and obsessive-compulsive disorder compared to healthy controls have been found (Slaap, Nielen, Boshuisen, van Roon, & den Boer, 2004).

In variance with the above mentioned theory that state hyperarousal to be specific to anxiety, short-term measures have demonstrated decreased HRV also in patients with major depressive disorder (MDD) compared to healthy controls (Agelink, Boz, Ullrich, & Andrich, 2002; Imaoka et al., 1985; Rechlin, Weis, Spitzer, & Kaschka, 1994), but no differences have also been reported (Lehofer et al., 1997; Rottenberg, 2007). The above mentioned Dutch research project also compared a large patient cohort with a current diagnosis of MDD (n=1075) with healthy controls and found reduced HRV in all indices in the clinical group (Licht et al., 2008). It has been debated whether the differences between standard HRV indices in patients with MDD versus healthy controls can be explained by co-morbid ADs (Tulen et al., 1996) and/or decreased physical activity (Watkins, Grossman, Krishnan, & Blumenthal, 1999). Psychotropic medication has been proposed to explain

decreased HRV (Lehofer, et al., 1997). In the Dutch studies mentioned above, all significant differences for AD disappeared and were strongly reduced for MDD, when psychoactive medication was accounted for (Licht, et al., 2009; Licht, et al., 2008). The literature on pharmacological treatments of MDD is inconclusive, and pharmacological improvements of depressive symptoms have also been associated with increased HRV (Balogh, Fitzpatrick, Hendricks, & Paige, 1993). A more thorough discussion on this topic follows below.

Depression and anxiety have been linked to a higher risk for cardiovascular disease (Rozanski, et al., 1999). Depression is present in about 20% of patients with postmyocardial infarction (Green et al., 2009). There are several possible links between depression and cardiac events (Carney, Freedland, Veith, & Jaffe, 1999). Smoking and hypertension is known risk factors that are more present in depressed patients. Another possible link is that depression is associated with poor adherence to cardiac rehabilitation. These links between depression and cardiovascular events deserve attention but has not been conclusively supported. A more promising link is that altered cardiac autonomic tone, which can be studied in HRV, plays a mechanistic part (Bleil, Gianaros, Jennings, Flory, & Manuck, 2008; Carney et al., 2005; Carney et al., 2001; Carney & Freedland, 2009; Carney et al., 2007). It is also important to bear in mind that cardiac autonomic tone has other implications than HRV that might be important to cardiovascular risk, such as coronary vasomotion and platelet activation (Carney, et al., 1999).

Unfortunately, treating depression successfully does not improve event free survival in initially depressed patients after myocardial infarction (Berkman et al., 2003). Furtermore, treating depression successfully doesn't normalise autonomic tone. A treatment for depression that also involves the mechanisms that contribute to cardiovascular morbidity and mortality is still lacking (Carney, et al., 1999).

The Neurovisceral integration model, mentioned above, has linked ANS dysregulation to the pathophysiology of anxiety and depression (Thayer, Hansen, Saus-Rose, & Johnsen, 2009; Thayer & Lane, 2000). According to this theory, the regulation of ANS is important for how we perceive, interpret and react to our environment, and it is central to cognitive, emotional and physiological adaptation. Thereby it integrates the CNS and the ANS. There is now support for the idea that hyperarousal, which is believed to be an important characteristic of AD, is the result of a deficit in the inhibitory activity of the PNS, rather than increased SNS. Recent data show that vagal tone is decreased in both AD and MDD, indicating an impairment of the descending vagal pathways (Friedman & Thayer, 1998; Greaves-Lord et al., 2007; Thayer & Lane, 2000).

All studies mentioned above are conducted on adults with MDD or AD. Empirical data of HRV in children or adolescents with anxiety and/or depression are sparse. Apart from study II, we found only one that specifically

addresses this connection (Tonhajzerova et al., 2010). This study found less HRV in depressed girls than in healthy controls. There are, however, many reasons to believe that several aspects of anxiety and depression in adolescents are different when compared to adults; among other things, the still maturing brain, further explored below, the amount of external influence and the duration of disease.

Lifestyle and HRV

Several lifestyle factors are related to HRV in adults. The most studied is physical exercise, which has been found to have a beneficial effect on autonomic control of the heart, with decreased resting HR and increased HRV (Felber Dietrich et al., 2006; Hottenrott, Hoos, & Esperer, 2006; Tuomainen, Peuhkurinen, Kettunen, & Rauramaa, 2005). Lack of sleep or disturbed sleeping patterns, which can result from lifestyle factors, also correlates with HRV. Shift workers, people with fragmented sleep or recurring nightmares and patients with sleep apnoea have deranged HRV (Furlan et al., 2000; Gula et al., 2003; Nielsen et al., 2010; Sforza, Pichot, Cervena, Barthelemy, & Roche, 2007). Smoking decreases HRV in healthy adults both acutely and long term (Alyan et al., 2008; Barutcu et al., 2005; Felber Dietrich, et al., 2006; Hayano et al., 1990; Karakaya et al., 2007). Alcohol has a negative impact on HRV while studies on caffeine show inconsistent results (Ingjaldsson, Laberg, & Thayer, 2003; Rauh, Burkert, Siepmann, & Mueck-Weymann, 2006; Sondermeijer, van Marle, Kamen, & Krum, 2002; Thayer, Hall, Sollers, & Fischer, 2006). When it comes to body mass index (BMI), the results are to date inconclusive (Antelmi et al., 2004; Molfino et al., 2009; Rabbia et al., 2003).

The relationship between HRV and lifestyle is not as well studied in children and adolescents. Furthermore, with some exceptions, it is not known even in adults whether exposure to these lifestyle factors contributes to a lower HRV or if some underlying factor may explain the results, for example psychosocial stress or some biological vulnerability which might lead to reduced HRV and affect lifestyle.

The influence of age, gender and genetics on HRV

There is a modification of HRV with age, which reflects the evolving ANS (Silvetti, Drago, & Ragonese, 2001). HF, reflecting a maturing PNS, increases from infancy to childhood and stabilises after the age of 10 but increases slightly still in adolescence (Silvetti, et al., 2001). This is accompanied by a decreased HR during the same ages, which also reflects a maturing PNS. A very similar pattern applies to more general and more sympatheti-

cally influenced variability. A small decrease in HRV can be seen already in early adulthood (Finley & Nugent, 1995). Thayer et al. established that the prefrontal cortical influence on HR evolves with age and argue that adolescence may be a critical age in this development (Thayer et al., 2009). When it comes to gender differences, data are inconclusive, but a higher HRV in boys is most frequently reported, which might be due to the established lower HR also found in boys (Faulkner, Hathaway, & Tolley, 2003).

Later in life HRV decreases linearly with age. Women are reported as having more HF between 40 and 50 years of age than men while men have more LF between 40 and 60. Thereafter no differences between men and women can be observed (Kuo et al., 1999).

HRV is hereditary. According to the Framingham Heart study, the covariates; age, BMI, HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and coffee, alcohol and nicotine consumption, explained between 13 – 40% of the variance among HRV measures, whereas genes accounted for 13 – 23%.

In addition to the factors explored in detail above, HRV is influenced by several somatic diseases, and cardiovascular disease and diabetic autonomic neuropathy are among the most studied (Task Force, 1996).

Stress response measures other than HR and HRV

As mentioned above, many aspects of our physiology apart from HR and HRV respond to stressors. In study I, some of these measures are used in parallel with HR and HRV. Skin conductance level (SCL) and peripheral temperature, resulting from muscles constricting the blood vessels, are highly influenced by ANS activity and, unlike HRV, mainly in the SNS. Respiration is regulated in a more complex way but partly influenced by the ANS. When exposed to stress, ventilation increases, which in turn results in a drop in plasma CO_2. The CO_2 level can therefore be used to assess if breathing is in excess of metabolic demands, which is the definition of hyperventilation (Ley, 1999). A change in CO_2-level is the result of changes in respiration rate (RR) and/or tidal volume. Some researchers have pointed out that CO_2 level can be an advantageous measure of psychosocial stress, since it can differentiate between metabolic and psychosocial demands, which in most other measures, such as HR, generate the same response (Schleifer, Ley, & Spalding, 2002). CO_2-level is often measured as end-tidal CO_2 ($EtCO_2$) which allows for assessment of breath by breath variation. Oxygen saturation (SpO_2) expresses how much oxygen is transported in the blood, i.e. the level of haemoglobin saturation. The amount of O_2 carried depends on factors such as the amount of O_2 available in the inhaled air, the temperature and the blood pH, which in turn is influenced by the CO_2-level.

