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ANXIETY AND DEPRESSION IN ADOLESCENT FEMALES - AUTONOMIC REGULATION AND DIFFERENTIATION

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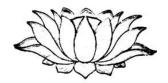


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The mind is the surface of the heart, the heart, the depth of the mind.

Hazrat Inayat Khan



ABSTRACT

The prevalence of anxiety and depression is on the increase in adolescent girls, as estimated by self-assessed symptom reports. There is a need for implementation of validated instruments to identify those in need of treatment. The concept of autonomic self-regulation may help us to elucidate possible pathophysiological pathways of anxiety disorders and depression. Heart rate variability (HRV) provides a tool to assess the descending vagal inhibitory tone, i.e. the capacity of autonomic self-regulation. This perspective gives a framework for evaluating practices of allostatic competence as possible methods for preventing and treating of anxiety disorders and depression in adolescent girls. The present work is intended to create a platform for future studies aimed in this direction.

Study I demonstrated that autonomic regulation measured by HRV is decreased in adolescent female psychiatric patients with anxiety disorders and/or major depressive disorder (MDD) compared to healthy controls, which was partly explained by selective serotonin reuptake inhibitor (SSRI) medication, but not by lack of physical activity or cardiovascular risk factors. It thus seemed as if depressive and anxious symptoms contributed to impaired vagal inhibitory control in adolescent girls.

Study II investigated whether lifestyle factors, that are accessible for intervention, are related to HRV in healthy adolescents and conclude that physical activity, but not eating habits, sleep pattern or smoking, was related to HRV, without contribution from gender, systolic blood pressure, plasma-glucose, body mass index or sociodemographic factors. The data provides a basis for future studies of interventional design.

Study III showed that the emotional subscale of Strengths and Difficulties Questionnaire (SDQ-em) and the putative salutogenic scale of Sense of Coherence (SOC) were equivalent or even superior to the specialized self-assessment scales for anxiety and depression in their ability to differentiate cases of anxiety disorders and major depressive disorder from non-cases in adolescent girls. The study thus supports the accuracy of SDQ-em as a screening instrument for anxiety and depression and as a tool to discriminate between caseness and non-caseness of emotional disorders in adolescent girls.

Study IV was an in depth investigation of the construct of Sense of Coherence (SOC) applied in adolescent girls, showing that it lacks a unique dimensionality as a salutogenic construct, but constitutes a sensitive inverse measure of persistent depressive and generalized anxiety problems similar to diagnoses such as major depressive disorder (MDD), dysthymic disorder (DD), generalized anxiety disorder (GAD) or generalized social anxiety disorder (SAD) according to DSM-IV. It was also demonstrated that a low SOC score was correlated to a decrease in HRV.

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CONTENTS

1	Intro	duction	1				
2	Prev	alence of anxiety and depression in adolescence	2				
3	Diagnostic considerations						
	3.1	Diagnosis of anxiety					
	3.2	Diagnosis of depression	4				
	3.3	Diagnosis of comorbidity of anxiety and depression	5				
	3.4	Diagnosis of stress-related disorders	5				
4	Etio	ological theories of anxiety and depression					
	4.1	Overview					
	4.2	Autonomic regulation	8				
		4.2.1 The brain-heart connection	8				
		4.2.2 Measures of heart rate variability	10				
	4.3	Neurotransmitter system dysfunction					
	4.4	The hypothalamic-pituitary-adrenal (HPA) axis					
	4.5	Genetic influences					
	4.6	The stress research paradigm	13				
	4.7	Salutogenesis – a complementary perspective					
		4.7.1 Background					
		4.7.2 Definition					
		4.7.3 Sense of coherence	15				
5	Trea	tment of anxiety and depression in adolescence					
	5.1	Treatment of anxiety					
	5.2	Treatment of depression					
6	Aim	S					
7		nodological considerations					
	7.1	Study overview					
	7.2	Description of the samples					
		7.2.1 The clinical sample					
		7.2.2 The non-clinical sample					
	7.3	Diagnostic interview					
	7.4	Methods of self-assessment					
		7.4.1 Psychiatric self-assessment					
		7.4.2 Salutogenic self-assessment					
		7.4.3 Lifestyle questionnaire					
	7.5	Heart rate variability (HRV) registration and processing					
	7.6	Salivary cortisol					
	7.7	Cardiovascular risk-factors					
	7.8	Ethics					
8		mary of studies I-IV					
O	8.1	Study I - HRV in adolescent girls with emotional disorders					
	8.2	Study II - HRV in relation to lifestyle in healthy adolescents					
	8.3	Study III - Caseness/non-caseness of depression and anxiety					
	8.4	Study IV - Discriminant validity of sense of coherence (SOC)					
9		ussion					
_		Autonomic regulation					

	9.2	Psychiatric self-assessment	42
	9.3	Limitations of the study	42
10	New	hypothesis and future perspective	48
	10.1	Psychiatric diagnosis based on etiology	48
	10.2	The concept of atypical depression	48
	10.3	Future methods of treatment	50
11	Acknowledgements		52
		rences	

LIST OF ABBREVIATIONS

ACTH Adreno Corticotropin Hormone ANS Autonomic Nervous System

ASD Acute Stress Disorder
AUC Area Under the Curve
BAI Beck's Anxiety Inventory
BDI Beck's Depression Inventory

BMI Body Mass Index

CAP Child and Adolescent Psychiatry
CBT Cognitive Behavioral Therapy
CDI Children's Depression Inventory

CBG Cortisol Binding Globulin

CRH Corticotropin Releasing Hormone

DSM-IV The Diagnostic and Statistical Manual of Mental Disorders 4th ed.

DAWBA Development and Wellbeing Assessment

DBP Diastolic Blood Pressure
DD Dysthymic Disorder
ECG Electrocardiography
EEG Electroencephalography
GAD Generalized Anxiety Disorder

HAD-anx Hospital Anxiety and Depression Scale, anxiety score HAD-dep Hospital Anxiety and Depression Scale, depression score

HF High Frequency heart rate variability
HPA Hypothalamic-Pituitary-Adrenal
HPG Hypothalamic-Pituitary-Gonadal
HPT Hypothalamic-Pituitary-Thyroid

HR Heart Rate

HRV Heart Rate Variability

ICD-10 International Classification of Diseases 10th rev.

IPT Interpersonal Psychotherapy

LF Low Frequency heart rate variability

MASC Multidimensional Anxiety Scale for Children

MBCT Mindfulness Based Cognitive Therapy
MBSR Mindfulness Based Stress Reduction

MDD Major Depressive Disorder

MFQ Mood and Feelings Questionnaire
OCD Obsessive Compulsive Disorder
PTSD Post Traumatic Stress Disorder
RSA Respiratory Sinus Arrhythmia

ROC-curve Receiver Operating Characteristic Curve

SA node Sinoatrial node

SAD Social Anxiety Disorder SBP Systolic Blood Pressure

SCARED Screen for Child Anxiety Related Emotional Disorders

SCAS Spence Children's Anxiety Scale

SDNN Standard deviation of inter-beat intervals

SDQ-em Strengths and Difficulties Questionnaire – emotional subscale SDQ-tot Strengths and Difficulties Questionnaire – total difficulties score

SDQ-imp Strengths and Difficulties Questionnaire – impact scale

SMD Severe Mood Dysregulation

SOC(29) Sense of Coherence Scale (29 items version) SSRI Selective Serotonin Reuptake Inhibitor

YSR Youth Self Report

5-HT 5-hydroxytryptamine/serotonin

5-HTT 5-hydroxytryptamine transporter/serotonin transport protein

1 INTRODUCTION

This study is an attempt to broaden and deepen the understanding of depression and anxiety in young females - the most common psychiatric problems in this group across cultures (Rutter, 2008). Relatively little research in the field of depression and anxiety in children and adolescents has been conducted in Sweden and elsewhere. Although embarking on such research requires a complex integrative and translational approach, there are good reasons to focus specifically onto the collectively neglected, but growing group of young women with depressive and anxious problems.

Initially this work was intended to create a platform for future studies of interventional design by providing (or pointing out the specific needs for) measureable end-points anchored in pathophysiological theories, with a specific focus on autonomic regulation. Along the way it became evident that questions of how to differentiate caseness of major depressive disorder (MDD) and/or anxiety disorders from non-caseness and how to differentiate MDD from anxiety disorders needed to be addressed. Other important issues, such as how to best identify the different anxiety disorders and how to differentiate "classical major depressive disorder" from "atypical depression" in this age group has not been studied, but are briefly discussed in the end of the thesis.

A short review of the current state of the art is given to provide a framework and a rational for the work.

2 PREVALENCE OF ANXIETY AND DEPRESSION IN ADOLESCENCE

Non-manual based clinical assessment of anxiety and depression in adolescents has low inter-rate reliability among clinicians and a golden standard for the diagnostic procedure is lacking. The prevalence of anxiety disorders and major depressive disorder (MDD) in adolescents should therefore be based on self-report questionnaires, utilizing the adolescent as well as parents or teachers as informants, in combination with clinical assessment according to structured interviews. This has not always been implemented, making prevalence numbers difficult to interpret and compare. It may also partially explain the great discrepancies in prevalence numbers reported in international studies of anxiety disorders based on clinical assessment in this age-group, ranging from 2.8-18.4 percent in 15-18 year olds (Fergusson et al., 1993, Feehan et al., 1994, Goodwin et al., 2004, Lewinsohn et al., 1998, McGee et al., 1990). A recent Swedish study conducted by self-report screening for social anxiety disorder show a point prevalence of 6.6% in girls vs. 1.8% in boys (Gren-Landell et al., 2009b). The range of lifetime prevalence of depression reported in the literature is also wide: from 9-20 percent at the end of adolescence (Reinherz et al., 1993, Fergusson et al., 2005, Costello et al., 2003, Lewinsohn et al., 1998).

Ten years ago in Sweden the 1-year prevalence of major depressive disorder based on self-report screening followed by clinical interview was 5.8% and the lifetime prevalence was 11.4% (Olsson and von Knorring, 1999). More recent prevalence data on anxiety disorders and depression in adolescents in Sweden is lacking, but there are several indications of increased prevalence, especially in adolescent girls. The percentage of female adolescents in the population with self-reported symptoms of anxiety and depression has more than doubled in twenty years, now reaching >30%. Hospital care for anxiety disorder and depression, but not for psychoses, has doubled, now reaching > 200/100 000 and hospitalization after suicide attempts and self-harming behavior has also increased dramatically for young women aged 16-24 compared to other age groups. In the adolescent male population self-reported symptoms of anxiety and depression, hospitalization due to anxiety disorders and MDD and the rate of suicide attempts have also increased but figures are still way below that of the young

female part of the population (The Swedish National Board of Health and Welfare, 2009b).

It is alarming that, compared to other age groups, adolescents and young adults now constitute the largest group of the total number of psychiatric patients in Stockholm, all age groups included (Dalman C, 2006). According to *Pastill**, the Stockholm CAP clinic database, female adolescents with anxiety disorders and MDD constitute the largest group (33%) of all CAP patients in Stockholm and sick leaves due to psychiatric disorders continues to increase in young females as opposed to other groups (Dalman C, 2006).

^{*} Pastill is a centralized clinical database including information about all public use of Child- and Adolescent Mental Health Services in Stockholm County (CAMHS) since 2000. The database comprises detailed data including the national identification number, residential area, symptoms and/or problems at time of contacting CAMHS, and type and frequency of provided care. Data has been collected through completion of standardized forms by care providers employed within CAMHS.

