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Neuroendocrine Studies in Patients with Affective Disorders

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“There are other worlds than these”

Stephen King

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ABSTRACT

Background

Affective disorders are common and a major cause for increased disability and mortality worldwide. Exogenous stressors and biological variables, including neuroendocrine factors, are assumed to contribute to an increased vulnerability to mood dysregulation. Affective disorders are highly heterogeneous and different neuroendocrine systems may play differential roles in the phenotypic expression of affective disorders in men and women.

Aims

The overall aim of this thesis was to study three neuroendocrine systems in relation to underlying behavioral endophenotypes (personality traits, self-directed and interpersonal violence, and psychiatric symptoms) in patients with affective disorders.

Methods

In **Study I** oxytocin plasma levels were assessed in 101 general psychiatric outpatients and followed-up in 36 patients after one month. Patients underwent diagnostic, symptomatic, and personality trait assessments.

In **Study II** insulin and glucagon levels in plasma and cerebrospinal fluid (CSF) were assessed in 28 patients hospitalized after a recent suicide attempt and 19 healthy controls. Study persons were assessed regarding lifetime violence expression, psychiatric diagnoses and symptoms.

In **Study III** serum levels of allopregnanolone, progesterone and estradiol were assessed in 14 women with severe postpartum depression and psychosis who, as previously reported, responded with rapid symptom remission during sublingual estradiol treatment. Hormonal and symptomatic assessment were performed before and after 4 weeks of estradiol treatment. 28 healthy postpartum controls were included for baseline comparison.

Results

I) Plasma oxytocin levels were positively associated with personality traits of impulsiveness (monotony avoidance) and negative emotionality (psychic anxiety) with potential gender differences.

II) Patients after suicide attempt had higher insulin (plasma and CSF) and lower glucagon levels (CSF) than healthy controls. Insulin levels (plasma and CSF) were higher and glucagon levels (plasma) were lower in patients and controls with higher levels of prior violence expression.

III) Serum allopregnanolone decreased in women with postpartum depression and psychosis during estradiol treatment. The ratio between allopregnanolone and progesterone was significantly lower in patients than in healthy controls at baseline and it remained unchanged after symptom remission.

Conclusion

Behavioral endophenotypes, rather than categorical diagnoses, of affective disorders were associated with neuroendocrine variation in three different cohorts of patients with affective disorder. Hormonal variation pointed towards an association with trait, rather than state like facets of affective behavior, constituting potential vulnerability markers for affective dysregulation.

Keywords: Affective disorder, Suicide attempt, Postpartum depression, Postpartum psychosis, Personality traits, Violence, Oxytocin, Insulin, Glucagon, Allopregnanolone, Progesterone, Estradiol

POPULÄRVETENSKAPLIG SAMMANFATTNING

Världen över drabbas 350 miljoner människor av unipolära depressioner och bipolära sjukdomar (affektiva sjukdomar). Patienter med affektiva sjukdomar dör cirka femton år tidigare på grund av kroppsliga sjukdomar och suicid. Upp till varannan patient försöker ta sitt liv och lika många svarar inte på behandling eller får återfall trots behandling. Det är mycket vanligt med sociala svårigheter som påverkar familj- och arbetsliv. Medan män har större risk att ta sina liv löper kvinnor ökad risk att göra suicidförsök och att utveckla depression. Efter en förlossning är risken att drabbas av svåra affektiva sjukdomar förhöjd som kan uttrycka sig i form av svåra depressioner, manier eller psykoser. Dessa tillstånd ökar risken för att modern tar sitt liv och i sällsynta fall även barnets liv.

Vissa människor är särskilt sårbara att utveckla affektiva sjukdomar. Sårbarheten påverkas av genetiska faktorer och livshändelser. Det är dock oklart hur patienternas emotionella, kognitiva och kroppsliga symtom uppstår och hur dessa hänger ihop med förändringar i hjärnan och generna. Ökad kunskap om dessa processer skulle sannolikt förbättra möjligheten att behandla och förebygga affektiva sjukdomar.

Patienter i gruppen affektiva sjukdomar är väldigt olika; de skiljer sig avseende emotionella, kognitiva och kroppsliga symtom, avseende risker för sjukdomsutveckling samt återfallsrisk och behandlingssvar. Ett sätt att försöka koppla sjukdomstecken och förändringar i hjärnan är att undersöka mer enhetliga grupper av patienter som till exempel patienter som gjort suicidförsök eller kvinnor efter förlossningen. Ett annat sätt är att undersöka särskilda underliggande aspekter som till exempel personlighet.

Hos många patienter med psykisk sjukdom har man hittat förändringar i stressystemet. Vid stress påverkas bland annat hormonella system. Hormoner påverkar inte enbart kroppens men även hjärnans funktion. Genom att undersöka kopplingen av hormonella faktorer med kroppsliga, mentala och beteendeuttryck kan man indirekt dra slutsatser om hjärnans funktion vid affektiva sjukdomar.

I den här avhandlingen har vi undersökt hur tre olika hormonella system är kopplade till särskilda underliggande aspekter av affektiva sjukdomar. Avhandlingen består av tre olika studier.
I den första frågade vi oss om oxytocin är kopplad till personlighetsdrag som har relevans för patienternas sociala svårigheter. Detta undersökte vi i en stor grupp av öppenvårdspatienter med olika psykiska sjukdomar.
I den andra ville vi veta om patienter som hade gjort självmordsförsök hade förändrade nivåer av insulin och glukagon och om detta var kopplad till våldsamt beteende.

I den tredje studien undersökte vi om kvinnor med svår depression och psykos efter förlossningen uppvisade förändringar av allopregnanolon och progesteron. Dessutom kunde vi undersöka förändringar av dessa hormon under behandling med estradiol när kvinnorna hade tillfrisknat.

I den första studien visade vi att patienter med psykiska sjukdomar som hade mer impulsiva och negativ emotionella personlighetsdrag hade högre oxytocin nivåer. Dessa patienter hade särskilda drag av ångest och var mer extroverta. Möjligen var dessa samband särskild tydliga hos män.
I den andra studien visade vi att patienter som hade gjort självmordsförsök hade högre nivåer av insulin i blodet och i ryggmärgsvätskan än friska kontroll-personer. Dessutom hade de lägre nivåer av glukagon i blodet. Högre nivåer av insulin och lägre nivåer av glukagon var kopplade till självrapporterat interpersonellt våld sedan femton års ålder hos patienter och friska kontroller.
I den tredje studien visade vi att allopregnanolon minskade under estradiol behandling för postpartum depression och postpartum psykos. Patienterna uppvisade både före och under behandlingen förändringar i relationen mellan allopregnanolon och progesteron jämfört med friska kvinnor.

Sammanfattningsvis tyder resultaten på att särskilda underliggande aspekter av affektiva sjukdomar är kopplade med förändringar i hormonella system. Dessa förändringar ter sig vara kopplade med långvariga drag hellre än akuta sjukdomsuttryck och kan på så sätt tyda på sårbarhetsfaktorer för affektiva sjukdomar. Resultaten bidrar till ökad förståelse om särskilda hormonella aspekter hos specifika grupper av personer med affektiva sjukdomar.

ORIGINAL PAPERS

I. Bendix M, Uvnäs-Moberg K, Petersson M, Gustavsson P, Svanborg P, Åsberg M, Jokinen J. Plasma oxytocin and personality traits inpsychiatric outpatients. Psychoneuroendocrinology (2015) 57, 102-110.

II. Bendix M, Uvnäs-Moberg K, Petersson M, Kaldo V, Åsberg M, Jokinen J. Insulin and glucagon in plasma and cerebrospinal fluid in suicideattempters and healthy controls. Psychoneuroendocrinology 81 (2017) 1-7.

Bendix M, Uvnäs-Moberg K, Petersson M, Kaldo V, Åsberg M, Jokinen J. Corrigendum to “Insulin and glucagon in plasma and cerebrospinal fluid in suicide attempters and healthy controls” [Psychoneuroendocrinology 81 (2017) 1–7]. Psychoneuroendocrinology (2018) 94, 168.

III. Bendix M, Bixo M, Wihlbäck AC, Ahokas A, Jokinen J. Allopregnanolone and progesterone in estradiol treated severe postpartum depression and psychosis. Manuscript.

ABBREVIATIONS

ASI	Anxiety Sensitivity-Index
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale
BSA	Brief Scales of Anxiety
CPRS	Comprehensive Psychopathological Rating Scale
CSF	Cerebrospinal fluid
DSM	Diagnostic and Statistical Manual of Mental Disorders
ELISA	Enzyme-linked immunosorbent assay
GABA	Gamma-aminobutyric acid
GAF	Global assessment of functioning
5-HIAA	5-Hydroxyindoleacetic acid
HPA	Hypothalamic-pituitary-adrenal
HPG	Hypothalamic-pituitary-gonadal
ICD	International Classification of Diseases
KIVS	Karolinska Interpersonal Violence Scale
KSP	Karolinska Scales of Personality
MADRS	Montgomery Åsberg Depression Scale
OGTT	Oral glucose tolerance test
PMDD	Premenstrual dysphoric disorder
PRIME-MD	Primary Care Evaluation of Mental Disorders
PVN	Paraventricular nucleus
RDoC	Research Domain Criteria
RIA	Radioimmunoassay
SCID	Structured clinical interview DSM
SD	Standard deviation
STAI	Spielberger State-Trait Anxiety Inventory

1. INTRODUCTION

1.1 Affective disorders - definition

Affective disorders are major psychiatric syndromes characterized by mood disturbances, changes in cognition and bodily functions (1). Bipolar disorders are separated from unipolar disorders since differences in course, pharmacologic response, and genetics became evident (2). Genetic studies have provided evidence for overlap between bipolar disorders, depression, schizophrenia and anxiety disorders (3, 4).

1.2 Scope

Depression affects 300 million and bipolar disorder 50 million people worldwide with depression being the leading cause of disability (5). Affective disorders are often comorbid with anxiety, personality and substance use disorders (6). Patients have 11-17 years reduced life expectancy mainly caused by suicide and somatic comorbidity (7-9). About 30-50% attempt suicide and 11% complete suicide (10-12) with increased risk for suicide attempt in females and suicide in males (13, 14). At least every second patient with major depression experiences social behavioral problems with severe impact on interpersonal and professional functioning (15). Every second patient does not respond to treatment or experiences recurrence despite treatment (16, 17). With the onset of puberty, the female to male ratio in depression doubles while it remains stable throughout life in bipolar disorders (18). However, gender dependent incidence rates for depression seem dependent on severity and subtype of depression (19). The risk for a first or recurrent episode of severe affective disorder is increased after delivery (20, 21). Postpartum onset major depression (3 months incidence 6.5% (22)) is a potential risk factor for conversion to bipolar disorder (23). The evidence is strong for an association between bipolar disorder and postpartum psychosis (1-2/1000 deliveries), characterized predominantly by depressive, manic or mixed episodes (24). In Sweden, 18% of maternal deaths are due to suicides, which are more often of a violent nature than during other periods in female life (25), and maternal suicides can be associated with infanticide (26).

1.3 Classification of affective disorders

The aim of clinical diagnostic systems is to have a high clinical utility – i.e. aid detection of disorders, guide management and predict outcome. Mental disorders are classified based on patterns of reported experiences and observed behaviors and lack biological underpinnings, clinical tests or causative criteria (27). Current revisions of the DSM and the ICD system anticipate though future inclusion of neurobiological measures (28).

1.3.1 DSM

DSM-III and IV defined mood disorders as a single category but DSM-5 separates bipolar and depressive disorders. DSM-5 redefined the postnatal specifier to ”with peripartum onset” (pregnancy to within 4 weeks after delivery) (29).

1.3.2 ICD

ICD-11 is harmonized with DSM-5 and classification of mood disorders are similar, although the supplementary code for perinatal disorders applies to pregnancy and within 6 weeks after delivery (30).

1.4 Phenotype in affective disorders

Core features of unipolar and bipolar depression are depressed mood, loss of interest, lack of reactivity, psychomotor retardation and agitation, impaired cognition (concentration, learning, memory), neurovegetative signs of appetite and weight change, as well as disruption of sleep and circadian rhythm (31). Manic episodes are characterized by uncontrollable excitation and increased motivation (32). High levels of anxiety (33) and psychotic symptoms, especially in bipolar disorder, are common (34).

The signs and symptoms of psychopathology are assumed to be caused by alterations in brain functioning in cortico-limbic circuits (35) which is ultimately dependent on proteins produced by individual genes. Affective disorders, especially bipolar disorder, are heritable, but genetic differences constitute only a susceptibility to develop illness in the setting of developmental and environmental challenges (36). Consequently, the phenotypic output of mental disorders can be conceptualized as the product of genotype, environment and epigenetic factors (37). (Figure 1)

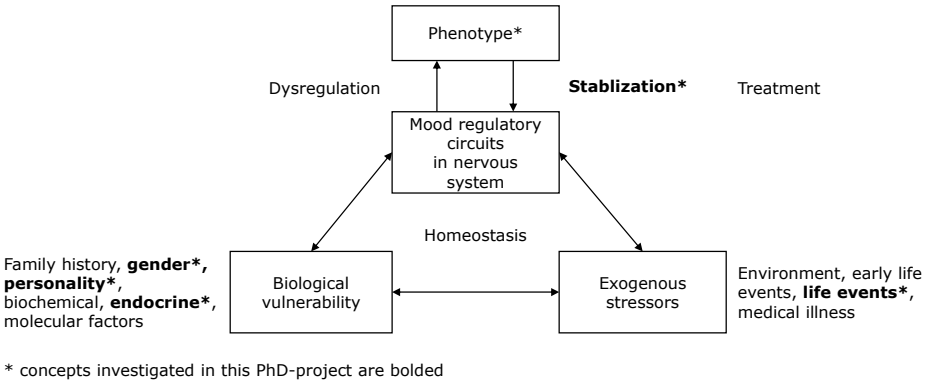


Figure 1. Sources of variance in phenotype (adapted from (38)).