Cortisol is a glucocorticoid and is released in response to stress. Its primary function is to increase the blood glucose level and it has important anti-inflammatory effects. It can be measured in serum, urine or saliva. To measure saliva cortisol is comfortable and painless and gives estimates of the fraction of free unbound cortisol, which is the biologically active form. Saliva samples are also advantageous compared to those of blood and urine in that they can be taken more frequently. Saliva cortisol is used to measure the responsiveness of the HPA-system to stressors. Several procedures have been applied, such as measuring at certain intervals distributed over the day, at certain activities or on waking and before going to bed. However, the most used is the response during the first hour of awakening measured by 3 – 5 saliva samples taken at certain intervals (Fekedulegn et al., 2007). These kinds of measure have been used to compare different clinical groups. Many studies have found an elevated response during the first hour of awakening in burnout syndrome, CFS, MDD and AD (Alderling et al., 2008; Bhagwagar, Hafizi, & Cowen, 2005; de Vente, Olff, van Amsterdam, Kamphuis, & Emmelkamp, 2003; Grossi et al., 2005; Wood, Wessely, Papadopoulos, Poon, & Checkleya, 1998) while the outcomes of other studies have revealed no differences or contradictory results (Huber, Issa, Schik, & Wolf, 2006; Mommersteeg, Heijnen, Verbraak, & van Doornen, 2006). High levels of morning cortisol are also associated with poor rest and recovery from work stress (Gustafsson, Lindfors, Aronsson, & Lundberg, 2008).

Cardiovascular risk factors

Among the most documented risk factors for cardiovascular disease are smoking, obesity, hypertension and diabetes mellitus (Wilson & Culleton, 1998). These risk factors have all been associated with decreased HRV (Hayano, et al., 1990; Jensen-Urstad, Reichard, & Jensen-Urstad, 1999; Rabbia, et al., 2003; Singh, et al., 1998).

Obesity is usually based on the BMI (BMI = weight (kg) / height^2 (m)). A value above 30 is often considered to indicate obesity. Besides HRV, obesity is also related to hypertension and high blood glucose values even in adolescence (Molfino, et al., 2009; Rabbia, et al., 2003). The results are, however, not conclusive (Antelmi, et al., 2004).

Hypertension is one of the most important risk factors for cardiovascular disease (Wilson & Culleton, 1998). Since blood pressure tends to increase with age, many people with high-normal blood pressure will develop hypertension with ageing. Blood pressure control is considered a main strategy for preventing cardiovascular mortality (Williams et al., 2004).

Fasting blood glucose level in the general population is also inversely correlated with HRV (Singh et al., 2000). High fasting blood glucose levels can be a sign of impairment in the glucose regulation and even undiagnosed dia-

betes. These findings may imply that impaired glucose regulation is also a risk factor for cardiovascular disease even when diabetes mellitus is not diagnosed. An intensive glucose control strategy can effectively reduce the risk of major cardiovascular events (C. Y. Zhang et al., 2010).

In the appended papers, an attempt has been made to control for the most important cardiovascular risk factors, which is especially important since they correlate with HRV.

SSRIs and cardiovascular risk

Cardiovascular disease is the leading cause of death overall and the prevalence of cardiovascular events tends to be higher in a psychiatric population. Several reasons for this have been proposed, such as a higher incidence of smoking, obesity, lack of exercise and stress. Given that there is an elevated risk of cardiovascular disease in psychiatric, especially depressed, patients and that psychotropic medications are among the most prescribed, one might speculate about the connection between these medications and cardiovascular disease. Earlier reviews and guidelines have reported cardiovascular effects and elevated risks of cardiovascular events from several psychotropic medications, but selective serotonin reuptake inhibitors (SSRIs) are generally considered safe both in normal use and overdose and even in children and adolescents (Cohen, Gibson, & Alderman, 2000; Feinstein, Khawaja, Nurenberg, & Frishman, 2002; Gutgesell et al., 1999; Kovacs & Arora, 2008). Protective properties, such as reduced cardiac workload, reduced risk of myocardial infarction in smokers and inhibition of platelet aggregation, have also been proposed in SSRIs (Feinstein, et al., 2002; Kovacs & Arora, 2008). Recently however, there have been studies indicating that taking SSRIs may be a risk factor for cardiovascular events, especially in women (Krantz et al., 2009; Whang et al., 2009). Some authors suggest the use of HRV to identify patients not suitable for this type of medication (Koschke et al., 2009). When evaluating these results, one should consider that the use of SSRIs, compared to non-use and the use of alternatives, may coincide with several other important factors, such as more depression and prescription of SSRIs in depressed patients with heart problems, since they are believed to be safer than alternative medications. It is also important that untreated depression is a risk factor for both mortality and low quality of life.

Cognitive performance

A common complaint in psychosocial stress and fatigue is cognitive dysfunction. The fatigue syndrome criteria used in study I include lacking mental energy and difficulties with attention and/or memory. Whether perform-

ance is actually impaired or whether these complaints are misperceptions is uncertain (Österberg, Karlson, & Hansen, 2009). Although inconclusive, some studies have found an association between the subjective complaints and objective performance in patients with CFS and burnout syndrome compared to healthy individuals in terms of worse performance when it comes to spatial working memory, sustained attention and non-verbal memory (Capuron et al., 2006; Marshall, Forstot, Callies, Peterson, & Schenck, 1997; Sandstrom, Rhodin, Lundberg, Olsson, & Nyberg, 2005).

The theory behind the Neurovisceral integration model, mentioned several times above, is proposed from data indicating that the decreased HRV in patients suffering from anxiety and depression is accompanied by problems in affective and attentional regulation (Thayer & Lane, 2000). This can be linked to dis-inhibition. The association between high HRV and low impulsivity in continuous performance tests has been demonstrated (Booij et al., 2006; Hansen, Johnsen, & Thayer, 2003). It has been speculated that impulsivity is the common characteristic in most conditions and syndromes that have low HRV, such as AD, MDD, attention-deficit/hyperactivity disorder, substance abuse, suicidal tendencies and hostility (Booij, et al., 2006).

Aims of the present thesis

Asking the initial question from 1989 about whether HRV is "noise or music" may now, in 2010, seem a little like preaching to the choir. Everyone agrees that meaning can be gathered from the HRV-signal. In recent decades, a considerable quantity of research has been produced involving HRV. A search in the PubMed database for articles with "Heart rate variability" included in the title gave 160 hits between 1980 – 1989, 1259 hits between 1990 – 1999 and 2277 hits between 2000 – 2009. These figures reflect a growing interest and a rapidly growing knowledge base.

The aim of the present thesis is to fill in some gaps in the knowledge about the connection between HRV and conditions with high allostatic load, including psychiatric problems, and lifestyle factors. In study I, the connection between HRV and stress-related fatigue is investigated. As described above, the question of whether there is a connection is to a large extent answered. In contrast to earlier studies, participants in study I were diagnosed according to clinical criteria instead of cut-off scores on self-rating scales. Furthermore, data collection was carried out during three standardized conditions, in combination with several other physiological and performance parameters in addition to HRV. This will make it possible to draw conclusions about whether or not the expected lower HRV will agree with other parameters and be valid during different conditions. A special focus will be on the link between impulsivity and HRV, since vagal activity is in essence inhibitory.

In studies II and III, findings in adults about the association between psychiatric disorders and lifestyle in connection with HRV will be reinvestigated, this time in adolescents. In study II, we also explore the relationship between HRV and antidepressants in adolescents, an area sparsely studied.

Cardiovascular disease is the leading cause of death worldwide and allostatic load present in stress-related fatigue and psychiatric disorders seems to increase the risk. HRV might be used to identify people at risk. The next step will be to find interventions to reduce this risk. Generally, any intervention will have a better prognosis if it can be applied early, at best before manifest morbidity.

The empirical studies

General method of measuring heart rate variability

In all three studies the same equipment and method were applied assessing HRV. The equipment was an I-330-C-2 physiological monitoring system (J&J Engineering; Poulsbo, WA) and c-Stress customized software (PBM Systems, Stockholm, Sweden). The ECG was recorded from electrodes placed on the left and right wrist with a sampling rate of 1024 Hz. For HR and HRV, IBIs were calculated on-line using an R-wave peak detection algorithm and stored on a PC for off-line processing. IBIs were scanned manually for ectopic beats, which were replaced using cubic spline interpolation. More than 5% missing or distorted data in any registered HRV segment resulted in exclusion of the participant in all analyses. Fourier analysis was performed on 5 minute (study I) or 2 minute (studies II and III) segments of detrended data passed through a Hamming window. The HRV measures analysed were HF, LF and SDNN. The values of LF and HF were analysed after logarithmic transformation.

Study I: Psychophysiological characteristics of women suffering from stress-related fatigue

Aims

The aim of study I was to investigate whether, compared to healthy controls, women suffering from stress-related fatigue would have (a) less HRV, (b) higher cortisol response upon waking and/or (c) inferior performance on a continuous performance task. Some other cardiovascular, respiratory and autonomic measures were studied in parallel.