3 DIAGNOSTIC CONSIDERATIONS

3.1 DIAGNOSIS OF ANXIETY

According to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, 2000), anxiety disorders are sub-categorized as: panic disorder with or without agoraphobia, agoraphobia without panic disorder, specific phobia, social phobia (referred to as social anxiety disorder, SAD in this text), obsessive compulsive disorder (OCD), post traumatic stress disorder (PTSD), acute stress syndrome, generalized anxiety disorder (GAD) and anxiety of somatic or substance related cause. Social anxiety disorder can be situational or more generalized. The current World Health Organization diagnostic classification system, the 10^{th} revision of the International Classification of Diseases (ICD-10, 2009), is not fully compatible with DSM-IV and has a different categorization. Under the heading "Neurotic, stressrelated and somatoform disorders" several subgroups are listed: "phobic anxiety disorders" including agoraphobia, SAD and specific phobias, "other anxiety disorders" including panic disorder, GAD and mixed anxiety and depression, "reaction to severe stress and adjustment disorder" including acute stress syndrome, PTSD and adjustment disorder and "obsessive compulsive disorder" as a separate category. Separation anxiety is classified as a disorder specific to children in both DSM-IV and ICD-10.

3.2 DIAGNOSIS OF DEPRESSION

The criteria for major depressive disorder (MDD) are specified in DSM-IV and ICD-10. The symptoms must cause decreased global functioning and persist for at least two weeks. MDD is further classified by severity and occurrence (as a single episode or as recurrent). If depressive symptoms persist for more than a year, it is labeled dysthymic disorder (DD). The criteria are basically the same for adolescents as for adults. DSM-IV presents several criteria for "classical" depression also in reversed form, thus allowing atypical features of depression within the context of MDD. ICD-10 on the other hand presents atypical depression as a specific category. In adolescence these atypical features are common. For example, the diagnostic criteria of weight loss and decreased appetite seen in adults is often conversely seen as weight gain in adolescence, early awakening, commonly seen in depressed adults, is seldom seen in adolescents, who instead have problems with insomnia, late sleep phase and

hypersomnia. In young depressed individuals, inhibition is not always present, but rather increased agitation and self-destructive behaviors are common.

Early onset of bipolar disorder is yet another important and often difficult differential diagnosis to consider as well as the recently described severe mood dysregulation syndrome (SMD) (Schapir and Zalsman, 2008, Youngstrom et al., 2008), which are not further discussed in this context.

3.3 DIAGNOSIS OF COMORBIDITY OF ANXIETY AND DEPRESSION

The differentiation of the diagnoses of MDD, GAD and generalized SAD is particularly difficult in adolescence. The diagnoses display high comorbidity (Angold et al., 1999) and comorbidity tends to generate higher severity scores (III). It seems as if the more generalized the anxiety problems get, the greater impact on the quality of life - in contrast to situational anxiety problems, which can probably be managed to a greater extent by avoidance or compensational strategies.

Primary depression and primary social anxiety may both be entry points to a vicious circle of increased depression and anxiety in this age group. Decreased social engagement in adolescence can be the result of different trajectories. It can be caused by a primary diagnosis of generalized SAD with/or without secondary depressive symptoms, or by primary MDD with/or without comorbidity of GAD or generalized SAD. Individuals with both GAD and MDD show an increased risk of subsequent death, and it may be that these disorders interact synergistically to affect mortality (Phillips et al., 2009). A common genetic predisposition has also been suggested (Middeldorp et al., 2005, Hettema, 2008).

3.4 DIAGNOSIS OF STRESS-RELATED DISORDERS

Differentiating anxiety and depression from stress-related disorders is a challenge in CAP for two reasons. Firstly, children's stress reactions may be different from that exhibited by adults. Secondly, acute and chronic stress - and consequently stress related disorders - may be involved as part of the pathophysiological mechanisms in the development of anxiety disorders and MDD in children and youth (for further discussion, see HPA-axis).

Stress-related DSM-IV and ICD-10 diagnoses that are relatively common in both CAP and adult psychiatric populations include acute stress disorder (ASD), post traumatic stress disorder (PTSD), and maladaptive stress disorder. In addition, other diagnoses such as burn-out syndrome, neurasthenia and chronic fatigue syndrome are stress-related disorders recognized in ICD-10, but not in DSM-IV. ASD and PTSD are listed under anxiety disorders in DSM-IV. The criteria overlap suggests that these disorders are not clear cut and there may be differential diagnostic difficulties in relation to both anxiety and depression.

4 ETIOLOGICAL THEORIES OF ANXIETY AND DEPRESSION

4.1 OVERVIEW

Several biological mechanisms are putatively related to etiology and symptom severity of anxiety and depression. Many of these have been targets for research, for example genetic and epigenetic mechanisms, serotonin, noradrenalin and dopamine metabolism, the hypothalamic–pituitary–adrenal (HPA)-, the hypothalamic-pituitary-gonadal (HPG)- and the hypothalamic-pituitary- thyroid (HPT) system, fatty-acid metabolism and the interconnected processes of inflammation (multiple inflammatory cytokines), oxygen radical damage and neuro-degeneration (IO&ND) (Maes et al., 2009) and brain morphological and functional correlates.

Psychological theories on attachment, subconscious inner conflicts, inter-relational behavior and cognition present models of anxiety and depression. At the level of the individual, studies have been made of subjective relational factors, stress load, family and school situation, socio-economic situation, parental education and the adaption to local health related behaviors and life styles. On a 'macro' level, research has also focused on socio-cultural instability, structural changes to society and lack of norms as contributing factors to anxiety disorders and depression.

An evolutionary perspective has also been considered suggesting that mood help us to achieve favorable environmental conditions. When individual investments do not result in progress towards a goal, dampened mood potentially facilitates the re-orientation process to less ambitious levels. If a person is incapable of giving up a goal i.e. there is inadequate re-orientation, then a dampened mood can develop into clinical depression (Pariante, 2009). This is in line with the finding that adolescent girls with high levels of actual ideal-discrepancy and a tendency to ruminate in response to stress and failure are particularly likely to report depressive symptoms (Papadakis et al., 2006).

In isolation, these models are only capable of explaining fractions of the whole, but since they do not exclude each other, they can be integrated to more complex level of understanding. A perspective with a life-span developmental approach to psychopathology is possible and may even be crucial for progress. The etiology is

likely to involve a complex interplay between genetic and biological factors and experiences of stressful or traumatic events.

4.2 AUTONOMIC REGULATION

4.2.1 The brain-heart connection

An emerging perspective on anxiety and depression is that dysfunction of the autonomic self-regulation is part of their pathophysiology (Thayer and Lane, 2000, Thayer et al., 2009). Autonomic self-regulation represents the interface of what we perceive, how we interpret it and how we react. It represents the capacity of cognitive, emotional and physiological adaption i.e. integration of the central nervous system (CNS) and autonomic nervous system (ANS).

According to Porges, vagal regulation of the heart has changed in the course of evolution. Uniquely to mammals, myelinated pathways from the nucleus ambiguus were developed in addition to the original unmyelinated descending pathways from the dorsal motor nucleus. The myelinated pathways in humans are connected to higher brain structures, including the prefrontal cortex and amygdala – the central network (figure 1). The output from the central network is thus under vagal inhibitory control by the myelinated vagus. Increased influence of the myelinated vagus slows down the heart rate, inhibits fight and flight activity, decrease the hypothalamic-pituitary-adrenal (HPA) axis response, inflammatory processes and glucose regulation and promotes social behavior (Porges, 2007). In other words, the prefrontal cortex and the amygdala are linked to the regulation of these allostatic systems via the vagus nerve (Thayer and Sternberg, 2006) (figure 1).

Descending vagal pathways from the central network, reach the sino-atrial (SA) node in the heart, which is the impulse-generating tissue of the heart. Via the brainstem the SA node also receives signals from respiratory- and cardiopulmonary structures and from arterial baro-reflexes. The interplay of these inputs to the SA node produces complex variability that characterizes the heart rate, so-called heart rate variability (HRV) (Benarroch, 1993, Thayer and Lane, 2000).

Cortical level:

- Medial prefrontal cortex
- Anterior cingulate cortex
- Insular cortex
- Paraventricular nucleus
- Central nucleus of the amygdala
- Lateral hypothalamic area

Midbrain level:

Periaqueductal grey

Pons level:

Parabrachial region

Brainstem level:

- Nucleus ambiguus efference via myelinated vagus.
- Ventrolateral medulla sympathetic efference.
- Nucleus tractus solitarius - efference via the myelinated vagus.

Spinal level:

- Stellate ganglia (C7) sympathetic
- The vagus nerve

Figure 1. Descending vagal pathways constituting "the vagal break" (Benarroch, 1993)

During fetal life the myelinated vagal fibers increase from 24 to 28 weeks gestation until full-term birth, and the myelinization process is then active during the first year of life. It has been hypothesized that deficits in the myelinization of the vagal break may be a contributing factor to dysfunctional autonomic self-regulation and impaired social development (Porges, 2007). Prematures show lower HRV parameters than full term infants and the most significant differences are observed in HRV parameters reflecting parasympathetic activity (RSA) (Longin et al., 2006). There is a modification of HRV with age, which reflects the development of the autonomic nervous system (Silvetti et al. 2001). HRV increases from 0–6 years and then a decrease of HRV follows until adulthood (Finley and Nugent 1995).

A genetic component is suggested for individual differences in HRV (Singh et al., 2002, Wang et al., 2009). There is support for a gender difference in HRV, with women having greater HRV than men (Snieder et al., 2007), and also displaying greater HRV response (decrease) to stress than males (Li et al., 2009).

The hyper-arousal that is seen in anxiety disorders was previously assumed to be caused by increased sympathetic activity. Later, the relative increase of arousal

observed in anxiety disorders has been shown to be the result of a deficit in the inhibitory activity of the parasympathetic nervous system, rather than only increased sympathetic activity. Recent data show that vagal tone is decreased in both anxiety disorders and depression, indicating an impairment of the descending vagal pathways, (I) (Thayer and Lane, 2000).

4.2.2 Measures of heart rate variability

There are different ways of measuring and calculating HRV. Holterelectrocardiography (ECG) measured with an ambulatory device to continuously monitoring during 24 hours is often used, mirroring HRV during all activities throughout the day, as well as during sleep. The long registration increases the risk of movement artifacts. Shorter registrations without interventions have been shown to give reproducible intra-individual HRV measures after 6 months (II) and are more easily managed in CAP clinics.

The easiest way to calculate HRV is by the standard deviation of the inter-beat intervals (R-R intervals) (figure 2), which reflects all the cyclic components responsible for variability during the time of the ECG recording, the so called SDNN.

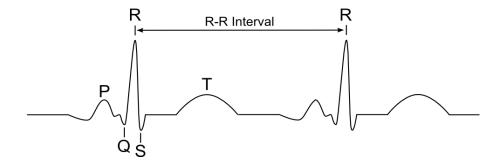


Figure 2. Electrocardiogram (ECG) showing the R-R interval (inter-beat interval)

In healthy individuals, the heart rate shows several simultaneous patterns of variability with different frequencies. By using Fourier transformation (spectral analysis) it can be estimated how HRV distributes as a function of frequency. In this way the level of variability within the different frequency domains can be identified. High frequency domain (HF) is defined by the interval 0.15-0.4 Hz and low frequency domain (LF)

by 0.04-0.15 Hz. Respiratory Sinus Arrhythmia (RSA), i.e. the deceleration of heart rate during exhalation and the acceleration of heart rate during inhalation, is captured in the HF domain, when the breathing rate is normal. In older literature, HF is said to measure vagal tone and LF interpreted as a quantitative marker for sympathetic modulations, or a reflection of both sympathetic and vagal influences (Berntson et al., 1997) as referred to in study II. More recent studies using pharmacological blockade of the vagal and sympathetic input to the heart respectively, suggest that both HF and LF mainly measures the input of the myelinated vagus (Porges, 2007, Thayer and Lane, 2000). This updated interpretation is referred to in study I.

