THYROID HORMONES, INTERPERSONAL VIOLENCE AND PERSONALITY TRAITS; CLINICAL STUDIES IN HIGH-RISK PSYCHIATRIC COHORTS

Cave Sinai
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Stockholm 2015
Cover picture: National flower of Paraguay - Mburucuyá, (in Guarani, a Tupi–Guarani subfamily of the Tupian languages in South America, meaning “fruit which serves”), Blue passion flower/Blå passionsblomma (Passiflora caerulea). PMID: 24140586

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Thyroid hormones, interpersonal violence and personality traits; clinical studies in high-risk psychiatric cohorts.

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Cave Sinai

Principal Supervisor:
Jussi Jokinen, Associate Professor
Senior Researcher, Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychiatry
Professor,
Department of Clinical Sciences, Umeå

Co-supervisors:
Tatja Hirvikoski, Neuropsychologist, PhD
Karolinska Institutet
Department of Women’s and Children’s health (KBH)
Division of Neuropsychiatry
Anna-Lena Nordström, Professor
Associated to Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychiatry

Opponent:
Soili Lehto, Associate Professor
University of Eastern Finland
Institute of Clinical Medicine
Department of Psychiatry

Examination Board:
Åsa Westrin, Associate Professor
Lund University
Unit for Clinical Suicide Research
Division of Psychiatry,
Department of Clinical Sciences, Lund

Mussie Msghina, Associate Professor
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychiatry

Kristina Melkersson, Associate Professor
Karolinska Institutet
Department of Molecular Medicine and Surgery
to Martina
ABSTRACT

Suicidal and violent behaviors as well as early life adversity are prevalent in clinical high-risk populations. Early life adversity is related to developmental dysregulation of behavioral and emotional traits. The neuroendocrine systems involved in the development of dysfunctional behavior and impulsive aggressive traits are not fully known. The overall aim of this thesis was to investigate the relationship between thyroid hormones and personality traits, as well as to exposure to interpersonal violence and violent behavior in two high-risk cohorts of patients with a history of suicide attempts.

In study I we investigated personality traits assessed by the Karolinska Scales of Personality in relation to peripheral thyroid hormones in 100 euthyroid suicide attempters.

In studies II and III, we studied the relationship between exposure to, and expression of interpersonal violence and adult levels of thyroid and cortisol hormones in 92 clinically euthyroid women with borderline personality disorder (BPD), with at least two prior suicide attempts. The Karolinska Interpersonal Violence Scale was used to assess exposure to, and expression of interpersonal violence. Baseline thyroid function was evaluated by measuring plasma free and bound triiodothyronine (FT3 and T3), thyroxine (FT4 and T4), and thyroid-stimulating hormone (TSH) with immunoassays. The FT3/FT4 ratio was used to estimate the peripheral deiodination. Plasma cortisol was also measured.

In study IV we investigated the screening validity of the Karolinska Interpersonal Violence Scale, in predicting post-traumatic stress disorder (PTSD) in 106 women with BPD, with at least two prior suicide attempts.

In study I, we found that in male suicide attempters, the T3/FT4 ratio was negatively correlated to Aggressiveness and positively correlated to Detachment. In study II, 67% of women with BPD reported Medium High or High levels of exposure to interpersonal violence as a child. The FT3/FT4 ratio showed a significant negative correlation with exposure to violence as a child. Patients with PTSD had significantly higher plasma cortisol levels. In study III, the mean expression of interpersonal violence as an adult was significantly higher in BPD patients as compared to healthy controls. Adult expression of interpersonal violence among females with BPD, showed a significant positive correlation with the T3 levels. T3 and comorbid diagnosis of alcohol abuse were independent predictors of adult expression of interpersonal violence. In study IV, the PTSD diagnosis was valid for (58%) women with BPD. The KIVS – exposure of lifetime interpersonal violence, displayed a fair accuracy of predicting diagnosis of PTSD.

Our findings indicate that peripheral thyroid hormones may be associated with early life adversity, adult aggressive traits and interpersonal violence in clinical high-risk psychiatric populations. Karolinska Interpersonal Violence Scale may be used for PTSD screening.
LIST OF SCIENTIFIC PAPERS


IV. Cave Sinai, Tatja Hirvikoski, Maria Wiklander, Anna-Lena Nordström, Peter Nordström, Åsa Nilsonne, Alexander Wilczek, Marie Åsberg and Jussi Jokinen. Predictive validity of the Karolinska Interpersonal Violence Scale in detecting Post Traumatic Stress Disorder, among women with Borderline Personality Disorder. *Manuscript*. 
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<th>Description</th>
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<tr>
<td>ANS</td>
<td>Autonomic Nervous System</td>
</tr>
<tr>
<td>AVP</td>
<td>Arginine vasopressin = Antidiuretic hormone (ADH)</td>
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<tr>
<td>AUC</td>
<td>Area Under Curve</td>
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<tr>
<td>BPD</td>
<td>Borderline Personality Disorder</td>
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<tr>
<td>CRH</td>
<td>Corticotropin Releasing Hormone</td>
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<tr>
<td>FT3</td>
<td>Free Triiodothyronine</td>
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<tr>
<td>FT4</td>
<td>Free Thyroxine</td>
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<tr>
<td>HPA</td>
<td>Hypothalamic-Pituitary-Adrenal Axis</td>
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<tr>
<td>HPT</td>
<td>Hypothalamic-Pituitary-Thyroid</td>
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<tr>
<td>KIVS</td>
<td>Karolinska Interpersonal Violence Scale</td>
</tr>
<tr>
<td>KSP</td>
<td>Karolinska Scales of Personality</td>
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<tr>
<td>ROC</td>
<td>Receiver Operating Characteristics</td>
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<tr>
<td>MDD</td>
<td>Major Depressive Disorder</td>
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<td>PCL-R</td>
<td>Psychopathy Check List-Revised</td>
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<tr>
<td>PMDD</td>
<td>Premenstrual Dysphoric Disorder</td>
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<td>PTSD</td>
<td>Posttraumatic Stress Disorder</td>
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<tr>
<td>PVN</td>
<td>Periventricular Nucleus</td>
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<tr>
<td>rT3</td>
<td>Reverse Triiodothyronine</td>
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<tr>
<td>SCID</td>
<td>Structured Clinical Interview For DSM Axis Disorders</td>
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<tr>
<td>SKIP</td>
<td>Stockholm county council and Karolinska Institutet psychotherapy Project for suicide-prone women</td>
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<tr>
<td>SNS</td>
<td>Sympathetic Nervous System</td>
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<tr>
<td>SSRI</td>
<td>Selective Serotonin Reuptake Inhibitor</td>
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<td>TBG</td>
<td>Thyroxine Binding Globulin</td>
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<td>Abbreviation</td>
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<tr>
<td>TH</td>
<td>Thyroid Hormones</td>
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<td>TRH</td>
<td>Thyroid Releasing Hormone</td>
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<td>Thyroid Stimulating Hormone</td>
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<td>T3</td>
<td>Triiodothyronine</td>
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<td>T4</td>
<td>Thyroxine</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine, serotonin</td>
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1 INTRODUCTION

1.1 STRESS

The human body aims for balance. Any stressor, be it a mentally perceived or physical direct form of challenge, illness or threat, will force the brain to adapt to or overcome this burden, thus returning to a state of equilibrium, maintaining bodily functions. From the smallest molecule to our more advanced mental imaginings, feelings and ideas our body aspires for survival, development and procreation. Our brain has astonishing physiological and cerebral flexibility to cope with nature and stress. These stressors are capable of stirring and remodel our mind, cognitive abilities, behaviors and physiology. The border between mind and body is progressively blurred in the light of our scientific reasoning and investigation, fitting well into humanity’s accelerated interest in the mind, brain and behavior. In the wake of every action or thought, there is a neurobiological counterpart, both capable of governing or being subordinate to our behavior. Differences in mental states whether healthy or unhealthy, functional or dysfunctional, sane or insane, tickle the interest and the neuroendocrinological involvement in these variances is especially intriguing. Many findings are ahead of us, with respect to the possible imminent interplay and concomitant greater mutuality between psychiatric-medical, psychological, social and philosophical epistemologies of the human behavior.

The human brains amazing accomplishments are really mediated through two mechanisms: direct muscular action and hormonal release. The former, all too obvious and easily apprehensible with our senses, but do we tenderly care for and appreciate our hormone secreting glands, as we do with our manifest body? The psycho-neuro-endocrinological aspects of daily living and importance is increasingly recognized and comfort our understanding of how to deal and dispense with daily stressors, relations and emotions, something that many people take for granted, but can be a cumbersome load for an individual with emotional unstable personality disorder.

1.1.1 Neuroendocrine responses to stressors

The human nervous system regulates under voluntary and involuntary control. The nervous system is divided into the central nervous system (CNS, the brain and spinal chord) and the peripheral nervous system (PNS, all neurons apart from CNS). The voluntary responses are mainly within movement and sensation. The involuntary system (autonomic system) is parted into two branches of which we have less conscious control over, including the sympathetic nervous system (SNS, innervating almost every organ-system in the body) and the more continuously active parasympathetic system (responsible for continuous maintenance of organ functions, also called rest-and-digest system). In humans, the major systems governing and mediating the body’s responses to physical burdens or emotional stressors are the SNS
and the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamic-pituitary-thyroid axis (HPT) is regarded as a slower hormonal reactor.

One of the different models/hypotheses of the human stress response involves a process of: stressor events, cognitive evaluation of the situation, a neurological triggering mechanism (in CNS and/or PNS), physiological mediation, target-organ activation and coping behavior (1).

In acute threat, the SNS responses (usually momentarily), by switching into lower energy consumption, pooling metabolites for the most vital tissues, thereby delaying costly anabolism. Once alerted, the preganglionic sympathetic neurons of the thoracolumbar spinal cord activates, projecting via paravertebral ganglia to the end organs. There is an immediately release of acetylcholine from the adrenal medulla, thereby mobilizing the catecholamines noradrenaline (norepinephrine) and adrenaline (epinephrine). Adrenergic neurons in CNS or SNS are also capable of secretion rather immediately. In contrast to the preganglionic sympathetic neurons capable of activation within milliseconds, medullary catecholamines are dispersed, and measureable after an approximate 20 second delay, into the bloodstream and serve as chemical mediators affecting a range of different organs for survival. Subsequently, within seconds after stress exposure, corticotrophin releasing hormone (CRH) is increased in peptidergic neurons in the hypothalamic paraventricular nucleus (PVN). Then released through hypophyseal portal system to the pituitary and, in conjunction with the synergistic effects of arginine vasopressin (AVP = antidiuretic hormone, ADH), acts as a regulator of the anterior pituitary adrenocorticotropic hormone (ACTH). ACTH, in turn, acts on the principal target organ, the adrenal cortex, secreting glucocorticoids (2). The secretion of the pleiotropic glucocorticoids, exert many different physiological effects throughout the body in order to adapt to the stressor or restore the organism into homeostasis (3, 4).

Other neuroendocrine systems are the somatotropic axis (including growth-hormone-releasing hormone and somatostatin), hormone release from the posterior pituitary (also called neurohypophysis, capable of release of vasopressin and oxytocin) and the focus of this dissertation: the hypothalamic-thyroid-axis.

There is an individual variability in our capability to tolerate this allostatic load and mobilize the response to acute or chronic stress. Failure or exhaustion of these systems may lead to enduring (mal-)adaptive alterations and may be one of the diverse biological accounts for progress and transformation into various diseases with physiological and psychological characteristics, such as posttraumatic stress disorder (PTSD) (5, 6).

### 1.1.2 Cortisol

Corticotrophin releasing hormone, the steroid hormone in the glucocorticoid class, is the key mediator of various stress-related responses. In the state of resting or habitual non-stressful settings, both CRH and AVP are secreted by parvocellular neurons of the PVN in a circadian and highly concordant pulsatile fashion (7), increasing their amplitude in the early morning, giving rise to increase in both amplitude and frequency of ACTH (8) and cortisol secretory
bursts in the general circulation. This diurnal variability is disrupted by changes in lightning, feeding schedules and stress (9). During acute stress the amplitude and synchronization of CRH and AVP pulsations into the hypophyseal portal system increase (10). The glucocorticoids (cortisol) secreted from the adrenal cortex, the final effectors of the HPA-axis and acting as key mediators of the stress system, can pass the blood-brain-barrier (BBB) thus acting on glucocorticoid receptors in hippocampus, prefrontal cortex, amygdala and hypothalamus. The two key sites for HPA feedback in the brain seem to be the PVN as well as the hippocampus, both involved in the feedback mechanism and regulation of CRH.

Essential for living and survival in adequate amounts, the excess of cortisol flow, wears and tears the body and brain and may be coupled to more prolonged altered cortisol levels and various psychopathologies (11) as depression (12), anxiety disorders (13), PTSD (14) and burnout (15, 16) in interplay with other signaling proteins like growth factors (17).

1.1.3 Thyroid hormones

1.1.3.1 Thyroid physiology

For the adult human two of the most vital functions of the thyroid gland are to regulate the overall rate of body metabolism including oxygen utilization and to establish effects on the cellular differentiation and development of the brain.

TH are essential in proper neurodevelopment (growth, neural differentiation, regulation of neuronal migration, dendritic arborization and myelination), metabolic regulation, and central nervous system functioning (18), including cognitive functions in adults (19) and children (20), as well as learning and memory (21) and have recently been hypothesized to be involved in autism (22). Congenital deficiencies of thyroid hormones, most often caused by maternal hypothyroidism, leads to the debilitating state of cretinism (stunted mental and physical growth). Dietary iodine deficiency leading to endemic cretinism is recognized as the single most common preventable cause of brain damage in the world by WHO (23).

In short the hypothalamic-pituitary-thyroid (HPT) axis can be described as follows: The thyrotropin-releasing hormone (TRH) (formerly named thyroid releasing factor until its structure was identified), is synthesized in neurons in the hypothalamic paraventricular nucleus (PVN), most of which projects to the median eminence. The median eminence connects to the anterior pituitary gland through hypothalamic-pituitary portal vessels, through which TRH is released and regulates the glycosylation pattern of the glycoprotein thyroid-stimulating hormone (TSH), thereby increasing its biological activity and half-life (24). Thyroid hormones are created by the thyroid gland located in the neck. The thyroid epithelial cells are arranged in spheres called thyroid follicles in which thyroid hormone is synthesized by the iodination of tyrosine residues in the glycoprotein thyroglobulin. TSH binds to thyroid follicle cells initiating several processes including production of triiodothyronine (T3) and the
prohormone thyroxine (T4), which is the major product. More than 70% of the thyroid hormone release from the thyroid gland is TSH stimulated T4 release. Thyroid hormones (TH) exert a negative feedback effect on the release of TSH and hypothalamic TRH neuron activity (25). Of the circulating T4 and T3 in the body, 70% is bound to thyroxine binding protein (TBG, the least abundant but most avid binder), 15-20% bound to albumin, 10-15% is bound to transthyretin (TTR, also called thyroxine-binding prealbumin), and 3% is bound to lipoproteins. TBG and TTR are acute phase proteins that can be decreased in acute or chronic illness.

The major mechanism regulating the bioavailability of thyroid hormones in tissues is the peripheral conversion of T4 to T3, performed by iodothyronine deiodinase selenoenzymes through a sequential monodeiodination reaction. If there is a shortage of iodine, then this mineral could be the limiting reagent in the production of active T3. T3 is several times more potent than the prohormone T4, and this peripheral conversion at the tissue level (26), is responsible for most of the TH actions and accounts for nearly 80% of T3 found in the circulation (27, 28). Thus, only 20% of T3 is distributed from the thyroid gland itself and means that our body is heavily dependent on peripheral conversion of T4 to T3.