Method

Participants

The diagnosis of stress-related fatigue was based on the following criteria suggested by the *National Board of Health and Welfare* as symptoms of *Fatigue syndrome* (2003): daily symptoms of fatigue lasting for at least 2 weeks that were related to a specific identified stressor that had been present for at least 6 months; lack of mental energy; impaired daily functioning; and physiological or behavioural symptoms such as headache, sleeping problems, irritability, or problems with attention and/or memory. These symptoms could not be related to substance abuse or other psychiatric or medical disorders. Women with stress-related fatigue were invited by advertisement to participate in a treatment study with an herbal extract, the results of which are published elsewhere (Olsson, von Schéele, & Panossian, 2009). Our final stress-related fatigue group comprised 36 women. Six regularly took SSRIs which is the first treatment option for this condition. Previous reports are inconsistent as to the extent to which these medications affect HRV and waking salivary cortisol (Bar et al., 2004; Harmer, Bhagwagar, Shelley, & Cowen, 2003; Kovacs & Arora, 2008; Licht, et al., 2008; Nadeem, Attenburrow, & Cowen, 2004).

Controls were nineteen healthy female volunteers who went through the same procedure as the clinical group. Controls had to state that they were generally healthy, did not have any serious disease and were not currently or had not been on sick leave for more than 14 days during the past year. The mean age of the controls was 40 years while the 36 women with stress-related fatigue averaged 41 years of age. Three women in the control group took an SSRI.

Procedure

The test leader conducted the tests in a room normally used for psychotherapy. Participants were provided with full information and signed an informed consent form prior to commencing the tests. The study was approved by the Ethics Committee at Uppsala University.

Participants completed the subjective rating scales and underwent the psychophysiological procedure, which included a computerized continuous performance test. They were then provided with four cotton rolls for the collection of saliva the next day.

Fatigue symptoms were quantified using Pines' Burnout Measure questionnaire (Hallsten, Bellaagh, & Gustafsson, 2002). Depressive symptoms were measured by means of the Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). Mental and Physical health was measured with the SF-36 questionnaire (Sullivan & Karlsson, 1998; Sullivan, Karlsson, & Ware, 1995).

After a 10 minute adaptation period, during which the participant was comfortably seated in an armchair connected to the equipment, the psychophysiological recording began. The first phase was a 10 minute baseline during which participants listened to an unexciting audio book in order to distract the participants from the recording procedure. The second phase was 14 minutes of continuous performance testing, where participants were instructed to press the mouse button as quickly as possible when a letter appeared at irregular intervals on a screen, with the exception of the letter "X". In the third phase, participants were asked to relax for 10 minutes. Throughout the procedure, $EtCO_2$, SpO_2 at the finger, RR, HR, finger temperature and SCL were measured continuously. Every 5 minutes, Subjective units of distress (SUD) on a scale from 1 (totally calm) to 10 (extremely distressed) were recorded. All data were scanned manually for artefacts, which were edited out except for IBIs, which were replaced as explained below. Participants with more than 5% distorted data in any parameter in any segment were excluded from analysis.

Measurements

The HRV was retrieved as described above (common method). Specific to this study, the mean of two 5 minute baseline segments represents baseline, the mean of two 5 minute segments from the continuous performance task phase represents stress (thus cutting 4 minutes of the non-stationary tails from the beginning and end of the test) and the mean of two 5 minute segments from the relaxation phase represents relaxation. All mean values were used statistically after logarithmic transformation to avoid skewed distribution. Transforming HRV-data is a standard procedure (Task Force, 1996).

$EtCO_2$ was identified as the peak of the CO_2 concentration at the end of exhalation and sampled from a nasal cannula. $EtCO_2$ corresponds well to arterial pCO_2 and can be used to identify hyperventilation (Gardner, 1994). RR was calculated as breaths per minute from CO_2 fluctuations. SpO_2 was recorded at 2 Hz from a finger sensor placed on the third digit of the left hand. SCL was measured from the middle phalanges of the digits 2 and 4 of the left hand using isotonic gel. Finger temperature was measured by a thermistor taped to the distal phalanx of digit 5 of the left hand. Blood pressure

was taken every 5 minutes. Mean blood pressures were calculated for each phase.

For collection of saliva samples, Salivette® cotton rolls (Sarstedt, Rommelsdorf, Germany) were used. Participants were instructed to hold them in the mouth for at least 1 min or until they were soaked through. The first sample was taken immediately upon waking while still in bed, and subsequent samples 15, 30 and 60 min after waking. The area under the curve (AUC) was calculated according to the trapezoidal formula with the first measurement as baseline. Cortisol levels, but not the AUC, were logarithmically transformed to avoid skewness. Three control participants were excluded: two had saliva samples that were dry upon arrival in the laboratory, and one was an outlier in cortisol level and AUC (> 4SD higher than the mean).

Cognitive performance was assessed using a computerized version of Conners' Continuous Performance Test II (CCPT-II; Conners, 2003; Conners, Epstein, Angold, & Klaric, 2003). Five indices were used: (a) omissions; not responding when a response is required (the unprocessed number of errors was used in the analysis); (b) commissions; responding when a response is not required (the unprocessed number of errors was used in the analysis); (c) hit reaction time for the correct responses measured in ms; (d) detectability, also known as d', where a high value indicates good ability to distinguish a signal from noise; and (e) response style, also known as β, which is a measure of impulsivity (the trade-off between speed and accuracy). A low value indicates a risky response style whereas a high value indicates that safety is a priority. d' and β are based on signal detection theory. One participant in the control group was excluded from the performance test analyses because her CCPT-II results were very atypical (> 5 SD from the mean).

Statistics

Two-way, between-within analyses of variance (ANOVA) were used to analyse the physiological measures and subjective units of distress. The two main effects indicate an overall group difference and an overall stress response, and an interaction effect indicates different responses to the experimental phases by the two groups. The response in saliva cortisol during the first hour after waking was post-hoc tested with Tukey HSD. Since the CCPT-II commission- and omission-errors were not normally distributed, the non-parametric Mann-Whitney U-test was applied when comparing the groups. Pearson product-moment correlations were used to analyse the relations between the main outcome measures and fatigue and depression respectively. For these analyses, the mean HRV for the full procedure (30 minutes) was used. Spearman rank order correlations were employed to analyse the relations between the main outcome measures and the CCPT-II -

indices. In these analyses, the HRV-measures during testing were used. The alpha level was set at $p < .05$.

Results

The fatigued group gave higher ratings of distress (SUD) throughout the experimental procedure as evidenced by a significant main effect of group ($F(1, 53) = 4.81$, $p = .03$). The test procedure raised SUD in both groups taken together, resulting in a significant main effect of condition ($F(2, 106) = 96.16$, $p < .0001$). There was no interaction effect in SUDS. All HRV measures were significantly lower in the fatigued group than in controls (LF: $F_{Group}(1, 53) = 4.67$, $p = .04$; HF: $F_{Group}(1, 53) = 4.49$, $p = .04$; SDNN: $F_{Group}(1, 53) = 7.76$, $p = .007$) and were significantly affected by condition (LF: $F_{Condition}(2, 106) = 5.86$, $p = .004$; HF: $F_{Condition}(2, 106) = 6.01$, $p = .003$; SDNN: $F_{Condition}(2, 106) = 3.63$, $p = .03$). Further, HF showed a significant group x condition interaction ($F_{Group\ x\ Cond.}(2, 106) = 3.44$, $p = .04$). It is noteworthy that the groups did not differ in IBI or RR (see *Figure 4*).

When it comes to the more exploratory measures, $EtCO_2$ and SpO_2 were lower, and finger temperature higher, in the fatigued group ($EtCO_2$: $F_{Group}(1, 53) = 4.99$, $p = .03$; SpO_2: $F_{Group}(1, 53) = 5.36$, $p = .02$; finger temperature: $F_{Group}(1, 53) = 5.43$, $p = .02$). Furthermore, $EtCO_2$, SpO_2, SCL, SBP and DBP were significantly affected by condition ($EtCO_2$: $F_{Condition}(2, 106) = 19.3$, $p < .0001$; SpO_2: $F_{Condition}(2, 106) = 5.47$, $p = .006$; SCL: $F_{Condition}(2, 106) = 28.0$, $p < .0001$; SBP: $F_{Condition}(2, 106) = 21.1$, $p < .0001$; DBP: $F_{Condition}(2, 106) = 23.7$, $p < .0001$).

Saliva cortisol showed no main group effect across the four time points, but a significant time effect ($F_{Time}(3, 150) = 12.93$, $p < .0001$) and a group x time interaction ($F_{Group\ x\ Time.}(3, 150) = 4.20$, $p = .007$) (see *Figure 5*). Post-Hoc testing with Tukey's HSD test reveals that the cortisol level at waking was significantly lower than all the other sample times in the fatigued group. AUC was also greater in the fatigued group than in the healthy controls ($t(50) = 2.77$, $p = .008$).

The correlations between ratings of fatigue and depression were highly significant in the two groups, both separately and when combined ($r = .72 – .88$, $p = .002 – .0001$, $n_{fatigue} = 36$, $n_{controls} = 19$). In the combined sample ($n = 55$), correlations between all the main outcome indices of HRV and cortisol response (AUC) on one hand and depression (MADRS) and fatigue (Pines) on the other, were significant (HRV: $r = - .27$ to $- .42$, $p = .049 – .002$; AUC: $r = .29$ and $.33$, $p = .04$ and $.02$). In the separate groups, none of these correlations were significant.