In summary, only the myelinated vagus contributes to the RSA, HF and LF, but the unmyelinated vagus and the sympathetic nervous system contributes to HRV in general. Subsequently the RSA, HF and LF specifically mirror the function of the vagal break and thus the capacity of physiological, emotional and cognitive self-regulation. These mechanisms are suggested to be involved in the previously described psychophysiological models of anxiety and depression (Thayer et al., 2009, Thayer and Lane, 2000, Porges, 2007).

4.3 NEUROTRANSMITTER SYSTEM DYSFUNCTION

Dysfunction within the serotonin, noradrenalin or dopamine neurotransmitter systems of the CNS are involved in the patophysiology of anxiety disorders and depression. However, associations between a specific lesion and the behavioral symptoms have been difficult to identify due to the full complexity of the processes involved (Brunello et al., 2003). Briefly summarized, a dysfunction on serotoninreceptor level is suggested as a key mechanism in major depressive disorder (MDD) (Ruf and Bhagwagar, 2009). This may explain the delayed treatment response of SSRI often seen in MDD, as up-regulation of the serotonin receptors takes several weeks. Reduced serotonin synthesis has been suggested as a mechanism in atypical depression, which usually has a more prompt treatment-response to SSRI medication (Antonijevic, 2006). The neurotransmitter systems are overlapping (Brunello et al., 2003) and hypernoradrenergic function is also suggested to be associated with major depressive disorder and hyponoradrenergic activity with atypical depression (Gold and Chrousos, 2002). Neurocircuits based in the amygdale region seem to play a crucial role in mediating anxiety symptoms and additional neurocircuits may play a role in specific anxiety disorders (Stein et al., 2002).

4.4 THE HYPOTHALAMIC-PITUITARY-ADRENAL (HPA) AXIS

Adverse experiences during fetal life, infancy and childhood can have consequences for stress regulation and behavior later in life (Herbert et al., 2006). Maternal stress during pregnancy (through epigenetic mechanisms), deprivation of maternal contact during critical periods of infancy or neglect and abuse in childhood, are examples of such adverse experiences. During fetal and child development excess glucocorticoides seem to increase the sensitivity of the HPA axis, resulting in long-lasting increased vulnerability to depression and anxiety (Halligan et al., 2004, Goodyer, 2008).

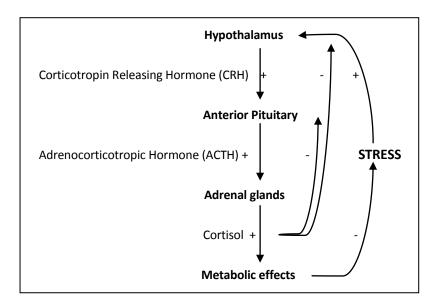


Figure 3. Schematic illustration of the Hypothalamic-Pituitary-Adrenal (HPA) axis

In adults, sustained over-activity in the HPA-axis, with increased secretion of corticotropin-releasing hormone (CRH) and a hypernoradrenergic function is considered to be the key mechanisms of major depressive disorder (MDD) (figure 3). The resulting hypercortisolemia contributes to sleep alterations, disturbed circadian patterns, enhanced anxiety, decreased appetite and cognitive impairment. Whether or not hypercortisolemia impairs serotonin receptor function is debated (Bhagwagar et al., 2003). In contrast, atypical depression in adults has been associated with attenuated CRH- and hyponoradrenergic activity and normal serotonin receptor function (Gold and Chrousos, 2002, Antonijevic, 2006). It is not yet known whether this is a premorbid vulnerability factor or a result of prolonged stress exposure (Rydmark et al., 2006).

4.5 GENETIC INFLUENCES

Thousands of genes influence the brain systems that regulate mood. Consequently, polymorphism at many loci will influence the vulnerability of depression and anxiety. Approximately 40% of vulnerability to depression is due to genetic differences, but no locus accounts for more than a few percent in variation (Levinson, 2006). Genetic effects on symptoms of anxiety and depression have been shown to be developmentally dynamic from middle childhood to young adulthood. Both genetic innovation and attenuation may be involved. Genetic innovation means that new genetic mechanisms are activated increasing the relationship between the genotype and the symptoms of anxiety and depression; attenuation means that the association between the genotype and symptoms of anxiety and depression decline over time. This implies that different genetic influences involved in the pathophysiology of anxiety and depression may occur during specific developmental periods. Differences in genetic risk factors in males and females may also increase during development (Kendler et al., 2008).

4.6 THE STRESS RESEARCH PARADIGM

Stress can be defined as the imbalance between external or internal stressors and the resources the individual can access to cope with them. A stress response is constituted of a general component, mainly associated with glucocorticoides and the autonomic nervous system and a specific component that defines the required individual physiological or behavioral response. The specific response is modulated by emotional control mechanisms. Together these components facilitate an adaptive response (Herbert et al., 2006) aiming to maintain balance. "Le milieu interieur" as defined by Claude Bernard in 1865 or homeostasis as described by Cannon in the 1920's is the ability of an organism to maintain balance during changing conditions. It is achieved by dynamic behavioral adjustments and physiological regulation mechanisms later defined as allostatis (McEwen, 1998).

Most research efforts so far have focused on external factors related to stress-load and the detrimental effects of self-perceived stress, for example, the sympathetic adrenal medullar system that mediates complex stress responses in most of our inner organs by the release of catecholamines. Adrenalin and noradrenalin can be measured in blood and urine and have been extensively studied as measures of 'stress'. Acute

stress leads to elevated blood levels, but during chronic stress a depletion of the noradrenergic system can be the result. In treatment of stress-related disorders methods such as cognitive behavioral psychotherapy have introduced strategies to improve resilience to stress. Less attention has been given to psychophysiological mechanisms of efficient restoration of homeostasis or methods and practices of allostatic competence.

There is scientific evidence for a causal relationship between the generic stress component (the sympathetic nervous system and HPA-axis) and development of anxiety and depression (Herbert et al., 2006), but this does not necessarily explain the increase of anxiety and depressive problems in the population. There is a common preconception that external stress load on the individual has increased in recent decades, causing the increase in anxiety and depressive problems in the population. Possible variations of the actual stress load in adolescents are difficult to measure and self-assessment of subjectively perceived stress can be affected by many other factors such as individual vulnerability, cultural influences and attitudes.

4.7 SALUTOGENESIS – A COMPLEMENTARY PERSPECTIVE

4.7.1 Background

As a complement to the perspective of pathogenic mechanisms as etiological models for adolescent anxiety disorders and depression, we were interested in studying protective parameters. Of specific interest are protective factors that are accessible for intervention, as these may counteract the development of anxiety and depressive problems in youth and represent possible targets for prevention. We therefore studied self-reported life style parameters in relation to autonomic regulation measured by heart rate variability in healthy adolescents (II). We also included the Sense of Coherence (SOC)-scale (III, IV) that has been frequently used in child and adolescent psychiatry as a salutogenic measure and has been shown to have predictive values for psychological health (Eriksson and Lindstrom, 2006).

4.7.2 Definition

The concept of salutogenesis (salus=health and genesis=origin) was introduced by Antonovsky (Antonovsky, 1987). He described the relationship between health and disease as a continuum. Factors or processes that move the individual towards the healthy end of the continuum were called salutogenic, where as pathogenic factors or processes move individuals towards the disease end of the continuum.

He suggested that the stress factors an individual may encounter in life can be pathogenic, neutral or salutogenic, depending on the individual's "generalized resistance resources". Thus, the ability to successfully cope with stressors is a basic salutogenic factor that protects the individual from disease by increasing resilience (Antonovsky, 1987). This implies that well-developed stress regulation, i.e. autonomic regulation, may enhance psychological and physical health and wellbeing, which is in line with previously described models of stress-regulation and current understanding of the pathophysiology of anxiety disorders and depression.

Antonovsky concluded that stress is harmful only in combination with insufficient generalized resistance resources. These can be strengthened by protective factors and weakened by risk factors, and he considered them to be qualitatively different, i.e. protective (salutogenic) factors are not merely the absence of pathogenic (risk-) factors.

4.7.3 Sense of coherence

Sense of coherence was also coined by Antonovsky as a theoretical model of the generalized resistance resources and defined as a global orientation to inner and outer stressors. He constructed a Sense of Coherence Scale that was intended to specifically measure three protective factors: 1. the extent to which individuals are likely to perceive stressors as predictable and explicable (comprehensibility), 2. the extent to which they have confidence in their capacity to overcome the stressors (manageability) and 3. the extent to which they judge it worthwhile to take on the challenge (meaningfulness). Together these constitute a global salutogenic factor.

The discriminant validity of SOC in relation to symptoms of anxiety and depression has previously been questioned in adults. Instead of assuming that protective and risk factors are dichotomous, i.e. qualitatively and dimensionally different, an alternative

interpretation may be that these factors are continuous variables within the same dimension.

This discussion is also relevant to adolescents, since SOC has been considered to gradually stabilize during adolescence and be a trait measure from young adulthood. It is well known that symptoms of anxiety and depression early in life are risk factors for future psychiatric problems and the absence of these symptoms may be important salutogenic factors expressed by a low sense of coherence. If a low sense of coherence simply mirrors anxious and depressive problems, evidence-based methods for treatment may prevent chronic development and enhance the individual's general resistance resources.

5 TREATMENT OF ANXIETY AND DEPRESSION IN ADOLESCENCE

5.1 TREATMENT OF ANXIETY

There is evidence for the clinical utility of cognitive behavioral therapy (CBT) in treating children and adolescents suffering from anxiety disorders (James et al., 2005) and also in long-term follow up (Barrett et al., 2001). Relative to placebo, antidepressants are efficacious for adolescent anxiety disorders (Bailly, 2009). The effects are strongest in non-obsessive compulsive anxiety disorders and intermediate in obsessive compulsive disorder (OCD) (Bridge et al., 2007). According to the Swedish classification of pharmaceuticals, SSRI treatment is recommended for OCD in this age group, but not for other anxiety disorders (FASS, 2008).

5.2 TREATMENT OF DEPRESSION

Since several studies show there is a relatively high response rate to placebo, brief supportive treatment and family education, these methods constitute the recommended first approach for mild adolescent depression (Birmaher et al., 2007, Rutter, 2008). For more persistent or severe depression either cognitive behavioral (CBT) or interpersonal therapy (IPT) are empirically validated psychotherapy methods (Weisz et al., 2006, Mufson et al., 1999, Mufson et al., 2004).

Medication with serotonin reuptake inhibitors (SSRI) (Birmaher et al., 2007) is also a validated treatment of adolescent depression. A combination of CBT and SSRI seems to have a more favorable risk/benefit balance than mono-therapy with only CBT or SSRI in this age group (Vitiello, 2009). Regulatory officials in US and Europe, have stated caution regarding the use of SSRI in treatment of adolescent depression, because of a suspected association to increased risk of impulsive and suicidal behavior (Emslie et al., 2006). This has resulted in the decreased use of SSRI for treatment of adolescent depression in the US (Libby et al., 2009). There is debate regarding the significance of this data and as to whether or not the decrease of SSRI prescription may have paradoxically contributed to an increase in suicides due insufficient treatment. In Sweden, the prescription of SSRI to adolescents has continued to increase (Melander and Rastad, 2007).