Triiodothyronin (T3) is regarded as the biologically most active hormone binding with 15-fold greater affinity than T4 to the cellular nuclear receptor, whereas T4 is minimally active, albeit longer lasting and acts as a reservoir, as a source for conversion to T3 in most tissues. At higher concentrations T4 can actually generate a biological effect, but this effect is minimal in physiological concentrations (29). T3 and T4 do not express a significant circadian variation, whereas TSH does, with highest concentrations after midnight with a gradual decline until commencement of nocturnal rising levels around 23.00 h.

Deiodination is accomplished by three deiodinases, responsible for the intra and extracellular levels of T3. The deiodinase type 1 (D1) is expressed in the pituitary, thyroid, kidney and liver (conversing T4 into either T3 or reverse T3), D2 is expressed in brain, pituitary, thyroid and heart and brown adipose tissue. D3 is expressed in brain, placenta and skin, and responsible for 80% of adult inactivation of T4 and T3(30). The cellular localization of the deiodinases is plasma membrane (D1 and D3) and membranes of the endoplasmic reticulum (D2), enhancing easy access for T3 to the nucleus.

1.1.3.2 Clinical and subclinical hyper- and hypothyreosis

Failure of thyroid gland to produce or secrete T4 in the amount that the body needs, can bring the individual to a state of hypothyreosis. Overt symptoms of hypothyreosis include: fatigue or lethargy, cold intolerance, constipation and dry skin. Subclinical hypothyreosis, defined as within reference range free levels of serum T3 (FT3) and T4 (FT4) and elevated serum TSH levels (31), may present with milder symptoms (31). In subclinical hypothyroidism, the upper limits for TSH (32, 33) as well as the scope of symptomatology justifying treatment is much under debate (31).
Hyperthyreosis (thyrotoxicosis) on the other hand has signs of elevated T3, T4 and suppressed TSH, and may most commonly present with goiter, nervousness, heat intolerance, sweating, palpitations, fatigue, weight loss, tachycardia and tremor. Subclinical hyperthyreosis is manifest with low or undetectable TSH but FT3 and FT4 within population reference ranges (31) and present milder symptoms than hyperthyreosis with low or undetectable TSH and normal FT3 and FT4. The most common cause of subclinical hyperthyreosis is accidental excessive replacement therapy or TSH suppressive treatment for malign or benign thyroid disease (exogenous subclinical hypothyroidism) in contrast to the endogenous forms: Graves’ disease, multinodular goiter, and solitary autonomously functioning thyroid nodules.

The psychiatric disorders and symptoms concomitant with different thyroid diseases (34), some of which remit along the correction of thyroid status, have been studied to be mostly within the anxiety spectra, such as panic disorder, generalized anxiety disorder and simple phobia (35). Almost one third of individuals with thyroid illness are displaying past or present major depressive disorder or present depressive affective temperament (35).

1.1.3.3 Peripheral thyroid hormone turnover and the T3/T4 ratio

The association between T3 and T4 in peripheral tissue is continually adjusted by the balancing of the T3/T4 ratio, buffering the differences in hormone activity due to the wide range of serum T4 (36). Of the total plasma T4 and T3, only 0.03% and 0.3% is in the free form respectively. Total serum T4 is a measure of free and bound hormone. Altered levels in thyroid hormone-binding serum proteins gives reciprocal changes in total T4, even though levels of physiologically active free T4 are unchanged. Hence, a patient may be physiologically normal but have abnormal total serum T4 levels. Measuring free T4 in the serum sidestep the difficulty of interpreting total T4 levels (37). Changes in T3 and T4 are generally concordant and measurement of only T3 is insensitive in identifying hypothyroidism since normal values persist until the disorder is far advanced (38), thus the HPT-axis seem to be wired to preserve T3 at a stable level (39) even under adverse situations (40). Sustained elevations in serum T3/T4 ratios have also been reported in athyreotic (without thyroid gland) subjects partially withdrawn from T4 therapy (41).

In peripheral tissue, it appears that the relationship between the serum levels of T4 and TSH, could be called the set point, (see figure 1). This set point is relatively stable for any single individual if measured repeatedly, but expresses a significant variation between individuals (42, 43).
Figure 1:
The straight line illustrates the log-linear relationship between serum TSH and FT4, demonstrating the set point of the hypothalamus-pituitary-thyroid axis. The slope $\alpha$ indicates the sensitivity of the HPT-axis for changes in FT4. The actual thyroid state is shown as the working point at the line. The localization of the working point of healthy euthyroid subjects expresses notable variability within the normal reference range (TSH 0.4 - 4.0 mU/l and FT4 10 - 21 pmol/l). Thus, this could have relevance in the clinical setting, for example; subclinical hypothyroidism (TSH > 4.0 mU/l but normal FT4) may be diagnosed at an earlier time in subject A than in subject B despite an equal decrease in serum FT4, (adapted from Benhadi et al. 2010)(43).

The working point of the HPT-axis in a particular individual can be pinned down fairly well from four independent morning blood samples withdrawn over a 4-week period (43). A very important but often neglected fact among endocrinologists is that the laboratory serum TSH reference range is twice the width of the individual reference range. (42). This makes it hard to compare any two individuals, let alone finding the true indicator for abnormal thyroid function for an individual having TSH in the upper margin or above the reference range, with concurrent T4 and T3 within laboratory reference ranges. The index of individuality (the ratio of intra- to inter-individual variance) for TH has been shown to be low, even in samples collected over a year (42). This gives us a hint that there is an individual genetic effect in the thyroid hormone pathway.
1.1.3.4 Central thyroid regulation

Little is known about central thyroid hormone regulation. For obvious ethical, technical and methodological reasons, most of the models are from rodent experiments. In the brain, the thyroid energy economy seem to be a biological priority, tightly regulated and mostly independent of peripheral shifts in thyroid function (44, 45) however this complex interplay with circulating T3 and T4 levels, transporter and deiodinase activities has not hitherto been elucidated (40). Local deiodination of T4 is the major source of nuclear T3 in the cortex and D2 and D3 deiodinases seem to act in distinct patterns in the CNS, being clustered into specific cell types (46). In rats, D2 activity seem to be highest in cortical areas, and lesser degrees in the midbrain, pons, hypothalamus and brain stem (47). D2, the major source of plasma T3 in euthyroid individuals (48), although this is lately under debate in favor of D1 (26, 27), has higher affinity than D1 to T4 and converts T4 to T3 by being mobilized in tanycytes (ependymal cells found in the third and fourth ventricle of the brain), and makes T3 available in the proximate neurons in the hypothalamus.

Thyroid hormones also modulate glucose transport processes across the BBB (49). Glial cells of the infundibular nucleus and median eminence region as well as tanycytes lining the third ventricle, express D2 immunoreactivity and this suggests that T4 is recruited by hypothalamic glial cells for conversion into T3, later transported to TRH producing neurons in the PVN. This calls for more research but give us a perspective of the central regulation and feedback mechanisms, apart from peripheral processes (50) which were measured in this thesis. Interestingly, in bipolar disorder there seems to be an association to a genetic polymorphism of the type II deiodinase gene (51), related to T3 and T4 levels. There are also indications that T3 is involved in norepinephrine metabolism in the adrenergic nervous system, as well as influencing serotonin (5-HT) and may have effects on neurotransmission at the level of the synapse (52).

1.1.3.5 Thyroid hormones in energy balance and stress

When measuring thyroid hormone levels in a euthyroid population and finding relationships to variables of various kinds as was performed in this thesis, one cannot disregard the impact of the individuality of resting metabolic rates (RMR). When studying humans in sickness, threat (as in exposure to interpersonal violence) or in balance with life and self, the resting state may be altered as is reflected in any living organism encountering stress in various ecosystems, including both physical parameters and biotic attributes. This is also reflected in how most organisms allocate its resources for maintaining homeostasis or reproduction. For example (although phylogenetically very different from humans), the well-studied C. Elegans larvae evolve through four life-stages labeled L1, L2, L3 and L4. After L4 it molts into the reproductive adult stage. But, if the external milieu is unfavorable, the L1 and L2 animals may sidetrack their development from reproduction into dauer formation. This larva is then able to exist into a state of inactivity in weeks (53), in order to survive harsh conditions. This kind of phenotypic plasticity has been studied in animals but to a lesser degree in humans with regard to energy homeostasis, let alone among thyroid hormones.
Being in a positive energy balance, such as in excessive intake of food and lack of exercise, is obviously known to be related to obesity. In contrast to hypothyroid individuals who may gain weight with concomitant lower T3 levels, obese individuals may express slightly elevated T3 levels as a compensatory adaptation to the enhanced metabolic demands of larger tissue mass (54). It is likely that different deiodinases are involved in terms of regulation in tissue and time, contributing to the energy turnover responses to dietary induced obesity (55). On the contrary, it has since long been known that in energy demanding situations, such as cold, the thyroid responses with altering its hormonal secretion (56, 57). As a matter of fact when displaying human beings to cold and energy restriction for over 60 h activates the HPT-axis (58), also called the Polar T3 syndrome (59, 60), characterized by symptoms of fatigue, interpersonal irritability, cognitive problems and negative affects. Euthyroid individuals with no inherent thyroid disease, being in residence in arctic climate, may express this form of hypothermic reactivity with elevated T3 (not always detected in serum since it may take place in tissues) and elevated TSH sensitivity to TSH.

What about permanently living in cold temperatures? It has been shown that indigenous circumpolar populations have a greater capability to raise the basal metabolic rate during severe cold than nonindigenous groups, suggesting a genetic component involved (61). Indigenous population from the tropics express lowered basal metabolic rates (62). Twin studies have also proposed not only heritable levels of thyroid hormones, but also genetically determined thyroid responses to environmental stressors (63). TSH expression in the hypophysiotropic neuron is contingent on T3 concentration, thyroid hormone receptors, the nutritional state of the individual as well as stress history (64), and the extent of hormonal and neuronal factors that discriminate the organisms basal metabolic state, thereby regulating TRH release and metabolism. The HPT-axis is altered in response to energy deficits or prolonged stress as previously mentioned with regard to the Polar T3 syndrome.

In the pathological state (also a form of stress) of hypercortisolemia in Cushing’s syndrome, it has been proposed that short-term or permanent glucocorticoid overload suppresses peripheral T4 to T3 conversion yielding lower values of total T3 (65) and free T3, thus reflecting a protective or adaptive cellular response to glucocorticoid excess (66). In starvation, the circulation of T3 is decreased, reflecting an adaptation with reduced energy spending, since nutritional substrates are lower. With prolonged illness, serum T4, T3 decreases, related both to central and peripheral changes. The pulsatility of TSH is reduced, with a special positive relationship with T3 decrease and the diminished TSH pulsatility, whereas in the periphery the low T3 syndrome can be observed, as D1 activity is reduced and D3 induced in liver and muscle (67).
The responsiveness of thyroid hormones to stress is dynamical and although the effects are not immediate as the medullary cortical secretion, it has been proposed that the thyroid system may respond to stress quickly with a maximum after 20 minutes (TSH) and 40 minutes (T3) and 60 minutes (T4), although the doses employed exceeded endogenously secreted hormones from the portal system (68). This may have very interesting and implications for individual susceptibilities in coping with stress and development of psychopathology, worthy of future research, as triiodothyronine may be part of an arousal signal, also being involved in noradrenergic transmission (69).

1.1.4 Thyroid hormones in psychiatric illness

The link between the thyroid (also termed “the gland of emotions”) (70) and emotions has been the focus of interest for nearly two centuries, with C.H. Parry’s early (1825) description of a woman developing thyrotoxicosis in the aftermath of a sudden stressor (71) and as early as 1925 the basal metabolic rate was measured among patients with anxiety or hysteria, with thyroid related emotional interplay depicted as:

“The energy governing mechanism of subtle emotional reactions should stimulate study of such a disease entity as exophthalmic goiter, the etiology of which seems definitely disputed, to determine what components of it may be due to the secretion of the thyroid and what may be due to a lowered threshold for emotional reactivity”

(Ziegler & Levine, 1925)(72)

The French physiologist Claude Bernard (proposing the concept of “le milieu interieur” in 1854 (73) along with Walter Cannon, one of the early investigators of physiological reactions to stress reactions, termed the notion of homeostasis. Cannon, in anticipation of the future field of psychoneuroendocrinology, encouraged already in 1928 the study of emotions and physiology:

“I propose to consider emotions in terms of nerve impulses... interest in this realm of medicine should not be relegated to cults, mental healers and the clergy. The doctor is properly concerned with the workings of the body and their disturbances and he should have, therefore, a natural interest in the effects of emotional stress and in the modes of relieving it.” [“Reproduced with permission from (74), Copyright Massachusetts Medical Society.]

In the 1930s, (75) high doses of dried out (desiccated) sheep thyroid glands were administrated and fruitfully relieved symptoms among patients with periodic catatonia and cyclic mood disorders. Later, in 1956, Dongier et al. (76) were among the first to measure thyroid reaction due to emotional stimuli in psychiatric patients in a laboratory setting, with stress interviews designed to break down psychological defenses (sic!).
In subsequent research, both building on and scientifically challenging the works of Hans Selye’s stress research and hypotheses (77), the late John Wayne Mason (1924-2014), enlightened the scientific community by considering the importance of psychological and psychiatric aspects of stress reactivity and interplay (78), with a special interest in thyroid hormones and psychological reactive patterns:

“Another need in this field is for more extensive investigation not only of acute disturbances and thyroid activity but also of possible relationships between chronic mean basal thyroid hormone levels and personality characteristics—particularly in relation to defensive organization in normal human subjects. Such studies have been among the most intriguing and provocative in recent psychoendocrine research on the pituitary-adrenal cortical system.”


1.1.4.1 Thyroid hormones in depression

In the psychiatric clinical setting, the use of thyroid hormones for augmentation of treatment with antidepressants has been rather intriguing, with Arthur J. Prange’s first observation of the amplification of the antidepressant imipramine (a tricyclic antidepressant) activity by thyroid hormones in 1968(79). This set forth a number of thyroid-related studies among depressive individuals in the next two decades, with studies involving acceleration (80) (speeding up the antidepressant response from the very beginning of treatment), supplementation studies (81) for patients with prior treatment with no or superficial antidepressant response, and prophylactic studies (designed to prevent anticipated future depressive episodes. For an excellent review see (82).

One of the first in the line of many following studies, made use of the antidepressant accelerative effect of liothyronine (the synthetic form of T3 used for treatment of hypothyroidism and myxedema coma) in combination with imipramine over a two week period, evident in women but not men (83). This raises the question whether a subgroup comprised of undetected subclinical hypothyroid women were fortuitously treated for that condition in addition to the depression. Was this treatable subclinical hypothyreosis, mistakenly manifested with depressive symptoms, supported by the fact of higher female prevalence and age-related increasing frequency of subclinical hypothyreosis (84)?
This is contrasted by two large population studies (with nearly 28,000 and 8,000 euthyroid controls respectively and over 300 and 500 subclinical hypothyreotic patients respectively), finding no significant differences in wellbeing, anxiety disorder or depression among these cohorts (85, 86). Thus, the explanatory link between subclinical hypothyreosis and depressive symptomatology is still unraveled.

In the beginning of 1970s several reports gave further impetus for thyroid hormones in mood disorder treatment, by administering T3 (83, 87-89), TSH (90) and TRH (91). In 1972, TRH was administered to five depressed patients with marked antidepressant outcome (92). They also noted that TSH responded with at blunt response to TRH and the hypothesis of a depression related abnormality of the HPT-axis was formed. This spurred several trials with TRH tests (showing TSH blunting among one third of depressed individuals and even more among patients with borderline personality disorder (BPD) (93), as well as observation of other thyroid hormones among depressed patients along the years, of which several were performed during the 1980s (94-98). It was postulated in a study (99), that the TSH blunting (among 10 patients with major depressive disorder, borderline or alcohol dependence diagnoses) was not depression specific, showed a reliable test-retest reliability, an altered thyroid hormone feedback control on TSH response among blunters and finally, that factors such as thyroid hormones, cortisol, weight, height and body surface was unrelated to the TSH blunting. Studies confirmed decreased TSH levels among depressed and blunted TSH responses to TRH (100), which at that time were thought of be of diagnostic value to discriminate among biologically confirmed depression and other states.