With regard to the cognitive test, the fatigued group performed differently from the healthy control group in that they made significantly more commission errors ($p = .004$) and responded faster ($p = .005$). Concerning the two signal detection indices, the fatigued group ($n = 36$) had both lower d' - ($p =$

.03) and β-values (p = .03) than healthy controls (n = 18), indicating difficulty distinguishing signal from noise as well as a more impulsive, risky response pattern in the fatigued group. Omission errors did not differ significantly between the groups (p > .05). There were significant negative Spearman´s rank correlations between commissions and HF and significant positive ones between d' and HF both for the total group (r_s = -.28 and .29 respectively, both ps = .04, n = 54) and for the fatigued group (r_s = -.35 and .41 respectively, p = .04 and .01, n = 36). No other correlations between the main outcome indices and the test results were significant.

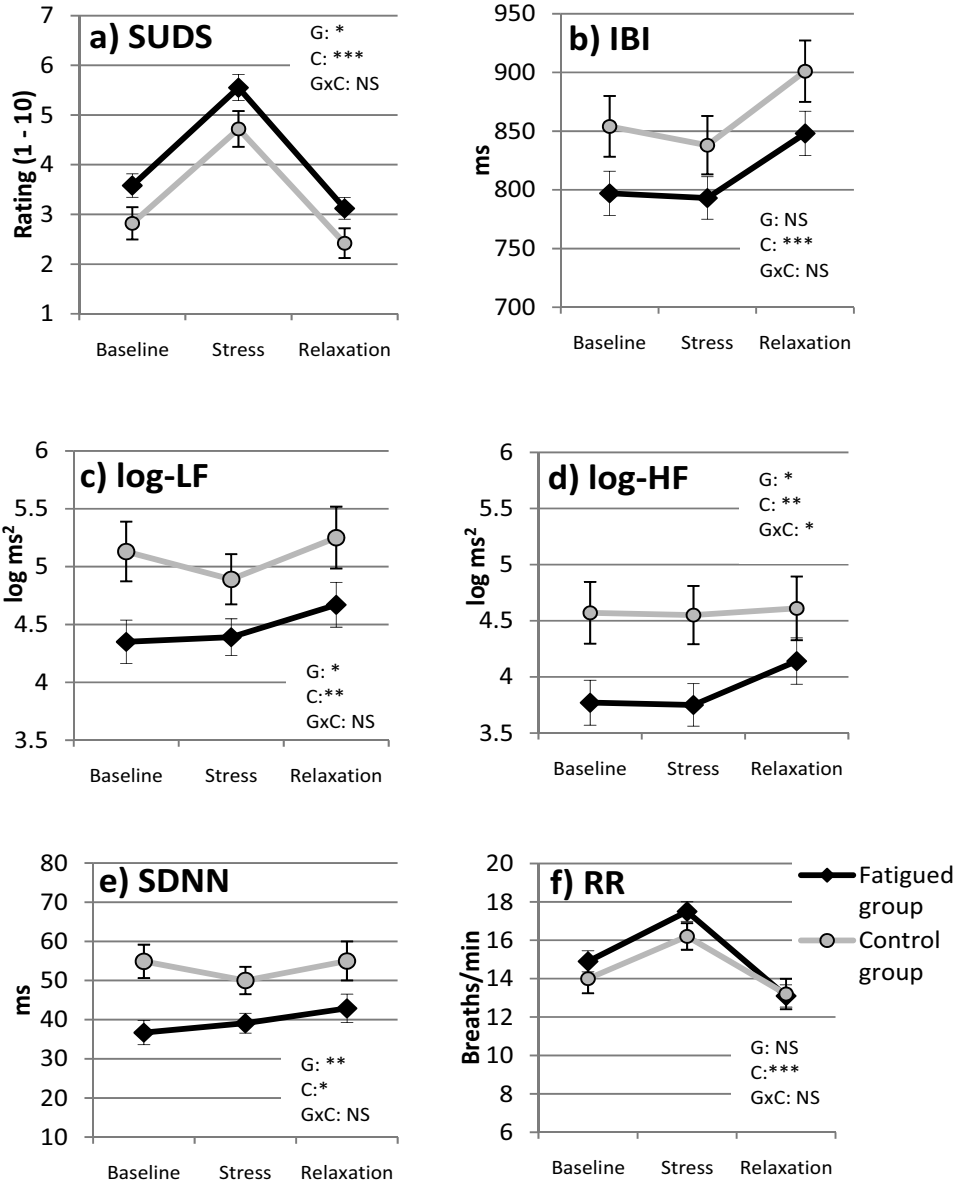

Figure 4. Subjective units of distress (SUDS; a), inter-beat intervals (IBIs ;b), log low frequency power HRV (log LF; c), log high frequency HRV (log HF; d), standard deviations of IBIs (SDNN; e) and respiration rate (RR; f) during the three experimental conditions. The significant effects of two-way, within-between, ANOVAs are indicated by G = main effect of group, C = main effect of condition and GxC = the interaction effect. NS = not significant, * = $p < .05$, ** = $p < .01$, *** = $p < .001$. Vertical bars denote standard errors.

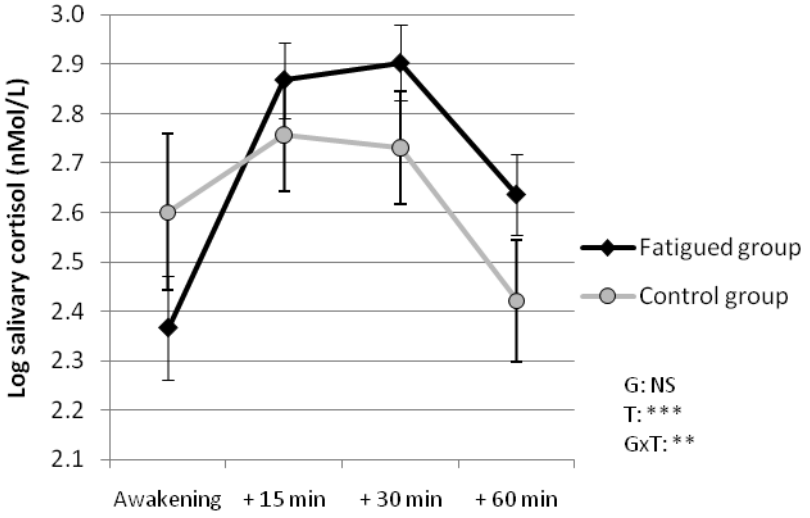

Figure 5. Cortisol response to waking showing log-transformed mean values of salivary cortisol over time after waking for patients with stress-related fatigue (n = 36) and healthy controls (n = 16). The significant effects of a two-way, within-between, ANOVA are indicated by G = main effect of group, T = main effect of time and GxT = the interaction effect. NS = not significant, ** = $p < .01$, *** = $p < .001$. Vertical bars denote standard errors.

Discussion

There were differences in ANS and HPA-axis measures between women with stress-related fatigue and healthy women in this study. In line with our hypothesis, all indices of HRV were lower in the fatigued group than in the healthy control group, which indicates less vagal influence on heart rate. These results support earlier research. Women with stress-related fatigue showed signs of cardiovascular hyperarousal that might be adaptive in the short term but which could take its toll in the longer term. A similar speculation is supported also by the HPA-axis measure saliva cortisol, which showed a greater response during the first hour of waking in women with stress-related fatigue than in controls. This finding was consistent in two separate analyses of the data and in line with earlier findings. Cortisol is an energy-mobilizing hormone and a greater response may be adaptive for coping with the increased demands of daily routines when being fatigued. The cost of enhanced energy mobilization in the morning could be exhaustion later in the day. The ANS and HPA-axis outcome measures are correlated with the level of fatigue and depression in the combined sample but not in the separate groups. This indicates that it is the between-group-differences that are reflected in the combined sample correlations.

Our hypothesis about task performance was also confirmed. The fatigued group made more errors, was less able to distinguish stimuli from noise and showed a more impulsive response style. Contrary to expectation, their reaction times were faster. There are data indicating that decreased HRV in patients suffering from anxiety and depression is accompanied by problems in affective and attentional regulation that can be linked to inhibitory processes (Thayer & Lane, 2000). There are also studies showing an association between HRV and performance on tests like the one used in this study (Hansen, et al., 2003). We also found linear associations between HF and commissions (negative) as well as detectability, or *d'*, (positive) both in the total group and in the fatigued group. These associations support earlier findings that there is a link between vagal activity and attentional processes. In our study this link is most evident in a fatigued population and of the two vagal systems; the myelinated vagus seems to be the one involved since the correlations involves HF rather than LF.

In the present study, participants' symptoms of fatigue were highly correlated with those of depression. Thus, it is possible that depression could account for our findings. Since our recruitment was based on fatigue as the major complaint, we do not know how these correlations would have appeared in a population with depression as the major complaint. We cannot exclude the possibility that in other studies fatigue was actually responsible for the correlations found ascribed to depression. There is evidence that fatigue explains some of the association often found between depression and myocardial infarction (Irvine et al., 1999). Whether depression causes fatigue or vice versa is an interesting question only answerable using a longitudinal study design. As mentioned in the introduction, there is an association between stress-related fatigue and cardiovascular disease. Longitudinal studies are required to determine whether lower HRV in the current study is an early predictor of later cardiovascular disease in women with stress-related fatigue.