1.5 Endophenotype and biomarker concepts in affective disorders

The pathway from gene to phenotype can be seen as a gradient of increasing heterogeneity and complexity where elements interact with each other and the environment (figure 2) (31, 39). It is thus unlikely that categorical diagnoses can be mapped to molecular events (40). The relationship between underlying behavioral and biological expressions may though be stronger, as proposed by the endophenotype concept (37). Behavioral endophenotypes, such as symptoms, behaviors or psychological traits, may therefore be better candidates to relate neurobiological measures than categorical diagnoses of affective disorders (31, 41). The RDoC (Research Domain Criteria) initiative expanded the endophenotype concept to psychopathology with the aim to classify mental disorders based on disruptions in biological function that are related to upstream genetics and downstream behavior (42). Patients with affective disorders may show alterations in several dimensional constructs, e.g. the negative (stress sensitivity, anxiety) or positive valence (reward), cognitive (attention, memory bias) or social processes domains with biological expressions at different levels of analysis (43).

Diagnostic categories	Psychopath. Behavioral phenotype	Symptoms Signs Traits Sex	Intermediate Phenotype	Endopheno-type	Circuits Neural systems	Cells Plasticity	Protein e.g. Receptor NT Hormone	Gene expression regulation	Gene hubs	Gene
			Biomarker							

Figure 2. Potential pathway from gene to diagnosis. Interaction occurs within and between levels and with environment (31, 39) NT=neurotransmitter.

All endophenotypes are by definition biomarkers, i.e. any characteristic such as a biological or psychological measurement that correlates with a biological, pathological or treatment associated response (44). Biomarkers do not necessarily mediate genetic pathways but can be clinically useful for guiding screening, diagnostics, disease staging, treatment selection, or prognosis (45). Promising biomarker candidates in mood disorders are related to neuroendocrine, inflammatory, neurotrophic and metabolic processes (46).

The identification of biological and behavioral biomarkers and endophenotypes in complex somatic disorders such as cardiovascular disease and cancer has had considerable implications for improvements in treatment selection and prognosis over the past decades (42). Based on these experiences - where endophenotypes often were prerequisites for the discovery of biological or genetic mechanisms - it has been proposed that endophenotype and biomarker patterns might parse heterogeneity and optimize patient outcomes also in mental disorders (47, 48). Taxonomies of markers from different biological levels together with information on environmental exposures, clinical signs and symptoms may have potential to stratify and personalize medicine in affective disorders and to inform on etiopathogenetic pathways (49, 50).

1.5.1 Psychopathological endophenotypes in affective disorders

Several core features of affective disorders are potential endophenotypes associated with underlying neurobiological processes: e.g. anhedonia related endophenotypes in association to dysfunctions in the reward system, neurovegetative endophenotypes associated with neurotransmitters and hormones involved in appetite and weight regulation, and psychomotor related endophenotypes associated with hypothalamic-pituitary-adrenal-axis (HPA-axis) and dopaminergic dysfunction (31, 41).

1.5.1.1 Personality traits

Personality is a broader construct that may better be explained by sets of endophenotypes as suggested by the intermediate phenotype concept (51). Personality traits are relatively stable patterns of thoughts, feelings and behavior which have strong genetic influences (52). There is support for a higher order structure of three to five traits including extraversion/positive emotionality, neuroticism/negative emotionality, conscientiousness/constraint, agreeableness and openness-to-experience, each including several lower-order traits (53). Neuroticism (a tendency for anxious and irritable distress and increased stress sensitivity) predicts internalizing disorders (54) and is one of the strongest candidate endophenotypes for depression (31).

1.5.1.2 Social behavior

Social deficits in mental disorders can be transient or trait like. Impairments of social affiliation, cognition and perception have been associated with alterations in evaluative, reward and cognitive brain systems and underlying biological changes in neurotransmitters and endocrine factors, notably the HPA-axis and oxytocin system (55). Social stress sensitivity, associated with HPA-dysregulation in patients with depression (56), is a strong candidate endophenotype (31). Increased sensitivity and reactivity to positive social stimuli may be a potential endophenotype specific for bipolar disorder (57).

1.5.1.3 Self-directed and interpersonal violence

Even though a majority of patients with affective disorders consider or attempt suicide, only a minority complete suicide (14). Risk factors for suicide attempt and suicide are similar in unipolar and bipolar disorders and include a temporal and dose-dependent association with depressive or mixed episodes, comorbidity with e.g. substance abuse or personality disorders, prior suicide attempts, early life adversities, and familial vulnerability (14, 58). A diathesis-stress model for predisposition to suicide has been proposed where psychopathology or life events act as stressors that interact with pre-existing vulnerability endophenotypes (59). Such endophenotypes may be found in certain personality dimensions, such as aggression and impulsivity that are associated with suicide attempt and completion (60, 61). These traits may predispose to either development of mental disorders (62) or directly, and independent from psychopathology, to suicidal behavior (60). As inter-personal and self-inflicted aggression are closely related (63) they may indicate an underlying co-occurring vulnerability which influences the risk for either one of these behaviors and is part of a suicide propensity endophenotype (60). Subgroups of suicidal patients with aggressive-impulsive behavior may share certain neurobiological vulnerabilities (64).

1.6 Neuroendocrinology of mood regulation

1.6.1 Neuroendocrine modulation of motivated behavior

The neuroendocrine system coordinates physiological and behavioral responses of the whole body in response to internal, behavioral and social triggers (65). Hormones secreted by cells in the central nervous system are released locally, into the blood stream, or via central projections in other brain regions (66). HPA-axis, hypothalamic-pituitary-gonadal-axis (HPG), as well as oxytocin interact with mood regulating circuits via effects on the autonomic nervous system, other neurotransmitters and brain areas such as the limbic system (67, 68). Hormonal release is dependent not only on current internal and external context (e.g. genes, age, sex, life stress) but also on historic context, such as early life stress, that can alter molecular context via epigenetic processes and thereby affect susceptibility to current events (66, 68). Hence the integrated endocrine output depends on

current context and experience, and it influences motivated behaviors that have physiological, behavioral and mental expressions (68). Behavioral expressions of affective disorders can in this way be accompanied by variations in neuroendocrine factors that mirror central dysregulation (69). (Figure 3)

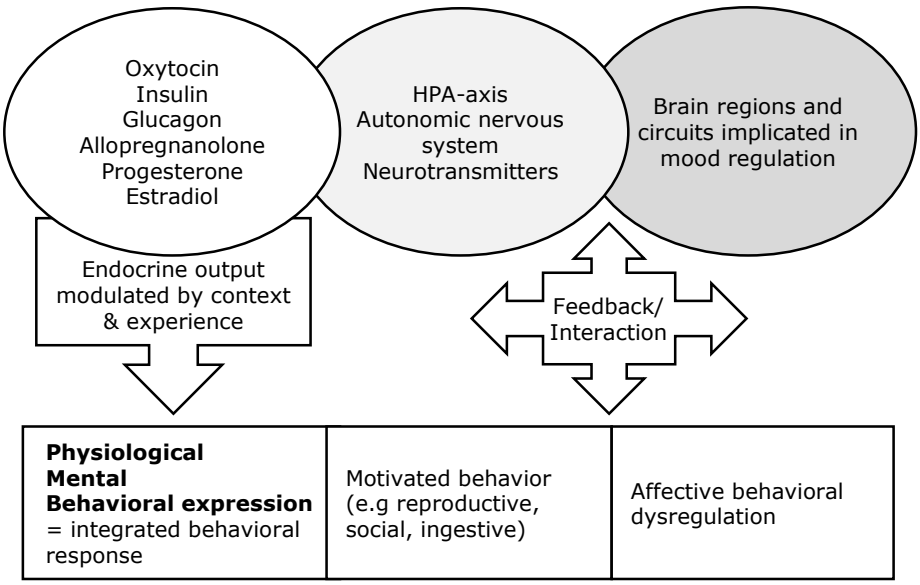


Figure 3. Neuroendocrine modulation of motivated behavior (66, 68).

1.6.2 Stress diathesis, HPA axis and autonomic nervous system

Perception of experienced or anticipated external and internal threats (physiological and psychological/social) triggers a stress response that aims to restore homeostasis (70). The stress response involves several allostatic systems, such as the HPA-axis and autonomic nervous system, which interact with e.g. oxytocin, reproductive, and metabolic hormones (71). An adaptive stress response is of limited duration and involves e.g. appropriate aggression and inhibition of feeding and reproduction (70). Dysregulation of the stress response is considered to be a common factor in many mental, emotional and behavioral disorders (72). Especially HPA-axis but also autonomic dysregulations have been associated with affective disorders (67, 73-75) and their interactions with other endocrine systems have probable implications for affective dysregulation (76-79).

1.6.3 Sex differences

The increased incidence of depression during reproductive female life may be associated with sex differences in brain morphology and circuit functioning that affect stress reactivity and social behavior (80, 81). Behavioral sex differences due to developmental gonadal hormone exposures are established in non-mammals but seem to be more subjective to environmental influences in humans (80). Many brain regions implicated in mood disorders are sexually dimorphic (e.g. hypothalamic nuclei, amygdala, hippocampus) (67). Reproductive hormones interact with several systems associated with mood regulation, such as the HPA-axis, other metabolic hormones, the autonomic nervous system, many neurotransmitters, and oxytocin (82). Gender differences in major depression may originate from endocrine exposures during fetal development (67).

1.7 The oxytocin system and motivated behavior

The nonapeptide oxytocin is mainly synthesized in the paraventricular nucleus (PVN) and supraoptic nucleus in the hypothalamus. Oxytocin is not only released into the blood circulation via the posterior pituitary but also directly into the brain, acting both as a hormone and a neurotransmitter. The hypothalamic nuclei receive inputs from, and have projections to, several brain areas, such as the forebrain, hypothalamus, amygdala, hippocampus, and brain stem which express oxytocin receptors. (Reviewed in (83)). Findings from animal studies support release dependent interactions with the HPA-axis, estrogen, dopamine, serotonin, and the autonomic nervous systems. Intracerebral release is region and stimulus dependent and can occur independently but also coordinated with peripheral release. Oxytocin is released in diverse settings, e.g. during birth, lactation, in response to touch, after food intake and during social interaction. It mediates effects consistent with an anti-stress pattern, promoting anxiolysis, sedation, decreased nociception, anabolism and bonding. It decreases stress-reactivity through action on HPA-axis and autonomic nervous system and decreases cortisol, and blood pressure. (Reviewed in (84, 85)). Oxytocin release can in threatening settings have anti-social effects, despite its general involvement in non-stressful and positive social situations (85, 86). Findings from oxytocin administration studies suggest that oxytocin increases the sensitivity to social cues; the interpretation of the cue is though dependent on contextual factors (such as sex, attachment style, early life experiences and psychiatric symptoms) (87) hence oxytocin may promote either prosocial or defensive anti-social emotions and behaviors (88). This salience and social sensitivity may be associated with genetic variability in the oxytocin system (89).

1.7.1 Oxytocin and affective disorders

Dysregulation in the oxytocin system may have a pathophysiologic role in several mental disorders with social and interpersonal dysfunction (90, 91). Even though the evidence seems stronger in autism and schizophrenia, oxytocin also has potential implications for emotional distress and social behavior in affective disorders (83). Its interaction with HPA-axis, autonomic and serotonin system may mediate physiological and psychological treatment effects (84, 92, 93). Genetic and epigenetic variation in the oxytocin system has been associated with depressive and anxiety symptoms, suicidal ideation, traumatic life events and changes in emotion regulating circuits (89, 94). Oxytocin plays a major role in depression related behaviors in animals (83). However, no consistent associations between affective disorders and oxytocin have been found in humans: Post mortem studies have shown elevated oxytocin neurons in the PVN of patients with major depression and bipolar disorder (95) and increased oxytocin mRNA levels in melancholic depression (96). In unipolar depression have though peripheral levels of oxytocin been found to be increased (97), decreased (98-101) or similar (93) compared with healthy controls. Peripheral levels in bipolar depression were found to be decreased compared with healthy controls (101) and similar (101) or increased compared with unipolar depression (102). After treatment, peripheral oxytocin levels increased in patients with bipolar depression in the study of Lien et al. (102) but not in the study of Ozsoy et al. (101) and levels remained unchanged in patients with unipolar depression in both studies (101, 102). Intranasal oxytocin modulated emotion recognition and processing in major depression (103, 104) but does not seem to have any treatment effects (105).

Most studies in affective disorders have assessed peripheral oxytocin levels which may affect findings as oxytocin does not cross the blood brain barrier easily (83). These controversial associations may also depend on contextual and developmental factors: Severity of depressive symptoms in major depression was negatively associated with plasma oxytocin levels (100, 106, 107) with higher levels of rumination strengthening the negative association in men (108). Compared with healthy controls, patients after suicide attempt had a trend for lower cerebrospinal fluid levels (CSF) of oxytocin, which was associated with suicide intent in males (109). Decreased oxytocin levels have been associated with history of attempted suicide, lifetime expression of aggression (110), early life stress in men (107), and in women with childhood abuse (111) and childhood trauma (112). An increased oxytocin response has been found in association with childhood trauma (113) and in women with major depression in response to affiliation associated imagery (114). Comorbid or contextual anxiety may moderate effects of depression on oxytocin levels (91). Oxytocin administration increased anxiety in response to unpredictable stress (115) but was found to decrease social stress associated anxiety (116) and amygdala activation (117).

1.7.2 Oxytocin and personality traits

Associations between oxytocin and personality traits have been found notably in relation to extraversion, novelty seeking and trait anxiety. Positive associations between extraversion and novelty seeking were reported in major depression (118) and healthy populations (119, 120). Self-perception of extraversion and openness to experience traits improved after intranasal oxytocin administration (121). Extraversion traits and plasma oxytocin correlated negatively with amygdala and hippocampus volumes in healthy populations (119). However, a study in healthy females found a negative association with novelty seeking (122) and there was no association between these traits and oxytocin in postnatal women (123, 124).

Trait anxiety was negatively associated with oxytocin in healthy women (125) and in the postnatal period (123, 124). Trait anxiety increased the negative association between oxytocin and childhood adversity in men (107). In children, higher levels of trait anxiety were associated with lower levels of oxytocin in plasma and CSF in response to a painful stressor (126).

Furthermore, has oxytocin been found to correlate positively with reward dependence in major depression (118), attachment anxiety (125), and harm avoidance and attachment in healthy women (122). Oxytocin was negatively associated with aggression and guilt in postpartum women (123, 124) and with aggression in women with emotional instability personality disorder where it correlated negatively with childhood adversity (112).