Other frequent thyroid abnormalities in depression are increased levels of T4 or FT4 (101), albeit within reference range (102), and associated with faster time to remission among men (103) which normalizes along treatment of depression (104) independent of TSH blunting (105). One hypothesis for this may be a secondary elevation due to depression-associated elevated cortisol (106). It could also be a compensatory reflection of antidepressant related inhibition of TRH secretion (107). With regard to triiodothyronine, which may improve the antidepressant response and outcomes (80), a low T3 syndrome has been suggested, with only 6% incidence (among 205 major depressives) of subnormal T3 levels among patients with major depression and no thyroid disease (108). In depression, the circadian rhythm of TSH seemed to be changed, with an absence of the expected nocturnal surge (109). Among unipolar depressed subjects, findings from the Netherlands Brain Bank (110) revealed a decrease in TRH mRNA, suggesting low TSH serum concentrations being related to diminished hypothalamic TRH drive, with in turn may be related to the mild hypercortisolism observed among depressed individuals, since rats exposed to glucocorticoids have shown a down-regulation of TRH mRNA in the paraventricular nucleus (111). This means that exploring the interaction of HPA-and HPT-axis is imperative for characterization of psychiatric related thyroid abnormalities. The literature in this specific subject is scarce and little interest has been shown to fully investigate HPA-HPT interplay.
1.1.4.2 Thyroid hormones and medication

There are multitudes of medications that can affect thyroid hormone levels. The most commonly encountered among doctors are lithium, glucocorticoids, amiodarone, and antiepileptic medications. Lithium may affect the thyroid by a variety of mechanisms: 1) inhibition of thyroid hormone discharge (by decreasing follicular droplet creation), followed by lowered T4 and T3 and increase of TSH; 2) lithium induced subclinical hypothyroidism, mostly among older women; 3) thyroid hormone changes leading to goiter among 50% of individuals starting lithium therapy. This also contributes to the fact that is hard to discriminate how much of the bipolar associated changes of the HPT-axis is associated to the affective disease (especially the rapid cycling type) as reviewed (112), and how much that is related to their coexisting lithium therapy. High doses of glucocorticoids (but seldom in long term therapy), are associated to central suppression of TSH secretion (although not as prominent as in hyperthyreosis). Amiodarone (an iodine-rich medication for anti-arrhythmic treatment), is a matter mostly for cardiologists, who encounter hypothyroidism among 10% of their treated patients and finally antiepileptics such as phenytoid and carbamazepine, which both decrease both free and total T4 and T3 (38).

Most of the studies investigating the effect on psychiatric medication on thyroid hormone levels have involved tricyclic antidepressants, rendering conflicting results. Some report a decrease in T4 or FT4 (113, 114), whereas other did not (115, 116). The antidepressant effect on thyroid hormones seems to be inconclusive with thyroid hormone alterations in any direction. Mirtazapine seem to increase FT3 levels, decrease FT4 and leaving TSH unchanged (117). Among selective serotonin reuptake inhibitors (SSRI), thyroid hormones can deviate into any direction (118) but generally a decrease in T3 and T4 and unaltered TSH has been seen (119).

1.2 BEHAVIOR

1.2.1 Traumatic stress

In neuroendocrine research the relationship between the adult psychiatric outcome of childhood traumatic experiences, for example posttraumatic stress disorder (PTSD), and alterations of human endocrine systems has been intriguing, and the aspect of causality is as yet, not clearly delineated. It is still not fully known by which specific mechanisms early-life stress-related changes in neuroendocrine responses lead to the development of mental disorders, nor do we know if, and which, specific individuals with possible inherited alterations are prone to develop psychopathology, due to severe stress and its concurrent impact on neurohormones (77, 120-123). There is an emerging field of investigation on early stressors related to chronic diseases in adulthood (124). Exactly how does early life surges of stressors burden the neuroendocrinological system and get under the skin and bones of the individuals, perhaps altering even the genome with prolonged effects even generations ahead? We are awaiting the future findings in the beating of the waves of rodent experiments showing the infant capable of learning maternally transmitted fear even before amygdala
odor-shock conditioning, in conjunction with the enduring character of these relationally conveyed memories. Amazingly, even before complete sensory and motor development has taken place, the infant can learn and grasp imminent environmental threats from their mothers (125).

1.2.1.1 Exposure to interpersonal violence

Domestic or interpersonal violence is a public health problem, prevalent in all countries. There is also an obvious gender difference with 35% of women in the world, experiencing intimate partner violence or sexual violence (within relationship or by any perpetrator). This is both a violation of human rights, but renders even more long-lasting individual consequences and burdens the whole society. Victimization risk factors are low education, witnessing parental violence, childhood abuse as well as attitudes of violence acceptance and gender inequality (126). The Swedish National Council for Crime Prevention reported in 2012 that 7% of the population (male or female) is subject to violent crime (127), and 85% of individuals exposed for physical violence report exposure for mental abuse, during the same period (127). Thus, physical and emotional abuse are intimately linked. Childhood sexual abuse, one form of interpersonal violence, is linked with significant adult levels of subsequent occurrence of major depression, suicide attempt, conduct disorder, alcohol and nicotine dependence, rape after age of 18 years, divorce and social anxiety (128).

1.2.1.2 Susceptibility and resilience to stress

Among all people exposed to extreme stressors, there are vulnerable individuals, who are at greater risk for developing illness (mental or physical) related to exposure violent interpersonal expressions. These individuals may be distinguished not only by clinical characteristics, but conceivably also by means of individualized physiological responses to stress, in terms of certain hormonal profiles or reactivity patterns. In contrary, there are more resilient individuals, biologically more fit to adapt to stressors, i.e. more resilient individuals. Resilience can be described as a dynamic and modifying process that aims for regain of homeostasis in conditions of stress. There are reports of past mildly stressful incidents associated with lower emotional distress during hospital admission, attenuated fearfulness in a preschool child-care setting and reduced cardiac responses to stressful laboratory tests (129).

On the other hand, there a number of different negative traits, such as anxiety, depression, hostility and aggressiveness being markers for example coronary heart disease, but also showing such overlap in the negative dispositions that the possibility of a general propensity in favor of negative affectivity may be even more relevant for disease risk than any specific negative affect (130). In contrast to the disease-prone personality, a self-healing personality has been proposed (131) with the essential notion of optimization of the interaction between the individual and his/her specific social ecosystem in order to maintain the biopsychosocial balance. In simple words: to fit an individual into the sort of environment that can best take a fruitful advantage of that individual’s certain reactivity patterns (behavior) and personality. In
resilience research, factors as secure attachment, experiencing positive emotions and having a purpose in life have been proposed to be the pivot points for resiliency (132). The scope of research in resiliency includes investigation of neurocircuits, gene-environment interactions, experience-dependent plasticity (including epigenetic regulations), early rearing conditions, adolescent stress and animal models attenuating disturbance after stress exposure (132).

1.2.2 Posttraumatic Stress Disorder

The diagnosis of posttraumatic stress disorder (PTSD) in the psychiatric setting has its origins in assessment of American veterans from combat war in Vietnam. However the notion of emotional symptoms arising in the aftermath of a disaster or war has been depicted since centuries ago. Even since Job’s lamentation in the Bible, of the traumatic events imposed upon him and his words “If only my anguish could be weighed and all my misery be placed on the scales!” (Job 6) (133). Little did he know that in centuries ahead humans would develop the notion of PTSD, to characterize the symptoms arising after a traumatic experience. Also, the 2000 years old Greek play “Ajax”, is presently used in the rehab process of American Veterans. The play, depicting a soldier returning from war, but tormented by the trauma (Greek: τραυμα = wound, damage) impersonates him as free at last from the war; but now carrying the war inside him.

The symptoms of stress reaction has also been noted in narratives from trench warfare in World War I with descriptions of “shell shock”, a name invented by the soldiers and recounted 1915 in The Lancet (134). The interest in traumatic related stress reactions faded somewhat between the world wars, but was revitalized again with the dawn of World War II (WW2), with descriptions of battle stress, combat fatigue, traumatic war neurosis and gross stress reaction, as well as the closure of the WW2 with Holocaust survivors expressing a special form of stress. Also in 1942, the Cocoanut Grove fire (135) gave rise to not only advances in medical care concerning fluid resuscitation techniques for burn victims or the use of penicillin, but also in the study of over 500 surviving patients by the Neurologist Alexandra Adler, who may be the first who systematically studied the psychological symptoms of a fire accident (136), adding impetus to future work in the field of PTSD. The conceptualization of PTSD in the present setting in DSM 5 has its origins in Freud’s notion of traumatic neurosis (137) and was first called Gross Stress Reaction in the DSM-I approved in 1951 and released in 1952. (138).

After the Second World War, psychiatrists gathered and expressed the need to define a consensus in describing the stress reactions. By that time, two main epistemological traditions dealt with this phenomenon. The biological constellation, fortified by Selye, who coined the term stress (as general adaptation syndrome, GAS) in 1936 (77, 139), reflected upon the relationship to the hypothalamic-pituitary-adrenal (HPA) axis. Selye’s description of the GAS was related to biologically healthy responses to stress, and traumatic neuroses were regarded as consequences of prolonged and severe stress. On the other hand, the psychological denomination, rooted in the psychodynamic tradition, stressed upon the role of
the unconscious, early life stress and repressed memories, with subsequent articulations of defense mechanisms related to illness.

In DSM-I, the stress syndrome was annotated to an exceptional physical or mental stress, such as a natural catastrophe or battle; occurring in individuals with no psychiatric disease and must have had diminished in days to weeks. In DSM-II, the diagnosis of gross stress reaction was omitted, with no clarification why. Thus, between 1968 and 1980, no formal diagnosis for stress reaction was available, until 1980 when PTSD was introduced into the DSM-III, in a time when great attention was allocated to post-combat stress disorders among Vietnam Veterans. DSM-II had little explanations of what distinguishes "overwhelming environmental stress" and if the individual did not recover from the experience, "another mental disorder is indicated", suggesting there is a pre-existing vulnerability that was not cognate to the traumatic event.

In contrast to DSM-I, the DSM-III defined the stressor relatively narrowly: “The person has experienced an event that is outside the range of usual human experience and that would be markedly distressing to almost anyone”. Also, in the DSM-III, the requirement of preexisting normality was abandoned, thus giving playroom for acknowledgement of individual variability of resilience and vulnerability. Now something interesting occurs among clinicians; being bestowed a new diagnostic category for traumatic consequences in individuals, other stressors like car-accidents or early life abuse, were gradually included in the definition of the stressor. The theory of dissociation was gradually emphasized, introducing a psychodynamic nuance not intended (140). Another clinically related change was that the temporal proximity between stressor and the individual responses were accepted to be longer, introducing the “delayed onset of PTSD”, thus giving rise to roughly defined descriptions of dissociative symptoms with scarce clinical documentation. Interestingly, now the diagnosis most related and intended for individuals surviving war, was increasingly being used among civilians in peacetime. As DSM-III-R (141) was released seven years later, many of these unplanned alterations were actualized in the manual.

With the DSM-IV (142) the concept of the stressor was further adjusted into not only imposing a threat to the individual in question; “a threat to the physical integrity of self or others”. Consequently, the perceived stressor was not a direct physical link between extreme stressor and the exposed individual; thus another dimension in human processing of stress was introduced: one that requires formation of the mental picture of a threat imposed upon others. When we formerly diagnosed PTSD according to the DSM-IV, we measured certain behaviors (the b, c and d criteria) and put them into a clinical context to determine whether it’s an illness and would cause enough suffering for the individual (according to DSM-IV: “cause clinically significant distress or impairment in social, occupational, or other important areas of functioning”) (142), thus enabled us to call this a psychiatric disease. The time-span between the traumatic event and evoked symptoms was not always easy to determine (DSM-IV describes it as “Symptoms usually begin within the first 3 months after the trauma,
although there may be a delay of months, or even years, before symptoms appear”). Thus the DSM-IV did not state a specific time limit between the stressful event and manifest symptoms, only a duration of at least one month for the symptoms itemized within the b, c and d clusters. If the duration of symptoms persisted more than three months, PTSD should have been classified as chronic, else it was specified as acute.

1.2.2.1 Neuroendocrinology and PTSD

Among the present findings in the field of research of the biological correlates of PTSD is its high comorbidity with medical conditions such as hypertension, cardiovascular illness, metabolic syndrome, chronic fatigue syndrome, fibromyalgia, gastrointestinal disorder, pain disorder and respiratory illness (143). Thus it may not be surprising that among patients with comorbid PTSD, the mortality rate is higher than patients without (144). The great majority of studies have observed low cortisol levels (and high norepinephrine) (14, 145, 146). A meta-analysis reviewing PTSD in relation to cortisol in urine, saliva and plasma (a.m. and p.m. samples) did find a systematic difference in basal cortisol levels between individuals with trauma exposure and no PTSD as compared to persons with PTSD (147), although no difference was found between PTSD and non-exposed controls. With regard to the rhythmicity of cortisol pulsation there seem to be a tendency of the diagnose of PTSD being related to lower than expected morning increase of cortisol (148), lower average value around which the hormone oscillates as well a less random oscillations in the single diurnal cycle studied (149).

1.2.2.2 Thyroid hormones and traumatic experiences

The literature with regard to thyroid hormones, in settings of extreme stress among individuals developing PTSD, is scarce. Even fewer studies have investigated the HPT-axis function in relation to reported traumatic experiences among individuals with personality disorders. The few studies available at hand, have mostly focused on two clinical groups: women with a history of childhood sexual abuse (with or without PTSD) and individuals suffering from combat related PTSD (150).

Earlier studies have reported elevated levels of free and total triiodothyronine (FT3 and T3) in individuals with PTSD as compared to a control group (151-154). Past studies with heterogeneous clinical populations have reported a positive association between FT3/FT4 ratios and a history of childhood trauma. Women with premenstrual dysphoric disorder (PMDD) and a history of sexual abuse showed a greater FT3/FT4 ratio, as compared to women with PMDD and no history of sexual abuse as well as healthy controls (155). Significant elevations in TT3/FT4 and a significant reduction in TSH, have been found in a community sample of 63 women with PTSD due to childhood sexual abuse as compared to 42 women without PTSD, of whom 17% also reported childhood sexual abuse (156), although the validity of this study could be questioned on the grounds that individuals were recruited from the municipality through poster advertisements, the newspaper and radio,
seeking volunteers who assumed they had experienced childhood sexual maltreatment and had current problems related to that abuse. In another study, no changes in TSH, T3, T4 or cortisol was found among hospitalized battered children in the acute stage of aggression, as compared to controls (157).

Furthermore, the study of Haviland et al. (158) of 22 adolescent girls with a recent exposure to sexual abuse, reported significant negative correlations between thyroid hormones (FT3 and TT3) within reference range and severity of PTSD symptoms. They even proposed evidence for a “low T3 syndrome” associated with the sexual traumatic stress. Plaza et al. (159), measuring only FT4 and TSH, found a higher history of physical and emotional abuse among post-partum women with thyroid dysfunction (defined as TSH outside the reference range), as compared to women without thyroid dysfunction. As summarized in a report with focus on the thyroid and traumatic experiences (150), elevated T3 levels have earlier been reported in Vietnam, Israeli, World War II and Croatian combat veteran samples with PTSD. Studies of Vietnam veterans have reported elevated FT3/FT4 and TT3/FT4 ratios, in participants with PTSD, as compared to the non-PTSD group (153, 154). In refugees from former Eastern Germany, annotated to have been living under chronic stressful situations, lower T4, FT4, T3, rT3 and notably also concomitant lower TSH (160) has been observed.

