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NEUROENDOCRINE STUDIES IN SUICIDE ATTEMPTERS AND IN HYPERSEXUAL DISORDER

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NEUROENDOCRINE STUDIES IN SUICIDE ATTEMPTERS AND IN HYPERSEXUAL DISORDER

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Early life adversity is associated with increased risk of high psychiatric disease, suicidal behavior as well as risky sexual behavior in adulthood. Altered functioning of several neurobiological systems, like the serotonergic system and the hypothalamic-pituitary-adrenal axis associated with suicidal behavior, may stem from both genetic and developmental causes. Adversity in early life has developmental effects on these systems that persist into adulthood. Other neuroendocrine systems such as oxytocin regulating social behavior and DHEA-S with multiple biological actions might also be implicated in suicidal behavior. Hypersexual disorder includes features of impulsivity, addiction, sexual desire deregulation and some aspects of hypersexual behavior are also associated with more suicidality. Neurobiological alterations in patients with hypersexual disorder are for the moment largely unknown.

The aim of this PhD project was to investigate neuroendocrine systems with focus on HPA axis, Oxytocin and DHEAS in suicide attempters and in patients with Hypersexual Disorder. Focus was on early life adversity and violent behavior in relation to neuroendocrine biomarkers.

Studies I-III: The clinical cohort consists of 28 medication free suicide attempters and 19 healthy volunteers who participated in this cross sectional and longitudinal study. CSF and plasma basal levels of oxytocin, cortisol, DHEA-S and CSF 5-HIAA levels were assessed. Suicide intent, depressive symptoms, interpersonal violence in childhood and adult life as well as childhood emotional climate were assessed with psychometric rating scales. All patients were followed up for cause of death.

Results: Suicide attempters showed a trend for lower CSF oxytocin levels compared to healthy volunteers, CSF and plasma oxytocin was significantly negatively related to suicide intent especially in men and showed a trend for negative correlation with lifetime violent behavior. Revictimized suicide attempters had lower plasma oxytocin and a more negative childhood emotional climate compared to non revictimized suicide attempters.

Higher CSF and plasma cortisol levels were also present in suicide attempters compared to healthy volunteers, whereas CSF DHEA-S levels were higher in male suicide attempters and CSF 5-HIAA levels lower in female suicide attempters respectively. CSF cortisol/DHEAS

ratio was inversely correlated with exposure to interpersonal violence as a child adjusted for age, gender and depression severity in a regression analysis.

In suicide prediction, suicide victims tended to have low CSF 5-HIAA and high CSF cortisol and suicide victims that were abused in childhood had higher CSF cortisol compared to suicide victims with low exposure to interpersonal violence as a child. Oxytocin or DHEA-S levels did not differ in suicide victims compared to survivors.

Study IV: The study includes 67 male patients with hypersexual disorder and 39 healthy male volunteers. Basal morning plasma levels of cortisol and ACTH were assessed and the dexamethasone (0.5 mg) suppression test was performed with cortisol and ACTH measured post dexamethasone administration. Multiple psychometric rating scales were used for assessing sexual behavior, depressive symptoms and early life adversity.

Results: Men with hypersexual disorder had higher DST-ACTH levels and were more often DST non-suppressors compared to healthy volunteers. Men with hypersexual disorder reported more depressive symptoms and early life adversity than healthy volunteers. Early life adversity and hypersexual behavior were negatively correlated with HPA axis measures in patients. In the regression analyses the diagnosis of hypersexual disorder was significantly associated with both DST non-suppression and higher plasma DST-ACTH even when adjusted for childhood trauma.

Conclusion: Early life adversity, interpersonal violence and suicide intent are risk factors for suicide and oxytocin by modulating prosocial behaviors might thus be protective in individuals with high suicide risk. The role of DHEA-S in suicidal behavior is proposed to be through the effects of early life adversity and its implication to the allostatic load while other possible mechanisms cannot be excluded. The study on male patients with hypersexual disorder reports for the first time HPA axis dysregulation.

LIST OF SCIENTIFIC PAPERS

- I. Jokinen J, **Chatzittofis A**, Hellström C, Nordström P, Uvnäs-Moberg K, Åsberg M. Low CSF oxytocin reflects high intent in suicide attempters. *Psychoneuroendocrinology*. 2012;37:482-490.
- II. **Chatzittofis A**, Nordström P, Hellström C, Arver S, Åsberg M, Jokinen J. CSF 5-HIAA, Cortisol and DHEAS levels in Suicide Attempters. *European Neuropsychopharmacology*. 2013;23(10):1280-1287.
- III. **Chatzittofis A**, Nordström P, Uvnäs-Moberg K, Åsberg M, Jokinen J. CSF and plasma oxytocin levels in suicide attempters, the role of childhood trauma and revictimization. *Neuro Endocrinology Letters*. 2014; 35(3):213-217.
- IV. **Chatzittofis A**, Arver S, Öberg K, Hallberg J, Nordström P, Jokinen J. HPA axis dysregulation in patients with hypersexual disorder. *Psychoneuroendocrinology*. 2016; 63:247-253.