There were six participants in the clinical group who took SSRIs. As we will see in study II, SSRI explains part of the HRV in depressed adolescents. In this study however, the medicated fatigued participants had non-significantly lower HRV. Closest to significance was LF HRV ($p = .1$). We found no significant differences between the medicated and non-medicated participants with regard to saliva cortisol or task performance measures. The aim of this study was not to study the effects of SSRI and the statistical power for detecting any differences was small.

As mentioned, our findings with respect to HRV and cortisol can be conceptualized as indications of generally greater physiological arousal or activation, which is consistent with the fatigued group's higher SUDS. $EtCO_2$ was lower in the fatigued group, indicating activation and hyperventilation (Gevirtz & Schwartz, 2003). Contradicting these results, this group had higher finger temperatures, which usually indicates relaxation, since activa-

tion accompanies SNS constriction of peripheral blood vessels, making the hands colder. This unexpected result of higher finger temperature was observed once before during ambulatory monitoring of participants with CFS, who were compared with depressed participants and healthy controls (Pazderka-Robinson, Morrison, & Flor-Henry, 2004). In the latter, CFS patients also had lower SCL, which we did not observe in our patients, nor did we find higher SCL that should accompany generalized stress activation. In conclusion, there is some evidence of an activated, aroused physiology. However, the measures most traditionally used to capture SNS activation, i.e. SCL, finger temperature, HR, RR, SBP and DBP, showed either no difference at all, or unexpected differences, between the groups.

Our finding of lower SpO_2 in the fatigued group is hard to fit in to what is known about stress activation. Some research has linked HRV, especially RSA, to gas exchange (Hayano, et al., 1996). We might speculate that the lower HRV observed in our fatigued group might have influenced gas exchange, lowering SpO_2 level. The lower $ETCO_2$ in the fatigued group indicate hyperventilation, but since there is no difference in RR this must be due to a higher tidal volume. The role of hyperventilation in CFS has been studied. There is support for a lower $EtCO_2$ in patients with CFS but whether this is of any importance for the development of the disease is debatable (Bazelmans, Bleijenberg, Vercoulen, van der Meer, & Folgering, 1997; Bogaerts et al., 2007).

Several labels are used to describe fatigue syndromes with different definitions. The validity and reliability of the diagnoses are therefore uncertain. In our sample of fatigued women, the scores on self-rated fatigue, depression and health were within the expected range and not explained by differences in age or BMI. Our study population was probably comparable to that of other studies investigating burnout syndrome, VE and work overload. We do not know whether our findings would be valid also for men. We focused on women since these problems are more prevalent in this group (Norlund et al., 2010). The fact that they were recruited by an advertisement for an herbal extract treatment study may have confounded the results but if this is the case, the effect is unknown.

Unexpectedly, three of the healthy control participants took SSRI medication. However, they did not report depression or anxiety in any of the screening questionnaires. Failing to screen out control participants who might have had past symptoms of depression may have increased the risk of making a type II error. With an even healthier group not taking any medications, differences might have been larger.

We suffered a substantial loss of data. We applied case-wise deletion, where a loss in one data point results in a lost case, and physiological measures were collected or summarized in more than 70 data points for each subject. For each of the main outcome measures, cortisol and HRV, four subjects had incomplete data sets and between one and five subjects had incom-

plete data sets on other variables. The choice of case-wise rather than pair-wise deletion of data is conservative, increasing the risk of type II errors. In total, data from 16 out of 71 (23%) eligible participants could not be used for these reasons. The main results for the three HRV indices and the cortisol response had similar or higher significance levels with pair-wise deletion: LF: $F_{Group}(1, 65) = 6.3$, $p = .01$; HF: $F_{Group}(1, 65) = 5.6$, $p = .02$; SDNN: $F_{Group}(1, 65) = 9.1$, $p = .004$; cortisol response: $F_{Group \times Time}(3, 186) = 3.3$, $p = .02$.

In summary, we found that women with stress-related fatigue had lower HRV and an elevated cortisol response upon waking, both signs of increased stress activation. Other parallel measures known to reflect SNS activity such as SCL did, however, not differ between the groups. HRV is sensitive to both branches of the ANS but, in short-term recordings, the vagal influence is the strongest. This leads us to believe that the hyperarousal indicated is probably the result of low PNS activity rather than increased SNS activity. According to earlier research and theory, a decreased PNS activity, which partly has its origin in the prefrontal cortex, may lead to decreased ability for neural inhibition, leading in turn to problems such as impaired impulse control and affective and attentional dysregulation (Thayer & Lane, 2000). This is in line with our results, where the women with stress-related fatigue showed a more impulsive, risky response pattern on the CCPT-II than their healthy counterparts.

General method of studies II and III

Participants

Healthy sample (controls for study II)

High/secondary school students (66 girls and 33 boys) constituted the original sample. Only the girls were included in study II. The participants were recruited from high/secondary schools: one in a small rural town, one in Stockholm city, one in an affluent northern suburb and one in a less affluent southern suburb with a large immigrant population. The participants were given oral and written information about the study and every participant and at least one parent gave their written consent. All participants had the measurements taken in the same order. These measurements were repeated after six months to evaluate the stability of the intra-individual HRV (results presented in study III). When both measurements were completed, the students were offered two cinema tickets each. Exclusion criteria were diabetes and thyroid dysfunction. Both studies were approved by the Regional Ethics Committee at the Karolinska Institute.

In study II, one participant was excluded because she matched one of the exclusion criteria and 12 additional participants had incomplete or distorted HR-recordings. The final control group in study II comprised 53 girls with mean age 16.4 years (age range 15.9 – 17.7 years). For study III the boys were also eligible. One of them matched one of the exclusion criteria and eight had incomplete or distorted HR-recordings. Five of the girls failed to attend the second measurement six months later and one additional girl had a bad HR-recording on this occasion, resulting in 71 participants, 47 girls and 24 boys, for analysis in study III with a mean age of 16.5 years (age range 15.9 – 17.7 years). Analysis of the excluded cases reveals that exclusions were unevenly distributed among schools, and that adolescents with both parents of foreign origin were overrepresented in the exclusions.

Procedure

In the healthy sample, the measurements were carried out at the school nurse's office by four nurses and one physician.

All participants, both the clinical group and the controls, were sitting upright, in silence, with no body movements allowed during the procedure. Use of tobacco or intake of tea, coffee, caffeine containing soft drinks or beta stimulant asthma medication was not allowed for one hour prior to the measurements. The HRV registration was preceded by 15 min of rest. HRV was measured during 2 x 2 minutes, in between which blood pressure was checked. A modified version of a 12 min protocol was employed (von Scheele, von Scheele, Hansson, Winman, & Theorell, 2005). In studies II and III SDNN was analysed after logarithmic transformation.

Study II: Heart rate variability is related to anxiety and depression in adolescent girls

Aim

The aim of study II was to investigate autonomous regulation measured by HRV in female adolescent psychiatric patients with only AD, only MDD and comorbidity of both these conditions compared to age matched controls. As mentioned above, relationships have been found in adults. Several aspects of anxiety and depression in adolescents differ from adults, such as the still maturing brain (adolescents) and the wear and tear of the stress involved in the disorders (adults). An additional aim was to assess the effect of SSRI on HRV. Other studies in adults have shown that medicated subjects have a more pronounced lower HRV compared to controls than unmedicated subjects (Licht, et al., 2009; Licht, et al., 2008). If HRV is decreased already in clinically depressed and anxious adolescents, future research should focus on whether they are also at risk of later cardiovascular disease and whether this can be prevented by early risk identification.

Method

Participants

The 53 participants in the control group and the HRV measurements are described above. The original clinical sample consisted of 73 adolescent girls, who were patients in child and adolescent psychiatry clinics and had a Development and wellbeing assessment diagnosis (DAWBA) of one or several ADs and/or MDD. Four participants were excluded because of medical conditions (pregnancy, diabetes and hypothyreosis), another five had distorted HR recordings and two did not show up for the physiological measurements, leaving a final sample of 60 adolescent girls with a mean age of 16.8 years (range: 14.5 y – 18.4 y). The participants had ongoing treatment contact at one of 13 outpatient child and adolescent psychiatry clinics situated in the centre of Stockholm, its suburbs and in smaller towns nearby. The patients were informed about the study and invited to participate by staff at the clinics.