1.2.3 PTSD among Borderline Personality Disorder

Traumatic experiences are often reported among individuals with borderline personality disorder (BPD) (161) and frequently include multiple forms of traumatization such as physical or sexual (162). These stressful events can contribute to different burdensome symptoms (such as re-experiencing, avoidant behavior and increased arousal) relating to the diagnosis of PTSD. The prevalence of PTSD has been reported to be as high as 54% among individuals with BPD (163). This is also almost eight times higher than in the general population in Sweden (7.4%) (164), similarly shown in an American cohort of patients with BPD (165) with prevalence seven times the general US population. The awareness of co-morbid PTSD as well as acknowledgment of past victimization and its posttraumatic consequences is vital for the choice of treatment strategies as well as the prognosis for patients with BPD. Absence of co-morbid PTSD among individuals with BPD is related to faster time-to-remission (166), while a history of sexual victimization is related to a less favorable course of PTSD, with lower likelihood of remission and higher risk of recurrence of PTSD (165).

1.2.4 Depression among individuals with Borderline Personality Disorder

Depression is one of the most prevalent of the mental disorders, carrying the heaviest burden of disability, with the gender difference revealing 50% more estimated burden among women worldwide (167). In the state of major depression, the brain has been shown to express an altered negative feed-back of the HPA-axis, increased cortisol levels, increased pituitary and adrenal size, hypersecretion of CRH, increased cerebrospinal CRH concentrations, impaired
glucocorticoid receptor function in blood cells and in the brain, as well as decreased hippocampal size (168).

The similarities of symptoms of major depression and BPD is not always clear-cut, and may give rise to questions of whether symptoms are more an expression of the state the individual is in, rather than personality traits. However depressive states are common in personality disorders and up to 85% of individuals in our cohort of individuals with BPD (study II and III) expressed any mood disorder. It has also been suggested that 85% of personality disorders with a history of depression, express recurrences in depressive states (169) as well as an odds ratio of 6.5 of having a mood disorder (170). Co-morbid PD can have a negative influence on the progress of mood disorder, but improvements in major depressive disorder (MDD) do not habitually affect the progress of personality disorder (169).

1.2.5 Suicide and attempted suicide

The global burden of suicide is almost a million deaths per year (171) and is a major health concern across all ages. In Sweden, with a population of approximately 9.7 million, an estimation of 1531 individuals committed suicide in 2014 (1044 men and 487 women) (172). Risk factors for suicide can be generally seen as distal; such as genetic loading, personality characteristics of impulsivity and aggression, restricted fetal growth and perinatal circumstances, early traumatic life events and neurobiological alterations (serotonin dysfunction or HPA disturbances), as well as proximal: psychiatric disorder, physical disorder, substance abuse, psychosocial crisis, availability of means and exposure to socially learned modeling effects of suicide occurring in the family or environment. Attempted suicide is also a globally recognized burden, with an estimate of 20 times the number of completed suicides (171), although this number can be questioned depending on country differences in available data. Women perform more suicide attempts than men, who are completing suicide more often. Depression and prior suicide attempts are the most important risk factors for completed suicide. Some proposed personality characteristics associated with suicide risk involve anger and aggression (173), anxiety proneness, impulsivity, low socialization (174) as well as certain personality and defense mechanism profiles such as being more socially introverted, depressed and psychasthenic (175). Among personality disorders, BPD is particularly associated with suicidal behavior (176). Childhood trauma is related to adult suicide attempts (177) as well as completed suicide, but the diagnose of PTSD has not been found to be indicative for suicide attempts, after controlling for BPD (178). Impaired decision is also related to suicide attempts (179) and individuals with BPD have been shown express impaired decision making (180) even in their non-affective executive functioning (181).
1.2.5.1 Thyroid hormones in suicide

The neurobiological relationship to suicide and suicide attempts involves a variety of different systems as neuroendocrine dysfunctions, glial and astrocytic dysfunction, inflammatory factors, glutamatergic and GABAergic alterations (182), serotonergic alterations (183), as well as genes coding for these systems. The interest in thyroid hormones in relation to suicide and suicide attempts, have been scarce but some finding exist, most of them among female depressed populations. A significant lower weight of the thyroid gland among individuals > 60 years of age, as compared to the general population, has been found (184). A lower TSH response to TRH has been associated suicidal intent, suicidal lethality and agitation (185). The maximal TSH response to TRH has shown an inverse correlation with CSF 5-HIAA, and it was lowest in the non-attempter group (186). Other findings of interest are lower FT3 levels in depressed suicide-attempters (187) and negative correlations between plasma T3 levels and suicide intent (as measured by the Suicide Intent Scale) as well as to depression severity (188).

1.3 PERSONALITY

Personality is a complex construct. There are many different ways of assessing and defining what it is and most people have a notion of what it is, but when asking any individual to pinpoint what it really is, the responses are quite diverse. Mostly we externally observe any individual’s behaviors and the sum of perceived behaviors and interaction with other’s over time defines a broad picture of what that specific personality is. Our approach to personality can on the trait, situational or interactional level, of which trait theory (dispositional theory) has the largest research background. A personality can be defined as possessing traits, which are stable over time, with biological or psychological propensities to manage our behavior in a variety of environments. Personality may change to a small but measurable degree over the life course (189), with genes in continuous interplay with family and environment (190), in healthy as well as pathological ranges.

1.3.1 Personality assessment

Personality is most commonly assessed, by asking the individuals themselves about their own perception of behavioral traits (i.e. by self-report inventories). Other possible methods are narratives or behavioral observations (mostly used in lab settings) or biological correlates to personality traits. All of these methodologies contribute to the characterization of the multifaceted phenomena called personality. There are many different psychological instruments to assess long-term traits and propensities to feel, think and act in particular ways, of which the five-factor model has been the most grounded in the literature (191). Its view is grounded on the notion that we have universal (non-culturally dependent and non-state dependent) dimensions in our personalities. These are comprised of: openness to experience, conscientiousness, extraversion, agreeableness and neuroticism (192).
1.3.2 Personality disorder

The proposed ICD-11 definition of personality disorder is “a relatively enduring and pervasive disturbance in how individuals experience and interpret themselves, others, and the world that results in maladaptive patterns of cognition, emotional experience, emotional expression, and behavior. These maladaptive patterns are relatively inflexible and are associated with significant problems in psychosocial functioning that are particularly evident in interpersonal relationships, manifested across a range of personal and social situations (i.e. not limited to specific relationships or situations). Personality disorder is of long duration, typically lasting at least several years. Most commonly, it has its first manifestations in childhood and is clearly evident in adolescence.” (193). The prevalence of personality disorder varies in different reports but an estimated 4-10% of the population has any form of personality disorder, with a variety in debilitating functioning (194-196). The DSM-IV definition of personality traits and disorder is “enduring patterns of perceiving, relating to, and thinking about the environment and oneself that are exhibited in a wide range of social and personal contexts. Only when personality traits are inflexible and maladaptive and cause significant functional impairment or subjective distress do they constitute Personality Disorders” (142).

1.3.2.1 Borderline Personality Disorder/Emotionally Unstable Personality Disorder

Emotionally unstable personality disorder (also called borderline personality disorder in DSM-III to DSM-5 manuals in contrast to the ICD-10 label, and is in this thesis being termed interchangeably), was initially described by the psychoanalyst Adolph Stern in 1938, finding some patients worsening their condition by therapy, with their pathology at that time imagined to be located on a “borderline” between neurosis and psychosis. His description of their clinical features was: “psychic bleeding”, inordinate hypersensitivity, difficulties in reality testing and relationships, some of which may apply to the diagnosis even today. By the introduction of DSM-III (197) the diagnosis was included on a separate axis. With regard to its symptomatology it is a heterogeneous disorder. It is comprised of nine criteria, and by identifying five of them in a thorough clinical examination the diagnosis is valid. The nine criteria according to DSM-IV-TR (198) are:

1) frantic efforts to avoid real or imagined abandonment.
   Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5
2) a pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation
3) identity disturbance: markedly and persistently unstable self-image or sense of self
4) impulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating).
   Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5
5) recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior
6) affective instability due to a marked reactivity of mood (e.g., intense episodic
dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than
a few days)
7) chronic feelings of emptiness
8) inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of
temper, constant anger, recurrent physical fights)
9) transient, stress-related paranoid ideation or severe dissociative symptoms

BPD is marked by a very high comorbidity with other disorders (166). The trait domains
underlying BPD correspond to: emotional dysregulation (or affective instability), impulsivity
or disinhibition and cognitive function. Another domain: problems in interpersonal
relationships, has been argued to possibly be a consequence of the other domains (199).
Traumatic experiences are often reported among individuals with borderline personality
disorder (BPD) (161) and frequently include multiple forms of traumatization such as
physical or sexual (162). These stressful events can contribute to the different burdensome
symptoms of PTSD (such as re-experiencing, avoidant behavior and increased arousal). The
prevalence of PTSD has been reported to be as high as 54% among individuals with BPD
(163).

1.3.3 Personality and biology

The search for individual differences in cortical arousability was one of the groundbreaking
proposals in this area (200, 201). Another proposal, have been existence of universal sets of
behaviors expressed by animals and humans, with habitual sensitivity of different parts of the
central nervous system determining personality (202). With an attempt to improve the
shortcomings of earlier personality models (emanated from factor analysis of behavior and
not taking consideration to fundamental biologic and social determinants), a psychobiological
model of temperament and character (203) has been proposed, including monoamine
modulators such as dopamine, serotonin and norepinephrine (204).

Investigation of neurobiological correlates related to personality traits vary from fields of
magnetic resonance imaging (205), positron emission tomography (206), molecular genetics
(207), electrophysiology, electrodermal activity or basal physiological measures such as
enzymes (208) relevant for neurophysiology, to psychoneuroendocrinology (209), and
recently to inflammatory physiology (210). In genetic personality research, problems with the
phenotype definition and measurement, have made the search for any specific genetic loci
difficult (211).

With the introduction of DSM-5, incorporating the spectrum model of disease and
introducing a dimensional-categorical model of personality disorder (bringing the specific
pattern of impairments for each of the six personality disorders to notice), the genetic,
endophenotypic and phenotypic data may be more easily integrated (212). An embryonic
field of imaging, the study of brain connectivity with Diffusion Tensor Imaging (DTI) might
also better disclose interesting individual personality characteristics (such as negative emotionality) (213), in the future. Discoveries from personality neurosciences are not yet fully interwoven into the practical clinical psychiatric setting, but is an emerging field of research (214).

1.3.3.1 Hormones and personality

Human hormones can assist and repress behavioral responses, have a diversity of effects, as well as affect complex behaviors. Moreover hormonal effects can depend on family, gender and developmental stage. Early life actions of hormones can have an influence on adult hormonal dynamics (124). Hormonal secretions and responses are affected by biological clocks. Spatial parameters influence hormonal effects on behavior and have different effects depending on site of action. In addition, hormone effects on behavior depend on context, for example, testosterone levels have been shown to be elevated among males winning a doubles tennis match (215). Personality traits can be affected by HPA functioning, linking depression to certain personality traits such as neuroticism (216). Experimentally elevating central oxytocin levels enhances positive social perception, with elevated trustworthiness and attractiveness ratings of unfamiliar faces as compared to controls (217). All in all, the interplay of these many factors influences both behavioral traits and ultimately both the composition and perception of an individual’s personality.

1.3.3.2 Thyroid hormones and personality traits

With regard to thyroid hormones in personality research, the literature is very limited and consists of heterogeneous groups with healthy individuals or psychiatric patients and makes use of different measurement instruments. Accordingly, well-grounded conclusions are hard to draw.

1.3.3.2.1 Thyroid hormones and personality traits – sensation seeking.

Although limited by a small number of subjects Arque et al. (218) found a negative correlation between sensation seeking and TSH, especially among those with highest TSH levels. They assumed that the possible TSH inhibition should be associated to the noradrenergic system in sensation seekers (218). A positive correlation between T4 and depression-anxiety traits was found. The scales used were Minnesota Multiphasic Personality Inventory (MMPI), Sensation-Seeking Scale (SSS) and Susceptibility to Punishment Scale (SP; a 36 item scale aiming to select individual who selectively responses to anxiety and fear stimuli). Balada et al. (219) found similar findings, with a negative relationship between T4 and SSS.
Furthermore, after doing a post-hoc test splitting the women in low-TSH and high-TSH groups, they observed a significant negative relationship between SP scores and plasma T4 and TSH, among healthy females in their early follicular phase.

1.3.3.2.2 Thyroid hormones and personality traits – antisocial traits.

Among institutionalized and criminally active juveniles, having grown up under extreme psychosocial pressure, Levander et al. (220) found significantly higher mean T3 levels (but not TSH levels), than non-delinquent controls. This spurred Alm et al. (221) to study a similar cohort of men, finding no relationship between T3 and psychopathy-related personality traits. On the other hand, they found that among former juvenile delinquents, crime was 3.8 times higher than those with low T3 levels (mean cut off between high/low T3 was determined by the mean T3 levels of the control group).

Stålenheim et al. (222) investigated a male cohort of euthyroid patients (diagnosed with DSM-III-R), having committed serious criminal acts, thus referred for major forensic examinations, in comparison with healthy controls. Among patients, significantly increased T3, decreased FT4 and no difference in TSH were found, as compared to controls. Within group analysis of the patients showed that patients with cluster A personality disorder expressed significantly elevated T3 levels, and no difference was found between cluster C and controls. The most prominent T3 elevation was found for the cluster B group comprised of borderline and antisocial PD patients. The latter group was also diagnosed with DSM-IV rendering a somewhat larger group and even higher T3 levels. An additional finding was that in contrast to non-violent criminal recidivists, the violent criminal recidivists expressed notably higher mean T3, as compared to controls. They also found a significant inverse correlation between T3 and FT4 only among research subjects. FT4 among patients expressed significantly lower levels as compared to controls, with antisocial PD being even lower than borderline PD. They conclude that the elevated T3 levels were most closely related to trait-related behavior within PCL-R factor 2 (reflecting chronically antisocial lifestyle and social deviance, as compared to PCL-R factor 1 linked to selfish, callous and remorseless psychopathic personality traits).

Gunilla Stålenheim (223) performed a follow up on the same cohort aiming for evaluation of the validity of the former findings over time, and further explore personality characteristics related to T3 and FT4, this time evaluated with Karolinska Scale of Personality (KSP, see section 3.2.1). She repeated the findings with higher T3 and lower FT4 as compared to controls. T3 was significantly positively correlated to KSP scores of Impulsiveness, Socialization, Irritability and Detachment. Among violent criminal recidivists, the relationship was even stronger to T3 for Detachment and Irritability respectively. Among non-recidivists, significant correlation to personality variables was found for neither T3 nor T4 levels.
Although not specifically assessing personality, Ramklint et al. (224) replicated the finding of higher serum T3 levels among criminals, this time among 61 men referred to forensic examinations by the courts. The finding was significant for men with previous conduct disorder (which is a robust predictor of adult personality disorder) (225), as well as finding lower FT4 than patients without conduct disorder. No differences were found for TSH levels between the groups. The highest T3 levels were found for men with conduct disorder and prior child and adolescent psychiatric contact. In another study, Söderström and Forsman (226) found that psychopathy scores measured with PCL-R correlated with the T3/T4 ratio, thereby indicating an increased deiodination as a possible mechanism behind the increased T3 and decreased T4 levels associated with callous personality traits.