1.8 Insulin, glucagon and motivated behavior

Glucose is the main energy substrate for the central nervous system, which consumes about 20% of the daily average (127). Insulin, primarily synthesized in pancreatic beta-cells, regulates glucose homeostasis through effects on peripheral organs, hypothalamic neurons and other systems involved in energy metabolism. It is also involved in non-metabolic central functions such as cognition, learning, memory, reward and neuroplasticity (128-130). Declining glucose levels activate hypothalamic regulatory factors, the autonomic nervous system, stimulate ingestive behavior and initiate progressive release of glucagon, adrenalin, cortisol and growth hormone that counteract insulin action (129, 131, 132). Glucagon is secreted from pancreatic alpha-cells also in response to adrenergic (133) and serotonergic stimulation (134). Circuits controlling energy balance and emotions are intertwined; several brain structures and circuits have dual functions in the homeostatic control of metabolic and emotional behavior (e.g. hypothalamus, limbic system, and dopamine system) (135).

1.8.1 Insulin and glucagon in affective disorders

Patients with mood disorders have increased risk for metabolic disorders, but it is difficult to parse environmental (e.g. medical care, medication, lifestyle) from genetic and pathophysiological influences (136). Patients with major depression and bipolar disorder seem to have decreased insulin sensitivity compared with healthy controls (137-139) with increased fasting glucose (137) and increased glucose and insulin reaction during oral glucose tolerance test (OGTT) (137-139). Glycemic abnormalities have been found already at onset in young treatment naïve patients with serious mental disorders (140). There is potential evidence for shared biological origins of affective disorders and metabolic diseases (141, 142).

1.8.2 Insulin and glucagon in self-directed and interpersonal violence

History of suicide attempt was associated with peripheral fasting glucose levels in the lower normal range (143). In the same study impulsive, histrionic and narcissistic personality traits were associated with lower glucose in men whereas females showed an association between higher glucose and histrionic traits (143). Female patients with prior or current self-harm had normal baseline glucose and glucagon levels but a lower glucose nadir during OGTT and they reported higher levels of physical aggression than healthy controls (144). In patients assessed after a suicide attempt, higher CSF-insulin levels were associated with violent nature of the attempt but not with diagnosis of major depression (145). Contrary to these findings reported Koponen et al. (146) that patients with major depression or dysthymia and current suicidal ideation and/or history of suicide attempt had hyperglycemia at baseline and during OGTT, but these findings were potentially confounded by higher body mass index (BMI), age and concurrent medication. A hypoglycemic tendency during OGTT has also been reported in habitually violent men (147) potentially associated with hyperinsulinemia (148) or hypoglucagonemia (149). Higher basal plasma-insulin levels predicted violent re-offense in violent offenders (150).

1.9 Reproductive hormones and female mood

Estrogens and progesterone are cholesterol derivates that are mainly synthesized in ovaries and placenta but also in peripheral tissues and in the brain (151, 152). They can pass the blood brain barrier and central and peripheral levels seem to be similar (153, 154). Estrogen and progesterone receptors are densely expressed in hypothalamus, amygdala, and hippocampus; reproductive hormones interact with neurotransmitter systems, autonomic nervous system and other neuroendocrine systems such as HPA-axis and the oxytocin system (155). Besides their role in reproductive behaviors, these steroids have also non-reproductive effects regarding e.g. memory, neuroplasticity, anxiety, and mood (155, 156). The progesterone derivate allopregnanolone is a neurosteroid which has anti-

depressive, anxiolytic, anticonvulsant, sedative and anti-nociceptive effects (157). Progesterone metabolizing enzymes are expressed peripherally and centrally (158) and allopregnanolone can cross the blood brain barrier (153). Allopregnanolone acts primarily through allosteric modulation of the $GABA_A$-receptor (159) and suppresses the HPA-axis (160). Dysregulations in GABA signaling and altered levels of progesterone and allopregnanolone have been reported in depression and bipolar disorder (161). Increased levels of allopregnanolone were found after treatment with certain SSRIs, antipsychotics, lithium and estradiol (161, 162). Consistent changes in the HPG-axis have not been found in female mood disorders but the combined evidence from animal, experimental, hormonal treatment and neuroimaging studies suggests that fluctuations in reproductive hormones can trigger affective dysregulation in vulnerable women in the postpartum period (163). Structural and functional alterations in mood networks seem to differ between major depressive and postpartum depressive disorder and these changes may be associated with alterations in hormones, inflammatory markers and neurotransmitters (164).

1.9.1 Estradiol treatment in postnatal affective disorders

There is no convincing evidence for the efficacy of estradiol treatment in postnatal affective disorders (165). However, the quick and large effects in some populations with severe postnatal affective disorders have been interpreted as potential evidence for hormone sensitive subgroups of women with affective disorders (163, 166, 167).

1.9.2 Allopregnanolone and progesterone in postnatal affective disorders

Neurosteroid dysregulation may have a pathophysiologic role in postpartum depression (168). Both withdrawal from high pregnancy levels of allopregnanolone and progesterone as well as failure to regulate $GABA_A$-receptor subunit composition have been suggested as potential mechanisms (169). Neurosteroids have been scarcely investigated in the perinatal period compared to premenstrual mood disorders where evidence of a dysregulation in the neurosteroid system is stronger (170). Intravenous allopregnanolone has been found to have rapid onset effect in phase 3 trials in postpartum depression (171). Decreased allopregnanolone levels were reported in women with baby blues (172) but not in women with postpartum depression (173, 174) and Hellgren et al. reported both decreased (175) and normal levels during pregnancy (176) compared with healthy controls. In pregnant women who developed postpartum depression, the allopregnanolone progesterone ratio - a biological relevant proxy for the conversion of progesterone into allopregnanolone - was associated with interaction between estradiol levels and oxytocin receptor methylation (177). Allopregnanolone was negatively associated with depressive symptoms in women

with a history of postpartum depression which recurred after add-back of estradiol and progesterone following experimental hypogonadism (169, 178). In women at-risk for development of postpartum depression, progesterone was elevated during the peripartum period (179) but there was no difference between women with postpartum depression compared with healthy controls (173).

2. AIMS

2.1 Overall aims

The overall aim of this thesis was to study three different neuroendocrine systems in relation to underlying behavioral endophenotypes (personality traits, self-directed and interpersonal violence, and psychiatric symptoms) in patients with affective disorders.

2.2 Specific aims

The specific aims of the individual studies in this thesis were:

Study I To assess the relationship between peripheral levels of oxytocin and personality traits in a large population of medication-free psychiatric outpatients with diminished functioning, taking gender effects into account. To assess the stability of oxytocin and the association with personality traits over time.

Study II To compare CSF and plasma levels of insulin and glucagon between patients after suicide attempt and healthy controls. To assess the relationship between these hormones and aggressive behavior.

Study III To compare peripheral levels of allopregnanolone and progesterone between women with severe postpartum affective disorders (severe postpartum depression and postpartum psychosis) and healthy controls. To assess differences, changes and interrelations of peripheral allopregnanolone, progesterone and estradiol levels during effective estradiol treatment in women with severe postpartum affective disorders.

2.3 Hypotheses

In Study I we hypothesized that extroversion related personality traits would be associated with peripheral oxytocin levels in psychiatric outpatients.

In Study II we hypothesized that patients after suicide attempt would have higher insulin and lower counter-regulatory glucagon levels compared with healthy controls. We further expected history of violent behavior to be associated with these hormonal changes.

In Study III we hypothesized that patients with severe postnatal affective disorders would have lower allopregnanolone levels than healthy controls. We expected that increasing levels of estradiol during estradiol treatment would increase allopregnanolone levels suggesting a potential mediation of estradiol treatment effect by allopregnanolone.

2.4 Research questions

The primary research questions of this thesis focus on neuroendocrine variation in relation to behavioral endophenotypes in affective disorder. Neuroendocrine variation in relation to categorical diagnoses and gender in studies I and II was assessed to address potential confounding.

Neuroendocrine variation in relation to behavioral aspects of affective disorder

Are peripheral levels of oxytocin associated with personality traits relevant for social behavior in heterogeneous psychiatric outpatients? (study I)

Differ peripheral and/or central levels of insulin and glucagon levels between patients after suicide attempt and healthy controls? (study II)

Are peripheral and central levels of insulin and glucagon correlated with expression of violent behavior in patients after suicide attempt and healthy controls? (study II)

Neuroendocrine variation in relation to dimensional affective symptoms

Are peripheral levels of oxytocin associated with symptoms of depression or anxiety in heterogeneous psychiatric outpatients? (study I)

Are peripheral and central levels of insulin and glucagon associated with affective symptoms in patients after suicide attempt? (study II)

Are peripheral allopregnanolone, progesterone or estradiol levels associated with depressive or psychotic symptoms before and during estradiol treatment in women with severe postpartum affective disorder? (study III)

Are changes in peripheral allopregnanolone, progesterone or estradiol levels associated with changes in psychiatric symptoms during estradiol treatment in women with severe postpartum affective disorder? (study III)

Neuroendocrine variation in relation to categorical diagnoses in populations with affective disorders

Are peripheral levels of oxytocin associated with a personality disorder diagnosis in heterogeneous psychiatric outpatients? (study I)

Are peripheral and central levels of insulin and glucagon associated with a diagnosis of mood disorder in patients after suicide attempt? (study II)

Are peripheral levels of allopregnanolone decreased in patients with postpartum psychosis or postpartum depression compared with healthy postpartum controls? Do patients have different peripheral progesterone levels compared with controls? (study III)

Differ peripheral levels of allopregnanolone and progesterone between symptomatic and remitted state in estradiol treated women with postpartum psychosis and depression? (study III)

Neuroendocrine variation in relation to gender in populations with affective disorders

Do female and male heterogeneous psychiatric outpatients differ regarding potential associations between oxytocin levels and personality traits? (study I)

Neuroendocrine interrelationships in populations with affective disorders

Are peripheral levels of oxytocin stable over time in heterogeneous psychiatric outpatients? (study I)

Are central and peripheral levels of insulin and glucagon correlated with each other in patients after suicide attempt and healthy controls? (study II)

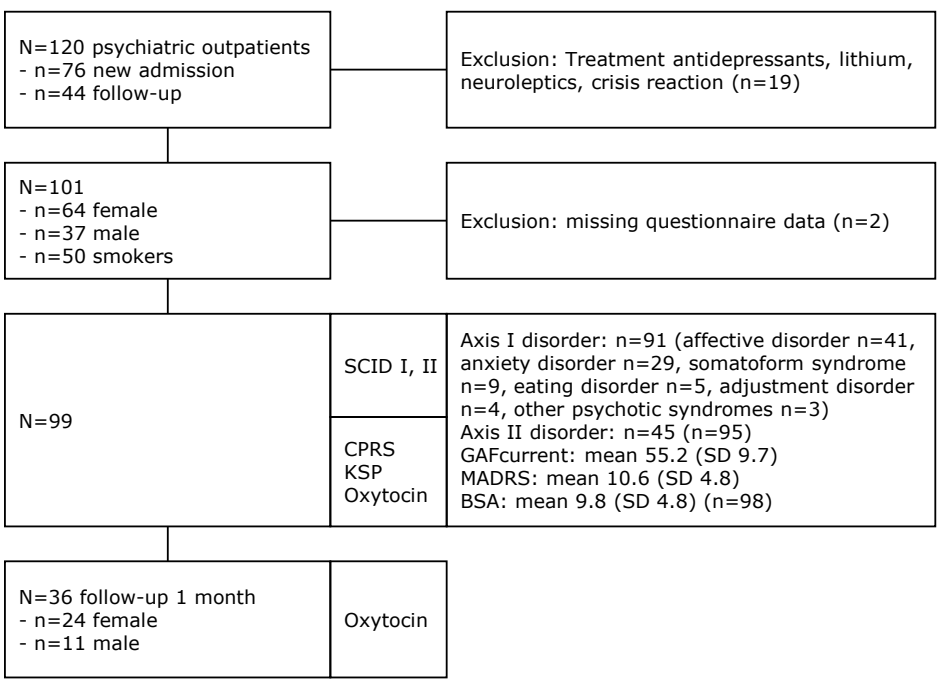
How relate peripheral levels of allopregnanolone, progesterone and estradiol to each other before and during estradiol treatment in women with postpartum affective disorder and controls? (study III)

3. METHODS

3.1 Study persons

3.1.1 Study I

Study I includes 101 medication-free psychiatric outpatients. Patients were recruited between 1991 and 1992 with the aim to assess the relationship between endocrine variables, psychiatric symptoms and personality factors. The study population consists of 37 men and 64 women (mean age 38 years, SD 12, range 19-76) who attended a general psychiatric outpatient clinic in Stockholm either at first-admission or follow-up. Patients treated with lithium, antidepressants or neuroleptics, as well as patients with severe crisis reactions, were excluded. Due to missing data in questionnaires, data from 99 persons were analyzed in this study. Ninety-one patients fulfilled criteria for axis I disorders, and 45 patients had a diagnosis of personality disorder. Smoking status (n=50 smokers) did not differ between gender. Follow-up data for oxytocin levels were available in 36 patients. The population has been described in (143, 180). (Figure 4).

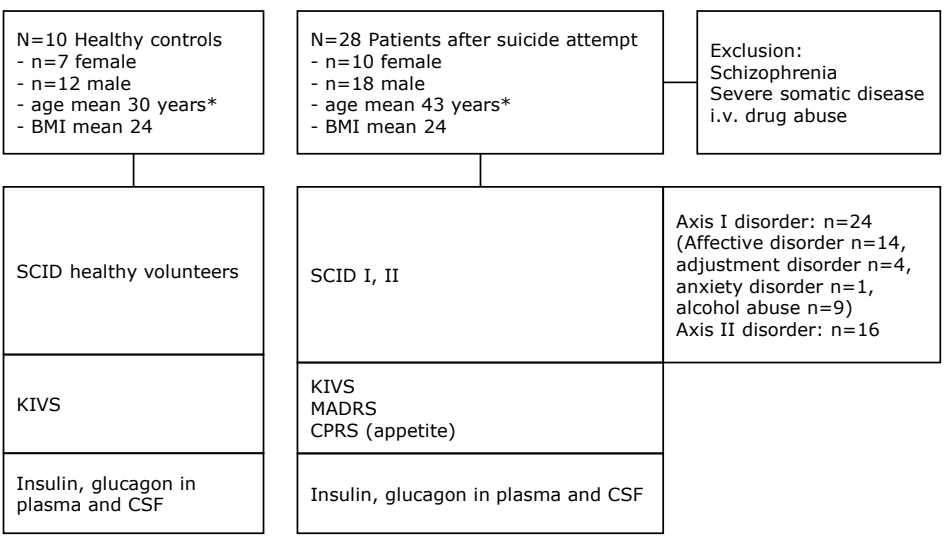


SCID=Structured clinical interview DSM-III, CPRS=Comprehensive Psychopathological Rating Scale, KSP=Karolinska Scales of Personality, GAFcurrent=Global assessment of functioning past month, MADRS= Montgomery Åsberg Depression Scale, BSA=Brief Scales of Anxiety

Figure 4. Flowchart Study I.