The benefit to risk ratio of SSRI treatment in adolescents varies as a function of indication, age, duration and study conditions. However, the benefits of antidepressants have generally been considered greater than risks from possible suicidal ideation or suicide risk due to the medication and the long term effects of medication with SSRI in adolescence has been considered lower than the risk of being depressed (Bridge et al., 2007) (March et al., 2007).

Nevertheless, there is recent evidence from animal experiments that blockage of the serotonin transport protein (5-HTT) prenatally or in infancy causes wiring defects in certain brain areas where 5-HTT is transiently expressed during development. The behavioral effects of serotonin blockade during development are different from the effects of blockade in adults, and perinatal administration of SSRI in rodents causes anxiety and depression-like behavior which persists into adulthood (Homberg et al., 2009).

Adolescent depression has a high rate of relapse, estimated at 30-70% within two years for clinical samples (Birmaher et al., 2002). In treatment of adolescent depression with any of the evidence-based methods, the rate of incomplete recovery is also high, which in turn increases risk of recurrent episodes (Kovacs, 1996). In these cases, reasons for continued depression such as rapid drug metabolism, non compliance and comorbidity must be ruled out.

National guidelines vary between USA and Britain. Britain has a more conservative approach to the use of SSRI's in treatment of adolescent depression and recommends psychotherapy three months prior to SSRI treatment in moderate to severe adolescent depression, advising that medication should not be prescribed without concomitant psychotherapy (Birmaher et al., 2007, Middleton et al., 2005). In Sweden, national clinical guide lines are lacking and the choice of treatment method is mainly based on personal preferences and accessibility (The Swedish National Board of Health and Welfare, 2009a).

6 AIMS

The primary aim of this study was to investigate how autonomic regulation is related to anxiety and depression in adolescent girls. Thus, from a longer term perspective, the aim was to create a basis for future studies of interventional design to investigate allostatic practices and the effect of life style changes as preventive and treatment methods for anxiety and depression in this age group.

The specific aims were to answer the following questions:

- Is autonomic regulation impaired in adolescent girls with anxiety disorders and/or major depressive disorder (MDD) compared to healthy controls? I
- Is autonomic regulation related to lifestyle factors that are accessible for intervention in healthy adolescents? **II**
- How do we best differentiate caseness of anxiety disorders and/or MDD from non-caseness in adolescent girls? **III**
- Does sense of coherence represent a salutogenic construct that is dimensionally different from measures of anxiety and depression in adolescent girls, and how is it related to autonomic regulation? IV

7 METHODOLOGICAL CONSIDERATIONS

7.1 STUDY OVERVIEW

Data was collected from two samples of adolescents – one recruited from schools and one recruited from CAP clinics. Data from the non-clinical (school) sample was collected on two occasions with a six-month interval during 2003-2004. Data from the clinical (CAP) sample was collected on one occasion during 2005-2008 (figure 4).

NON-CLINICAL SAMPLE

Measurement 1 6 months Measurement 2 Girls (n=66) Girls (n=66) 2004 Mean age of 16.5 range 15.9-17.7 2003 Boys (n=33) Boys (n=33) 2004 Mean age 16.3 range 16.0-17.5 2003 **CLINICAL SAMPLE** Girls (n=73) (6 DAWBA excl) Mean age 16.8 range 14.5-18.4 2005-2008 Boys (n=8)

Figure 4. Schematic illustration of the sampling procedure

Study I, III and IV have cross-sectional designs and compare the clinical sample of girls versus the non-clinical sample. Study II was based on repeated measures only of the non-clinical sample including both boys and girls. Data on psychiatric self-assessment of depressive and anxious symptoms, i.e. symptom severity scores,

salutogenic self-assessment and life style and health-related parameters, heart rate variability (HRV) as a measure of autonomic regulation, saliva cortisol with four samples over one day as a measure of HPA-axis function and physiological cardiovascular risk factors represented by body mass index (BMI), blood pressure and plasma (p)-glucose were collected from the non-clinical sample on two occasions with a six months interval and on one occasion from the clinical sample (table 1).

Table 1. Overview of all parameters used in the study

Questionnaires	Autonomic regulation (heart rate variability)	HPA-axis function	Physiological cardiovascular risk factors
Psychiatric self-assessment Beck's depression Inventory Beck's Anxiety Inventory Hospital Anxiety and depression Scale Strengths and Difficulties Questionnaire	High frequency Low frequency Standard deviation of inter-beat intervals	Salivary cortisol x 4	Body Mass Index Systolic blood pressure Diastolic blood pressure Plasma-glucose
Salutogenic self-assessment Sense of coherence Lifestyle and health related parameters questionnaire			

7.2 DESCRIPTION OF THE SAMPLES

7.2.1 The clinical sample

Since the majority of CAP patients did not have a proper ICD-10 or DSM-IV diagnosis, patients with a non-manual based clinical diagnosis of depression or anxiety or simply labeled as "depressed" were asked to participate. The diagnoses were then validated by the "Development and Wellbeing Assessment" (DAWBA), a semi-structured internet-based diagnostic interview, which was carried out by one of the co-workers of the study at the patient's CAP clinic. Parents and teachers were not interviewed. The computer generated DSM-IV diagnoses were then rated again and accepted or rejected by assessment of two independent child and adolescent psychiatrists. Only patients with a validated DAWBA-diagnosis of one or several anxiety disorders and/or MDD were included in the study.

Anxiety disorders in this study were defined by a compromise between DSM-IV, and ICD-10 categorizations and included panic disorder with or without agoraphobia, social anxiety disorder (SAD, also referred to as social phobia), post traumatic stress disorder (PTSD), generalized anxiety disorder (GAD) and separation anxiety, but not acute stress reaction, obsessive compulsive disorder (OCD) or anxiety caused by somatic or substance-related causes. Agoraphobia without panic disorder was referred to as specific phobias. Major depressive disorder (MDD) was defined by the DSM IV criteria, thus allowing symptoms of atypical depressive symptoms.

Exclusion criteria for the clinical sample were mental retardation, severe autistic disorder and severe anorexia nervosa. In study I and II, in which HRV was the main outcome parameter, patients with > 5% distorted HRV data and medical conditions such as anemia, thyroid disorders, diabetes and pregnancy were also excluded. Inclusion criteria for the clinical sample were 15-18 years old CAP patients with main diagnoses of anxiety disorders and/or MDD, validated by DAWBA.

Since only eight boys were recruited in the clinical sample they were excluded from all analyses in study I, III and IV in which only female psychiatric patients remained. (In contrast, boys were included in study II, where only the non-clinical sample was assessed.)

After DAWBA validation 73 adolescent female psychiatric patients with a mean age of 16.8 years (range 14.5-18.4 years) remained (figure 6a). They all had a diagnosis of one or several anxiety disorders and/or MDD. No patients had a diagnosis of bipolar disorder. The DAWBA interview concluded that 19.2 percent of the subjects fulfilled the criteria for MDD only, 32.9 percent for one or several anxiety disorders only, and 47.9 percent were diagnosed with comorbidity with both MDD and one or several anxiety disorders. The most common diagnoses were MDD and general anxiety (GAD) and social anxiety disorder (SAD). Co-morbidity of several anxiety disorders was common, approximately 30% of the total sample suffered from two or more anxiety disorders (figure 5).

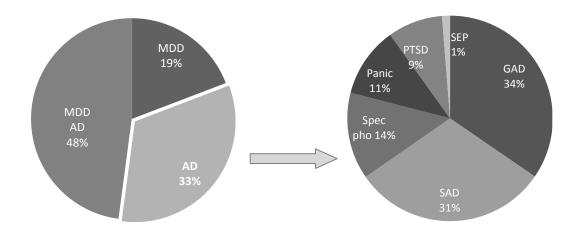


Figure 5. Schematic description of the distribution of MDD and anxiety disorders in the clinical sample. The right circle represents a breakdown of the 33% of the original sample who only had anxiety disorders: general anxiety disorder (GAD), social anxiety disorder (SAD), specific phobias, panic disorder, post traumatic stress disorder (PTSD), separation anxiety (SEP)

In addition to MDD and anxiety disorders approximately 27% of the total clinical sample had another co-morbid psychiatric diagnosis. The majority of these patients had one other psychiatric diagnosis in addition to the anxiety disorder and/or depression and two patients had two additional psychiatric diagnoses. The clinical sample thus included two patients with conduct disorders, three with Asperger's syndrome, two with OCD, one with anorexia nervosa, nine with bulimia nervosa and twelve with eating disorders, UNS (table 2). The subgroup of the clinical sample exhibiting comorbidity with psychiatric diagnoses other than anxiety disorders and MDD did not show extreme scores on any of the assessment scales. The subgroup exhibiting comorbidity with anxiety disorders and MDD had the highest severity scores on the psychiatric self-assessment scales, whereas the subgroup only exhibiting anxiety disorders had the lowest scores on all psychiatric self-assessment scales, and the one only exhibiting MDD medium scores.

Table 2. Description of the comorbidity in the clinical sample

	No other diagnoses	Eating disorder UNS	Bulimia nervosa	Anorexia nervosa	OCD	Aspberger's syndrome	Conduct disorder	Total
Anxiety disorder	17	4	1		1	1	1	25(24) ¹
MDD	8	1	3		1	2		15(14) ¹
Anxiety disorder and MDD	21	7	5	1			1	35
Total	46	12	9	1	2	3	2	75(73) ¹

¹ The total number of subjects in the clinical sample was 73, but two patients had two diagnoses in addition to anxiety disorder and/or depression explaining the total number of 75.

The subjects had ongoing treatment contact (median duration 11 months) at one of 13 open psychiatric clinics for children and adolescents situated in the centre of Stockholm, its suburbs and in smaller towns nearby – located in proximity to the schools that were the recruitment base for the non-clinical sample. The first author informed the staff at the clinics (doctors, psychologists and social workers) about the study and the staff then asked their patients about participation and gave them written information. From what the staff reported 85% of the informed patients participated. The reasons for declining participation were fear of blood sampling or parents not approving of the procedure.

7.2.2 The non-clinical sample

The inclusion-criterion for the non-clinical sample was simply that participants had to be in their first year of "gymnasieskola" (Swedish equivalent to upper secondary school, year 10). The exclusion-criteria were the same as for the clinical sample. For the non-clinical sample, both boys and girls were recruited from four "gymnasieskolor"

representing four socio-demographically different areas: a small rural town, Stockholm City, an affluent northern suburb and a less affluent southern suburb with a large immigrant population. About 80% of the informed students participated, the participation ratio being similar for all schools. The main reasons for declining to participate were fear of blood sampling and reluctance to miss school-hours. The mean age was 16.5 years (range 15.9 – 17.7 years).

The non-clinical sample was not a true population-based sample, which limited the inferential power. This may be considered as a limitation, especially in study II, where we aimed to generalize the results to the population level. In study I and III, the female part of the non-clinical sample constituted the control group to which the clinical sample was compared. In study IV the non-clinical sample and the clinical sample were studied separately (figure 6b).

7.3 DIAGNOSTIC INTERVIEW

In this study, validation of the psychiatric diagnoses of the clinical sample was made using the Development and Wellbeing Assessment (DAWBA), chosen because it is an internationally used tool, validated for Swedish use, internet-based and easily manageable. DAWBA is a semi-structured diagnostic interview designed to generate ICD-10 and DSM-IV psychiatric diagnoses in 5-17 year olds. DAWBA has consistently generated reasonable estimates of prevalence and association with risk factors (Goodman et al., 2000). When compared to clinical diagnoses, DAWBA diagnoses support good validity (Goodman et al., 2000, Alyahri and Goodman, 2006, Mullick and Goodman, 2005). In this study, the information was only collected from the patients and not from parents and teachers.