Although not fitting in the above categories but involving thyroid hormones from a personality perspective, Frey et al. (227) found, among 121 healthy men and women, no relationships between the thyroid hormones TSH, FT4, FT3 and extraversion, openness, agreeableness or conscientiousness, neither a correlation between FT4 or FT3 and neuroticism, although they did find a negative relationship between TSH and neuroticism (a marker for depressive vulnerability (228).

1.3.3.3 Thyroid hormones and aggression

Aggression is a multifaceted construct to measure. Aggression can be reactive (i.e. in response to threat), emotional or impulsive, all of these flavored with emotional aspects. Aggression can also be premeditated, instrumental, deliberate or planned in advance, thus lacking the apparent emotional underpinnings. Most of the neuroendocrine findings in aggression research have been within hormones in the stress system, as well as testosterone and monoamines (229).

Research with a specific regard to thyroid hormones and aggression among humans is very limited, although some observations have been made, with various forms of measurement methods for characterization of aggressive or aggression-related traits.

Ozsoy et al. (230) found thyroid dysfunction, as noticed by lower levels of FT3 and FT4, in highly aggressive alcohol dependent patients, but also acknowledging the difficult issue of discriminating between state or trait behavior, with regard to their alcohol-dependence related to development of aggressive behavior, or aggressive individuals being more prone to more severe alcohol dependence with possible concomitant thyroid dysfunction. Dmitreva et al. (231) found on the other hand higher FT3 levels among young individuals with conduct disorder, also reported to display aggressive behavior, along with impulsivity and restlessness. Their finding was more specifically positively related to fidgeting and increasing Conners ratings (a screening scale for attention deficit and hyperactivity disorder).

Moreover, Daly et al. (232) have performed one of the few observations with serial measurements, aiming at illustrating the dynamics of thyroid hormones. They observed increasing aggression (with a visual analogue scale measuring anger, violent feelings and
irritability) being significantly correlated to increasing FT4 and TSH levels among 23 men receiving high doses of methyltestosterone; with FT4 returning to baseline and TSH continuing to increase in the withdrawal phase, whereas T4 decreased and returned to baseline and T3 decreased and continued to be lower than baseline.

Lastly, Eklund et al. (233) has measured higher T3 levels in males with early behavioral risk patterns who did commit subsequent violent offences, as compared to individuals with the same risk who did not express further violent offending.

More findings related to aggressive behavior and thyroid hormones could be found among rodent experiments and will not be reviewed here.
2 AIMS

The overall aim of this thesis is to investigate the relationship between stress-related hormones and personality traits, as well as to exposure to interpersonal violence and violent behavior in two high-risk cohorts of patients, with a history of suicide attempts.

More specifically, the questions addressed in the thesis were as follows:

- Is there a relationship with thyroid hormone levels and personality traits among men and women with a history of suicide attempt?
- Is there a relationship with history of exposure to interpersonal violence and adult levels of thyroid and cortisol hormones, among 92 euthyroid women with borderline personality disorder, and a history of at least two suicide attempts?
- Is the violent behavior among 92 euthyroid women with borderline personality disorder related to adult peripheral thyroid hormone levels?
- What is the screening validity of the Karolinska Interpersonal Violence Scale, in predicting posttraumatic stress disorder among women with borderline personality disorder?
3 MATERIALS AND METHODS

3.1 STUDY PARTICIPANTS

3.1.1 STUDY I: Suicide attempters

Patients having their clinical follow-up after attempted suicide at the Suicide Prevention Clinic of the Karolinska University Hospital were invited to participate in the study of biological and psychological risk factors for suicidal behavior. Patients were recruited during the years of 2001 - 2005. The Regional Ethics Review Board in Stockholm approved the study protocol (Dnr. 00-194, 2001-06-19) and the participants gave their written informed consent to participate.

The study was originally designed to answer the questions: Are there relationships between biological serotonin-system markers and psychological/psychiatric/personality-related factors, which in other studies have been associated with elevated suicide risk? Are any of the studied biological or psychological/psychiatric markers, being able to predict completed or repeated serious suicide attempts?

Consecutive patients, with a recent history of suicide attempt under treatment at the suicide-prevention clinic at Karolinska Hospital psychiatric clinic, were invited by their doctor to participate in the project. A total of 100 suicide attempters (33 men and 67 women) were enrolled in the study. Inclusion criteria were a recent suicide attempt (a time limit of 1 month), a fair capacity to communicate verbally and in writing in the Swedish language and age 18 years or older. Exclusion criteria were schizophrenia spectrum psychosis, dementia, mental retardation and intravenous drug abuse. A suicide attempt was defined as a self-destructive act with some degree of intent to die. The mean age of the patients was 34 years (SD = 12.4; range 18 - 67) and did not differ between men and women.

The suicide-prevention clinic admitted non-psychotic patients with no serious drug abuse from Solna-Sundbyberg (in the Stockholm area), and was giving voluntary treatment only. If eligible and approving to participate, they were interviewed by a psychiatrist involved the project, with a diagnostic interview according to DSM-IV (SCID-interview), structured Karolinska Self Harm History Interview (unpublished manuscript) and risk-rescue assessment of the index-suicide attempt. The pharmacological history was recorded. The patients were assessed by a psychologist, with regard to the SCID Axis II diagnoses, history of violent behavior, as well as their social functioning level.

A non-fasting sample of approximately 100 ml venous blood, were taken by a nurse, in most cases with the patient lying down to eliminate risk of fainting. The nurse also disposed personality formulas for the patients to complete.
3.1.2 STUDIES II-IV: Women with borderline personality disorder and prior suicide attempts (SKIP-study).

Stockholm county council and Karolinska Institute Psychotherapy project for suicide-prone women (SKIP) is a three-arm randomized controlled trial, aiming to compare the efficacies of the two psychotherapeutic methodologies, dialectic behavioral therapy (DBT) (234), an adapted version of transference focused therapy, called “object relations therapy” and finally general psychiatric care (treatment as usual).

Female patients with a diagnosis of BPD were recruited between June 1999 and December 2004. Inclusion criteria were a history of at least two suicide attempts (defined as a self-destructive act with some degree of intent to die), borderline diagnosis according to DSM-IV, a fair capacity to communicate verbally and in writing in the Swedish language, age between 18 and 50 years, and planning to stay in the Stockholm county during the upcoming years. Exclusion criteria were schizophrenia spectrum psychosis, melancholia, mental retardation, drug abuse, severe anorexia, major depressive illness with melancholic features, evidence of dementia or any other irreversible organic brain syndrome.

This study aims to find and evaluate accomplished treatments for individuals belonging to the patient group of BPD, who were the most difficult to treat and required more psychiatric care. BPD with comorbid major depressive disorder have been associated with more interpersonal triggers for the first and subsequent suicide attempts, expressing elevated life-time aggression, impulsivity and hostility as well as a higher count of lifetime suicide attempts (235). The participants were thus selected upon the basis of having engaged in two or more lifetime suicide attempts. At least one of them should have happened within a six-month time-span prior referral to the study. In addition to suicide and suicide attempts, behavior of self-harm is common in this patient group. In order to confirm the validity of suicide-attempts, the psychiatric scenery and circumstances around their history of self-destructive occasions were thoroughly scrutinized in the interviews.

A total of 162 women with BPD were invited to take part in the SKIP study. Of these individuals, 14 declined to join the study, 41 were furthermore excluded due to not fulfilling inclusion criteria or to fulfilling exclusion criteria and one completed suicide before joining the study. Thus, out of 162 women, 106 (65%) took part in the SKIP study. We obtained laboratory data for 97 of 106 individuals; 92 patients were euthyroid (TSH reference range: 0.4 - 3.5 mE/l, Karolinska University Laboratory) and thus included in the statistical analyses described in paper II-III in this doctoral thesis. By this procedure we tried as to exclude possible hypo- or hyperthyreotic women. In paper IV, all 106 women were included in the statistical analyses since no biological variable was of interest.

The mean age of the 106 patients was 30 years (median = 28.5, SD = 7.6; range 19-50). All participants were interviewed by a trained psychiatrist, with the exception of two cases where it was performed by psychologists, using the SCID I research version interview to establish the DSM-IV diagnoses (236). The PTSD diagnosis according to DSM-III and/or DSM-IV
was assessed by SCID interviews. Along with the SCID interview, 78 of the patients were interviewed by the “suicidal history” interview (Karolinska Self Harm History Interview, unpublished manuscript) and all patients performed the Parasuicide History Interview (PHI) (237). Trained psychiatrists and clinical psychologists established Axis II diagnoses by DIP-I interviews (238). All self-rating scales were completed under the supervision of a research nurse. In addition to the baseline scoring and interviews, the women were invited to a 12 and 24-month follow up, for assessment. The great majority of the patients qualified for several comorbid psychiatric DSM-IV diagnoses. This is characteristic for BPD patients and finding individuals with isolated BPD only, without any other comorbid psychiatric diagnosis is uncommon (239, 240).

3.1.3 Healthy controls

Fifty-seven healthy women were recruited for another study (241). They were screened by a psychiatrist to verify the absence of any current mental disorder. The mean age for healthy volunteers was 39.4 years (S.D. = 10.7; range, 18 - 54).

3.1.4 Ethical considerations

The Regional Ethical Review Board in Stockholm approved the study protocols: (Dnr. 95-283, 1995-09-18), (Dnr. 00-194, 2001-06-19), (2008/61-31/4) and all participants gave their written informed consent to the study. The psychiatric cohorts concerned can be considered “high-risk”, with annotation to their acute and/or chronic suicide-risk and vital need for adequate psychiatric treatment for survival. The risks and benefits of the studies had been taken into account beforehand, given the sensitive nature of approaching an individual in mental distress with suicidal behavior. It was also taken into consideration that some patients may hypothetically feel obliged or being contingent on participation in the study, due to the treatment given. Some patients may also by the nature of their psychiatric illness and relational difficulties, have been particularly vulnerable or emotionally dependent on the caregivers. Before initiation of the projects, it was concluded that common psychiatric experience does not argue for matters of dependency and all patients were offered the means and opportunity to decline the project throughout the whole process of recruitment, treatment and follow-up, without having to worry that this would affect the provided treatment.

With regard to matters of confidentiality, this is deeply rooted and exercised within the psychiatric and psychological practices both abiding within the laws of the Swedish Health and Medical Services Act (regarding respect, integrity and secrecy), as well as due to obligations within licenses of practices. The essential need for and gains from suicide-risk research were considered to be a prerequisite for suicide prevention development and would widely outweigh the patients’ eventual discomfort and additional time span spent with their psychiatric contacts. Given the common standards of routine interviewing processes in psychiatric wards and other settings, it was not conceived that there would be any harm occurring to the patients. On the contrary, this opportunity was of great gain for these individuals with severe illness, being prioritized for thorough investigation and treatment, in
an effort to alleviate their mental distress and treat additional comorbidities. Moreover, participation was voluntary and the patients were given information about their individual outcome in the psychiatric and psychological investigations.

3.2 CLINICAL ASSESSMENTS

3.2.1 Karolinska Scales of Personality

The Karolinska Scale of Personality (KSP) (242, 243) is a self-rating questionnaire useful in research related to the investigation of biological correlates of relevant and stable personality traits. There is evidence of reliability and validity of this scale (244), and its psychometric properties are have been validated in a large number of studies (245). The inventory consists of 135 items grouped into 15 different scales, with each item given as a statement with a four-point response format, ranging from ‘does not apply at all’ to ‘apply completely’. The development of the inventory’s scales has been fueled by a blend of approaches (246) involving empirical-external, rational-deductive and psychometric-inductive approaches, all merged to constitute a psychometric means for psychopathy research.

The subscales are known to intercorrelate (244) and to reduce the risk of multicollinearity, the scales can be grouped into six factors as follows: Anxiety Proneness; in which KSP scales related to anxiety load on (Somatic Anxiety, Psychic Anxiety, Muscular Tension, Psychasthenia and Inhibition of Aggression). Aggression; the five aggression-related subscales (Verbal aggression, Indirect Aggression, Irritability, Suspicion and Guilt) load on this factor. Impulsivity; comprises the KSP Impulsiveness and Monotony Avoidance scales (avoiding routine, need for change and action). Impulsiveness is annotated to relate to the cognitive content of impulsive behavior such as lack of pre-planned actions (i.e. acting or making decisions at the spur of the moment), whereas Monotony Avoidance accredit motivational facets such as an inability tolerating boredom or dull routines (i.e. having “ants in pants” or impatient behavior). Both Impulsiveness and Monotony avoidance scales have manifested stability over time (247). The three subscales not included in any of the factors above are: Detachment; reflecting avoidance of involvement with other, being withdrawn, or having a need for privacy, but also involving emotional aspects such as showing indifference to people. Social desirability; reflects conformity aspects such as being socially conforming, friendly and helpful. Socialization; implies positive childhood experiences and satisfaction with present situations, and this scale has expressed a notable stability over time (247).

The KSP has been revised and refined with regard to its psychometric properties, is now called The Swedish universities Scales of Personality (SSP), and includes 91 items divided into 13 scales (248).
3.2.2 Karolinska Interpersonal Violence Scale

The Karolinska Interpersonal Violence Scale (KIVS) (241) contains four subscales with direct questions with concrete examples of exposure to violence and expressed violent behavior in childhood (aged 6-14 years) and during adult life (15 years or older), (see table 1).

The ratings are filled in during a structured interview to elicit a comprehensive lifetime trauma and victimization history and history of lifetime expressed violent behavior. Interviews and ratings (0-5 for each subscale, total 20) were performed and assessed by trained psychiatrists. The inter-rater reliability of the KIVS subscales has shown to be high ($r = 0.9$). The KIVS-scales has been validated against several other rating scales measuring aggression and acts of violence (241).

In study II, the KIVS scores were grouped into three levels of exposure to interpersonal violence as a child: Low = score 0 and 1, representing “no exposure or mild level of exposure”, Medium High = score 2 and 3 representing “medium high level of exposure”, and High = score 4 and 5 representing “high level of exposure”.

Table 1. The Karolinska Interpersonal Violence Scale

The steps of this scale are defined by short statements about violent behavior. On the basis of an interview with the subject, use the highest score where one or more of the statements apply.

A. Used violence.

As a child (6–14 years)
0  No violence.
1  Occasional fights, but no cause for alarm among grown-ups in school or in the family.
2  Fighter. Been in fights a lot.
3  Often started fights. Hit a comrade who had been bullied. Continued hitting when the other had surrendered.
4  Initiated bullying. Often hit other children, with fist or object.
5  Caused serious physical injury. Violent toward adult(s). Violent behavior that led to intervention by social welfare authorities.

As an adult (15 years or older)
0  No violence.
1  Slapped or spanked children on occasion. Shoved or shook partner or another adult.
2  Occasionally smacked partner or child. Fought when drunk.
3  Assaulted partner drunk or sober. Repeated corporal punishment of child. Frequent fighting when drunk. Hit someone when sober.
4  Instance of violent sexual abuse. Repeated battering/physical abuse of child or partner. Assaulted/attacked other persons frequently, drunk or sober.
5  Killed or caused severe bodily harm. Repeated instances of violent sexual abuse. Convicted of crime of violence.

B. Victim of violence.

Childhood (6–14 years)
0  No violence.
1  Occasional slaps. Fights in school, of no great significance.
2  Bullied occasionally for short period(s). Occasionally exposed to corporal punishment.
3  Often bullied. Frequently exposed to corporal punishment. Beaten by drunken parent.
4  Bullied throughout childhood. Battered/beaten up by schoolmates. Regularly beaten by parent or another adult. Beaten with objects. Sexually abused.
5  Repeated exposure to violence at home or in school that resulted at least once in serious bodily harm. Repeated sexual abuse, or sexual abuse that resulted in bodily harm.