3.1.2 Study II

Study II consists of 28 medication-free patients (10 women, 18 men) hospitalized after a suicide attempt and 19 healthy controls (7 women, 12 men). The study population was recruited between 1988 and 1991 with the aim to study risk factors for suicidal behavior. Suicide attempt was defined as any non-fatal, self-injurious behavior with at least some intent to die. Patients with schizophrenia spectrum disorder or intravenous drug abuse were excluded. Twenty-four patients fulfilled criteria for axis I disorder (14 patients with mood disorders) and 16 patients had a diagnosis of personality disorder. Patients were significantly older (mean 43 years, range 23-66) than controls (mean 30 years, range 23-48). BMI (kg/m^2) was similar between the groups (patients mean 24.0, SD 2.9; controls mean 24.0, SD 4.9). Assessment in patients was performed after wash-out of psychopharmacological treatment (mean 8.6 days (SD 3.8) after the suicide attempt). The population has been described in (109, 181). (Figure 5)



* significant difference between controls and patients
SCID=Structured Clinical Interview DSM-III, KIVS=Karolinska Interpersonal Violence Scale, MADRS= Montgomery Åsberg Depression Scale, CPRS=Comprehensive Psychopathological Rating Scale (appetite rating only) CSF=cerebrospinal fluid

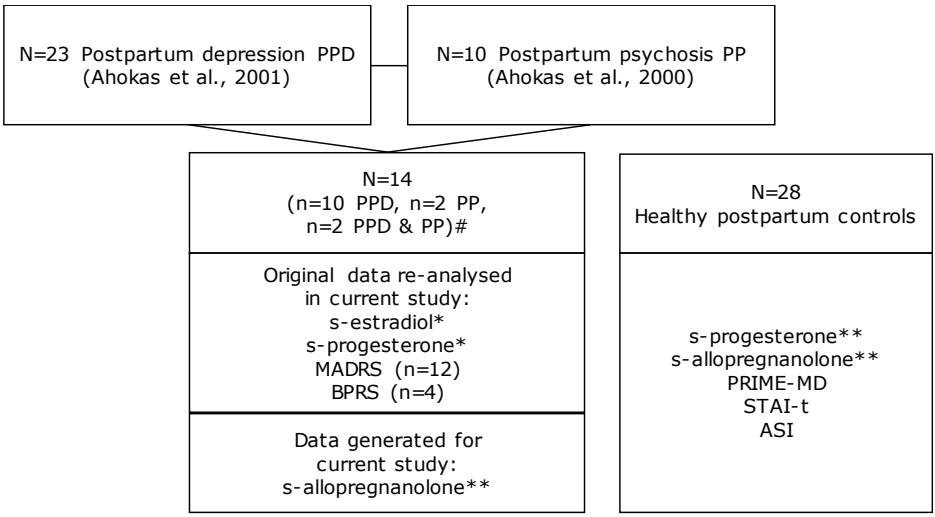
Figure 5. Flowchart study II

3.1.3 Study III

Study III includes 10 women with postpartum depression and 4 women with postpartum psychosis. Patients were part of two larger samples consecutively recruited at the duty unit/psychiatric emergency department at Helsinki City Hospital, Finland with the aim to study estradiol treatment effects (182, 183). Out of ethical reasons there was no placebo-treated group. The current study is based on the availability of remaining blood samples before start of treatment. We also included 28 healthy postpartum controls from an ongoing study with the aim to study neurosteroid levels in the perinatal period. (Figure 6)

Inclusion criteria were either a diagnosis of major depression (ICD-10) (with debut within 6 months postpartum according to psychiatric interview, Montgomery-Åsberg-Depression-Scale (MADRS) ≥22, serum-estradiol concentration ≤200 pmol/L) or postpartum psychosis (ICD-10)). Two women with psychotic postpartum depression were included in both original studies but analyzed only once in the current study. Exclusion criteria in women with postpartum depression were a history of gynecologic, breast or thromboembolic disease (no woman was excluded), use of hormonal preparations (n=2 excluded) and irregular use of study medication (n=1 excluded). No women with postpartum psychosis were excluded. Baseline assessment was performed significantly earlier after partus in controls (mean 6, SD 3 days) than in patients (mean 94 SD 57 days). Follow-up assessment in patients took place after mean 26, SD 7 days. Baseline assessment of hemoglobin, red and white blood cells, sedimentation rate, C-reactive protein, thyroxin and thyroid stimulating hormone were in the normal range.

Treatment consisted of sublingual 17beta-estradiol 1 mg with goal serum-concentration estradiol 400 pmol/L. Treatment effects within two weeks were reported in the original studies: remission of depression occurred in 19 of the 23 women with postpartum depression (183) and psychotic symptoms declined according to Brief-Psychiatric-Rating-Scale (BPRS) from 78.3 to 4.1 in the women with postpartum psychosis (182). Four out of 10 women in the original postpartum psychosis study (182) tapered neuroleptics during the first treatment week. Two out of 23 women in the original postpartum depression study started antidepressants treatment week 3 (183). Data on breastfeeding were not available in the remaining study population investigated in this study. Women in control group and study population had not resumed menstruation neither at baseline nor at follow-up.



* Analyzed at Helsinki City Hospital, Finland
** Analyzed at Umeå Neuroendocrine Centre, Umeå University, Sweden
# Among four women with postpartum psychosis two presented with psychotic depression. These were reported in both original studies but included only once in the current study
PPD=postpartum depression, PP=postpartum psychosis
MADRS=Montgomery Åsberg Depression Scale, BPRS=Brief Psychiatric Rating Scale
PRIME-MD=Primary Care Evaluation of Mental Disorders, STAI-t=Trait subscale of Spielberger State-Trait Anxiety Inventory, ASI=Anxiety Sensitivity-Index

Figure 6. Flowchart study III.

3.2 Psychometric instruments

3.2.1 Psychiatric diagnosis

3.2.1.1 Study I

Standardized psychiatric diagnostic evaluation was performed with the Structured Clinical Interview (SCID) I and II according to DSM-III-R. The interviews were performed by two experienced psychiatrists blinded for self-assessment data except from the SCID II screen after blood sampling and breakfast.

3.2.1.2 Study II

The patients were diagnosed after standardized assessment with SCID I and II interviews (Research Version) performed by trained psychiatrists according to DSM-III. Controls were assessed with the SCID interview for healthy volunteers in order to exclude current or prior psychiatric or somatic disorders.

3.2.1.3 Study III

Standardized psychiatric diagnostic assessment was performed according to ICD-10. Controls were assessed with the self-administered versions of the Primary Care Evaluation of Mental Disorders (PRIME-MD) (184).

3.2.2 Psychiatric symptoms

3.2.2.1 Study I

Symptom severity was assessed by interview with the Comprehensive Psychopathological Rating Scale (CPRS) (185). The CPRS items used in the study are those that are included in the subscales Montgomery-Åsberg-Depression-Scale (MADRS) and the Brief Scale for Anxiety (BSA) (186).

3.2.2.2 Study II

Patients' depressive symptom severity was rater-assessed with the Montgomery-Åsberg-Depression-Scale (MADRS) (185). Patients self-reported appetite levels were assessed with the Comprehensive Psychological Rating Scale (CPRS) (187).

3.2.2.3 Study III

Symptom severity was assessed at baseline and weekly with a) Montgomery-Åsberg-Depression-Scale (MADRS) in women with postpartum depression and b) the Brief-Psychiatric-Rating-Scale (BPRS) in women with postpartum psychosis. Controls self-assessed trait anxiety with the Spielberger-State-Trait Anxiety Inventory (STAI; 20-item, 1-4 points per item) (188) to exclude current mental disorders and anxiety proneness at inclusion and follow-ups and the Anxiety Sensitivity Index for assessment of anxiety symptoms (ASI; 16-item, 0-4 points) (189) at inclusion.

3.2.3 Personality traits

3.2.3.1 Study I

Personality traits were assessed by self-report with the Karolinska Scales of Personality (KSP). The KSP was constructed to measure personality traits in biological research (190). The personality inventory consists of 135 items grouped into 15 subscales. Each item in the subscales is given as a statement with a four-point response format ranging from "Does not apply at all" to "Applies completely." The KSP raw scores were transformed into T scores (population mean=50, SD=10) based on an age and gender-stratified Swedish normative sample (191). We used the same subscale based four-factor structure as described in this population by Svanborg et al. (180). Factor I, negative emotionality (somatic anxiety, psychic anxiety, muscular tension, psychasthenia, lack of assertiveness, guilt); factor II aggressiveness/nonconformity (verbal aggression,

indirect aggression, social desirability); factor III interpersonal aversiveness (suspicion, irritability, detachment, socialization) and factor IV impulsiveness (monotony avoidance, impulsiveness subscale). The psychometric properties of the KSP and its subscales have been reported to be good and the scales measure longitudinally stable personality traits (192, 193).

3.2.4 Violent behavior

3.2.4.1 Study II

Patients and healthy volunteers were interviewed with the semi-structured Karolinska Interpersonal Violence Scale (KIVS) (63) for assessment of lifetime violence exposure and expression. The KIVS includes four subscales (range 0-5) measuring exposure to and use of interpersonal violence as a child (6-14 years old) or adult (15 years of age or older). In this study, only the two violence expression subscales were analyzed. Violence expression ranges from occasional low-grade violence (1) to causing serious injury or conviction for violent crimes (5). The KIVS has shown good validity and the inter-rater reliability was r=0.91 and 0.92 in the violence expression subscales (63).

3.3 Biological analyses

3.3.1 Study I

Plasma samples were collected at 8 a.m. after fasting since midnight (two blood samples with a 30 second interval to test reliability of the analyses). A third blood sample was taken after one month to test the stability of the hormone levels. The samples were stored at -80°C until oxytocin levels were determined by radioimmunoassay (RIA) (69, 76, 194). The detection limit was 3.2 fmol/L.

3.3.2 Study II

Blood and CSF sampling were performed between 8 a.m. and 9 a.m. after fasting in bed since midnight. Venous blood samples were collected 15 minutes before lumbar puncture. Lumbar puncture was performed after measurement of the neuraxis in sitting position between lumbar vertebrae IV and V. Liquor and plasma were kept frozen at -80°C until analyzation of insulin and glucagon levels with RIA (76, 194). In four patients and one control data for CSF insulin and glucagon were missing. The detection limits were 0.2 mikroU/ml (=2 pMol/L) for the insulin assay and 15 pg/ml for the glucagon assay.

3.3.3 Study III

Fasting blood samples were collected between 7 a.m. and 9 a.m. at baseline and weekly before administration of the morning dose of sublingual estradiol. In this study assessments from baseline and treatment week 4 were used. Allopregnanolone in patients and controls was analyzed with standard radioimmunoassay (RIA) after diethylether extraction and celite chromatographic purification at UNC (Umeå Neuroendocrine Centre, Umeå University, Sweden). The assay has a sensitivity of 25pg and the methods are described in detail in Bixo et al. (195). Serum-estradiol and progesterone levels in patients were available in the original dataset after analysis at the laboratory in Helsinki, Finland. Progesterone serum levels in controls were measured with a sequential competitive immunoassay (Immulite®). All analyse kits were purchased from Diagnostic Products Corporation, Corporate Offices, Los Angeles, CA, USA.

3.4 Statistical analyses

In studies II and III hormonal levels for CSF-insulin and plasma-progesterone fell below the detection limit in some of the study persons (CSF-insulin: 19 controls, 9 patients; plasma-progesterone: 5 patients). These were substituted with a constant – in study II we employed by mistake the detection limit in pmol/L instead of mikroU/ml, thus the value 2 instead of 0.2 was imputed (196, 197). In study III we divided the detection limit 0.8 nmol with sqr2 for plasma progesterone as suggested by Hornung and Reed (198). In study III, the missing progesterone value for one patient at the 4-week follow-up was imputed from the 3-week and 6-week measurements, assuming a linear relationship. In study III, the ratio between allopregnanolone and progesterone was calculated as an index for the metabolism of progesterone to allopregnanolone as a post-hoc analysis.

Initial analyses were carried out to evaluate skewness and kurtosis of the distributions with the Shapiro-Wilks test. Non-normally distributed data were log transformed before analyzation as dependent variables with parametric methods -oxytocin (study I), insulin, glucagon (study II), allopregnanolone, and progesterone (study III). Data from individuals in studies I-III that were identified as univariate and/or multivariate outliers (199) were excluded and as this did not affect the significance of the analyses they remained in the analyses. CSF-Insulin levels (study II) showed a bimodal distribution why data were split into high and low CSF-insulin levels and tested for group differences. Patients in study II were significantly older than controls and we performed sensitivity analyses which did not change the significance of the group differences for insulin and glucagon in plasma and CSF.

Study I: To analyze the association between plasma oxytocin and the KSP assessed personality factors (negative emotionality, aggressiveness/ nonconformity, interpersonal aversiveness and impulsiveness) multiple regression (forced entry) analysis was performed adjusted for age, gender and smoking status. Finally, correlation analyses (Pearson's r) or (Spearman rho) were used for an ad hoc analysis of KSP subscales and plasma oxytocin levels. Fisher's z test was used to compare correlation coefficients (Pearson's r).

Study II: To assess for group differences in continuous variables the Wilcoxon two-sample test was used. The potential effect of the confounding factors was tested with correlational analyses (Spearman rho). Standard regression analyses (forced entry) were conducted to assess if suicide attempt was a predictor for hormone levels in CSF and plasma and to adjust for BMI and age.

Study III: To assess independent group differences between patients and controls at base-line, dependent group differences in patients between base-line and follow-up, and relation- and interrelationships between hormones and psychological variables non-parametric methods were used. To adjust for differences in timing of assessment after birth in patients and controls, multiple linear regressions were performed.

The p value was set at <0.05 in all studies. Statistical analyses of studies I and II were performed with the software package JMP 11 (SAS Institute Inc., Cary, NC, USA) and of study III with the SPSS software, version 24 (IBM Corp., USA).