Figure 6 a. Exclusion procedure for the clinical sample

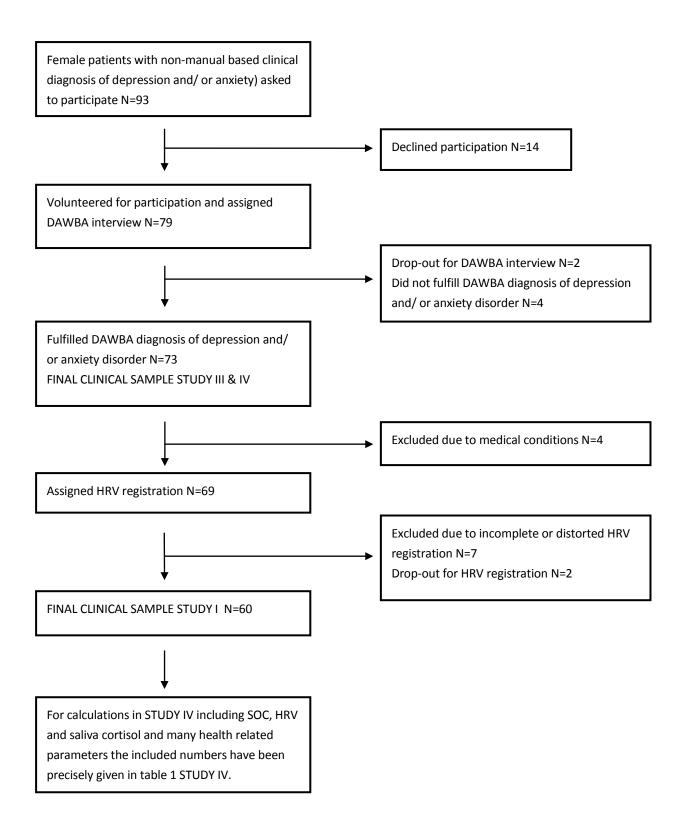
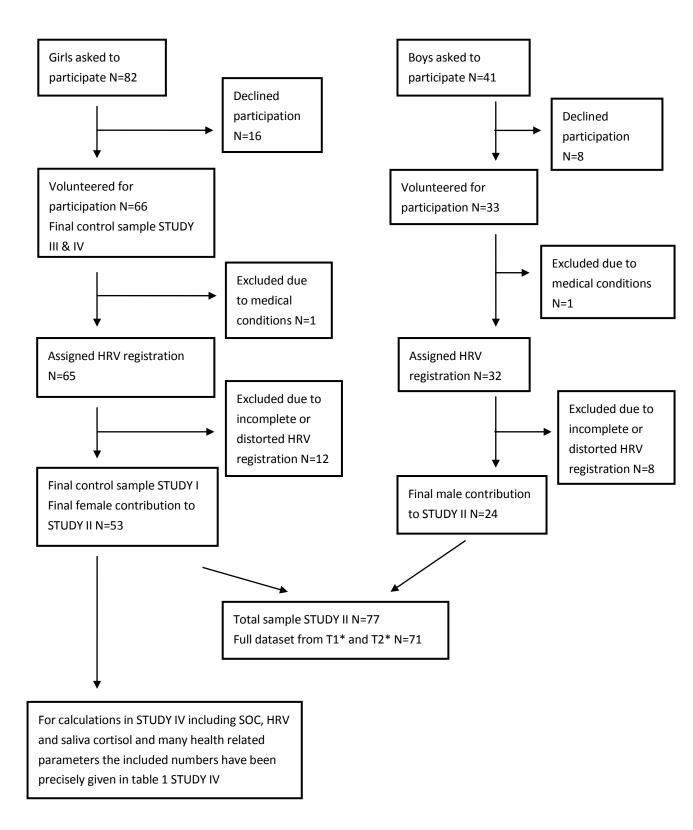


Figure 6 b. Exclusion procedure for the control sample



^{*}T1=first measurement, T2=repeated measurement six months later

7.4 METHODS OF SELF-ASSESSMENT

7.4.1 Psychiatric self-assessment

In this study, psychiatric self-assessment scales were used in order to evaluate the severity of anxiety and depressive symptoms in the samples in the study. At the time of designing the study (2002), the questionnaires detailed below, were translated and used in CAP, but only SDQ was validated for adolescents. Several other self-assessment scales were also in use at the time and since then new scales have been translated, validated for Swedish use in this age group and to some extent implemented; had we designed the study again the choice of self-assessment scales may have been different. An update of presently used self-assessment scales is presented in the discussion.

Hospital Anxiety and Depression Scale (HAD) includes seven questions about depression and seven about anxiety (Zigmond and Snaith, 1983). Each question scores 0-3 points. A total score of 8-10 points indicates mild to moderate symptoms; above 10 indicates a clinically significant condition.

Beck's Depression Inventory (BDI) consists of 21 items rated on a 4-point scale and yields a total score by summation of the ratings for the individual items (Beck, 1961). The total score ranges from 0-63 points and high scores indicate more severe depression. When this study was designed, the BDI-II had not yet been validated for the Swedish version and therefore BDI-A1 was used in this study.

Beck's Anxiety Inventory (BAI) contains 21 items assessing the degree to which the respondent has been affected by the physical or cognitive symptoms of anxiety during the past week (Beck, 1988). BAI items are also meant to reflect panic attack symptoms. The total score ranges from 0-63 points and high scores indicate more severe anxiety.

Strengths and Difficulties Questionnaire (SDQ) is an internationally-used screening instrument for mental health problems in children and teenagers (Goodman, 2001). It comprises 25 statements regarding psychological attributes and behaviours, forming five subscales: hyperactivity/inattention, emotional symptoms, conduct problems, peer problems and pro-social behaviours. Every item is rated on a three-point scale and all subscales, except the pro-social scale, are summarized to generate a total difficulties

score. In this study, only the self-report version was used. Acceptable psychometric properties for the self-report version of SDQ for adolescents have been shown in previous studies (Svedin and Priebe, 2008, Lundh et al., 2008).

7.4.2 Salutogenic self-assessment

When the study was designed we wanted to be able to assess protective and salutogenic factors for anxiety and depression and how they were related to autonomic regulation. The Sense of Coherence (SOC)-scale was therefore included, as it has been frequently used in CAP research.

Sense of Coherence (SOC) contains 29 items measuring putatively salutogenic factors (Antonovsky and Sagy, 1986, Antonovsky, 1993). Every item is rated on a 7-point scale giving a maximum score of 203. In adult populations, the average has been estimated to be 140 points. High scores indicate a good sense of coherence.

7.4.3 Life-style questionnaire

We aimed to clarify whether certain lifestyle factors and health-related behaviors were related to autonomic regulation in adolescence. No validated instrument matched the information that we required, so a simple questionnaire was put together that covered the following questions:

Psychosomatic health was measured by frequency of having headaches, back pain, stomach problems and sleeping problems defined on a five-point scale in terms of "never", "seldom", "1-2 days per week", "3-4 days per week", "every day".

The level of subjectively perceived stress in relation to total life situation, in relation to schoolwork and in relation to parents' life situation was assessed by a three-point scale defined in terms of "never accurate", "sometimes accurate" and "always accurate".

Sense of support (by teachers and parents) **and sense of satisfaction** (likes to be in school and likes to be with friends) were assessed by a three-point scale defined in terms of, "never accurate", "sometimes accurate", "always accurate".

Health behaviors were assessed by the frequency of physical activity (hard breathing, sweating), and going to bed after midnight ("never", "seldom", "once a week", "twice a week", ">twice a week") and by the frequency of skipping breakfast and smoking of cigarettes ("never", "seldom", "1-2d/week", "3-4d/week" or "every day"). Estimated number of hours spent watching TV per week was also reported.

Socio-demographic background was assessed by two-alternative questions: "One or both parents born in Sweden/both parents born abroad", "living with both parents/living with single parent", "both parents employed/one or both parents unemployed".

7.5 HEART RATE VARIABILITY (HRV) REGISTRATION AND PROCESSING

Heart rate variability (HRV) was used as a measure of autonomic regulation in this study. It was measured by a short ECG-registration with portable equipment. The subjects sat upright, in silence, and no body movements were allowed during the procedure. None of the subjects had clinical signs or symptoms of infectious disease. Use of tobacco or intake of tea, coffee, caffeinated soft drinks or beta stimulant asthma medication was not allowed 1 hr prior to the measurements. This was a practical compromise, since a longer abstinence would have been preferred to ensure lack of influence on HRV. The registration was preceded by 15 min of rest. The equipment comprised the I-330-C-2 Physiological Monitoring System (J&J Engineering; Poulsbo, WA), and c-Stress customized software (PBM Systems, Stockholm, Sweden). The electrocardiogram (ECG) was recorded from electrodes placed on the left and right wrist with a sampling rate of 1024 Hz. Inter-beat intervals were calculated online using an R-wave peak detection algorithm and stored on a PC for off-line processing. Fourier analysis was performed on 2 x 2-min segments of detrended data passed through a Hamming window. Fast Fourier Transformation (FFT) may be suboptimal for low frequency measures in short registrations and very low frequency HRV was therefore not included. The HRV mean values were logarithmically transformed and inter-beat intervals scanned manually for ectopic beats and artifacts. The main problem was the high number exclusions due to missing beats or distorted data.

7.6 SALIVARY CORTISOL

Plain baseline salivary cortisol values are usually presented by a day-curve comprised of several samples to describe the variations over the day. However, the curve of

baseline salivary cortisol is difficult to interpret and the clinical relevance questioned, especially in children and adolescents (Jessop and Turner-Cobb, 2008). In this study, the area under the curve between the first measurement (at awakening) and second (30 min after awakening) - in relation to baseline, the so-called 'awakening response' was calculated as an approximation of the HPA-axis reactivity, which in several studies have demonstrated an association to psychosocial factors, stress and health (Clow et al., 2004).

An advantage of measuring salivary cortisol rather than total serum cortisol is that it eliminates the need to account for within-subject changes or between-subject differences in cortisol binding globulin (CBG) (Gozansky et al., 2005). In serum >90% of the cortisol is bound to CBG, but in saliva only the free fraction is represented, which is the biologically active form. Salivary cortisol concentration is directly proportional to the serum unbound cortisol concentration (Vining et al., 1983).

Salivary cortisol was collected in the course an ordinary school-day, the first sample shortly after waking up (still in bed), the second sample 30 min later, the third in the afternoon and the fourth before going to bed. For saliva sampling, the Salivette sampling device with no preservative (Sarstedt) was used. The tube consisted of a plastic sampling vessel with a suspended insert containing a sterile neutral cotton wool swab, which had to be chewed for about 30 sec and then returned to the insert. The subjects noted the exact date and time for each sample on the test tubes, stored them in their freezer and posted them to the laboratory the following day. The saliva samples were stored at the laboratory at -20C and analyzed by batches. Both written and verbal instructions were given. The subjects were requested not to collect saliva if they had a cold or were ill, and not to smoke cigarettes or use oral tobacco within two hours before sampling.

Orion Diagnostica SPECTRIA^R Test Cortisol RIA was used in order to determine the cortisol concentration in the saliva samples. The test is based on a competitive immunoassay principle. The test tubes are coated with polyclonal rabbit anti-cortisol antibodies. A known amount of labeled cortisol and an unknown amount of unlabelled cortisol compete for a limited number of binding sites in the coated SPECTRA test tube. When the unbound cortisol has been washed away the amount of labeled cortisol in the test tube is reversely proportional to the amount of cortisol in the sample. The

concentration of unknown samples is estimated from a calibration curve. The method is routinely used for quantitative in vitro estimation of cortisol in serum, urine and saliva.