The DAWBA-interview was used to obtain valid diagnoses for the participants. DAWBA is a semi-structured diagnostic interview designed to generate ICD-10 and DSM-IV psychiatric diagnoses in 5 – 17 year olds. In this study, ADs were defined by a compromise between DSM-IV and ICD-10 categorizations and included PD with or without agoraphobia, specific phobia, social anxiety disorder, PTSD, general anxiety disorder and separation anxiety, but not acute stress reaction, obsessive-compulsive disorder or anxiety caused by somatic or substance-related causes. MDD was defined by the DSM-IV criteria, thus allowing for atypical depressive symptoms. Pa-

tients with severe autism or psychotic symptoms were not considered for inclusion in the study. The DAWBA interviewers employed computerized versions of the test in which all information was used to predict the likely diagnosis. Almost half of the participants had both an AD and MDD, a third had only an AD and the remaining had only MDD (see *Figure 6* for details).

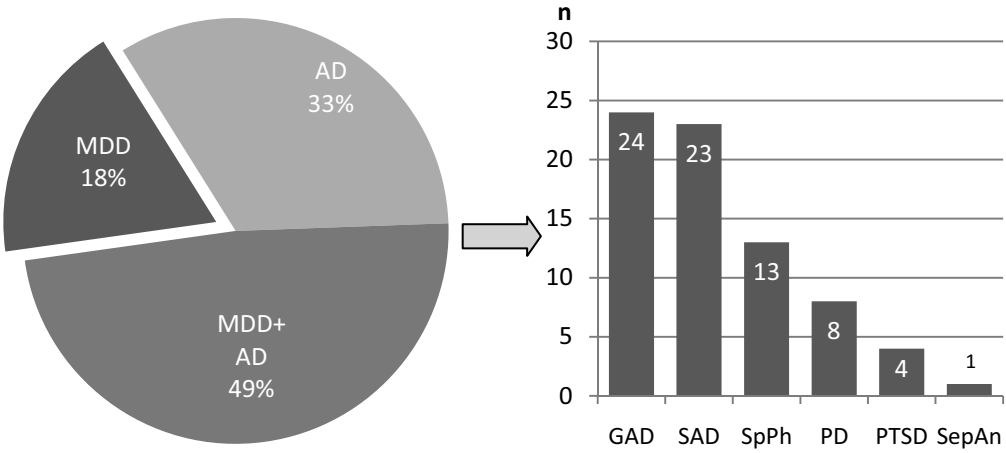

Figure 6. Schematic description of the distribution of major depressive disorder (MDD) and anxiety disorders (ADs) in the clinical sample (n = 60). The right-hand histogram describes the frequency distribution of the diagnoses of the 49 patients who had an AD. Some patients had more than one AD. GAD = general anxiety disorder, SAD = social anxiety disorder, SpPh = specific phobia, PD = panic disorder, PTSD = post-traumatic stress disorder and SepAn = separation anxiety.

Procedure

The measurements for the clinical group were carried out at the patient´s clinic and followed the same order in all participants. The HRV registration procedure is described above and was the same in both groups.

Measurements

Capillary p-glucose was analysed with a portable Heamocue Glucose System (Banauch et al., 1975). Weight and length were measured and BMI calculated. The same equipment was used throughout the study for measuring weight and blood pressure.

The DAWBA interview has consistently generated sensible estimates of prevalence and association with risk factors and, when compared to clinical diagnoses, DAWBA diagnoses demonstrate good validity (Goodman, Ford, Richards, Gatward, & Meltzer, 2000).

The Strengths and difficulties questionnaire (SDQ) is an internationally used screening instrument for mental health problems in children and teenagers (Goodman, 2001). It consists of 25 statements regarding psychological

attributes and behaviours, forming five subscales: hyperactivity/inattention, emotional symptoms, conduct problems, peer problems and pro-social behaviours. In this study, only the emotional scale (SDQ-em) was used, where high scores indicate more problems. Acceptable psychometric properties for the self-report version of SDQ for adolescents have been found as well as for the Swedish translation (Lundh, Wangby-Lundh, & Bjarehed, 2008; Svedin & Priebe, 2008).

Beck depression inventory (BDI) contains 21 items assessing depressive symptoms during the past week rated on a 4-point scale and yields a total score by summation (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). High scores indicate more severe depression.

Beck anxiety inventory (BAI) contains 21 items assessing the physical and cognitive symptoms of anxiety during the past week on a 4-point scale and yields a total score by summation (Steer, Kumar, Ranieri, & Beck, 1995). BAI items are also intended to reflect panic attack symptoms. High scores indicate more severe anxiety.

Physical activity was reported on a five-point scale as frequency of exercise while experiencing hard breathing and sweating (never, seldom, once a week, twice a week, >twice a week).

Statistics

Groups were compared with unpaired *t*-tests. When normal distributions were absent, Mann-Whitney's *U*-test was used. One way factorial ANOVAs were used for comparison between the three diagnostic subgroups and between SSRI-medicated patients, unmedicated patients and controls. Significant ANOVAs were post-hoc tested with Tukey's HSD tests. Partial correlations were used to remove the effect on HRV of BMI, systolic and diastolic blood pressure, p-glucose, and physical activity.

Results

Unpaired *t*-tests showed that HF, LF and SDNN were significantly lower in the clinical sample with diagnoses of AD and/or MDD compared to the controls (see *Figure 7*). HR was found to be non-significantly higher in the healthy controls compared to the clinical group (m_{controls} = 76.2 bpm, $m_{\text{clinical grp.}}$ = 73.2 bpm, $t(111) = 1.66$, $p = .10$). No significant differences in terms of HF, LF or SDNN were found between the diagnostic subgroups; AD, MDD and the group with AD/MDD comorbidity (all Fs < 0.70 and all ps > .50).

The clinical group was split into two groups, regardless of diagnosis; one with the participants who took SSRI medication (n = 23) and one who did not (n = 37). These two clinical groups and the healthy controls were compared. There were significant main effects for all HRV measures (LF: $F(2, 110) = 4.21$, $p = .02$; HF: $F(2, 110) = 5.80$, $p = .004$ and SDNN: $F(2, 110) = 5.65$, $p = .005$). The post-hoc tests revealed significant differences between

the SSRI medicated group and the controls in all the HRV measures, but in none of the indices for the non-medicated group compared to controls or between the two clinical groups (see *Figure 8*). Medication with SSRI explained 15.5% of the total variance of HF, 3.0% of LF and 6.5% of SDNN between the clinical sample and the controls when adjusted for BMI, SBP, DBP, p-glucose and physical activity. The subgroups of patients with SSRI medication compared to patients without SSRI medication did not have significantly different BDI or BAI scores, but SDQ-em showed higher scores, indicating more problems, in the group without medication (z = -2.0, p = .04).

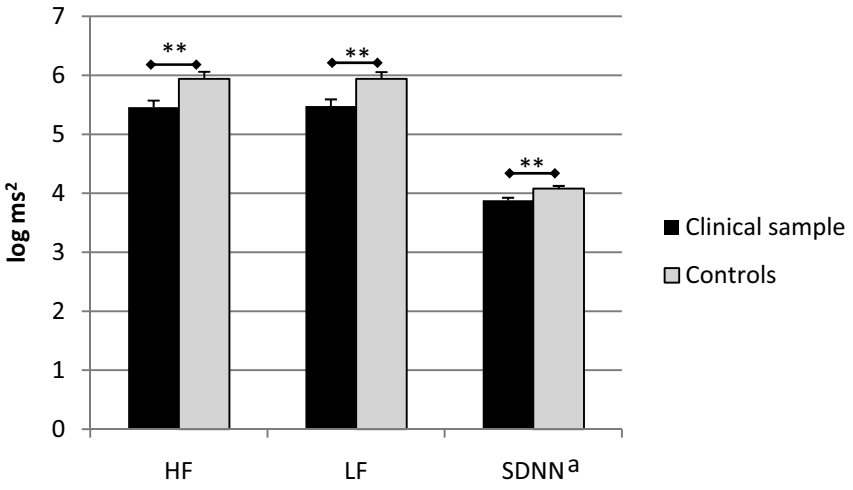

Figure 7. Unpaired *t*-tests showed significant differences in HF, LF and SDNN between the non-clinical sample and the clinical sample. ** = $p < .01$. $n_{\text{clinical grp.}} = 60$, $n_{\text{controls}} = 53$. Vertical bars denote standard errors.
[a] Unit for SDNN is log ms.

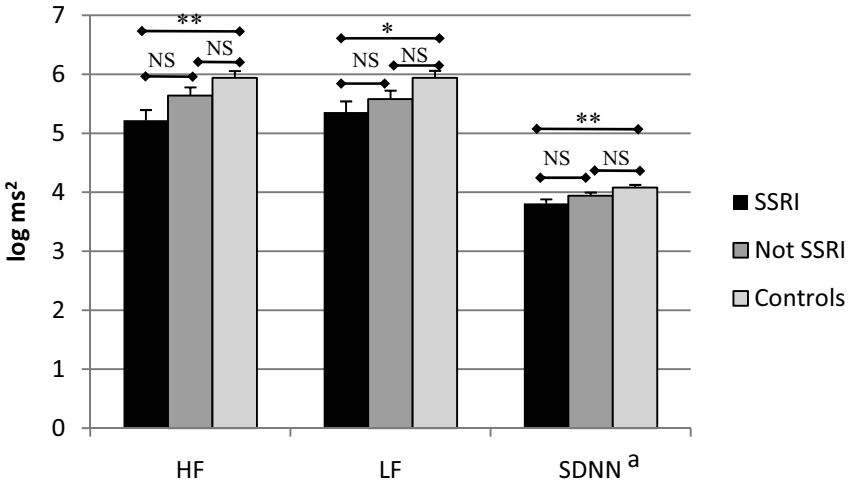

Figure 8. Post-hoc testing with Tukey's HSD test showed significant differences in HF, LF and SDNN between the controls and the clinical subsample on SSRI medication, but not between the controls and the non-medicated subsample, nor between the two clinical groups. NS = not significant, * = $p < .05$, ** = $p < .01$. $n_{\text{SSRI.}} = 23$, $n_{\text{not SSRI.}} = 37$, $n_{\text{controls}} = 53$. Vertical bars denote standard errors.
[a] Unit for SDNN is log ms.