3.5 Ethical approval

3.5.1 Study I

The Regional Ethical Review Board in Stockholm approved the study protocol (Karolinska Hospital ethical committee Dnr: 90:279) and the patients gave written informed consent.

3.5.2 Study II

The Regional Ethical Review Board in Stockholm approved the study protocols and the study persons provided written informed consent (Dnrs: 88-216; 91-96; 2010/3:4).

3.5.3 Study III

The Ethical review committee at the Helsingfors City Hospital approved the original study (06/1998) and patients gave written and informed consent. For the purpose of investigating neuroendocrine variables in collaboration with the original research group ethical approval was granted by the Regional Ethical Review Board in Umeå (Dnr: 2016/170-31). Neurosteroid levels in healthy postpartum controls came from another ongoing study (Dnr: 2011-146-31M).

3.5.4 Ethical considerations

Patients with mental disorders constitute vulnerable populations where it must be motivated that research aims to improve diagnostic, preventative or therapeutic methods that are relevant for the vulnerable population investigated, that risks and discomfort are minimized and that research cannot be performed in less vulnerable populations (200). Study I aimed to assess associations between personality traits and several peptide hormones with the aim to improve diagnostic understanding which could not have been performed in less vulnerable populations. These principles were followed also in study II and III where knowledge gain in high risk populations was not possible without investigating the population itself.

Further, especially concerning psychiatric high-risk patients in study II and III, decreased autonomy requires that research must be of direct gain for the study persons involved (200). Patients that had made suicide attempts in study II received a more rigorous assessment and special care was taken in information of patients to minimize risk for feeling coerced to participate. In study III patients were severely affected by psychotic and depressive symptoms and several were resistant to established treatments. Information was performed by clinicians with good knowledge of and access to alternative treatments. Researchers had from prior case studies knowledge on risks and benefits of the treatment and monitoring of potential negative side effects was included for a subgroup of patients.

In study III even potential harm of the neonate has to be included in the ethical consideration (201). The separation of mothers and children was inevitable due to severity of the disorders irrespective of participation in the study but potentially minimized due to the treatment. Mothers with postpartum psychosis were not able to breastfeed which was associated with disease severity rather than study participation. Mothers with postpartum depression continued to breastfeed and potential negative effects on the children were monitored.

For healthy controls in studies II and III the ethical principles for research (autonomy, beneficience, non-maleficience, justice) (202) were followed.

For research to be ethical the employed methods must guarantee sustainable scientific results involving, amongst other, aspects of methodologic power (200). Study III includes only few study persons and even the originally included study persons were few, especially concerning women with postpartum psychosis. Bearing in mind that postpartum psychosis is rare (1-2/1000 births), that it has very severe clinical implications and that the scientific literature is small, findings from this study have potential to inform knowledge but careful interpretation of findings is warranted. The severity of the disorder also implied that an inclusion of a placebo group was not ethically possible.

4. RESULTS

4.1 Neuroendocrine variation in relation to behavioral aspects of affective disorder

4.1.1 Results of study I

Plasma oxytocin was positively associated with personality traits of impulsiveness (monotony avoidance) and negative emotionality (psychic anxiety) in heterogeneous psychiatric outpatients.

The personality factor impulsiveness (KSP) showed a significant positive correlation in the bivariate analyses with the logarithm of oxytocin plasma levels in psychiatric outpatients (Pearson's r=0.22, p=0.039, (CI95 0.011-0.420) (n=84)). The personality factors showed a considerate degree of expected intercorrelation. (Table 1)

Table 1. Correlations between personality traits (factors) and plasma log oxytocin (Pearson's r) in psychiatric outpatients (203).

	Oxytocin	I	II	III	IV
I Negative emotionality	0.17	-			
II Aggressiveness/Nonconformity	0.04	-0.08	-		
III Interpersonal aversiveness	-0.03	0.44**	-0.36**	-	
IV Impulsiveness	0.22*	-0.19	0.22*	-0.16	-

* p<0.05, ** p<0.001

The factors impulsiveness and negative emotionality were independent predictors of log oxytocin after adjusting for age (n.s.), gender (n.s.), and smoking status (p=0.041) in a multiple linear regression (F=2.2, p=0.044, R^2=0.17, adjusted R^2=0.09) (table 2). The final regression model (without the non-significant predictors age, gender, aggressiveness/nonconformity and interpersonal aversiveness) was significant (F=3.8, p=0.013) and accounted for 9% of the variance of plasma oxytocin levels (adjusted R^2).

Table 2. Personality traits (factors) as predictors for log plasma oxytocin in psychiatric outpatients (203).

	t ratio	*p* value
Negative emotionality	2.22	0.029*
Aggressiveness/nonconformity	-0.30	0.76
Interpersonal aversiveness	-0.55	0.58
Impulsiveness	2.36	0.021*
Gender	1.20	0.23
Age	1.19	0.24
Smoking	2.08	0.041*

*p<0.05

According to an ad-hoc subscale analysis of the significant factors impulsiveness (subscales monotony avoidance and impulsiveness) and negative emotionality (subscales somatic anxiety, psychic anxiety, muscular tension, psychasthenia, lack of assertiveness, guilt) the logarithm of plasma oxytocin showed a significant positive correlation with monotony avoidance (Pearson's r=0.27, p=0.013 (CI95 0.060-0.460) and with psychic anxiety (r=0.23, p=0.036 (CI95 0.016-0.420)). (Figure 7)

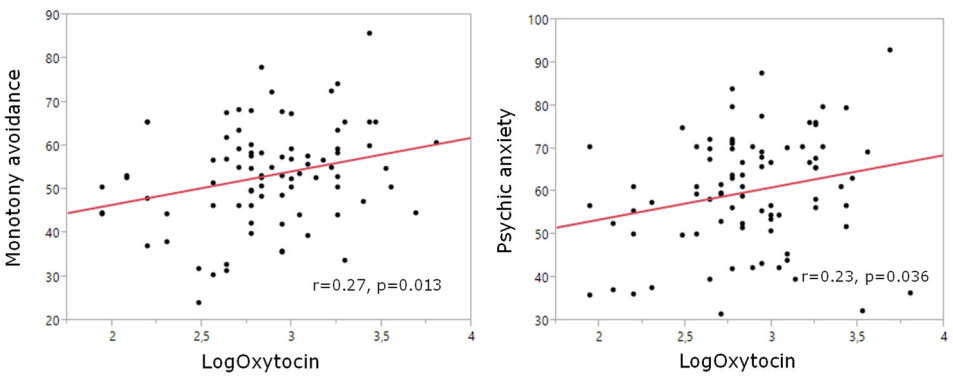


Figure 7. KSP subscale correlation monotony avoidance and psychic anxiety with log oxytocin in psychiatric outpatients (203).

4.1.2 Results of study II

Plasma and CSF insulin were higher and CSF glucagon levels were lower in patients after a recent suicide attempt compared with healthy controls.

Patients after suicide attempt had significantly higher levels of insulin in plasma and in CSF than healthy controls in the unadjusted analyses (Wilcoxon signed rank test). CSF insulin fell below the detection level of the assay 0.2 mikroU/ml in all controls. (Table 3; Figure 8)

Patients had significantly lower levels of glucagon in plasma and in CSF than healthy controls in the unadjusted analyses. (Table 3; Figure 8)

Table 3. CSF and plasma levels of insulin µU/ml and glucagon pmol/L in patients after suicide attempt (n=28) and healthy controls (n=19) (197).

Endocrine Measure	Patients after suicide attempt				Controls				Statistics[a] p-value unadjusted (adjusted)[b]
	Mean	Median	SD	Range	Mean	Median	SD	Range	
P-Insulin (n=24/19)	13.63	11.5	7.83	3-38	7.63	8	2.36	4-13	Z= -3.58 **p=0.0003 (p=0.011)**
CSF-Insulin (n=24/18)	3.29[#]	3.5[#]	1.16[#]	2-5[#]	2.00[#]	2.00[#]	0.00	2-2[#]	Z= -4.01 **p<0.0001 (p=0.0001)**
P-Glucagon (n=24/19)	236.88	235	38.39	178-304	325.84	301	148.28	26-742	Z= 3.02 **p=0.001** (p=0.10)
CSF-Glucagon (n=24/18)	63.71	53	19.46	45-108	77.72	68	28.25	43-160	Z= 1.98 **p=0.047 (p=0.041)**

[a] Wilcoxon
[b] Adjusted for age and BMI (P-glucagon, logP-insulin and logCSF-insulin) and BMI (logCSF-glucagon). Significant group differences are bolded.
[#] Imputing 2 µU/ml

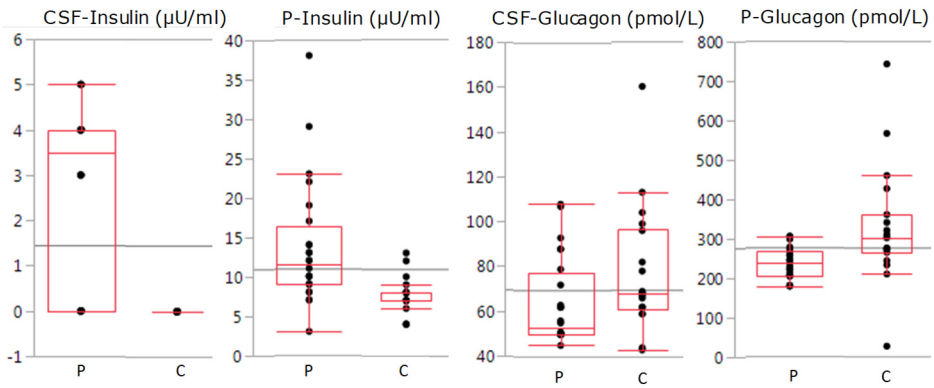


Figure 8. Insulin and glucagon levels in 24 patients in CSF and plasma and 18 (CSF), respective 19 (plasma) controls. Data points are overlapping as recorded without decimals and as all controls and 9 out of 24 patients fell below the limit of detection of the assay concerning CSF insulin. (196)

We adjusted for BMI and age if they were at least trend significantly correlated with insulin and glucagon in plasma or CSF. The regression models with suicide attempt, age and BMI as predictors of plasma insulin (RSq=0.45, RSq adjusted =0.41, DF=3, p<0.0001) and CSF-insulin (RSq=0.48, RSq adjusted =0.44, DF=3, p<0.0001) were significant. Suicide attempt (t-ratio=2.66, p=0.011) and BMI (t-ratio=3.39, p=0.0016) were significant unique predictors of plasma-insulin levels, but age was not. Only suicide attempt (t-ratio=4.67, p<0.0001) was significantly associated with CSF-insulin levels.

The regression model with suicide attempt, age and BMI as predictors of plasma glucagon was significant (RSq=0.19, RSq adjusted=0.13, DF=3, p=0.042), but neither suicide attempt, age, nor BMI were significantly associated with plasma glucagon levels. The regression model with suicide attempt and BMI as predictors of CSF-glucagon was significant (RSq=0.15, RSq adjusted=0.11, DF=2, p=0.043). Only suicide attempt was significantly associated with CSF glucagon (t-ratio=-2.12, p=0.041). (Table 3)

Plasma and CSF insulin correlated positively and plasma glucagon negatively with violence expression during adulthood in patients after suicide attempt and healthy controls.

Patients after a recent suicide attempt reported significantly higher levels (Z=-2.83, p=0.0047) of violence expression since age fifteen (KIVS) (mean 1.96, SD 1.22, median 2, range 0-5) than healthy controls (mean 0.47, SD 0.77, median 0, range 0-2).

Violence expression since age fifteen (KIVS) correlated positively with insulin levels in plasma (Spearman's rho=0.46, p<0.05) and in CSF (rho=0.50, p<0.05) and negatively with glucagon levels in plasma (rho=-0.39, p<0.05) but not in CSF (rho=-0.30, p<0.1) in patients and controls.

4.2 Neuroendocrine variation in relation to dimensional affective symptoms

4.2.1 Results of study I

Plasma oxytocin was not associated with depressive or anxiety symptoms in heterogeneous psychiatric outpatients.

In heterogeneous psychiatric outpatients the correlations between plasma oxytocin levels and depression severity (MADRS mean 10.6, SD 5.1 (n=99)) and anxiety (BSA mean 9.8, SD 4.8 (n=98) were not significant (Pearson´s r=0.05, p=0.65 (CI95 -0.16 to 0.26); r=0.04, p=0.73 (CI95 -0.18 to 0.25)).

4.2.2 Results of study II

Plasma glucagon was negatively correlated with depressive symptoms in patients after suicide attempt.

Depression severity (MADRS) in patients after a recent suicide attempt was significantly negatively correlated with plasma glucagon levels (Spearman's rho =-0.44, p=0.034).

CSF insulin was negatively associated with appetite in patients after suicide attempt.

Lower appetite levels (CPRS) were associated with higher CSF insulin levels (Spearman's rho = 0.43, p=0.039).

4.2.3 Results of study III

Plasma allopregnanolone, progesterone and estradiol were not associated with depressive or psychotic symptoms in women with postpartum affective disorder before or during estradiol treatment.

Neither at baseline nor after clinical recovery correlated depressive symptoms (MADRS) and psychotic symptoms (BPRS) in women with postpartum depression and psychosis with plasma allopregnanolone, progesterone or estradiol levels. (Table 4)

Table 4. Correlations between depressive (MADRS) and psychotic symptoms (BPRS) and allopregnanolone, progesterone, and estradiol levels at baseline and follow-up (Spearman rho).

	Allopregnanolone	Progesterone	Estradiol
MADRS baseline	0.09 (p=0.78) n=12	-0.18 (p=0.59) n=11	-0.33 (p=0.30) n=12
MADRS follow-up	-0.11 (p=0.73) n=12	-0.33 (p=0.32) n=11	-0.18 (p=0.57) n=12
BPRS baseline	0.60 (p=0.40) n=4	-0.50 (p=0.67) n=3	1.00 (p n.a.) n=4
BPRS follow-up	-0.78 (p=0.23) n=4	-0.54 (p=0.46) n=4	-0.26 (p=0.74) n=4

Changes in plasma allopregnanolone, progesterone and estradiol were not associated with change in depressive symptoms (MADRS) during estradiol treatment in women with postpartum affective disorder.

Change (measurement at follow-up minus measurement at baseline) in depressive symptoms (MADRS) in women with postpartum depression and psychosis was not associated with change in plasma levels of allopregnanolone (Spearman's rho -0.05, p=0.87, n=12), progesterone (rho -0.02, p=0.97, n=10) or estradiol (rho -0.29, p=0.37, n=12).