7.7 CARDIOVASCULAR RISK-FACTORS

Overweight, hypertension and diabetes are cardiovascular risk factors that are known to decrease heart rate variability, and are therefore potentially confounding factors when studying the relationship between psychiatric symptoms and autonomic regulation.

BMI, systolic and diastolic blood pressure and p-glucose were measured so that these factors could be controlled for in later analyses.

Weight and height were measured in order to calculate Body Mass Index (BMI =weight (kg)/height (m²)). Blood pressure was checked before, during and after the ECG registration. P-glucose was measured with a portable Heamocue Glucose System device (Banauch et al., 1975). The capillary samples were drawn right after the HRV measurement. Since no food or drinks were allowed one hour prior to the registration, the samples did not constitute proper fasting samples.

7.8 ETHICS

All the participants and their parents received verbal and written information about the study and an informed consent was signed by each participant and at least one parent. The study was approved by the Regional or Central Ethics Committee.

8 SUMMARY OF STUDIES I-IV

8.1 STUDY I

HRV IN ADOLESCENT GIRLS WITH EMOTIONAL DISORDERS

The primary aim of this study was to investigate autonomic regulation measured by heart rate variability (HRV) in a clinical sample of female adolescents with anxiety disorders and/or major depressive disorder (MDD) compared to healthy controls. A second aim was to assess effect of selective serotonin reuptake inhibitors (SSRI) on HRV. We found that high frequency (HF), low frequency (LF) heart rate variability and the standard deviation of inter-beat intervals (SDNN) were significantly lower in the clinical sample compared to the controls (Cohen's d for HF= 0.57, LF 0.55, SDNN 0.60) (figure 7). This was not explained by body mass index (BMI), blood pressure or lack of physical activity. Plasma-glucose differed between the groups but contributed only marginally to the differences of HRV.

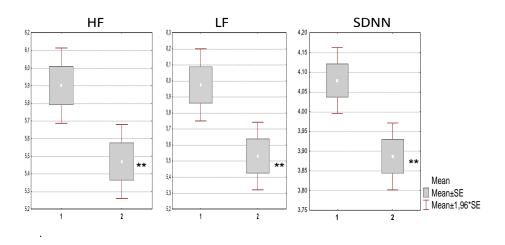


Figure 7. Unpaired t-test showed significant differences in high frequency (HF), low frequency (LF) heart rate variability (HRV) and the standard deviation of inter-beat intervals (SDNN) between the non-clinical sample (1) and the clinical sample (2)

Medication with SSRI explained 15.5% of the total variance of HF, 3.0% of LF and 6.5% of SDNN (figure 8 a-c). No significant differences in HF, LF and SDNN were found between the diagnostic subgroups, which may be due to the small sample sizes.

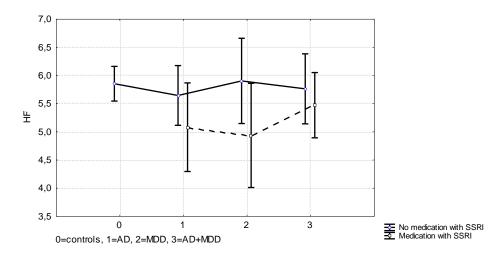


Figure 8 a. High frequency heart rate variability (HF) in the subgroups of the clinical sample - anxiety disorders (AD), major depressive disorder (MDD) and comorbidity of AD and MDD and in the controls

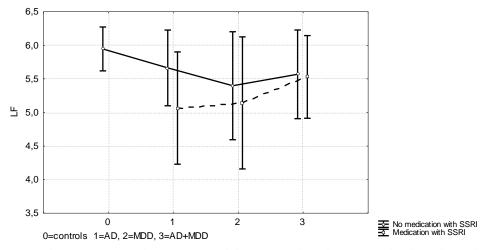


Figure 8 b. Low frequency heart rate variability (LF) in the subgroups of the clinical sample - anxiety disorders (AD), major depressive disorder (MDD) and comorbidity of AD and MDD and in the controls

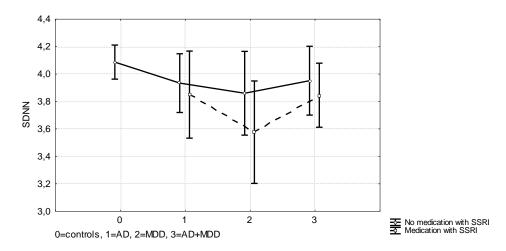


Figure 8 c. Standard dev. of inter-beat intervals (SDNN) in the subgroups of the clinical sample - anxiety disorders (AD), major depressive disorder (MDD), comorbidity of AD and MDD and in the controls.

No differences were found when severity scores (BDI, BAI and SDQ-em) were introduced as co-variates. Vertical bars denote 0.95 confidence intervals.

Interestingly, the clinical sample showed significantly higher non-fasting p-glucose levels, which could have partly explained the difference of HRV between the samples. The mean p-glucose value in the non psychiatric sample was 5.28 mmol/l for the first measurement and 5.52 mmol/l for repeated measurements, whereas the psychiatric sample had a mean value of 6.66 mmol/l. Initially, known diabetes cases were excluded from the study, but the higher mean in the psychiatric sample was partly explained by four subjects with incipient diabetes as estimated by non-fasting p-glucose. However, linear regression models showed that significant differences in HRV between the samples remained after adjustment for p-glucose. It is known that HRV is reduced in patients with diabetes and impaired fasting glucose levels (Singh et al., 2000) and it has also been shown that 48 hour, modest hyperinsulinemia induced by intravenously administered glucose decreases heart rate variability in healthy subjects (Petrova et al., 2006). Whether adolescent girls with anxiety disorders or MDD have an impaired glucose metabolism compared to healthy peers, and whether this is related to a decrease in HRV needs to be confirmed in greater samples, as do the putatively involved mechanisms.

8.2 STUDY II

HRV IN RELATION TO LIFESTYLE IN HEALTHY ADOLESCENTS

This study investigated whether there is a relationship between heart rate variability (HRV) versus lifestyle factors that are accessible for intervention and risk factors for cardiovascular disease in a population of healthy adolescent boys and girls. HRV was registered for 4 min in sitting position in 99 healthy adolescents, 33 girls and 66 boys, with an age range of 15 years 11 months-17 years 7 months. The measurements were repeated after 6 months.

On both occasions there were significant correlations (p < 0.05) between physical activity and HRV, with respective r values for high frequency heart rate variability (HF) 0.26, 0.30, low frequency heart rate variability (LF) 0.35, 0.29 and standard deviation of inter-beat intervals (SDNN) 0.28, 0.37 (figure 9). There was no significant interaction between first and second measurements. In contrast, there were no correlations to sleep patterns, eating habits and smoking. Risk factors for cardiovascular disease such as body mass index (BMI), systolic blood pressure (SPB) and p-glucose did not show any repeatable significant correlations to HRV.

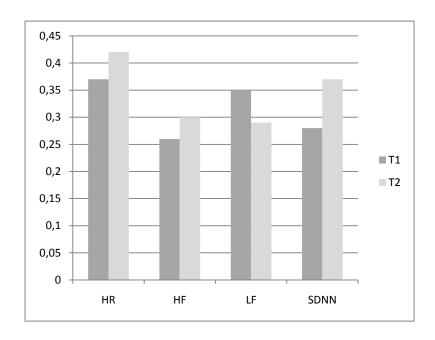


Figure 9. Correlations between heart rate variability (HRV) and physical activity on the first measurement (T1), and the repeated measurement 6 months later (T2). Correlation coefficients (y-axis) and heart rate (HR) and the HRV indices HF, LF, SDNN (x-axis)

Multiple regression models showed that physical activity was a predictor for HF, LF and SDNN in both measurements (table 3). In conclusion, HF, LF and SDNN were reproducible after 6 months and were related to physical activity on both occasions. Our data supports that HRV from only 4 minutes of registration in a non-clinical setting allows for the early identification of subclinical cardiac autonomic changes in healthy adolescents.

Table 3. Multi regression analyses (best subset model) showing the contribution of physical activity to heart rate (HR) and heart rate variability (HRV) on the first measurement (T1) and the repeated measurement 6 month later (T2)

	T1 Multiple R ²	T2 Multiple R ²
HR	0.13	0.21
HF	0.06	0.13
LF	0.11	0.16
SDNN	0.13	0.14

This cross-sectional designed study cannot prove any causal relationship, but it provides the basis for future studies of interventional design. As physical activity has been shown to be positively correlated to HRV on repeated measurements the next step would be to test physical activity as a preventive strategy or treatment method for those with decreased HRV and coexisting symptoms of anxiety and depression. It may be added that we found no relationship between HRV and physical activity in the clinical sample of girls with anxiety disorders and/or MDD, which is probably explained by the smaller sample size and the effect on HRV by the psychiatric disorder.

8.3 STUDY III -

CASENESS/NON-CASENESS OF DEPRESSION AND ANXIETY

This study aimed to validate the ability of frequently used self-assessment scales in Swedish child and adolescent psychiatric practice to differentiate between adolescent girls with manifest anxiety disorders and major depressive disorder from those with less severe symptoms, i.e. to separate caseness form non-caseness. Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI), the Hospital Anxiety and Depression Scale (HAD), Strengths and Difficulties Questionnaire, the emotional subscale (SDQ-em), the impact subscale (SDQ-imp) and the total difficulties score (SDQ-tot) were included as psychiatric self-assessment scales. Moreover, the complete Sense of Coherence scale with 29 items (SOC-29) was also included to investigate the complementary perspective of salutogenesis. The Receiver Operating Characteristic (ROC) curve was calculated by plotting sensitivity against specificity and the area under the curve was used as a measure of the discriminative ability of each assessment scale. For example, the discriminative ability of the SOC-scale to identify cases of emotional disorder (anxiety disorders and/or MDD) was estimated to 0.90 by ROC-analysis (figure 10).

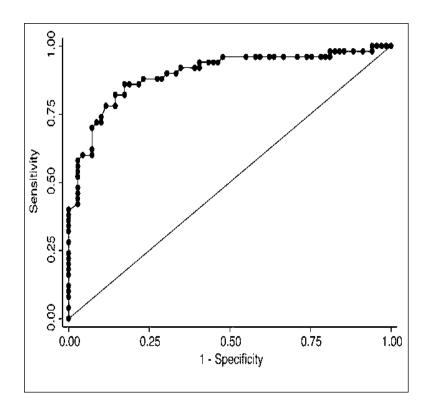


Figure 10. ROC-curve for the SOC-scale showing the ability to discriminate cases of emotional disorders from non-cases. Area under the curve (AUC)=0.90

In differentiating cases of emotional disorders (all cases of anxiety disorders and/or MDD) from non-cases SOC, SDQ-em, SDQ-imp, SDQ-tot and BDI showed similar ability (0.90-0.84), significantly better than BAI, HAD-anx and HAD-dep. In differentiating cases of MDD from non-cases all scales had similar abilities (0.93-0.81), except BAI that had a significantly lower ROC-AUC. In differentiating cases of anxiety disorders from non-cases SOC, SDQ-em, SDQ-imp and SDQ-tot and BDI were significantly better (0.84-0.75) than the specialized scales for anxiety, BAI and HAD-anx. Finally, in the ability to differentiate the comorbid cases with both anxiety disorders and MDD from the non-cases SOC, BDI, SDQ-em and SDQ-imp were significantly better (0.94-0-92) than SDQ-tot, HAD and BAI (figure 11).