Adulthood (15 years or older)
0  No violence.
1  Threatened or subjected to a low level of violence on at least one occasion.
2  Beaten by partner on occasion. Victim of purse snatching. Threatened with object.
3  Threatened with a weapon. Robbed. Beaten by someone other than partner. Frequently beaten by partner.
4  Raped. Battered.
5  Repeatedly raped. Repeatedly battered. Severely battered, resulting in serious bodily harm.

© Copyright 2010, Jussi Jokinen, MD, PhD. The Swedish version of the Karolinska Interpersonal Violence Scale (KIVS) was translated into English by an authorized bilingual translator; the English version of the KIVS was then back-translated into Swedish and the equivalence was checked by the original authors. Copies can be obtained from the author.
3.3 HORMONE ANALYSES

3.3.1 Thyroid hormones in the laboratory setting

In study I, baseline thyroid hormone sampling was evaluated by measurement of TSH, T3 and FT4 levels. At baseline thyroid hormone sampling in study II and III, one test-tube went for thyroid analysis, one for freezing after centrifugation. Baseline thyroid function was evaluated by measuring plasma free and bound T3, T4 as well as TSH levels. The FT3/FT4 ratio was used to estimate peripheral deiodination. Venous blood was drawn and immediately frozen in aliquots at – 70° C or below until analyzed. The samples were thawed and analyzed by immunoassays (Unicel Dxi 800 Beckman Coulter, for FT4, FT3 and TSH and Auto-Delfia, for T4 and T3) in the year 2010. Karolinska Laboratory at Karolinska University Hospital performed all analyses according to accredited routines. No prior thawing of the frozen plasma samples had been performed. More than 80% of laboratory error can be accredited to the pre-analytical phase of the clinical laboratory testing, which include the patient’s health status, as well as sample collection, shipping, processing, and placement on the analyzer (249). For FT3, we found a relationship with sample storage time, not found in other thyroid parameters, indicating that the molecule of free T3 or deiodinases in serum, may be especially fragile to the storage process, whether it may be freezing, thawing, or any other factor.

3.4 STATISTICAL ANALYSIS

3.4.1 Study 1

We analyzed the association between the thyroid hormones (TSH, T3, FT4, T3/FT4) and the KSP factors (Anxiety Proneness, Aggressiveness, and Impulsivity) and the subscales (Detachment, Social Desirability and Socialization), by a series of multiple regression (forced entry) analyses, performed separately for males and females, adjusted for age, diagnosis of alcohol abuse and use of medication. The residual scatterplots were examined to check the assumptions of normality, linearity and homoscedasticity between the predicted dependent variable scores and errors of prediction, and the assumptions were deemed to be satisfied (250). Furthermore, we performed the Durbin-Watson test statistic expressing no correlation in adjacent residuals, and the variance inflation factor (VIF) and tolerance statistic indicated no problem with multicollinearity. The alpha level was set at $p < 0.05$. The statistical analysis was performed using the SPSS statistical software package (version 16.0, SPSS™ Inc., Chicago, IL).
3.4.2 Study 2

Correlation analyses were used to determine associations between the clinical ratings and biological variables. Initially, tests of nonparametric or parametric correlations were performed using Spearman’s rho or Pearson’s r. Some variables were analyzed by both non-parametric as well as parametric statistical methods due to the non-normality of sample distributions. Group differences were computed with one-way ANOVA or with Wilcoxon test in continuous variables. For categorical variables, the group comparisons were calculated using the Chi-square test. Effect sizes for significant Chi-square tests were expressed as Kendall’s tau-c and interpreted as weak association (0.10 - 0.20), moderate association (0.20 - 0.40), relatively strong association (0.40 - 0.60), strong association (0.60 - 0.80), or very strong association (0.80 - 1.00). If the expected number was < 5 in any of the cells, the Chi-square test was not performed. Based on the results of bivariate analyses, the association between FT3/FT4 ratio and exposure to interpersonal violence as a child was computed with multiple regression analysis adjusted for age, PTSD, plasma cortisol and sample storage time. The residual scatterplots were examined to check the assumptions of normality, linearity and homoscedasticity between the predicted dependent variable scores and errors of prediction, and the assumptions were deemed to be satisfied. Furthermore, the Durbin-Watson test statistic expressed no correlation in adjacent residuals and the variance inflation factor and tolerance statistic indicated no problem with multicollinearity. The alpha level was set on < 0.05 while p-values 0.05 < p < 0.10 were regarded as statistical trends. The statistical analysis was performed using the SPSS statistical software package (IBM, SPSS™, version 22).

3.4.3 Study 3

Group differences in expressed adult interpersonal violence were analyzed with the Mann–Whitney U test. Correlation analyses (Spearman’s rho, two tailed test) were used to determine associations between the clinical ratings and the biological variables. The significance of association between the categorical variables comorbid alcohol diagnosis (current and/or remitted versus no lifetime alcohol diagnosis) and diagnosis of PTSD was tested with a χ² test. Based on the results of the bivariate analyses, the association between T3 and expressed interpersonal violence among patients was analyzed with a multiple regression analysis, adjusted for age, cortisol, sample storage time, and comorbid alcohol diagnosis. The selected covariates showed significant correlations with either T3 levels (age, cortisol, sample storage time) or with expressed interpersonal violence (comorbid alcohol diagnosis). The residual scatterplots were examined to check the assumptions of normality, linearity and homoscedasticity between the predicted dependent variable scores and errors of predictions, and the assumptions were deemed to be satisfied. Furthermore, the Durbin–Watson test statistic expressed no correlation in adjacent residuals. The alpha level was set on p < 0.05. The statistical analysis was performed using the SPSS statistical software package (IBM, SPSSSTM, version 22).
3.4.4 Study 4

Prevalence of true positives, false positives, true negatives and false negatives were calculated for relevant KIVS cut-off scores. The screening accuracy of the KIVS was assessed by plotting the receiver operating characteristic (ROC) curve, which plots sensitivity versus 1-specificity. Presence or absence of PTSD was used as the state variable against which the KIVS performance was tested. The general accuracy of the test was estimated as the area under the curve (AUC) (251). The significance of the association between the categorical variables types of traumatic events (sexual vs. any other traumatic event) and diagnosis of PTSD were tested with a $\chi^2$ test. Correlation analyses (Spearman’s rho, two tailed test) were used to determine associations between the number of traumatic events and the KIVS ratings. Group differences in KIVS exposure to interpersonal violence (childhood, adult and lifetime), between individuals with sexual vs. any other traumatic event, were analyzed with the Mann-Whitney U test. The statistical analysis was performed using the SPSS statistical software package (IBM, SPSS™, version 22) and JMP version 11.

4 SUMMARY OF STUDIES

4.1 STUDY I

Thyroid hormones and personality traits in attempted suicide

4.1.1 Study setting

The aim of this study was to investigate personality traits assessed by the Karolinska Scales of Personality (KSP) in relation to serum levels of hormones in the hypothalamic-pituitary-thyroid (HPT) axis in 100 euthyroid suicide attempters. Standard multiple regression analyses were performed with TSH, T3, FT4, and the T3/FT4 ratio, respectively, as the dependent variable and KSP factors (Anxiety Proneness, Aggressiveness, and Impulsivity) and subscales (Detachment, Social Desirability, and Socialization) as independent variables.

4.1.2 Results

4.1.3 Regression model for the T3/FT4 ratio in males

For males, the $R$ for regression of the T3/FT4 ratio ($n = 28$) was significantly different from zero $F(9, 13) = 2.82, p < 0.04$, with $R^2$ at 0.66, (see table 2). The adjusted $R^2$ value of 0.43 indicates that 43% of the variability in the T3/FT4 ratio was predicted by the model. Two regression coefficients were statistically significant predictors of the T3/FT4 ratio in the regression model; Aggressiveness, $p = 0.01$, and Detachment, $p = 0.04$, with Aggressiveness being the most important predictor due to the high $\beta$-value (- 0.98). The size and direction of the relationships suggest that a low T3/FT4 ratio was associated with high scores on the trait Aggressiveness and low scores on Detachment.
For the bivariate correlation between Aggressiveness and the T3/FT4 ratio, see figure 2.

The Social Desirability score and the T3/FT4 ratio expressed a significant bivariate correlation, but dropped to below significance in the regression model, which may be explained by shared variance among the predictors.

Figure 2: Correlation between the T3/FT4 ratio and Aggressiveness within the male group (n = 23 having data on both the T3/FT4 ratio and the KSP).

4.1.4 Regression model for FT4 in males

The regression model for FT4 (n = 29) approached but did not reach statistical significance ($p < 0.06$). Two regression coefficients were statistically significant predictors of FT4 in the regression model; Aggressiveness, $p = 0.03$, and Detachment, $p = 0.03$. High FT4 level was associated with high scores on the trait Aggressiveness ($\beta = 0.82$) and low scores on Detachment ($\beta = -0.45$).

4.1.5 Regression model for the T3/FT4 ratio in females

The regression model for females did not reach statistical significance $F_{(9, 38)} = 1.78$, $p = 0.11$), (see table 3). Anxiety Proneness, $p = 0.03$, and Social Desirability, $p = 0.04$, were significant predictors of the T3/FT4 ratio. A high T3/FT4 ratio was associated with high Anxiety Proneness and low Social Desirability.
**Table 2:** Correlation matrix and results of the multiple regression analyses for KSP traits and T3/T4 in females.

<table>
<thead>
<tr>
<th></th>
<th>Anxiety Proneness</th>
<th>Aggressiveness</th>
<th>Impulsiveness</th>
<th>Detachment</th>
<th>Social Desirability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>0.13</td>
<td>0.05</td>
<td>0.02</td>
<td>0.14</td>
<td>0.31</td>
</tr>
<tr>
<td>Social</td>
<td>0.04</td>
<td>0.00</td>
<td>0.00</td>
<td>0.29</td>
<td>0.02</td>
</tr>
<tr>
<td>Desirability</td>
<td>0.22</td>
<td>0.08</td>
<td>0.16</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>0.49</td>
<td>0.07</td>
<td>0.07</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>Detachment</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>0.37</td>
<td>0.02</td>
<td>0.02</td>
<td>0.27</td>
<td>0.02</td>
</tr>
</tbody>
</table>

**Table 3:** Correlation matrix and results of the multiple regression analyses for KSP traits and T3/T4 in males.

<table>
<thead>
<tr>
<th></th>
<th>Anxiety Proneness</th>
<th>Aggressiveness</th>
<th>Impulsiveness</th>
<th>Detachment</th>
<th>Social Desirability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>0.43</td>
<td>0.06</td>
<td>0.11</td>
<td>0.15</td>
<td>0.49</td>
</tr>
<tr>
<td>Social</td>
<td>0.06</td>
<td>0.00</td>
<td>0.00</td>
<td>0.29</td>
<td>0.02</td>
</tr>
<tr>
<td>Desirability</td>
<td>0.35</td>
<td>0.08</td>
<td>0.16</td>
<td>0.02</td>
<td>0.15</td>
</tr>
<tr>
<td>Impulsiveness</td>
<td>0.49</td>
<td>0.07</td>
<td>0.07</td>
<td>0.19</td>
<td>0.20</td>
</tr>
<tr>
<td>Detachment</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Aggressiveness</td>
<td>0.37</td>
<td>0.02</td>
<td>0.02</td>
<td>0.27</td>
<td>0.02</td>
</tr>
</tbody>
</table>
4.1.6 Regression model for T3 in females

The regression model for T3 \((n = 57)\) in females did not reach, but approached statistical significance \(F(9, 44) = 2.0, p = 0.06\). The personality trait Social Desirability \((p = 0.05)\) was a significant predictor of T3. High T3 was associated with low scores on the trait Social Desirability \((\beta = -0.34)\). Anxiety Proneness showed a statistical trend to be a significant predictor \((\beta = 0.35, p = 0.07)\).

4.1.7 Regression model for T3 and TSH in males and FT4 and TSH in females

In the regression models, none of the investigated personality traits expressed any significant relationship to thyroid hormone variables: T3, and TSH, for males \((n = 28)\) respectively, and FT4 \((n = 53)\) and TSH \((n = 58)\) among females respectively.

4.1.8 Conclusion:

These results indicate that HPT function may be related to personality traits associated with Aggressiveness and Detachment, as measured by KSP, in male suicide attempters. This may imply that altered peripheral deiodination may be a possible biological covariate.
4.2 STUDY II

HYPOTHALAMIC PITUITARY THYROID AXIS AND EXPOSURE TO INTERPERSONAL VIOLENCE IN CHILDHOOD AMONG WOMEN WITH BORDERLINE PERSONALITY DISORDER.

4.2.1 Study setting

The aim of the present study was to assess relationships between thyroid hormone measures and exposure to violence in childhood in women with BPD. A total of 92 clinically euthyroid women with BPD (53% with comorbid PTSD) diagnosis and at least two prior suicide attempts were assessed with the Karolinska Interpersonal Violence Scales (KIVS). Baseline thyroid function was evaluated by measuring plasma free and bound triiodothyronine (FT3 and T3), thyroxine (FT4 and T4), and thyroid-stimulating hormone (TSH) with immunoassays. The FT3/FT4 ratio was used to estimate peripheral deiodination. Plasma cortisol was also assessed.

4.2.2 Results

4.2.3 Clinical assessments

KIVS ratings were available from 92 euthyroid participants. The mean exposure to interpersonal violence as a child was 2.6 KIVS scale points (SD = 1.9, median = 3, range 0-5). Numbers of KIVS ratings are depicted in figure 3.

Figure 3. Number of women with borderline personality disorder with assessed Low, Medium High and High scores of exposure to interpersonal violence in childhood, as measured by the Karolinska Interpersonal Violence Scale.
There were no significant differences between the three exposure groups concerning age, any use of medication or frequency of Axis I diagnoses. PTSD diagnosis was significantly more frequent in the High exposure group as compared to the Low (p < 0.05) and Medium High groups (p < 0.05) (see Table 4). There were no significant differences between the three exposure groups concerning age, any use of medication or frequency of Axis I diagnoses. PTSD diagnosis was significantly more frequent in the High exposure group as compared to the Low (p < 0.05) and Medium High groups (p < 0.05) (see Table 4).

### Table 4: Clinical characteristics of the three KIVS groups

<table>
<thead>
<tr>
<th>KIVS group</th>
<th>d</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (n = 30)</td>
<td>0.055</td>
<td>2.9 (23%)</td>
</tr>
<tr>
<td>Medium High (n = 22)</td>
<td>0.36</td>
<td>2.9 (67%)</td>
</tr>
<tr>
<td>High (n = 40)</td>
<td>0.96</td>
<td>2.9 (67%)</td>
</tr>
</tbody>
</table>

Table 4: Clinical characteristics of the three KIVS groups.
4.2.4 Adult hormone levels and relationship to exposure to interpersonal violence in childhood.

None of the thyroid hormones T3, FT3, T4, FT4, TSH, nor the stress hormone cortisol, expressed a relationship to exposure to interpersonal violence in childhood.

4.2.5 Adult thyroid hormone ratios and relationship to exposure to interpersonal violence in childhood.

The FT3/FT4 (Pearson’s $r = -0.25$, $p = 0.02$) but not the T3/T4 ratio (Pearson’s $r = -0.2$, $p = 0.08$) expressed a significant negative bivariate relationship to KIVS exposure to interpersonal violence in childhood. For the FT3/FT4 ratio, a significant difference between the exposure groups (Low, Medium High and High), was found ($F_{(2,89)} = 3.3$, $p = 0.04$).

Post hoc analysis with the LSD test showed that the high exposure group had significantly lower FT3/FT4 ratio (mean = 0.47, SD = 0.08) as compared with the low exposure group (mean = 0.53, SD = 0.12) ($p = 0.02$) (see figure 4).

![Figure 4: The FT3/FT4 ratio in female BPD patients with Low, Medium-High, and High levels of exposure to interpersonal violence as a child.](image-url)
The correlation between FT3 and FT4 in the three groups of KIVS exposure to interpersonal violence as a child is shown in figure 5.