Change in psychotic symptoms was not assessed due to limited data in the bivariate correlations.

4.3 Neuroendocrine variation in relation to categorical diagnoses in populations with affective disorders

4.3.1 Results of study I

Plasma oxytocin levels did not differ in psychiatric outpatients depending on personality disorder diagnosis.

Categorical diagnoses were assessed to address potential confounding of associations between personality traits and oxytocin. Plasma oxytocin levels did not differ between patients with and without personality disorder diagnosis according to DSM-III (mean 19.3 fmol/mL, SD 7.4 vs. mean 18.8 fmol/mL, SD 7.6, t(df=84) =0.37, p=0.65, Cohen's d=0.07).

4.3.2 Results of study II

Plasma and CSF glucagon and insulin were not associated with a concurrent diagnosis of mood disorder in patients after suicide attempt.

Categorical diagnoses were assessed to address potential confounding of associations between personality disorder and insulin and glucagon. Among patients after suicide attempt, 50% fulfilled criteria for a diagnosis of affective disorder according to DSM-III (unipolar major depression (single episode or recurrent), bipolar disorder (latest episode depression), dysthymia). Plasma and CSF levels of insulin and glucagon were not significantly different in patients with and without diagnosis of affective disorder (all p-values above 0.11).

4.3.3 Results of study III

Patients with a diagnosis of postpartum depression and psychosis showed a trend for decreased plasma allopregnanolone levels compared with healthy controls but did not differ concerning plasma progesterone levels.

In women with an ICD-10 diagnosis of postpartum depression and postpartum psychosis, allopregnanolone plasma levels were significantly lower (Mann-Whitney-U test $p<0.001$) compared with healthy postpartum controls before starting estradiol treatment (table 5). After controlling for days since parturition in a multiple linear regression ($F(2,38)=9.90$, $p<0.001$, $R^2=0.34$, $R^2adj=0.31$), there was only a trend significant effect of patient status on allopregnanolone levels ($t\text{-ratio}_{patient}= -1.73$, $p=0.091$, $t\text{-ratio}_{time}= -1.12$, $p=0.271$).

Progesterone levels were similar in patients and controls in the unadjusted (Mann-Whitney-U test, $p=0.628$) and for time since parturition adjusted analyses (Multiple linear regression, $p=0.141$). (Table 5)

Table 5. Unadjusted and adjusted differences of allopregnanolone (nmol/L) and progesterone (nmol/L) levels between patients with postpartum depression and psychosis and healthy postpartum controls.

	Controls (n=28) Mean (SD), median (IQR)	Patients (n=14) Mean (SD), median (IQR)	p-value (adjusted)
Allopregnanolone			
- baseline	3.59 (3.93), 2.08 (5.48) (n=27)	0.58 (0.35), 0.48 (0.22) (n=14)	p<0.001 (p=0.091)
Progesterone			
- baseline	2.06 (2.20), 0.98 (2.07) (n=27)	1.64 (1.55), 1.20 (1.00) (n=13)	p=0.628 (p=0.141)

SD= Standard deviaion, IQR= Interquartile range

Plasma allopregnanolone was significantly lower during estradiol treatment while plasma progesterone levels did not differ from baseline levels.

In accordance with the treatment results in the larger original study populations (169, 170) the decline in depressive symptoms (MADRS) during estradiol treatment in postpartum depression was significant and implied remission (188). Due to few study persons, the considerate decline in psychotic symptoms (BPRS) was not significant but implied clinical recovery. Plasma levels of allopregnanolone decreased significantly from baseline while progesterone levels at follow-up were not different from baseline levels. (Table 6)

Table 6. Difference of allopregnanolone (nmol/L) and progesterone (nmol/L) levels in patients between baseline and follow-up.

	Patients baseline Mean (SD), median (IQR)	Patients follow-up Mean (SD), median (IQR)	Wilcoxon-signed-rank test
Allopregnanolone	0.58 (0.35), 0.48 (0.22) (n=14)	0.40 (0.11), 0.39 (0.13) (n=14)	**Z= -2.67, p=0.008** (n=14)
Progesterone	1.64 (1.55), 1.20 (1.00) (n=13)	1.11 (0.50), 1.00 (0.98) (n=13)	Z= -1.60, p=0.109 (n=12)
MADRS	41.5 (2.5), 41.0 (5) (n=12)	1.7 (1.7), 1.5 (3) (n=12)	**Z= -3.07, p=0.002** (n=12)
BPRS	77.5 (7.0), 78.5 (13) (n=4)	0.8 (1.5), 0 (2) (n=4)	Z= -1.83, p=0.068 (n=4)

Significant differences **bolded**

SD= Standard deviaion, IQR= Interquartile range

4.4 Neuroendocrine variation in relation to gender

4.4.1 Results of study I

Plasma oxytocin correlated positively with the personality trait impulsiveness in male but not in female psychiatric outpatients and the correlation in males remained trend significant after one month.

Gender was assessed to address potential confounding of associations between personality traits and oxytocin. Plasma-oxytocin levels did not differ significantly between males (mean 20.1 fmol/mL, SD 8.8, median 19, range 7-45) and females (mean 18.0 fmol/mL, SD 6.6, median 17, range 7-35) in psychiatric outpatients.

An ad-hoc analysis of gender dependent associations between plasma oxytocin and the personality factors impulsiveness and negative emotionality (that were significant predictors of oxytocin levels in the whole group (see 4.1.1)) showed that the positive correlation between plasma oxytocin and impulsiveness was significant in males (r=0.39, p=0.035, CI95 0.032-0.66, n=29) but not in females (r=0.09, p=0.49, CI95 -0.18-0.35, n=55). The correlations between negative emotionality and oxytocin were non-significant in males and females (Fisher's z=1.39, n.s.).

Plasma oxytocin measured after one month showed a trend for significant positive correlation with the impulsiveness factor in males (r=0.60, p=0.052, CI95 -0.003-0.88, n=11) but not in females (r=-0.13, p=0.55, CI95 -0.51-0.29, n=24) (Fisher's z=1.98, p<0.05, (two-tailed)). (Figure 9)

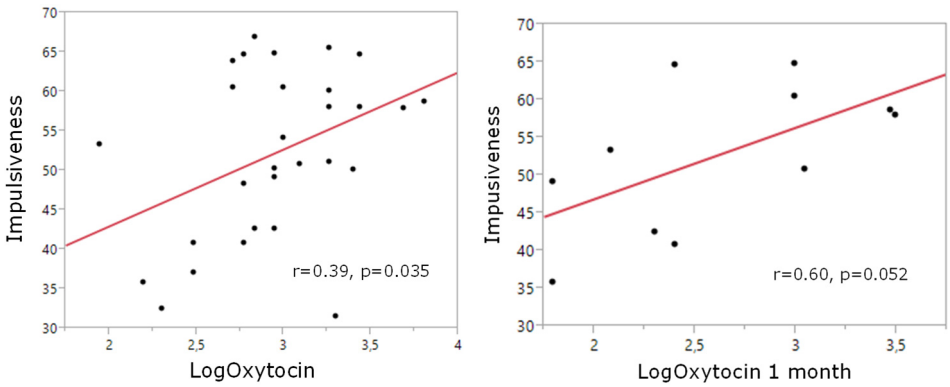


Figure 9. Correlations between the personality factor impulsiveness and log oxytocin in males at baseline and after one month (203).

4.5 Neuroendocrine interrelationships in populations with affective disorders

4.5.1 Results of study I

Plasma oxytocin levels at baseline were significantly positively correlated with levels after one month in heterogeneous psychiatric outpatients.

Plasma levels of oxytocin at baseline correlated significantly with levels after one month (rho=0.64, p<0.0001, CI95 0.35-0.78, n=35) in psychiatric outpatients. (Figure 10)

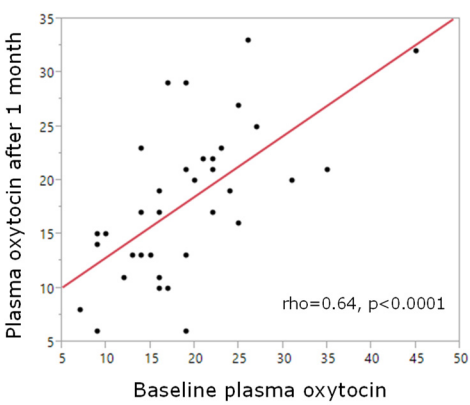


Figure 10. Correlations between plasma oxytocin at baseline and after one month in males and females (203).

4.5.2 Results of study II

There was no significant correlation between plasma and CSF levels of either insulin or glucagon. Negative correlations between insulin and glucagon were significant in both plasma and CSF.

In patients after suicide attempt and healthy controls, there was no significant correlation between plasma and CSF levels of either insulin (Spearman's rho 0.28, $p<0.1$) or glucagon (rho 0.24, n.s.). Insulin in plasma correlated negatively with glucagon in plasma (rho -0.33, $p<0.05$). Insulin in CSF correlated negatively with glucagon in CSF (rho -0.55, $p<0.001$) and plasma (rho -0.56, $p<0.001$).

4.5.3 Results of study III

Plasma allopregnanolone levels in patients with postpartum affective disorders showed a positive correlation with levels measured at follow-up during estradiol treatment.

Plasma levels of allopregnanolone in patients with postpartum depression and psychosis at baseline were significantly positively correlated (Spearman's rho 0.63, $p=0.017$) with levels at follow-up, assessed after mean 26 days of estradiol treatment.

Allopregnanolone was positively correlated with progesterone at baseline in the whole group and in controls. In patients, allopregnanolone correlated significantly with progesterone only at follow-up.

Plasma levels of allopregnanolone were significantly positively correlated with progesterone in the whole group (Spearman's rho 0.39, $p=0.014$) and in controls at baseline ($rho=0.57$, $p=0.002$). In patients, allopregnanolone correlated significantly with progesterone only at follow-up (rho 0.56, $p=0.045$) but not at baseline (rho 0.45, $p=0.12$).

The ratio between allopregnanolone and progesterone was significantly lower in patients with postpartum affective disorders than in healthy controls at baseline.

Patients with postpartum depression and psychosis had a significantly lower allopregnanolone progesterone ratio at baseline compared with healthy postpartum controls (Mann-Whitney U test $p<0.001$). The difference remained significant (t-ratio=-3.04, $p=0.004$) after adjustment for time since parturition (t-ratio=0.40, $p=0.70$) in a multiple linear regression ($F(2,36)=10.75$, $p<0.001$, $R^2=0.37$, $R^2adj=0.34$). (Table 7, Figure 11)

Table 7. Unadjusted and adjusted differences of the allopregnanolone/progesterone ratio between patients with postpartum depression and psychosis and healthy postpartum controls.

	Controls (n=26) Mean (SD), median (IQR)	Patients (n=13) Mean (SD), median (IQR)	p-value (adjusted)
Allopregnanolone/Progesterone ratio			
- baseline	**2.29 (2.33), 1.44 (1.59)**	**0.45 (0.19), 0.42 (0.24)**	**p<0.001 (p=0.004)**
- follow-up		0.40 (0.16), 0.34 (0.24)	

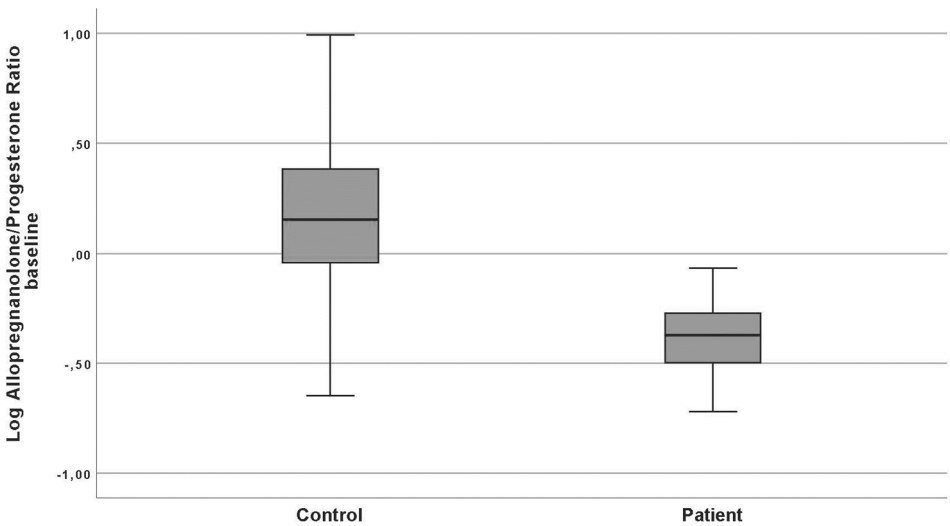


Figure 11. Log allopregnanolone/progesterone ratio in controls and patients with postpartum depression and psychosis at baseline.

The allopregnanolone/progesterone ratio assessed in patients at baseline did not differ from assessment after clinical recovery during estradiol treatment.

The allopregnanolone/progesterone ratio assessed at follow-up in patients during estradiol treatment was not significantly different from the baseline measurement (Wilcoxon signed-rank test Z= -0.63, p=0.530, n=12) (table 7).

The allopregnanolone/progesterone ratio showed no correlation with depressive or psychotic symptoms at baseline or after clinical recovery in women with postnatal affective disorders.

In patients, the allopregnanolone/progesterone ratio assessed at baseline and follow-up showed no significant correlation with concurrent depressive (MADRS) (baseline: Spearman's rho 0.074, p=0.829, n=11; follow up: rho 0.552,

p=0.078, n=11) or psychotic (BPRS) symptoms (baseline: rho 1.0, p n.a., n=3, follow-up: rho 0.258, p=0.742, n=4).

Change in allopregnanolone/progesterone ratio from treatment to follow-up was not associated with change in depressive symptoms during estradiol treatment in women with postpartum depression.

In women with postpartum depression change in the allopregnanolone/ progesterone ratio from baseline to follow-up during estradiol treatment was not correlated with change in depressive symptoms (MADRS) (Spearman's rho 0.142, p=0.695, n=10).

Change in psychotic symptoms was not assessed due to limited data in the bivariate correlations.