Discussion

This study found that HRV was significantly reduced in a group of adolescent psychiatric female patients with AD and/or MDD compared with healthy controls. There were no differences between the diagnostic subgroups, which means that the present data do not support the hypothesis that physiological hyperarousal, indicated by decreased HRV, is specific to AD. When the clinical group was divided into those who were taking SSRI-medication and those who were not, the only difference that remained significant was between the medicated group and controls. This supports earlier findings in adults, where the use of psychotropic medication (including SRRIs) was crucial to the finding of decreased RSA and SDNN in patients diagnosed with AD and strongly influenced the same finding in patients diagnosed with MDD (Licht, et al., 2009; Licht, et al., 2008). However, in neither this nor any of the above mentioned studies were patients experimentally assigned to using psychotropic medication or not. There might be several factors differentiating the groups, such as the level of depressive symptoms prior to beginning medication, symptom tolerance, socio-demographic factors or an impulsive behaviour pattern. In the present study, there was no difference in the post-medication level of depression or anxiety between the groups but, according to the SDQ-em ratings, a higher level of emotional behaviour problems was evident in the non-medicated group.

The HRV-registration method with 4 recorded minutes may seem short but a similar method was used in a population based study (Greaves-Lord, et al., 2007). Furthermore, as is shown in Study III, 4-minute registration of HRV has intra-individual stability over 6 months in this age group.

In conclusion, adolescent females with AD, MDD and comorbidity of AD/MDD show decreased HRV compared with healthy controls. Patients on SSRI-medication fundamentally influence this effect. If psychiatric patients at cardiovascular risk can be identified early in life, then there is greater opportunity for therapeutic treatments such as psychotherapy, pharmacotherapy and lifestyle change.

Study III: Heart rate variability is related to self reported physical activity in a healthy adolescent population

Aim

The aim of Study III was to investigate whether there is an impact of lifestyle (physical activity, eating habits, sleeping patterns and smoking) on HRV in healthy adolescents, at an age when lifestyle associated cardiovascular disorders are not yet frequent. The impacts of known cardiovascular risk factors (systolic blood pressure, p-glucose and BMI) on HRV were also studied.

Method

The study population, the procedure and the HRV-measurement details are described above. All participants who constituted the healthy controls in Study II participated in this study with the following alterations: boys were included while six girls were excluded, either for failing to attend or for having bad HR-recordings during the repeat measurement, leaving a final sample of 47 girls and 24 boys.

Lifestyle was self reported by means of a form using a five-point scale (never, seldom, once a week, twice a week, > twice a week). Sleeping patterns were defined by the frequency of going to bed after midnight, food habits by the frequency of skipping breakfast and/or lunch, physical exercise by the frequency of exercising intensely enough to induce hard breathing and sweating, and smoking as daily smoking or not.

Statistics

Pearson product-moment correlation was used to assess bi- and multi-variate relations. Partial correlations were employed to remove the effect of confounding variables. Groups were compared with independent, and timely differences with dependent, *t*-tests.

Results

Significant correlations were found between the first and the repeat measurement 6 months later for LF ($r = .62$, $p < .0001$, $n = 71$), HF ($r = .54$, $p < .0001$, $n = 71$) and SDNN ($r = .64$, $p < .0001$, $n = 71$). The correlations between measurements were significant also when controlled for HR. Furthermore, the correlations between the first and repeat measurements were significant for BMI ($r = .94$, $p < .0001$, $n = 70$), SBP ($r = .69$, $p < .0001$, $n = 71$) and p-glucose ($r = .32$, $p = .004$, $n = 71$). No significant ($p > .05$) differences between the two measurements were found in any HRV measure or in sociodemographic and lifestyle parameters.

Significantly higher frequency of physical activity was found in boys ($t(69) = 4.44$, $p < .0001$) and a higher frequency of skipping meals was found in girls ($t(69) = 3.03$, $p = .003$). No gender differences were found in sleeping patterns. Seven participants were daily smokers, of whom six were girls. BMI and p-glucose showed no gender differences. As expected from gender specific reference values, SBP was higher in boys ($t(69) = 3.79$, $p = .0003$) and HR was higher in girls ($t(69) = 2.77$, $p = .007$). No significant differences were found in LF, HF or SDNN ($p > .05$). Further analyses were therefore carried out with both sexes treated as a single group.

Significant correlations were found in both the first and the repeat measurement between self reported physical activity and LF ($r = .35$, $p = .002$, $n = 71$ and $r = .29$, $p = .01$, $n = 70$), HF ($r = .26$, $p = .03$, $n = 71$ and $r = .30$, $p = .01$, $n = 70$), SDNN ($r = .28$, $p = .02$, $n = 71$ and $r = .37$, $p = .002$, $n = 70$) and HR ($r = -.37$, $p = .02$, $n = 71$ and $r = -.42$, $p = .0003$, $n = 70$). The correlations between physical activity and LF remained significant when controlled for HR. This was not the case for HF and SDNN. Late sleeping patterns, poor eating habits and smoking revealed no significant correlations with HRV in any of the measurements. BMI, p-glucose and systolic blood pressure did not indicate any significant correlations with HF, LF, SDNN or HR in any of the measurements except for p-glucose, which showed a negative correlation with LF in the repeat measurement ($r = -.25$, $p = .04$, $n = 71$).

Discussion

The results of this study showed significant correlations between self reported physical activity and HRV in a healthy population of adolescents. This result was found in two consecutive measurements six months apart. There were however no associations between HRV and eating habits, sleeping patterns or smoking on either of the measurements. Of the known cardiovascular risk factors, only p-glucose showed a significant correlation with LF but only in one of two measurements, while BMI and systolic blood pressure did not correlate with any HRV index on any measurement. The repeated measures demonstrated that the results obtained were robust within the sample. The significant associations between physical activity and both HF and SDNN respectively disappeared when HR was controlled for. This does not, however, necessarily imply that PNS is less linked to physical activity since lower HR is also a sign of more vagal activity.

These results are in line with findings in adults where regular aerobic exercise led to an increase in autonomic efferent activity with enhanced vagal influence observable as increased HRV and decreased HR (Hottenrott, et al., 2006; Tuomainen, et al., 2005). In children, however, research shows that high intensity intermittent training over a 7 week period does not affect HRV (Gamelin et al., 2009). In the present study, the participants were older and the self-reported level of exercise probably reflects a longer duration of regu-

lar training than seven weeks, which may explain the impact on HRV. No relationship between sleeping patterns and HRV was found. This is in contrast to what has been reported in adult samples (Furlan, et al., 2000). There are several aspects of sleep that might be of interest, such as sleep quality and sleep deprivation, and sleep is known to be difficult to subjectively report (L. Zhang & Zhao, 2007). Furthermore, our sleep measure was not directed towards sleep deprivation but rather measured a shift in diurnal rhythm. All these factors may explain why we found no differences. Future research including both objective and subjective measures of sleep is required to demonstrate the effect of sleep on HRV in adolescents. With regard to smoking, the statistical power was very low since only seven daily smokers participated in the study. Moreover, the reliability of self-reported tobacco use in this age group is known to be low (Hennrikus et al., 2005). The lack of correlations between BMI and SBP versus HRV was possibly due to lack of sensitivity, as the sample showed little variation in these aspects.

As in Study II, 4-minute registrations without any standardized interventions were used. Our data showed that these recordings were stable over a period of six months. Short-term recordings (compared to 24 hours) of HRV have obvious advantages for screening purposes.