**Figure 5**: Correlation between FT3 (pmol/L) and FT4 (pmol/L) in the three groups of KIVS exposure to interpersonal violence as a child

Since the correlation between KIVS exposure to interpersonal violence as a child and the FT3/FT4 was significant, we further investigated what other factors that may modify or be biologically involved in this relationship. We thus performed a multiple regression analysis with FT3/FT4 as the dependent variable and the KIVS subscale “exposure to interpersonal violence in childhood”, age, PTSD diagnosis, serum cortisol as independent variables. In addition, the sample storage time was included as an independent variable, since the blood samples had been sampled during a period of more than 4 years between 1999-2004, and had been kept frozen until 2010, when the samples were thawed and analyzed.
The correlation matrix and results of the multiple regression analysis are presented in table 5. The overall model was significant (F (5, 85) = 5.1, p = 0.0004) with R = 0.48, R² = 0.23 and adjusted R² = 0.18, which implies that the model accounted for 18% of the variance in FT3/FT4 ratio.

### Table 5. Correlation matrix and results of the multiple regression analysis for KIVS exposure to interpersonal violence in childhood and FT3/FT4 in female patients with borderline personality disorder

<table>
<thead>
<tr>
<th></th>
<th>FT3/FT4</th>
<th>KIVS exposure</th>
<th>Age</th>
<th>PTSD</th>
<th>Cortisol</th>
<th>B</th>
<th>SE B</th>
<th>β</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIVS exposure</td>
<td>-0.25*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.019</td>
<td>0.005</td>
<td>-0.38*</td>
</tr>
<tr>
<td>Age</td>
<td>-0.06</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td>0.001</td>
<td>0.1</td>
</tr>
<tr>
<td>PTSD</td>
<td>0.14</td>
<td>0.36*</td>
<td>-0.02</td>
<td></td>
<td></td>
<td>0.02</td>
<td>0.02</td>
<td>0.26*</td>
</tr>
<tr>
<td>Cortisol</td>
<td>0.21*</td>
<td>0.08</td>
<td>-0.26*</td>
<td>0.29*</td>
<td></td>
<td>0.000</td>
<td>0.000</td>
<td>0.16</td>
</tr>
<tr>
<td>Sample storage time</td>
<td>0.24*</td>
<td>0.05</td>
<td>-0.26*</td>
<td>-0.09</td>
<td>0.11</td>
<td>0.000</td>
<td>0.000</td>
<td>0.29*</td>
</tr>
</tbody>
</table>

All tests are two-tailed. KIVS Exposure = Karolinska Interpersonal Violence Scale; exposure to interpersonal violence in childhood. *p < 0.05.

Three independent variables were statistically significant predictors of the FT3/FT4 ratio: KIVS exposure to violence as a child (p = 0.0004), diagnosis of PTSD (p = 0.018) and sample storage time (p = 0.005). The standardized value of β (for KIVS childhood interpersonal exposure to violence) = -0.38 indicates a negative relationship to the FT3/FT4 ratio; thus, higher scores on KIVS exposure to interpersonal violence were associated with a lower FT3/FT4 ratio. The Durbin-Watson statistic was 2.1, thus the assumption of independent errors was met. We finally performed a regression model, dropping the non-significant predictors age and cortisol, and the overall model was significant (F (3, 87) = 7.4, p = 0.0002) and still accounted for 17.4% of the variance of the FT3/FT4 ratio.

### 4.2.6 Diagnosis of PTSD in relation to hormone levels

None of the thyroid hormones expressed a significant relationship with the diagnosis of PTSD. In contrast, cortisol levels were significantly higher (Z = -2.4, p = 0.014) in patients with PTSD (mean = 458 nmol/L), as compared to patients without PTSD (mean = 344 nmol/L), although both means were within Karolinska Laboratory reference range for cortisol at noontime (300-800 nmol/L), (see table 6).

The correlation between KIVS exposure to interpersonal violence as a child and FT3/FT4 ratio was significant only in patients with comorbid PTSD (Pearson’s r = -0.44, p = 0.001), (see figure 6). Furthermore, in patients with comorbid PTSD, exposure to interpersonal violence as a child also showed a significant negative correlation with FT3 (Pearson’s r = 0.41, p = 0.004).
Table 6.

<table>
<thead>
<tr>
<th>Variables</th>
<th>PTSD</th>
<th>Non-PTSD</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>Median (Range)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>n</td>
<td>n</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.7)</td>
<td>Z = -0.9 (p = 0.35)</td>
</tr>
<tr>
<td></td>
<td>1.2 (0.5–3.0)</td>
<td>1.1 (0.4–3.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 49</td>
<td>n = 43</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1.9 (0.3)</td>
<td>1.9 (0.4)</td>
<td>Z = -0.1 (p = 0.96)</td>
</tr>
<tr>
<td></td>
<td>1.8 (1.4–2.5)</td>
<td>1.9 (1.2–2.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 43</td>
<td>n = 40</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>104 (20)</td>
<td>102 (16)</td>
<td>t = 0.5 (p = 0.64)</td>
</tr>
<tr>
<td></td>
<td>105 (65–140)</td>
<td>103 (70–135)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 45</td>
<td>n = 39</td>
<td></td>
</tr>
<tr>
<td>FT3</td>
<td>4.7 (0.6)</td>
<td>4.6 (0.8)</td>
<td>Z = -1.2 (p = 0.23)</td>
</tr>
<tr>
<td></td>
<td>4.8 (3.5–6)</td>
<td>4.5 (3.1–7.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 49</td>
<td>n = 43</td>
<td></td>
</tr>
<tr>
<td>FT4</td>
<td>9.4 (1.4)</td>
<td>9.7 (1.7)</td>
<td>Z = -1.0 (p = 0.31)</td>
</tr>
<tr>
<td></td>
<td>9 (7–13)</td>
<td>10 (6–14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 49</td>
<td>n = 43</td>
<td></td>
</tr>
<tr>
<td>T3/T4</td>
<td>0.02 (0.003)</td>
<td>0.02 (0.003)</td>
<td>Z = -0.2 (p = 0.84)</td>
</tr>
<tr>
<td></td>
<td>0.02 (0.01–0.02)</td>
<td>0.02 (0.01–0.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 42</td>
<td>n = 39</td>
<td></td>
</tr>
<tr>
<td>FT3/FT4</td>
<td>0.5 (0.1)</td>
<td>0.49 (0.1)</td>
<td>Z = -1.6 (p = 0.12)</td>
</tr>
<tr>
<td></td>
<td>0.5 (0.4–0.7)</td>
<td>0.46 (0.34–0.89)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 49</td>
<td>n = 43</td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>458 (224)</td>
<td>346 (127)</td>
<td>Z = -2.4 (p = 0.014)</td>
</tr>
<tr>
<td></td>
<td>429 (140–1,070)</td>
<td>340 (168–600)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n = 49</td>
<td>n = 43</td>
<td></td>
</tr>
</tbody>
</table>

TSH (mE/L), T3 (nmol/L), T3 (pmol/L), T4 (nmol/L), FT3 (pmol/L), FT4 (pmol/L), cortisol (nmol/L).

**Figure 6:** The correlation between KIVS exposure to interpersonal violence as a child and FT3/FT4 ratio, in women with borderline personality disorder and comorbid PTSD.
4.2.7 Diagnosis of PTSD in relation to childhood exposure of interpersonal violence

As clinical expectation would imply, patients with higher scores of exposure to interpersonal violence in the KIVS scale (score 1-5, without grouping) were more likely to have a diagnosis of PTSD ($Z = -3.6$, $p = 0.0004$), as well as with the KIVS clustered into Low, Medium-High and High groups respectively ($\chi^2 = 17$, $p = 0.0002$).

4.2.8 Thyroid hormones and cortisol

Cortisol expressed a relationship only with T3 ($\text{rho} = 0.3$, $p = 0.006$) and the FT3/FT4 ratio ($\text{rho} = 0.21$, $p = 0.05$) in correlational parametric analyses with the thyroid hormones in the study.

4.2.9 Conclusions

Posttraumatic stress disorder, but not psychopharmacological use or comorbid Axis I diagnoses occurs significantly higher among women with the highest reported childhood exposure to interpersonal violence, as measured by the Karolinska Interpersonal Violence Scale. Among women with BPD, those with comorbid PTSD and highest reported exposure to childhood interpersonal violence seem to have a lower individual set-point for thyroid turnover or lower thyroid peripheral deiodination (as measured by FT3/FT4 ratio or FT3 solitarily). Although within reference range, serum cortisol seems to be higher among individuals with BPD and comorbid PTSD, as compared to BPD without PTSD.

4.3 STUDY III

THYROID HORMONES AND EXPRESSION OF INTERPERSONAL VIOLENCE AMONG WOMEN WITH BORDERLINE PERSONALITY DISORDER.

4.3.1 Study setting

This study aimed at investigating the relationship between thyroid hormones and expressed adult interpersonal violence in female patients with borderline personality disorder (BPD). Furthermore, expressed adult interpersonal violence in female BPD patients was compared to healthy female controls. A total of 92 clinically euthyroid women with BPD and 57 healthy women were assessed with the Karolinska Interpersonal Violence Scales (KIVS). Among patients with BPD, baseline thyroid function was evaluated by measuring plasma free and bound triiodothyronine (FT3 and T3), thyroxine (FT4 and T4), and thyroid-stimulating hormone (TSH) with immunoassays in patients. Plasma cortisol was also measured.
4.3.2 Results

4.3.3 Clinical assessments

The mean expression of interpersonal violence as an adult was significantly higher in BPD patients (mean KIVS score = 1.3, SD = 1.3, median = 1, range 0 - 4), as compared to healthy controls (mean 0.4, SD = 0.8, median = 0, range 0 - 3), \( p = 0.001 \). Neither the patients, nor the controls did score the highest level (KIVS score = 5) of expressed adult interpersonal violence (see figure 7).

![Figure 7: Levels of expression of adult interpersonal violence among individuals with BPD and controls.](image)

Patients (mean age = 29.5 years) were significantly younger than controls (mean age = 39 years) \( p = 0.0001 \) which could be a confounder when estimating expressed violent behavior, but the correlations between age and the KIVS ratings were not significant in either patients \( p = 0.23 \) or controls \( p = 0.89 \).

Patients with BPD and comorbid diagnosis of alcohol abuse \( (n = 35, \) remitted and/or current) reported significantly higher expressed interpersonal violence as an adult (mean KIVS score = 1.74), as compared to patients with BPD and without comorbid alcohol abuse (mean KIVS score = 1.0; \( n = 56, Z = -2.6, p = 0.008 \)). Levels of adult expression of interpersonal violence did not differ between patients with or without comorbid diagnosis of PTSD \( (Z = -1.8, p = 0.07) \). Current alcohol abuse was not more frequent among women with PTSD \( (\chi^2 = 0.19, p = 0.66) \).
4.3.4 Associations between cortisol and thyroid hormones

Correlational analyses were performed between cortisol and thyroid hormones. Only T3 (rho = 0.3, p = 0.006) and FT3/FT4 ratio (rho = 0.21, p = 0.05) expressed a significant positive correlation with serum cortisol, whereas TSH, T4, FT4 and FT3 did not, (see table 7).

4.3.5 Association between neuroendocrine measures and expressed interpersonal violence

Among patients, the only thyroid hormone showing a significant correlation to scores of expression of interpersonal violence was T3 (rho = 0.23, p = 0.04). The correlations between the other hormone parameters and KIVS scores of expressed adult interpersonal violence were all non-significant, (see table 7). Therefore, T3 was further analyzed in a multiple regression analysis with expressed interpersonal violence as an adult, as dependent variable and T3, age, cortisol, sample storage time and comorbid alcohol abuse diagnosis (current and/or remitted) as independent variables. The overall model was significant (F(5, 81) = 3.1, p = 0.012) with $R = 0.41$, $R^2 = 0.17$ and adjusted $R^2 = 0.12$, which implies that the model accounted for 12% of the variance in expressed adult interpersonal violence.

Two independent variables were statistically significant predictors of KIVS expressed interpersonal violence as an adult: T3 ($p = 0.03$) and comorbid diagnosis of alcohol abuse ($p = 0.02$). The standardized value of $\beta$ for T3 = 0.27 indicated that higher T3 levels were associated with higher scores of KIVS expressed adult interpersonal violence. We finally performed a regression model, dropping the non-significant predictors (age, cortisol, and sample storage time) and the overall model was significant (F(2, 81) = 5.3, p = 0.007) and accounted for 10% of the variance of the expressed interpersonal violence as an adult.

4.3.6 Conclusions

It appears that women with borderline personality disorder report higher adult expression of interpersonal violence, as compared to healthy controls. This seems to be even more prominent among individuals with BPD and comorbid current and/or remitted alcohol diagnosis, as compared to BPD without alcohol-related substance disorder. Furthermore, adult interpersonal violence seems to be positively related to T3 levels, indicating either higher basal set-point in peripheral thyroid turnover, or higher state-dependent peripheral deiodination of T4, among more women with BPD and higher reported expression of interpersonal violence. Adult expression of violent interpersonal behavior seems to be to a certain degree associated with alcohol abuse and serum T3 hormones.
Table 7: Hormone levels (TSH (mE/L), T3 (nmol/L), T4 (pmol/L), T4 (nmol/L), FT3 (pmol/L), FT4 (pmol/L), Cortisol (nmol/L)), and Spearman's correlation between hormones and KIVS subscale: adult expression of interpersonal violence, among women with BPD.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean (S.D.)</th>
<th>Correlation between cortisol and HPT-axis parameters</th>
<th>Correlation between KIVS adult used violence and hormone parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (Range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>1.35 (0.67)</td>
<td>0.17</td>
<td>-0.055</td>
</tr>
<tr>
<td></td>
<td>1.2 (0.4–3.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>1.9 (0.34)</td>
<td>0.30**</td>
<td>0.23*</td>
</tr>
<tr>
<td></td>
<td>1.9 (1.2–2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>103 (18)</td>
<td>0.18</td>
<td>0.08</td>
</tr>
<tr>
<td></td>
<td>104 (65–140)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT3</td>
<td>4.7 (0.7)</td>
<td>0.20</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>4.6 (3.1–7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT4</td>
<td>9.6 (1.6)</td>
<td>-0.08</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>9 (6–14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3/T4</td>
<td>0.02 (0.003)</td>
<td>0.15</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>0.02 (0.01–0.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FT3/FT4</td>
<td>0.5 (0.1)</td>
<td>0.21*</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>0.5 (0.34–0.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol</td>
<td>406 (193)</td>
<td></td>
<td>-0.04</td>
</tr>
<tr>
<td></td>
<td>361 (140–1070)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=92</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p ≤ 0.05
** p ≤ 0.01
4.4 STUDY IV

PREDICTIVE VALIDITY OF THE KAROLINSKA INTERPERSONAL VIOLENCE SCALE IN DETECTING POST TRAUMATIC STRESS DISORDER, AMONG WOMEN WITH BORDERLINE PERSONALITY DISORDER

4.4.1 Study setting

This study aimed to determine the validity of the KIVS, as a screening tool for PTSD, among women with borderline personality disorder and severe suicidal behavior. 106 women with BPD and at least two suicide attempts were assessed with the Karolinska Interpersonal Violence Scale (KIVS) for exposure to interpersonal violence as a child and as an adult. PTSD was diagnosed with a SCID interview. Number and types of trauma were retrieved from a structured interview sheet preceding the assessment of PTSD. The screening ability of the KIVS for correct PTSD diagnosis was analyzed using receiver operating characteristic curve analysis (ROC).