4.6 Summary of main findings

4.6.1 Study I

- Plasma oxytocin was positively correlated with personality traits of impulsiveness (monotony avoidance) and negative emotionality (psychic anxiety) in a population of heterogeneous psychiatric outpatients.
- Plasma oxytocin levels were stable over one month.
- The positive correlation between oxytocin and impulsiveness was significant only in male patients and it remained trend significant after one month.
- Plasma oxytocin levels were not associated with diagnosis of personality disorder or symptoms of anxiety or depression.

4.6.2 Study II

- Plasma and CSF insulin were higher and CSF glucagon levels were lower in a population of heterogeneous psychiatric patients assessed shortly after a suicide attempt compared with healthy controls.
- Plasma and CSF insulin correlated positively and plasma glucagon negatively with degree of violence expression during adulthood in patients and controls.
- Plasma-glucagon levels were negatively associated with depressive symptoms and CSF-insulin levels were negatively associated with appetite in patients.
- Plasma and CSF glucagon and insulin were not associated with a concurrent diagnosis of affective disorder.

4.6.3 Study III

- Patients with diagnosis of severe postpartum depression and psychosis showed a trend for decreased plasma allopregnanolone levels compared with healthy controls.
- The ratio between allopregnanolone and progesterone was significantly lower in patients than in healthy controls.
- Plasma allopregnanolone was significantly lower after four weeks of estradiol treatment when patients had recovered clinically.
- The allopregnanolone/progesterone ratio assessed in patients at baseline did not differ from assessment during estradiol treatment.
- Allopregnanolone was positively correlated with progesterone at baseline in the whole group and in controls. In patients, allopregnanolone correlated significantly with progesterone only at follow-up.

5. DISCUSSION

5.1 General discussion

The aim of this thesis was to investigate behavioral endophenotypes in affective disorders in relation to three endocrine systems. We focused on behavioral endophenotypes in two populations with affective disorders with a high degree of comorbidity that have biologically valid associations with potential dysregulations in two endocrine systems - social behavior in relation to the oxytocin system and aggressive-impulsive behavior in relation to insulin and glucagon. Evidence from these studies points to associations between neuroendocrine variation and underlying trait behavioral endophenotypes rather than state presentations of affective disorders. As expected, we found little evidence for associations between categorical psychiatric diagnoses and neuroendocrine variation in these populations (study I and II). In study III, we chose to focus on a homogenous postnatal population with an assumed reproductive hormonal sensitivity. Even here, we found evidence for hormonal dysregulation associated with potential trait rather than state aspects of affective disorders.

5.2 Oxytocin

5.2.1 Main findings of study I

Half of the patients in this large cohort of heterogeneous psychiatric outpatients with diminished functioning fulfilled criteria for personality disorders, in line with other studies in psychiatric outpatients (204). Dysregulation in the oxytocin system has been associated with diminished social and interpersonal function (90) but we found no evidence for variation in peripheral oxytocin levels relative to a diagnosis of personality disorder. Dysregulation of oxytocin in patients with personality disorder has been found in relation to underlying aspects such as aggression (110) and childhood trauma (112). Personality disorder diagnosis per se, as assessed in our study, is probably too heterogeneous in regard to social behavioral difficulties. A rather dimensional nature of impairment may be difficult to detect with categorical personality disorder assessment (205). We though found significant associations between oxytocin dysregulation and two personality traits relevant for social behavior. Impulsiveness and negative emotionality accounted for a significant part of the variance in plasma oxytocin levels.

Oxytocin was positively associated with impulsiveness and more specifically the underlying trait of monotony avoidance that has been found to correlate with the extent of leisure activities in depressed patients (206). Monotony avoidance in

the KSP reflects inclination to excitement and change and avoidance of routine activities. It mirrors novelty and sensation seeking which are related to extraversion (207) and impulsivity (208). The positive association between monotony avoidance and oxytocin is partly in line with the studies of Bell et al. (118) - who reported a positive correlation with novelty seeking and reward dependence in patients with depression - and of Andari et al. (119) and DeDreu et al. (120) who reported positive associations with novelty seeking and extraversion in healthy populations. However, studies in healthy women have reported negative association between plasma oxytocin and monotony avoidance (123) and novelty seeking (122). When we re-analyzed the data dependent on gender the positive association between oxytocin and impulsiveness was only significant in males and despite a limited number of individuals in the follow-up assessment after one month this association remained trend significant. Due to different release patterns of hormones and interactions with fluctuating gonadal hormones that interact with oxytocin release (209) analyses in women are difficult without control for hormonal status and treatment.

In this study, plasma oxytocin levels were also positively associated with the personality factor negative emotionality and more specifically the underlying trait of psychic anxiety. The KSP psychic anxiety subscale reflects social and cognitive dimensions of anxiety proneness which may explain the lack of association between oxytocin and measurements of anxiety with the BSA that does not include social aspects of anxiety (186). Psychic anxiety has been associated with interpersonal problems (210). Higher social anxiety symptoms were positively associated with oxytocin in patients with social anxiety disorder (211). But several studies have found negative associations between trait anxiety in women (123-125), men (107) and children (126). These differences may relate to different functions of oxytocin dependent on gender (212) or current and historical context (e.g. social salience (213), stress predictability (115), attachment development (214), childhood trauma (112)). The biological function of the oxytocin system seems to motivate, mediate and reward behaviors and cognitions that promote relationships between individuals but depending on the relationship this can imply an increase in anxiety and motivation to solve negative interactions or a decrease in anxiety and promotion of social affiliation (87). Oxytocin is released dependent on socio-emotional stress (83) and an increased release in response to psychosocial stressors has been associated with childhood trauma (113). Findings in our study may imply that individuals with personality traits oriented towards novel situations have difficulties to habituate anxiety through social affiliation (215) during stress associated with mental illness.

5.2.2 Strengths & limitations of study I

The strengths of this study are a rather large population of heterogeneous and diagnostically well characterized psychiatric outpatients with diminished functioning. Only few patients had to be excluded due to concurrent medication which has been found to affect plasma oxytocin levels (92). Data on smoking status revealed that smoking is a significant confounder of plasma oxytocin levels as reported by Chiodera et al. (216). Personality traits were assessed with the KSP, a measure constructed for assessment of personality in biological research (190), and shown to measure longitudinally stable personality traits (192, 193). Fasting plasma oxytocin levels were assessed after extraction with an independently developed RIA, validated in different populations (69, 76, 109, 217) and levels were similar to those reported by other groups using the same method. RIA after extraction is considered gold standard compared to the faster ELISA methods (218). Assessments of oxytocin were reliable according to multiple measurements including reassessment after one month.

Limitations of this study in regard to the population are that some patients already had a follow-up contact at the outpatient department and despite being medication-free may psychological or social support have affected the oxytocin levels. In regard to female patients, we lacked data on menstrual cycle or postmenopausal data and contraception. The study lacked a control group and simultaneous measurement of oxytocin and personality traits occurred only once. A major limitation is that only peripheral oxytocin levels were assessed and related to presumed behavioral effects of the central nervous system. Oxytocin seems to cross the blood brain barrier only to a very limited amount (83) and a relationship between plasma and CSF levels probably implies simultaneous co-release. Furthermore, intracerebral release can also occur independently of coordinated co-release in certain brain regions, thus even CSF levels only approximate central actions (83). To some degree a relationship between central and peripheral levels has been found in humans (126, 219) and peripheral administration leads to increased levels of both peripheral and CSF levels in sheep (220). Increasing levels of peripheral oxytocin have been found to affect personality traits during breastfeeding (69); behavioral effects were also reported after peripheral administration (221) potentially mediated via vagal afferences (222). Finally, no assumptions on causality of variations in oxytocin on personality traits can be made due to the cross-sectional study design but it is unlikely that hormones cause personality; endocrine variation can rather be seen as an expression for central control systems that affect stable socio-emotional, behavioral and endocrine outputs (69).

5.3 Insulin and glucagon

5.3.1 Main findings of study II

Patients in this study had about one week prior to assessment made a suicide attempt and 44% fulfilled criteria for affective disorders. We could not find any evidence that basal levels of plasma and CSF insulin and glucagon differed depending on a concurrent diagnosis of affective disorder. Several studies have reported glycemic dysregulation in patients with affective disorder diagnoses during OGTT challenges (137-140). But evidence for baseline dysregulation of insulin and glucagon levels is limited, and also Westling et al. (145) found similar levels in patients after suicide attempt irrespective of mood disorder diagnosis.

In comparison with healthy controls, patients had higher levels of peripheral and CSF insulin and lower levels of CSF glucagon. This was most apparent regarding CSF insulin levels as all controls had undetectable levels. Patients had, compared with controls, significantly more often used severe forms of violence since age 15. The mean and median of two points in the KIVS refers to "Occasionally smacked partner or child. Fought when drunk" and the range in violence in patients included also most severe expressions: "Killed or caused severe bodily harm. Repeated instances of violent and sexual abuse. Convicted of crimes of violence". In comparison, violence in controls ranged only to two points with a median of 0. A study in patients after suicide attempt reported similar distributions for controls (63) but patients had lower levels of expressed adult violence. But patients in their study who completed suicide (about 5% of the study population) reported significantly higher levels of expressed adult violence. In this cohort about 20% of patients had committed suicide until 2010 (223), thus potentially representing a more violent subpopulation of patients with suicidal behavior. Hormone levels in patients and controls correlated significantly with degree of expressed violence, positively for insulin in plasma and CSF and negatively for glucagon in plasma. Associations between violent behavior and insulin and glucagon have been reported in both suicidal and forensic populations. Patients with violent compared to non-violent suicide attempts had higher CSF insulin levels (145) and reported higher expression of interpersonal violence (63). Higher plasma insulin levels were associated with risk for violent re-offense in male forensic patients with alcohol disorders (150). Lower plasma glucagon levels have been reported in violent offenders compared with healthy controls (149). However, in women with deliberate self-harm, plasma insulin and glucagon levels did not differ from healthy controls (144). In healthy women, an inverse association between plasma insulin and aggression related personality traits has been reported (69). These discrepancies may be associated with differences in severity of suicidal behavior and/or gender. Svanborg et al. (143) did not find any associations between personality traits and plasma glucagon in psychiatric outpatients but reported fasting glucose levels in the lower normal range in association with impulsive traits. Hypoglycemic tendencies have also been found

in forensic violent populations (148, 149) and skipping meals in adolescents was associated with suicidal ideation and depressive symptoms (224). It is unclear if aggressive personality traits correspond to behavioral expression of violence or if there are differences in the propensity to act on aggressive thoughts in healthy compared to diseased populations. Aggressive-impulsive personality traits have been suggested to have a mediating role in the diatheses from predisposing to proximal factors in suicide risk of individuals (225). Early developmental stressors increase risk for psychopathology, violent and suicidal behaviors (60, 226, 227). A hyperinsulemic metabolic pattern has been associated with early developmental exposures such as malnutrition or increased exposure to glucocorticoids (228, 229). Restricted fetal growth has been found to be a risk factor for suicide attempt and completion (230) and for violent suicide attempts in men (231). Developmental stressors may affect neuroendocrine development and function in several allostatic systems (232) which have parallel effects on mental and metabolic health (141). Impulsive aggression in suicidal behavior is associated with reduced central serotonergic activity (233). Serotonin regulates insulin (234) and glucagon secretion (235) and decreased glucose and glucagon release has been found in association with a loss of function mutation in the serotonin receptor 2 (134). According to prior publications in this study population, patients had decreased oxytocin levels and female patients had decreased 5-HIAA in CSF (109, 181). Serotonin and oxytocin affect insulin and glucagon levels through actions at the dorsal vagal complex in rats (236). Thus, hypersecretion of insulin and hyposecretion of glucagon with risk for hypoglycemic states and associated impulsivity and aggression may mirror dysregulation in the autonomic nervous or other central nervous systems (69).

5.3.2 Strengths & limitations of study II

The strengths of this study are a well characterized medication-free population of patients assessed shortly after a suicide attempt with high risk for suicide completion (181). Insulin and glucagon were assessed in both plasma and CSF also in healthy controls that were similar to patients in regard to BMI.

Limitations regarding the study population that might affect generalizability are a relatively small sample size (which is often the downside in studies of patients with severe disorders) with increased risk for type II errors, imprecise estimates and inflated effect sizes. We lacked information on the total number of eligible patients during the study period. The proportion of females is relatively low considering that suicide attempts are more common in women but the gender distribution may be related to severity of suicidal behavior. A further potential selection bias may apply also to controls as healthy participants undergoing experiments implying lumbar puncture have been found to have more impulsive personality traits (237). We lacked data on smoking status and the control group was significantly younger which we adjusted for in the analyses. Only the patients were hospitalized which may have influenced hormonal variation due to

differences in nutrition and activity levels (238). Violent behavior was assessed retrospectively with risk for differential recall bias in healthy and controls. We had no glucose levels or OGTT measurement for further assessment of metabolic function. We did not analyze potential associations with method of suicide, gender or suicide completion to avoid spurious positive findings due to multiple analyses. We cannot exclude that increased sympathetic activity in healthy due to stress in the situation of lumbar puncture leads to an increased inhibition of insulin secretion (239). We found no correlation between central and peripheral levels of the investigated hormones. According to the literature the insulin measured in CSF is most likely of peripheral origin (even though central secretion might occur) but it is not clear how insulin from the peripheral circulation enters the CSF and to what extent CSF levels can approximate brain levels (240). A gradient of 10-20 times higher plasma than CSF levels has been reported which is consistent with our findings (240). As all 19 controls and 9 out of 24 patients had undetectable CSF insulin levels, we aimed to impute the detection limit of the assay (0.2 mikroU/ml=2 mMol/L) for statistical analysis. By mistake we imputed 2 instead for 0.2 (as mikroU/ml values were used in the study) and thus employed a more conservative threshold than recommended for handling of data below detection level (detection level/sqr²) (198). Considering that CSF-insulin levels in controls lie between 0 and 0.2 mikroU/ml and in patients between 0 and 5.0 mikroU/ml, our approach to impute 2 instead of level of detection 0.2 leads to an absolute smaller, but still highly significant Z-value (-4.01 instead of -4.385). Even though the lower bound of the distribution and also the upper bound in controls cannot be estimated, the distributions are clearly different from each other and we thus chose to report p-values. Unfortunately, the mean, standard deviation and range for CSF insulin in patients (196) were reported without imputation even though the statistical analyses had been made with the imputed values. Thus the originally reported levels were correct but the presentation was confusing and we decided to publish a corrigendum with data shown as in table 3 in this thesis (section 4.1.2) (197). In general, measurement of insulin with RIA seems to be similar to ELISA (241) but may differ concerning glucagon measurements (242). We found higher levels of glucagon in relation to other studies. As the levels are similar to those reported by Svanborg et al. (143) who used the same method in the same laboratory, these discrepancies may be due to the binding potential of the antibody employed that did not discriminate between glucagon and glucagon-like peptides. This did though not affect interpretation of the differences between healthy and control subjects. Finally, this is a cross sectional study and no assumptions on causality can be made.