General discussion

In studies I and II we found evidence for hyperarousal in adult women suffering from stress-related fatigue and in adolescent girls with AD and/or MDD. Previous studies indicate that this was to be expected. However, theoretically, it is not clear why fatigue, depression and anxiety should share the same physiological activation pattern. Furthermore, the review of the literature presented in the introduction shows that HRV is reduced in a large variety of diagnoses. Consequently, decreased HRV has been suggested as a marker for unspecified disease (Task Force, 1996). This resembles Hans Selye's GAS-syndrome, which Selye described as "the syndrome of just being sick" (Selye, 1951). The body follows a general response pattern to a variety of damages and stressors, and some treatments seem to cure a wide variety of diseases. This response pattern is known as the stress response. Many of these general effects studied by Selye were caused by HPA-axis activity. In Study I we found evidence for an affected HPA-axis response in women suffering from stress-related fatigue. The GAS-theory was developed and modernized using the concept of allostasis. HRV is less frequently mentioned as a marker of allostatic load but it compares favourably to other allostatic measures (Thayer & Sternberg, 2006; Weber, et al., 2010). A recent study on a large population based sample used Structural equation modeling to test a hypothesized metafactor model of allostatic load composed of a number of biological system factors. In this model, HRV was one of six biological systems found to fit the data (Seeman et al., 2010). Three responses are described to constitute allostatic load: (1) frequent activation, (2) failed shut-down and (3) inadequate response (McEwen, 1998). Failure to turn on is not mentioned as a fourth category but when it comes to vagal activity, this seems be the case. To summarize this paragraph, several illnesses and psychiatric conditions are stressful, psychologically and physiologically, to the persons experiencing them. This builds up an allostatic load of which HRV seems to be a sensitive marker. There are several possible links between allostatic load and morbidity and mortality.

HRV in short-term recordings mainly indicates vagal activity. In their Neurovisceral integration model, Thayer and Lane propose that deficient inhibitory activity is central to many affective problems (2000). They point out that what may look like sympathetic activation could equally well be lower activity in the PNS and therefore dis-inhibition. In their model, autonomic, attentional and affective systems are integrated and they state that

"low HRV is associated with poor affective information processing" (Thayer & Lane, 2000). In Study I we included some other measures that are often related to SNS activation, for example HR, RR, blood pressure, SCL and peripheral temperature. However, none of these measures indicated more activity in the fatigued group. Peripheral temperature was even significantly higher in the fatigued group, indicating less SNS activity. Apart from decreased HRV, we found significantly lower $EtCO_2$, indicating hyperventilation, and lower SpO_2. None of these measures are unambiguous SNS parameters. Of these measures, only HR, SBP and DBP are included in Study II but none of these indicated a higher SNS activity in the clinical group characterized by decreased HRV. The girls with MDD and/or AD had in fact non-significantly lower HR than the controls. According to the Neurovisceral integration model, cognitive attentional systems are negatively influenced by prefrontal dis-inhibition, which can be traced in decreased HRV. In Study I we found that the fatigued group both had decreased HRV and worse performance on a test of continuous attention, displaying a more impulsive, dis-inhibited response pattern. We also found a correlation between HF, HRV and two of the performance indices. As HF is mainly influenced by the myeliniated vagus it seems like this system is the one most involved in this kind of attentional processes. According to the Polyvagal theory this is the system also involved in social interaction strategies (face muscles, voice intonation etc.). The Polyvagal theory, like the Neurovisceral integration model, argues for the importance of autonomic activity, and especially vagal, for behaviour (Porges, 2007).

In Study II the participants were adolescents. This means that decreased HRV is less likely to be a result of the cumulative wear of the psychiatric disorder. As previously mentioned, it is more likely to be the immediate stress of the disorder, building up the allostatic load, which affects HRV. As the link between allostatic load and disease is supported (Mattei, Demissie, Falcon, Ordovas, & Tucker, 2010; McEwen, 2004), it would be of benefit to identify people at risk early in life when the possibilities for change are greater. We found decreased HRV in adolescent girls with psychiatric problems, although other known cardiovascular risk factors did not show any differences at this age. HRV might therefore be a useful measure for identification of young people at risk of cardiovascular disorders and possibly other types of morbidity. However, as will be discussed below, more research is needed before we know whether this is a possibility.

So far, we have focused on the risks and problems associated with decreased HRV. Is there anything we can do to increase HRV? In Study III it is indicated that physical exercise correlates positively with HRV in adolescents. This evidence is in line with findings in adults where physical exercise had a positive influence on HRV, even though not all studies are in agreement (Buchheit & Gindre, 2006; Tuomainen, et al., 2005). Physical exercise is also known to have a positive, stress-reducing effect on allostatic systems

(Tsatsoulis & Fountoulakis, 2006). As the participants in our study were young, a long sedentary life has clearly not been a factor. We cannot, however, draw the causative conclusion that an increase in physical exercise will also raise HRV. There may be other issues contributing to some adolescents being more physically active than others. However, BMI and some other lifestyle factors were ruled out in our study.

As research about HRV and the vagal system has proliferated over the past three decades, behavioural therapeutic ideas about how to stimulate vagus have been proposed. Apart from dietary methods, exercise and relaxation (Mozaffarian, Stein, Prineas, & Siscovick, 2008; Tuomainen, et al., 2005; van Dixhoorn, 1998), direct HRV-biofeedback has been suggested. HRV-biofeedback means regular sessions where patients watch their heart rate on a monitor as it varies with breathing and relaxation, the goal being large HR variation in phase with breathing. Specific breathing rates are often applied. This intervention has some support in a wide range of conditions including PTSD, MDD, asthma, fibromyalgia, hypertension and heart failure (Hassett et al., 2007; Karavidas et al., 2007; Lehrer et al., 2004; Nolan et al., 2010; Nolan et al., 2005; Swanson et al., 2009; Zucker, Samuelson, Muench, Greenberg, & Gevirtz, 2009). Several self-help products for this kind of biofeedback have become available commercially, such as the Stresseraser® (Helicor Inc., New York). Future research will reveal whether or not these kinds of treatment are effective. We know that successful treatments for depression do not seem also to lower the elevated risk for cardiovascular disease found in depression. Perhaps addition of methods focusing more direct on the cardiac autonomic tonus can be more successful.

There is evidence that psychotropic medication may influence HRV negatively, which is also indicated in Study II. In previous studies, this relationship is most noticeable in the Dutch cohort studies frequently mentioned above (Licht, et al., 2009; Licht, et al., 2008). It is interesting that these medications reduce symptoms of emotional dysregulation while simultaneously reducing HRV. The same is true also for electroconvulsive therapy (Schultz, Anderson, & van de Borne, 1997). The overall data on mood, affect and wellbeing in relation to HRV suggest the opposite, namely that emotional health promotes high HRV (Thayer & Lane, 2000). If psychotropic medication *does* reduce HRV, the question that arises is: *does it* also increase cardiovascular risk? The literature indicates a risk for cardiovascular disease with psychotropic medication but SSRIs are generally believed to be safe or even protective (Cohen, et al., 2000; Feinstein, et al., 2002; Kovacs & Arora, 2008; Krantz, et al., 2009; Smoller et al., 2009). There are special, empirically based published guidelines for children and adolescents receiving psychotropic medication and they rate SSRIs as having minimal cardiovascular effects (Gutgesell, et al., 1999). Suggestions have been made that measuring HRV could be a way to minimize risks when prescribing psychotropic medication (Koschke, et al., 2009). It is important to remember

that what may seem to be an effect of SSRI medication in our study may as well be the result of some background variable associated with both decreased HRV and taking SSRIs, such as more depressive or anxiety symptoms prior to pharmacological treatment, lower symptom tolerance, sociodemographic factors or a more impulsive behaviour pattern.

Limitations

There are several aspects of the above studies that limit their inferential power. The sample sizes are relatively small, and the controls in Studies I and II were not recruited from population based samples. Furthermore, in Study I the participants were recruited by an advertisement for an herbal extract treatment study, which may have influenced the results. When subsamples were compared, as in Study II when investigating the effect of SSRI-medication, the sample sizes were very small, which has reduced the statistical power. We excluded a considerable number of cases due to distorted ECG registration. The HRV measures in the frequency domain depend on an undisturbed timeline and are therefore sensitive to excluded data. It is also very important to scan and exclude ectopic beats since they can fundamentally influence variability. In Study III we did not find evidence for lifestyle parameters other than physical activity as having an association with HRV. This may be due to our insufficiently sensitive measures for lifestyle parameters. In addition, there were few daily smokers and very few obese participants in our studies.

The cross-sectional nature of the present studies implies that we cannot draw any causal conclusions. For example, we do not know whether physical exercise causes higher HRV or whether the result is affected by background factors. We don´t even know if vagal dysfunction results in a psychiatric illness or if the distress of these illnesses result in autonomic changes. The goal of much HRV research has been to find a way to reduce the risk of cardiovascular morbidity and, ultimately, mortality. However, since much of the research on HRV is cross-sectional, the causal links between, for example, behaviour change and increased HRV, and between increased HRV and decreased risk for cardiovascular events, are not clear. HRV might be a mediator between certain conditions (e.g. MDD) and cardiovascular disease but it can also be a symptom of a dysfunctional heart. It might well be prudent to invest energy in activities that increase HRV but we are still not sure whether any such increase will lower the risk of cardiac morbidity.

Future research

Experimentally designed studies on therapy (behavioural or other) aimed at increasing HRV need to be carried out, focusing on groups with enhanced risk of cardiovascular disease, for example coronary patients with MDD. Longitudinal research is required to explore whether such a change decreases the risk of cardiovascular morbidity and mortality. Longitudinal research is also necessary to obtain knowledge about whether low HRV at a young age is prognostic of cardiovascular disease later in life.

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