4.4.2 Results

4.4.3 Clinical assessments

4.4.3.1 Participants and comorbidity

Among all women, 90 (98%) of the participants had at least one current Axis I psychiatric diagnosis. Among the Axis I diagnoses, 93 (88%) of the patients met the criteria for mood disorders (unipolar major depressive disorder, single episode or recurrent, bipolar disorder, depressed or dysthymic disorder), 92 (87%) for anxiety disorders. 61 (58%) patients met the criteria of posttraumatic stress disorder (PTSD). 27 (25%) had a comorbid eating disorder; of whom 19 (18%) with bulimia, eight (8%) with anorexia nervosa and two (2%) with eating disorder not otherwise specified. The criteria for conduct disorder were met in eight (8%) of the women. Eight women (8%) had a diagnosis of alcohol abuse and 30 (28%) in early or sustained full remission. 57 (54%) women had an additional personality disorder, (see figure 8).
Figure 8: Percentage of additional personality disorder among 106 women with borderline personality disorder (any patient can have more than one additional diagnosis of personality disorder).

4.4.3.2 Clinical assessments of PTSD diagnosis and the KIVS ratings

PTSD diagnosis was valid for 61 (58%) women with BPD. KIVS ratings for childhood and adult exposure to interpersonal violence were available from all 106 participants. The mean KIVS exposure to interpersonal violence as a child was 2.7 (SD = 1.9; median = 3, range, 0-5). The mean KIVS exposure interpersonal violence as an adult was 2.5 (SD = 1.9; median = 3; range, 0-5) and the mean KIVS exposure to lifetime (childhood and adult) interpersonal violence was 5.2 (SD = 3; median 5; range, 0-10).

Additional interview information of number and type trauma exposure was available in 76% of patients. Of these, only 9% of the patients reported absence of lifetime traumatic event, 39% reported one traumatic event, while 52% reported two or more traumatic events. Only patients with PTSD reported more than two traumas. Concerning the type of reported traumatic exposure, 60% of the women reported sexual traumatization.

Being exposed to two or more traumatic events was not significantly more related to PTSD diagnosis as compared to exposure to one trauma only ($p = 0.17$), while sexual traumatization was significantly more prevalent in women with PTSD diagnosis compared to other types of
traumatic events ($\chi^2 13.0, p = 0.0003$). Among women with and without PTSD, the number of traumatic events showed a significant positive correlation with the KIVS lifetime exposure score ($\rho = 0.33, p = 0.003$). In comparison to exposure to any other trauma, women with sexual traumatization scored significantly higher in KIVS exposure to interpersonal violence as a child and lifetime exposure ($p = 0.008; p = 0.002$), while there was a trend for higher adult exposure ($p = 0.07$).

### 4.4.3.3 ROC analysis of the KIVS ratings in the prediction of PTSD diagnosis

To estimate which threshold level of the KIVS ratings of childhood, adult and lifetime exposure to interpersonal violence that optimally predicted PTSD diagnosis, we analyzed the ROC curves and the ROC tables. For the KIVS rating of lifetime exposure to interpersonal violence, an optimal cut-off score of 4 achieved the best mean of the sum of sensitivity (90%) and specificity (62%) and yielded 75% correct positive and 82% correct negative predictions with the AUC = 0.79 (95% CI 0.71–0.88, $p < 0.001$), (see figure 9).

**Table 8** shows the optimal thresholds for the two KIVS subscales and lifetime exposure for the prediction of PTSD diagnosis.

![Figure 9](image-url)  
*Figure 9*: Receiver operating characteristics (ROC) curve for cut-off scores and for area under the curve (AUC) of the Karolinska Interpersonal Violence Scale – total lifetime exposure (childhood and adult exposure) score to predict post-traumatic stress disorder or no PTSD, among women with BPD.
Table 8: Optimal thresholds for the two KIVS subscales and lifetime exposure, for the prediction of PTSD diagnosis.

<table>
<thead>
<tr>
<th>Test</th>
<th>Cut-off</th>
<th>PTSD +</th>
<th>PTSD -</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>AUC [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIVS Exposure</td>
<td>≥4</td>
<td>40</td>
<td>7</td>
<td>66%</td>
<td>84%</td>
<td>85%</td>
<td>0.76 [0.66, 0.86]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>childhood</td>
<td></td>
<td></td>
<td></td>
<td>(40/61)</td>
<td>(38/45)</td>
<td>(40/47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;4</td>
<td>21</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIVS Exposure</td>
<td>≥4</td>
<td>35</td>
<td>8</td>
<td>57%</td>
<td>82%</td>
<td>81%</td>
<td>0.72 [0.62, 0.82]</td>
<td>=0.0002</td>
</tr>
<tr>
<td>adult</td>
<td></td>
<td></td>
<td></td>
<td>(35/61)</td>
<td>(37/45)</td>
<td>(35/43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;4</td>
<td>26</td>
<td>37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIVS Lifetime</td>
<td>≥4</td>
<td>55</td>
<td>17</td>
<td>90%</td>
<td>62%</td>
<td>76%</td>
<td>0.79 [0.71, 0.88]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>exposure</td>
<td></td>
<td></td>
<td></td>
<td>(55/61)</td>
<td>(28/45)</td>
<td>(55/72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;4</td>
<td>6</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: PPV = positive predictive value, or the portion of test positives that have PTSD; KIVS = Karolinska Interpersonal Violence Scale; AUC = area under curve within the ROC analysis; PTSD = post traumatic stress disorder diagnosis.
4.4.4 Conclusions

Both the construct and face validity of KIVS subscale exposure to violence seem to be good. There is a good overall accuracy of the KIVS lifetime exposure to interpersonal violence score for PTSD screening purposes, in this cohort of female suicide attempters with borderline personality disorder with a high prevalence of PTSD. This cohort expressed an expected high comorbidity with mood disorders as well as additional personality disorders, as measured by the DSM-IV standards. The prevalence of PTSD was 58%, which is somewhat higher than the reported prevalence of 25-54% in the literature. More than any other type of traumatic events, reported sexual traumatization seems to be closely related to the diagnosis of PTSD.
5 GENERAL DISCUSSION

5.1 CONCLUSIONS

The studies of this thesis, with the focus on finding biological correlates to our personality and behavior have found some relationships with the peripheral deiodination process among individuals with a high psychiatric burden. Among male suicide attempters we found personality traits of aggressive nature to be negatively related to serum levels of thyroid hormones. We also found a positive relationship to Detachment, as measured with a personality scale (KSP) initially designed for observation of biological correlates to relevant personality traits in psychopathy. The findings show that there are biological underpinnings related to our behavior both with regard to aggression as well as being withdrawn or emotionally cold.

We have also illustrated how early life exposure to interpersonal violence is related to traits qualifying them for diagnosis of PTSD well as adult functioning of thyroid turnover, at least among women with borderline personality disorder with a history of at least two prior suicide attempts. This was revealed by the observation of both a significantly higher frequency of PTSD as well as a lower peripheral thyroid turnover, among those with the highest reported childhood exposure to violence. The same cohort of women seem to report significantly higher adult expression of violence as compared to a sample healthy individuals from the general population. Aggressive behavior among these women with BPD, as measured with the Karolinska Interpersonal Violence Scale, seem to a certain degree be positively and independently related to both alcohol abuse as well as their peripheral thyroid hormone levels as measured with T3.

The finding of higher peripheral thyroid hormone levels, as compared to controls, has earlier been shown in male forensic populations with antisocial traits, as well as to violent offending. This could possibly argue for some gender similarities in peripheral deiodination processes in these different populations (antisocial men vs. women with BPD). We have shown that there is a markedly high number of both additional personality disorders as well as a high occurrence of PTSD (58%) in women with BPD and a history of at least two suicide attempts. This will argue for the importance of recognizing the diagnosis of PTSD among these women, for optimal treatment purposes. The screening ability for PTSD with the Karolinska Interpersonal violence scale showed both a good sensitivity as well as specificity.
5.2 STRENGTHS AND LIMITATIONS

The strength of these studies is the thorough and meticulous interviewing processes the patient had been offered. Competent and experienced psychiatrists and psychologists assessed them all, which is especially important given the sensitive nature of questions of expression of and exposure to interpersonal violence. This gives good reliability for accuracy of diagnostic processes and renders a rather homogenous group of individuals for study, given the complex nature of the diagnosis of borderline personality disorder. These cohorts can most certainly be regarded as high-risk from a psychiatric perspective. This is the first time such a large group of individuals (male and female) with a history of suicide attempts as well as women BPD has been investigated with regard to thyroid hormone levels. The study population is relatively homogenous also with regard to age, gender, and history of suicidal behavior, which could have lowered the variance due to unique adaptive metabolic mechanisms between individuals.

Among the limitations is the lack of thyroid measures in the normal population, as a control group, which limits our understanding whether this finding is specific for BPD patients, or if this may be a reflection of the depressive state since 85% of the cohort in study II and III, fulfilled the criteria for mood disorder. The cohorts were not intended to investigate thyroid hormones per se in the original study design, but there was available data for a majority of the patients with regard to thyroid hormones, which were included in our analyses. Thus these cohorts could be regarded as convenience samples. Another limitation is the cross-sectional sampling of hormones, at least with regard to TSH levels, which expresses a circadian rhythm.

5.2.1 Methodological considerations

5.2.1.1 Thyroid hormone sampling.

The patients in this doctoral thesis were all euthyroid, since we selected only individuals within TSH reference interval, for statistical univariate and multivariate analysis. However it cannot be left out of consideration that some of these patients may have presented with an undetected mild subclinical hyper- or hypothyroidism. The degree of symptomatology required before treatment is still under debate both in Sweden and internationally (252). However, in clinical practice doctors should be guided by their clinical judgment (253) although pregnant women and patients above age of 60 should be prioritized for further investigation and treatment (254). Interestingly the term subchemical hypothyroidism has been proposed, and fine-needle aspiration cytology is regarded having a higher diagnostic sensitivity than antibody assay, for individuals with clinical hypothyroidism not meeting conventional biochemical criteria with regard to TSH levels (255).
Another pitfall in antibody assay measurement of TSH levels is the diurnal variability which may vary up to 50% of mean values (256) and signs of 40% variation on same-time-of-day serial sampling (257). This is indicative for me to consider performing several samples in future studies involving TSH levels in analytical settings. In addition 95% percent of individuals without indication of thyroid disease have TSH levels below 2.5 mIU/l (258) and lowering the upper threshold for TSH levels to 2.5 mIU/l has been proposed (33). This is supported for several reasons: firstly, the normal reference range distribution of TSH values is skewed to the right in values 3.1- 4.12 mIU/L, the mean and median values of 1.5 mIU/L are closer to the lower limit than the upper and finally when risk factors for thyroid disease are excluded the upper reference limit is slightly lower (254). At this date of writing, the most recent (2013-09-13) change of range of TSH reference interval by the Karolinska University Laboratory in Solna, Stockholm was for adults (>19 years of age) from 0.4 - 4.7 to 0.3 - 4.2 mE/l for analyze method ModularE (ModE). The patients in this doctoral study were all re-analyzed, by thawing of frozen blood-samples, in 2010 by the DxI instrument with reference range 0.4-3.5 mE/l.

In the last 40 years, radioimmunoassay methods have been used to measure T4 and T3. The majority of the measured free fractions of the hormone in the laboratory process are actually dissociated hormone derived from the in vivo moiety. A distorted association between total and free concentrations may be due to 1) a change in binding protein concentration or affinity 2) occupancy of circulating binding sites by other ligands that dislocate T4 and T3. The estrogen-induced thyroxine binding globulin (TBG) increase, due to enhanced glycolysis that impedes clearance, is the most common (38). We had no data on the estrogen levels among the individuals in the cohorts in our studies, in order to check for this factor when analyzing the results.

5.2.1.2 Measuring traumatic history

The KIVS scale is a gradual increasing report of exposure to, or expressed actions of interpersonal violence (measuring actual incidents and not subjective feeling of events, which is a methodological gain of study II-IV), more similar to a Guttman scaling, rather than a Likert scale, which measures opinions or beliefs. On the other hand it could not be called a complete Guttman cumulative scaling either, since the respondent may not agree/report if lower ordered questions have happened but may confirm only one single higher item of violent exposure. Thus, the patient’s level of experience of the reported attribute is designated by the highest item yielding a confirmatory response. Furthermore, equally strong causal relations amid the latent variable (the degree of violent exposure) and each of the KIVS items is challenging to assume, neither can the scale scores be considered to be weighted equally at measures of equidistance. If the KIVS may discriminate true (and presumably linearly correlated) differences in the underlying attribute (the degree of violent exposure), is worth another study, not only with biomarkers for correlational analyses, but also including individual past or present patterns of physiological reactivity, stratified timing (responding to
which developmental stage prior incidents did occur) and duration of past stressors/violent behavior, as well as inter-rater reliability aspects under those conditions.

In the item pool in developing the scale, aspects with regard to neglect was not included, which may have refined the scale, provided we consider lack of emotional stimulus or genuine neglect a form of “silent violence”. Events that fundamentally threaten an individual’s core identity (i.e. being raped) may be even more likely to develop long lasting consequences, such as PTSD (259). This leads to another question of interest. Do all kind of violence has to be “acted out”. Are there more inconspicuous and maybe even more malicious kind of violent behavior, with respect to eliciting fear and stressful horror within the victim? This ultimately leads to more the more fundamental question of what violence really is, which probably cannot be answered without involving not only the neurobiological stress-response perspective, but also its subjective nature and individual meta-levels of perception of situational threat.

5.2.1.3 Missing data

In study I, there was some missing data among the participants, e.g. missing any of the thyroid hormone values or not having completed the KSP, which appeared to be missing completely at random. In order to preserve most of the sample size and statistical power this was handled by pairwise, and not listwise deletion in the statistical analyses (250, 260).

5.3 FUTURE DIRECTIONS

Another issue worth mentioning is the difference between central and peripheral thyroid physiological processes. We did measure peripheral thyroid hormones. But what goes on in the brain itself? Do these women with BPD possess a certain hormonal peripheral profile with distinct reactivity patterns influencing thinking, emotions and behavior? Or, rather, given the brain’s abundant deiodinase D2 concentration (mostly astroglial cells and tanyocytes), whose main purpose is maintaining local adequate T3 levels if circulating concentrations of T4 and T3 decline (261, 262), are we missing out (or have possibly found a link to), processes more deeply rooted to cerebral energy metabolism and perhaps emotion regulation?

In stress research, the individual’s perception of the stress and the magnitude of stress response are related to personality traits (263). Stress reactivity is a complex matter shared by cognitive, emotional, physiological and behavioral aspects. Some of the differences in Selye’s and Mason’s view with regard to the stress response was that in addition to Selye’s notion of instrumental and unspecific responses to stress, Mason already added in 1968, new some psychologically interesting ideas such as that 1) there are individual differences in psychoendocrine responses to the same stimulus (thus one cannot rely on group mean
responses in studies on neurohormonal reactivity patterns), 2) the grading of affective intensity, do not adequately capture the psychological response, since we all possess different “coping mechanisms” as it is presently called (he called it styles and effectiveness of psychological defenses, as well as “dynamic factors”), 3) longitudinal studies should be performed in order to follow the biological variability interlinked to psychiatric outcome, 4) introducing human subjects to adaptation to new testing environments since a novel surrounding may give a “first-experience” effect, 5) accounting for social factors or the “milieu” of the psychiatric setting. These mentioned factors are complex to operationalize, although it could be done.

Neurohormones act through both genomic as well as non-genomic modifications of the brain and body’s architecture, shaping the way we interact with the world, either in a functional or dysfunctional level. The field of psychoneuroendocrinology is rapidly expanding and new findings of the brains structural and functional relationship with early stressors and adult psychopathology gives incitement for both public awareness of the detrimental impact of childhood traumatic events, with hopefully greater prevention emphasis particularly for children and youth displaying recognized risk factors, as well as promotion of more research into the biological field of psychiatry.
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