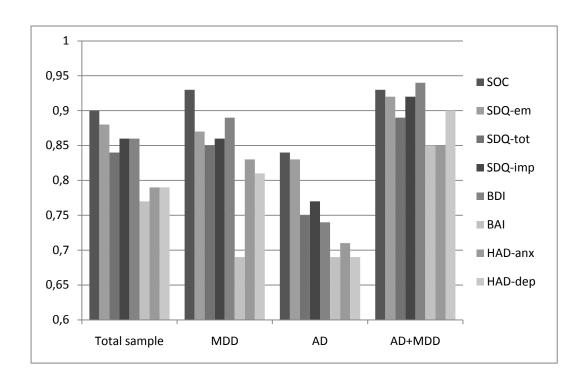


Figure 11. Area under the Receiver Operating Characteristic (ROC)-curve (y-axis) for each assessment scale for the total clinical sample (i..e. caseness of emtional disorder), the group with only major depressive disorder (MDD), the group with only anxiety disorders (AD) and the group with comorbidity of MDD and AD

Thus, SOC, SDQ (em, imp, tot) and BDI seemed to be the most valid tools for identifying girls with emotional disorders (anxiety disorders and/or MDD), without having the ability to differentiate between anxiety disorders and depression. This was an unexpected finding since SOC is supposed to be a salutogenic instrument and BDI a specialized depression scale. The finding supports the use of SDQ (em, imp, tot) as a screening instrument for emotional disorders in adolescent girls. SDQ also has the advantage of having brief subscales also for other psychiatric problems.

One would have expected the specialized scales for depression (BDI and HAD-dep) to be superior in their ability to differentiate caseness of MDD from non-caseness compared to SOC and SDQ, which was not the case. To differentiate caseness of anxiety disorders from non-caseness SOC, SDQ (em, imp, tot) and even BDI were superior compared to the specialized scales for anxiety. Consequently, better self-assessment scales are needed when screening specifically for MDD or anxiety disorders, and also for diagnostic aid.

The fact that SOC showed the highest ROC-AUC for differentiating cases of emotional disorders, anxiety disorders and MDD from non-cases compared to all other scales was a surprising finding, that leads us to further investigate what the SOC-scale actually measures (IV).

8.4 STUDY IV -

DISCRIMINANT VALIDITY OF SENSE OF COHERENCE (SOC)

The aim of this study was to challenge the concept of sense of coherence (SOC) as a distinct salutogenic construct separated from measures of anxiety and depression. In this paper we explored in depth the SOC construct based on data from the previous study.

In the non-clinical sample the correlation coefficients between SOC and Beck's Depression Inventory (BDI), Beck's Anxiety Inventory (BAI) and the Strength and Difficulties Questionnaire, the emotional subscale (SDQ-em) were -0.86***, -0.78 *** -0.73*** and in the clinical sample -0.74***, -0.70***, -0.53*** respectively. SOC versus BDI, BAI and SDQ-em showed similar patterns of correlation to self-reported and physiological health-related parameters in both samples. SOC was the most stable measure over six months.

Multivariate analyses failed to isolate SOC as a separate construct. On the contrary, principal component analysis showed that SOC and measures of anxiety and depression were in the same dimension (figure 12). Hierarchical cluster analysis performed on all items from all the scales revealed that 17 of the BAI items and 1 SDQ-em item that addressed severe situational anxiety and physiological reactions of fear constituted a separate cluster. All SOC and BDI items remained in the other cluster, indicating that persistent and generalized symptoms of depression and anxiety, but not severe situational anxiety and fear, are measured by these scales in combination.

Hierarchical cluster analyses solely applied to SOC items did not confirm any categories of meaningfulness, manageability and comprehensibility.

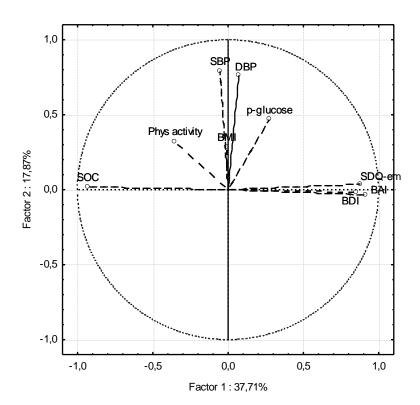


Figure 12. The projection of the scores of SOC, BDI, BAI and SDQ-em and physical activity, systolic (SBP) and diastolic blood pressure (DBP), body mass index (BMI) and p-glucose on the factor plane calculated by principal component analyses (orthogonal decomposition).

In conclusion, the findings indicate that SOC lacks a unique dimensionality as a salutogenic construct, instead constituting a sensitive inverse measure of comorbidity for persistent depressive symptoms and generalized anxiety/or generalized social anxiety. These symptoms were better captured with SOC than by the specialized scales for anxiety and depression. Self-assessment scales that adequately identify adolescent girls with persistent depressive symptoms and generalized anxiety need to be implemented and comorbidity identified, because of the corresponding severe symptomatology and impaired global function. The study also revealed that HRV and the awakening-response of saliva cortisol showed higher correlations to SOC than to BAI and BDI. This is in line with our finding that SOC but not BDI and BAI measures generalized anxiety, since persistent anxiety but not situational anxiety in adolescents is associated with a increase in the awakening response (Greaves-Lord et al., 2007). The finding is also in line with previous data showing that vagal tone is decreased in adult patients with GAD (Thayer and Lane, 2000).

9 DISCUSSION

9.1 AUTONOMIC REGULATION

The theory of autonomic self-regulation, measureable by HRV, as a pathophysiological model for anxiety and depression does not propose that the vagus is the ultimate cause for these disorders. On the contrary, emotion and social engagement behaviors are regulated by several complex neural circuits (Porges, 2007).

Nevertheless, the model is useful for several reasons. Firstly, a dysfunction of the descending vagal inhibitory pathways will have a negative impact on the individual's autonomic self-regulation and be mirrored in the capacity of cognitive, emotional and physiological adaption, resulting in symptoms of anxiety and depression as well as somatic symptoms (Thayer and Lane, 2000, Thayer et al., 2009). Study I verifies that the function of the vagal break is already impaired early in the life of individuals who suffer from anxiety and depressive symptoms, when it is unlikely that the heart rate variability is affected by ischemic heart disease. Secondly, the function of the descending vagal pathways can be measured objectively by their influence on the heart rate, as simply recorded by ECG. Thirdly, it seems possible to restore and improve the function of the descending vagal pathways with different treatment methods and practices described under "future treatment methods". As shown in study II, frequent physical activity is related to an increased HRV in healthy adolescents. The next step would be to investigate whether an intervention with physical activity improves HRV and simultaneously reduces symptoms of anxiety and depression. It is worth noting that in study I, SSRI medication paradoxically explained part of the decrease in HRV in the clinical sample. It is intriguing that SSRI reduces symptoms of emotional dysregulation while simultaneously causing a decrease in heart rate variability, and the clinical implication of this is not yet understood.

9.2 PSYCHIATRIC SELF-ASSESSMENT

Psychiatric self-assessment scales can be used in several contexts which demand different profiles and abilities. When used to screen for psychiatric symptoms or disorders in the population, the scale is preferably brief and cover several disorders. The items of the Strengths and Difficulties Questionnaire (SDQ) constitute subscales covering the most common child and adolescent psychiatric problems. Our data (III)

supports the choice of SDQ, when screening for anxiety and depressive problems, but one should remember that the emotional subscale does not differentiate between anxiety and depressive problems.

There are several reasons for more widespread screening for symptoms of anxiety and depression in adolescents. Firstly, it is likely that many adolescents with anxiety and depression never get diagnosed or treated. In the US it is estimated that 76% of children and adolescents with anxiety disorders and 61% with depression never receive treatment (Keller et al., 1992, Wu et al., 1999). Possible explanations are that adolescents with anxiety and depression do not perceive themselves as having a psychiatric disorder, or do not want to be perceived as being psychiatrically ill; that they are unaware that treatment is available or that surrounding adults, such as parents and teachers, often find it difficult to assess whether the symptoms of anxiety and depression are signs of a psychiatric disorder or a normal expression of teenage behavior. Secondly, there exists a relation between mild psychiatric symptoms such as suicidal thoughts, minor/sub-threshold depression, or dysthymia, and an increased risk of further severe psychiatric disease (Fergusson et al., 2005, Ljungdahl, 2007). Early onset of chronic depression also has a more malignant course and is associated with greater comorbidity compared to late (adult) onset (Klein et al., 1999). By assessing young adults, it has been shown that individuals who suffered from anxiety and depression as teenagers had a significantly lower rate of employment and education than those who did not. Likewise, a significantly higher percentage of the former group was currently receiving psychiatric treatment compared to a peer group who had not suffered from psychiatric problems during adolescence (Last et al., 1997, Pine et al., 1998). Thirdly, when depression and anxiety disorders in adolescents remain untreated, there is an increased risk of impact on self-confidence, relationships, learning abilities and psycho-social development and also an increased risk of recurrent episodes and suicide (Rutter, 2008).

Psychiatric self-assessment scales may also be used to make intake routines at CAP clinics more efficient, helping to identify those who need psychiatric treatment. Moreover, in this context ease and practicality of the procedure is essential, and we have shown in study III that the emotional subscale of SDQ has excellent abilities to discriminate between caseness and non-caseness of emotional disorders despite its brief format.

For diagnostic aid and assessment of treatment outcome new scales have been translated and validated since this study was designed, thus deserving an update. The Youth Self Report (YSR) has been frequently used, but does not contribute to better differentiation between anxiety and depression (Broberg et al., 2001).

Regarding specialized scales for depression the Swedish version of Children's Depression Inventory (CDI) does not have sufficient indications of being a valid and reliable measure of depression in adolescence (Ivarsson et al., 2006). The Swedish translation of the Depression Self Rating Scale (DSRS) was shown to be a reliable and valid measure of depression in adolescence, both for screening in the population (Ivarsson and Gillberg, 1997) and in a clinical setting (Ivarsson et al., 1994). However, the most promising scale may be the Mood and Feelings Questionnaire (MFQ) (Daviss et al., 2006), which is translated but not yet validated in the Swedish version.

For assessment of anxiety disorders the Spence Children's Anxiety Scale (SCAS) has been developed to assess the severity of anxiety symptoms broadly in line with the dimensions proposed by the DSM-IV and the English version has been validated up to the age of 14 (Spence et al., 2003). There is a Swedish version in use for age 13-18, which is not yet validated. For assessment of adolescent anxiety, including subscales for different anxiety disorders, the Multidimensional Anxiety Scale for Children (MASC) has recently shown been shown to be valid and reliable in the Swedish version (Ivarsson, 2006). The Screen for Child Anxiety Related Emotional Disorders (SCARED) is another promising instrument (Birmaher et al., 1997, Bodden et al., 2009), which has been translated but not yet validated for Swedish use. The Social Phobia Screening Questionnaire for Children (SPSQ-C) is a short DSM-IV based questionnaire for screening of SAD in adolescents that has recently validated in Swedish (Gren-Landell et al., 2009a).

In current Swedish CAP practice, diagnoses are mainly based on clinical assessments without the use of structured interviews (The Swedish National Board of Health and Welfare, 2009a), which makes the psychiatric diagnosis unreliable. The semi-structured and internet-based diagnostic interview DAWBA, which was used in our study to validate the clinical diagnoses, may be helpful to gain more information for diagnostic aid. For further and more detailed clinical assessment and future research a

more thorough interview such as the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (Kiddie-SADS-PL) or for older adolescents, the SCID Clinical Version or the more extended research version may have additive value. The SCID child edition is not yet in use in Sweden. In a recent meta analyses of several diagnostics interviews the K-SADS-PL appeared to be the instrument with best test-retest reliability for anxiety disorders and affective disorders (Renou et al., 2004).