5.4 Allopregnanolone, progesterone, and estradiol

5.4.1 Main findings of study III

In women with severe postnatal affective disorders we found significantly decreased peripheral allopregnanolone levels compared with healthy postpartum controls. Gonadal steroids decline quickly and considerately after parturition (243) and as the healthy controls were assessed significantly earlier this impacted the findings and the time adjusted difference fell below the significance level ($p=0.091$). Studies assessing controls and postnatal affective patients within similar postnatal timeframes could neither find differences between peripheral allopregnanolone levels and depressive states (173, 174). We could not find differing progesterone levels between patients and controls similar to prior reports (173). Allopregnanolone levels declined significantly in patients during estradiol treatment and the positive correlation between baseline and follow-up levels ($r=0.63$) implies a consistent reduction for the individuals in the study group. It is possible that this difference resulted from the physiological decline, but the majority of patients were included about three months after birth when levels have already stabilized. Allopregnanolone levels were comparable to luteal phase levels of menstruating women (244) and we found no association with time in patients. Estradiol could have suppressed allopregnanolone and it is theoretically possible that levels would have increased after termination of estradiol treatment but other studies suggest increasing levels in response to estradiol treatment (245). By the time of follow up, patients had recovered clinically but as neither baseline nor follow-up allopregnanolone nor change in levels was associated with mental symptoms we cannot conclude that the decline was associated with mood stabilization. The treatment effect reported in the original studies were likely associated with decreased treatment, as relapse or decreased effectiveness were associated with decreased estradiol serum levels (182, 183). But estradiol levels were not associated with depressive or psychotic symptoms in this subsample. As depressive and psychotic symptoms fell into a very narrow range both at baseline and after recovery this may though have affected the analyses.

Decreased levels of allopregnanolone have been associated with mood stabilization in premenstrual dysphoric disorder (PMDD) where negative mood symptoms and allopregnanolone seem to have an inverted U shape relationship (246). Such bimodal mood effects of allopregnanolone in PMDD have been associated with changes in GABA receptor sensitivity and plasticity (170, 247). Postpartum depression and PMDD may be part of a reproductive subtype of depression characterized by a distinct biological vulnerability to hormonal fluctuation (163) and associated with dysregulations in $GABA_A$-receptor plasticity (248). As gonadal steroids and their metabolites affect $GABA_A$-receptor composition (247), it is possible that estradiol treatment or decreased levels of

allopregnanolone may be associated with $GABA_A$-receptor changes, affecting neurotransmission and mood stabilization (248).

Decreased allopregnanolone levels may be a trait marker for women with severe postnatal affective dysregulation during periods of stress or hormonal change. Neurosteroids are involved in the homeostatic control of the HPA-axis (160) and failure to increase allopregnanolone may exacerbate HPA dysregulation which has potential pathologic implications for postpartum affective disorders (167). Most prior studies that investigated allopregnanolone in perinatal women have excluded patients who are at high risk for postnatal affective dysregulation, i.e. patient with prior or current severe depressive, bipolar, psychotic or suicidal episodes. Some of the studies that also included high-risk patients found decreased allopregnanolone levels during pregnancy (175, 249) and associations between change of allopregnanolone levels during pregnancy and epigenetic variation in estrogen responsive genes (250). The lack of correlation between progesterone and allopregnanolone during the symptomatic state as well as the decreased allopregnanolone progesterone ratio may suggest changes in allopregnanolone biosynthesis. Progesterone is metabolized into allopregnanolone by the enzymes 5-alpha-reductase and 3-alpha-hydroxysteroiddehydrogenase - the latter has been associated with depressive symptoms during pregnancy (176) and with paranoid ideation in women with bipolar disorder (251). The lack of correlation in the symptomatic state was in line with results from women with postpartum blues (172) and correlation in the recovered state may suggest a more efficient metabolism of progesterone that may be related with estradiol treatment as it affects activity of both enzymes (245). But the allopregnanolone progesterone ratio did not change during estradiol treatment. This may be related to a risk trait for affective postnatal dysregulation as Kimmel et al. (177) found that the association between estradiol levels and the allopregnanolone progesterone ratio was dependent on methylation at the oxytocin receptor (that was associated with childhood abuse) in pregnant women at risk for development of postpartum depression.

5.4.2 Strengths & limitations of study III

The strengths of this study are that the study group consisted of women with severe postpartum onset affective disorders that were part of two larger cohorts which included patients with treatment resistance to pharmacologic and psychotherapeutic interventions and a few of them had a history of recent suicide attempts (182, 183). None of the women resumed menstruation over the study period. We were able to assess neurosteroids in relation to high dose estradiol exposure longitudinally and had follow-up clinical data when patients had recovered clinically. We were able to use data from neurosteroid assessments in well characterized healthy controls from another study as the original study populations did not have a control group.

Limitations in regard to the study groups are that only a small subsample of the original groups with postpartum depression and psychosis could be analyzed based on plasma sample availability and that also the original cohorts were small with lack of information regarding the total number of eligible patients during the study period. Considering that women had severe depressive and psychotic symptoms, this cohort is though probably representative of patients with severe postnatal affective disorders. These are difficult to recruit based on the literature which comprises mainly studies of moderate postpartum depression. As data on breastfeeding were not available in the patients, we were not able to match the controls. We had no data on smoking status, blood pressure, pregnancy weight gain and BMI which can confound allopregnanolone levels (176, 252-254). Controls were assessed significantly earlier during a period when hormone levels are still increased after birth. We could not confirm whether the four patients that tapered neuroleptics during the first week or the two patients that started antidepressants after three weeks were part of our subsample. Thus, we cannot fully exclude that the pharmacological agents affected the neurosteroid levels. Allopregnanolone in patients was analyzed in samples that remained frozen for several years. Even though neurosteroid levels seem to be stable over time according to experience we cannot exclude that this affected the integrity of the samples. Progesterone analysis in patients and controls was performed in different laboratories, and despite employing immunoassays in both cases, levels may differ. Baseline levels of allopregnanolone were similar to those reported with RIA at approximately the same postnatal time points (174) while progesterone levels in our study were higher in patients and lower in controls than those reported by Pearson Murphy et al. (174) at 6 weeks and 2-7 days, respectively. Only peripheral levels were assessed. Neurosteroids cross the blood brain barrier easily and most but not all studies have reported similar plasma and CSF concentrations (159). The study was not placebo controlled and effects of estradiol on mood and neurosteroids cannot be assumed to be causal. Furthermore, estradiol affects multiple mood regulating systems (e.g. HPA-axis, immune, and serotonin system (167)) and potential treatment effects of estradiol would unlikely affect only neurosteroids. We did not correct for multiple comparisons in accordance with reasoning from Rothman (255) as the small sample size would likely have increased the type II error which would have precluded potentially relevant findings, motivating further research of neurosteroids in severe postnatal affective disorders.

5.5 Neuroendocrine dysregulation in affective disorder

The investigated hormones in this study are associated with each other and these interdependencies have probable implications for affective dysregulation. Oxytocin and allopregnanolone have similar actions in relation to their anxiolytic, sedative, anti-nociceptive and anti-aggressive effects. Oxytocin has a positive acute relationship with insulin, glucagon and glucose (256) though chronically increased levels of oxytocin lead to decreased insulin levels, associated with potential changes in alpha-adrenoceptor functioning (76). Furthermore, estradiol has estradiol been found to impact oxytocin and gastrointestinal hormone secretion. Estrogen stimulates release of oxytocin (85) and the anxiolytic effect of oxytocin is enhanced by estrogen (257). But progesterone and allopregnanolone seem to modulate this relationship (258). All hormones exert effects on the HPA-axis, autonomic nervous system and on several neurotransmittor systems implicated in affective disorders.

Certain hormonal patterns may be associated with maladaptive behavioral endophenotypes in affective disorders. Due to the hormonal interrelations a tendency for decreased levels of oxytocin, glucagon, and estradiol and increased levels of insulin and changes in neurosteroid metabolism may support a pattern consistent with central stress dysregulation in subpopulations with affective disorder. Such dysregulated hormonal patterns may be of genetic origin or secondary to prenatal or early life events that impact central affective regulation (259). The population of patients with suicide attempt (study II) has been investigated in other studies in relation to endocrine, serotonin and HPA variation. Decreased oxytocin levels were found in suicide attempters that had been revictimized (223) and were associated with higher suicide intent in males (109). Patients had higher cortisol levels and female patients had lower 5-HIAA levels (181). In male patients MAO-B levels were negatively associated with violence expression and exposure (260). Other studies in patients after suicide attempt found higher levels of extroversion related personality traits in males (261). Few studies have investigated gonadal steroids in suicidal patients but indirect associations with decreased estradiol and progesterone (262) and allopregnanolone metabolism (263, 264) have been reported. Some of these factors have been implied in completed suicide or reattempts. There are only few studies in severe postnatal affective populations but some of the findings may support similar patterns regarding oxytocin (265), gonadal steroids (266), personality traits (267) and dysregulation in central stress regulating systems (268). In order to further explore such potential patterns it would be necessary to have larger sample sizes with focus also on gender differences

6. CONCLUSION

6.1 Conclusions and clinical implication

Neuroendocrine variation was associated with underlying behavioral endophenotypes in three different cohorts of patients with affective disorders. Hormonal variation pointed toward trait rather than state expressions of affective behavior, thus constituting potential vulnerability markers for affective dysregulation.

Peripheral oxytocin levels were associated with personality traits that are relevant for social functioning in psychiatric outpatients - impulsiveness, monotony avoidance, negative emotionality and psychic anxiety. These personality traits were independent predictors of oxytocin levels and explained together with smoking 9% of the variation in plasma oxytocin. Considering that patients in this cohort had diverse psychiatric disorders this finding suggests clinical relevance in regard to differences in social sensitivity and motivation irrespective of categorical psychiatric disorder but potentially dependent on gender. Larger effects of personality traits on peripheral oxytocin levels have been reported in studies investigating gender separately and including measures of state anxiety, HPA-reactivity and potential underlying mediating factors such as attachment and early life adversity (269, 270). Based on this study peripheral oxytocin levels may be a biomarker related to impulsiveness in men with clinical implications e.g. concerning suicidality, substance abuse disorders, depressive phenotypes (271), or help seeking behavior (272). Only few studies have investigated effects of intranasal oxytocin in affective disorders - as personality traits have been found to moderate effects in healthy populations also effects in clinical populations might differ depending on these personality traits. Also, effectiveness of psychotherapeutic treatment may differ depending on socially relevant personality traits (273).

Insulin levels were increased, and glucagon levels were decreased in patients after suicide attempt compared with healthy controls. Suicide attempt uniquely explained 44% of the variation in insulin levels irrespective of age or BMI but due to small sample size the size of the effects can be assumed to be inflated. Patients had expressed higher levels of violence during adult life than controls, which was associated with higher insulin and lower glucagon levels. The findings confirm and extend prior findings of dysregulations of insulin and glucagon in association with suicidal and violent behavior and may imply insulin as a biomarker for interpersonal and self-directed violence in subgroups of patients with suicidal behavior. A potential tendency for hypoglycemia can be of developmental origin and may have clinical implications in regard to need of regular nutrition. Metabolic dysregulation in affective disorders seems to have implications not

only for mortality due to suicide but also due to metabolic disorders and should be taken into account in clinical practice.

Peripheral allopregnanolone levels decreased during treatment with estradiol and do not seem to have a mediating role in estradiol treatment effects in severe postnatal affective disorders. We found a decreased allopregnanolone progesterone ratio in patients, implying potential differences in progesterone metabolism, that was unrelated to symptomatic state and which may be a trait marker for women at risk of severe postnatal affective dysregulation. Intravenous allopregnanolone treatment is forecasted to receive approval within the coming months by the Food and Drug administration as treatment for postpartum depression. If findings of potential dysregulations in allopregnanolone metabolism in this study are associated with the severity of affective spectrum dysregulation clinical effects may differ compared to phase 3 trials that excluded patients with bipolar disorder and psychotic and suicidal symptoms.

6.2 Implications for future research

Not only the behavioral but also the biological expressions of affective disorders are utterly complex and in constant interaction with physical and social environments. Classic reductionistic explanations will most probably not be found and eventual etiopathogenetic explanations will likely include behavioral, environmental and biological variables from several levels of analysis. Despite these challenges, improvements in identification, treatment selection, and prognosis can be achieved even without concise knowledge of biological and genetic mechanisms through identification of biomarkers and endophenotypes. Like in complex medical disorders the use of combinations of biomarkers assessed at different biological levels, and combined with information on exposures, signs, symptoms and course of disease may not only optimize patient outcomes but also generate knowledge for discoveries concerning etiopathogenetic pathways.

The assessment of endocrine factors in psychiatric research has shown that valid findings are dependent on thoroughly characterized study populations in regard to physical and environmental contexts. Especially gender has important implications for several endocrine factors and might better be taken into account by gender stratified studies. Furthermore, can study designs that employ withdrawal and/or substitution designs, or provocation methods (both physical and neuropsychological) inform on relationships between phenotypes and endocrine system functioning. Different methods of hormonal analyses can result in large discrepancies between studies and gold standard definitions would be useful to compare results across studies. For only few hormones relationships between peripheral and CSF levels are known and even CSF levels and the regional distribution in the central nervous system can differ. Thus, CSF levels, neuroimaging and animal studies are necessary to relate behavioral endophenotypes with brain functioning. Many hormones have close associations

with molecular functioning in several other systems and epigenetic variation can have profound effects on behavioral responses.

Specifically, findings from study I raise questions concerning treatment effects dependent on personality traits associated with oxytocin variation. Findings from study II may support further research of autonomic and metabolic dysregulation and associations with developmental and epigenetic factors in suicide research. In postnatal affective disorders (study III) a greater focus on the most severe forms is warranted, not only because of their severe clinical implications but also as clinical risk factors for severe affective dysregulation are known which occurs in a specific time frame during natural hormonal variation. In this context important interactions with other systems can be investigated that have potential to result in more stratified treatment approaches.

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