In summary, there is still a need to implement instruments that have the ability to specifically identify caseness of MDD and anxiety disorders in adolescent girls. Moreover, there is a need for scales that have the ability to differentiate between different anxiety disorders. Such tools may aid the identification of comorbidity for MDD, GAD and generalized SAD. Since adolescents with concurring MDD, GAD or SAD often have a profound decrease of global functioning and low quality of life (III) they are important to identify and prioritize for treatment. Finally, self-assessment scales that have the ability to differentiate classical major depressive symptoms from symptoms of atypical depression would be helpful in future clinical work and research.

9.3 LIMITATIONS OF THE STUDY

As previously mentioned, the non-clinical sample was not a true population-based sample, and thus limited inferential power. This may be considered to be a limitation, especially in study II, where we aimed to generalize the results from the non-clinical sample to population level. The representativity of the non-clinical sample was however supported by comparison with SDQ data from other Scandinavian population based studies (III).

There were a large number of exclusions due to missing heart beats and distorted ECG registrations, often caused by body movements during registration.

Nevertheless, movement artifacts were minimized by having as short a registration period as possible - only four minutes – a time period which the result from study II show was sufficient, since the HRV result were replicable after six months.

It has been suggested that the use of a normalization procedure during ECG registration, with paced breathing or statistically correcting for breathing permits more

accurate inference of sympathetic and vagal modulation of the SA node by controlling the respiratory sinus arrhythmia (RSA). In that context RSA is described as the major index of vagal tone (Pagani et al., 1986). However, according to Porges, cardiac vagal tone, by definition, represents influences from both the nucleus ambiguus and the dorsal motor nucleus vagal nuclei to the SA node, while RSA reflects only the vagal pathways from the nucleus ambiguus. The vagal influence from the dorsal motor nucleus of the vagus is not included in the calculation of RSA, although it contributes to heart rate. With this understanding it becomes clear that corrections related to respiration can not improve the sensitivity of RSA to cardiac vagal tone. If the aim (as it was in our study) is to specifically measure the influence of the vagal break, that is to say the myelinated vagus, the high frequency and low frequency domains of HRV seem to be appropriate measures and not only the RSA (Porges, 2007).

It may be argued that using baro-receptor sensitivity (BRS) as a measure of autonomic regulation in this study in addition to HRV could have added information. Depressed adult patients show an impairment of BRS (La Rovere et al., 2008), which has been suggested to constitute the link between depression and cardiac risk (Davydov et al., 2007). Nevertheless, this link was not the primary focus of this study, but rather the aspect of autonomic self-regulation in relation to emotional disorders. Since HRV is still a more frequently used measurement of autonomic regulation in relation to psychiatric conditions in this age group it was considered the best parameter.

There was a major loss of salivary cortisol data, especially in the clinical sample, for which the "homework" of sampling often failed. Diurnal rhythm disturbances with a late sleep-phase were common, especially in the clinical sample and added insecurity in the assessment of the awakening response of the saliva cortisol. Instead of the awakening response a more precise method to measure HPA-axis function would have been preferred. The dexamethasone suppression test is the most frequently used measure of HPA-axis function in psychiatric disorders (Sher, 2006). Dexamethasone is a synthetic steroid that reduces ACTH release in a healthy individual due to negative feedback on the pituitary level of the HPA-axis, which results in a decrease in cortisol levels. Lately, a combined challenge test has been developed in which corticotropin-releasing hormone (CRH) stimulation is given after dexamethasone treatment (the combined Dex-CRH test). This test has proved to be an even more

accurate method of investigating HPA-system regulation in depressed patients (Sher, 2006). However, none of these methods were manageable in this study due to practical reasons.

In retrospect, a greater effort could have been made to translate and validate more accurate self-assessments scales for application in this study. The selection of scales was simply based on what was used in the CAP clinics at the time of designing the study. The problem with a random use of assessment scales has recently been highlighted in a nationwide Swedish CAP survey. It points out major inconsistencies between different CAP clinics regarding which psychiatric self-assessment scales that are used (The Swedish National Board of Health and Welfare, 2009a). Being able to discriminate between different anxiety disorders and separate major depressive disorder and atypical depression would have been of great value in this study. We would also have gained more secure data on lifestyle, health-related behaviors, quality of life, subjectively perceived stress and sleeping problems if instruments validated for this age group had been available in Swedish.

10 NEW HYPOTHESIS AND FUTURE PERSPECTIVE

10.1 PSYCHIATRIC DIAGNOSIS BASED ON ETIOLOGY

As described above, the prevailing diagnostic systems of mental disorders are based on a descriptive phenomenological approach. So far, this may have been the only possible approach regarding anxiety disorders and depression because of the complex and multifactorial mechanisms involved. Anxiety and depression are unspecific symptoms that may be the endpoint of several different pathophysiological processes. From this perspective it is evident that the current treatment methods are suboptimal, since different subgroups of anxiety and depression based on etiology are likely to have differences in optimal treatment.

By increasing knowledge, it may be possible to base the diagnoses on etiology. Autonomic regulation, HPA-axis- and immune function are probably important parameters to consider, when attempting to elucidate the pathophysiological pathways of anxiety and depression, and developmental (ontogenetic) aspects must be considered in order to understand different trajectories. Developmental and behavioral psychology may also contribute to a better understanding of vulnerability and resilience factors.

It is important to further study the complex interplay of biological mechanisms that contribute to the increased female vulnerability to anxiety and depression. The effect of gonadal hormones on the serotonin metabolism, inflammatory response, HPA-axis function and autonomic regulation needs to be investigated.

10.2 THE CONCEPT OF ATYPICAL DEPRESSION

When assessing the data on depressive and anxious symptoms, psychosomatic symptoms and stress-related problems in our clinical sample it seems the girls with DSM-IV diagnosis of MDD mainly suffered from atypical depressive problems. The study was not originally designed to differentiate classical MDD from atypical depression. Using the data from the assessment scales and DAWBA to retroactively differentiate the patients with diagnosis of MDD into a subgroup with classical melancholic symptoms and one subgroup with atypical features has not yet been managed.

Unpublished data from our study shows that the girls with anxiety disorders and MDD had significantly decreased awakening response and lower baseline salivacortisol during the day compared to the non-psychiatric controls, implying a HPA-axis function similar to that described in atypical adult depression. The clinical sample also showed increased insomnia, daytime tiredness/sleepiness, headache, back-pain and stomach problems compared to the controls.

A dramatic predominance of mood disorders (often with atypical features) in females emerges at the onset of puberty (Angold et al., 1998) and the female predominance of depression in adults seems to be restricted to the atypical subtype in premenopausal women (Angst et al., 2002, Silverstein, 2002) This contrasts with the pattern for postmenopausal women, for whom "classical MDD" is predominant and no gender differences have been identified (Antonijevic, 2006).

There are several indications that the pathophysiological mechanisms involved in atypical depression in adults are similar to those in the most common form of depression in adolescent females. Recent literature describes differences in HPA axisfunction, serotonin and noradrenalin function, immune activation and treatment response between MDD and atypical depression (Angst et al., 2006, Antonijevic, 2008).

As previously described, it is hypothesized that individuals who have experienced a sensitization of the HPA-axis may respond to an emotional stressor with HPA-hyperactivity, leading to symptoms of major depressive disorder. Conversely, individuals with reduced reactivity of the HPA axis, would not respond to a stressor with elevated corticosteroid levels, thus allowing a sustained inflammatory activation and the development of atypical depression (Anisman and Merali, 2003). This is in line with the finding that patients with chronic atypical depression show a persistent increase in pro-inflammatory cytokines (Anisman and Merali, 2003).

Recent meta-analyses on HPA-axis function in depressed children and adolescents show similar patterns to that in adults with MDD. The depressed youths exhibits higher baseline cortisol values, an overactive response to psychological stressors and atypical responses to the dexamethasone test, implying dysregulation in the feedback system and CRH-production of the HPA-axis rather than on the pituitary and adrenal

level (Lopez-Duran et al., 2009). However these analyses included both genders and pre-pubertal age groups and did not differentiate between symptoms of MDD and atypical depression.

The clinical relevance of the concept of atypical depression is that adolescent females with atypical depressive symptoms may need a modified treatment. Reduced serotonin synthesis has been suggested as a mechanism in atypical depression, which usually has a prompt treatment-response to SSRI medication, in contrast to the delayed response in classical MDD. Interestingly the ascending serotonin pathways seem to be influenced by gonadal hormones and inflammatory factors and this prompts further studies to elucidate the relationship between the effect of the hormonal changes in female puberty, serotonin synthesis and the risk of developing symptoms of atypical depression (Antonijevic, 2006).

This idea is relevant also from the perspective of the potential side effects of SSRI. It would be interesting to investigate whether adolescent patients with classical MDD show different side effects compared to those with atypical depression. Whether heart rate variability differs in patients with MDD compared to those with atypical depression is yet another question that remains answered.

Since patients with atypical depressive symptoms show an increased sensitivity to stress allostatic practices may be of specific importance to this group in preventing and counteracting anxious and depressive problems. It is also tempting to speculate that anti-inflammatory medication/diet and physical activity proven to have systemic anti-inflammatory effect (Mathur and Pedersen, 2008) may be adequate methods of prevention and treatment in this specific group.

10.3 FUTURE METHODS OF TREATMENT

According to the theories of autonomic regulation vagal afference may be of importance in treatment of depression and anxiety, since the descending vagal pathways (the vagal break) receives afferent feedback via the sensory vagus (tractus solitarius). There is already evidence that cognitive behavioral therapy (Thayer and Lane, 2000), physical activity (Blake et al., 2009), biofeedback (Karavidas et al., 2007), and certain meditative practices (Servant et al., 2009) increases HRV and reduce symptoms of anxiety and depression. If shown to be effective in adolescence,

the advantage of these alternative interventions is that the patients acquire methods for self-treatment that enhances autonomy and self-confidence.

Throughout the world, techniques that have been extracted from the tradition of yoga have been modified and applied as "yoga-therapy" or contemplative methods for treatment of anxiety and depression. The purpose of the classical yoga, according to the Patanjali's yoga Sutras, is to reach enlightenment (Baba, 1976); the capacity for autonomic self-regulation, resilience to outer stress and allostatic ability are merely side effects. In the west, these "side effects" have become the main focus and purpose for practice. According to the International Yoga Federation (www.fiy.yoganet.org) more than 300 million people regularly practice yoga today. Some of these methods are being extensively studied and evidence based for certain diagnosis, for example mindfulness based cognitive therapy (MBCT) for the prevention of relapse in depression (Kuyken et al., 2008) (Coelho et al., 2007) or for the treatment of GAD (Evans et al., 2008) and mindfulness based stress reduction (MBSR) for stress management (Praissman, 2008). In contrast, MBSR and MBCT have not been shown effective for other anxiety disorders or for acute depression (Toneatto and Nguyen, 2007). Some of the techniques are now also being evidence based for adolescents (Biegel et al., 2009). Other yoga techniques are in the process of being evaluated for treatment of anxiety and depression such as pranayama (breathing) techniques (Brown and Gerbarg, 2005) or asana practice (Shapiro et al., 2007).

Current research is aiming towards a better understanding of the bio-neurological mechanisms involved in these treatment methods, but many studies still have limitations to overcome. Many of the available findings need to be confirmed and the specificity and generalizability of the interventions determined (Chiesa and Serretti, 2009).

Heart rate variability as a measure of autonomic regulation, together with the improved diagnostic tools and classification systems that have been suggested as a result of the investigations in this study, may aid the future exploration and possible integration of new methods for the prevention and treatment of adolescent girls with anxiety and depression.

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