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LIST OF ABBREVIATIONS

5-HIAA	5-Hydroxyindole Acetic Acid
5-HT	Serotonin
ADHD	Attention Deficit Hyperactivity Disorder
AUC	Area Under the Curve
CAS:HD	Current Assessment Scale-Hypersexual Disorder
CSF	Cerebrospinal fluid
CTQ	Childhood trauma Questionnaire
DHEA	Dehydroepiandrosterone
DHEA-S	Dehydroepiandrosterone sulphate
DSM-III-R	Diagnostical and Statistical Manual of Mental Disorders, 3rd ed., revised
DSM-5	Diagnostical and Statistical Manual of Mental Disorders, 5 th ed.
DST	Dexamethasone Suppression Test
HPA	Hypothalamus Pituitary Adrenal
HD	Hypersexual Disorder
KIVS	Karolinska Interpersonal Violence Scale
KTA	Karolinska Trial Alliance
MADRS	Montgomery-Åsberg Depression Rating Scale
MADRS-S	Montgomery-Åsberg Depression Rating Scale-Self rating
MINI	Mini International Neuropsychiatric Interview
SCID	Structured Clinical Interview for DSM
SCS	Sexual Compulsivity Scale
SIS	Suicide Intent Scale

1 INTRODUCTION

1.1 SUICIDAL BEHAVIOR

Suicide is defined as the fatal result of a self-injurious act of which there is some evidence of the intent to die and a suicide attempt is the behavior that is considered potentially self-injurious with at least some intent to die (Turecki and Brent, 2015). Completed suicides as well as suicide attempts are a major health problem with World Health Organization (WHO) reporting that there are more than 800 000 suicide victims every year and suicide is the second leading cause of death in young people age 15-29. Consequently, suicide became a priority in the WHO Mental Health Action Plan 2013-2020 aiming at a 10% decrease in the rate of suicide by 2020.

1.2 RISK FACTORS AND BIOMARKERS FOR SUICIDE

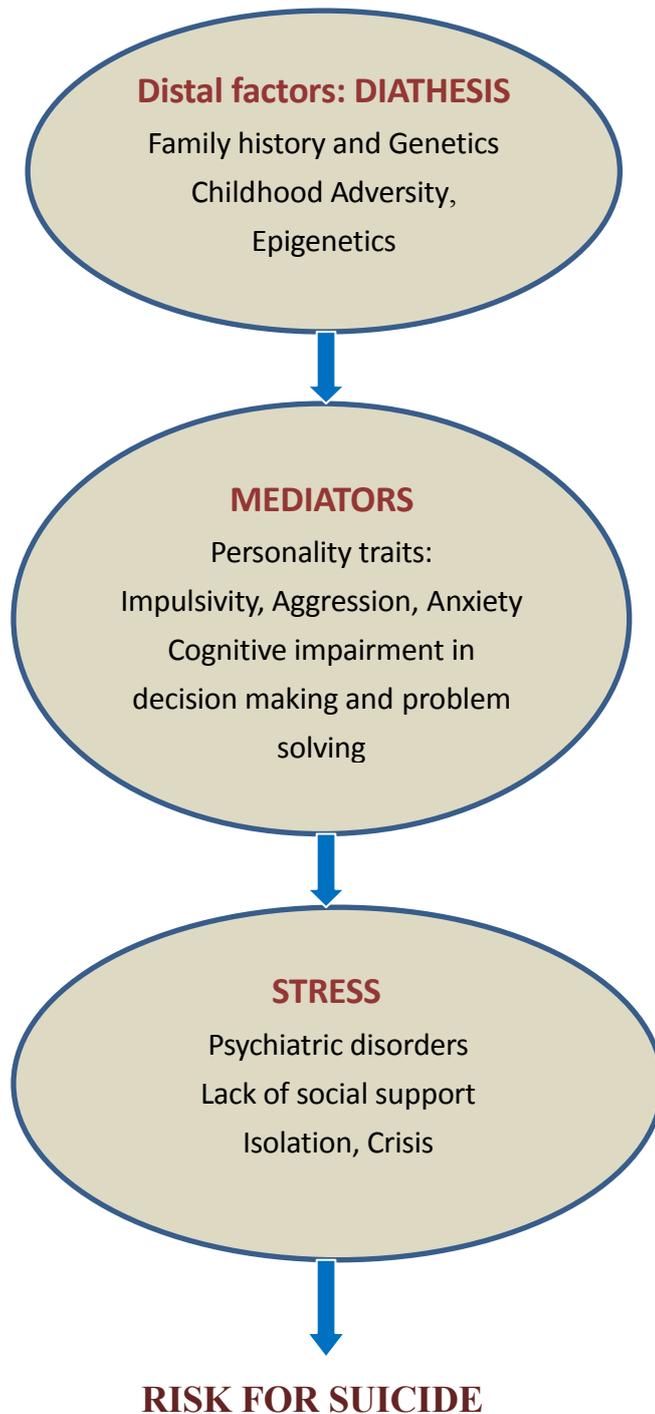
As suicide is a major health problem there has been a need to identify both risk factors as well as biomarkers. The ultimate goal is to identify the individuals at risk so that prevention can take place as well as to be able to give the proper treatment to suicide attempters. A previous suicide attempt is the most important risk factor for a completed suicide in the future (Turecki and Brent, 2015). In that aim research has revealed a number of risk factors for suicide.

These contributing factors to suicide can be better understood in the stress-diathesis model for suicidal behavior (Mann, 2003; van Heeringen and Mann, 2014). This model gives the possibility to illustrate the relationship between different biological systems with clinical correlates of suicide behavior (Mann, 2003; van Heeringen and Mann, 2014).

The different risk factors can be categorized into three groups (Turecki and Brent, 2015). First, the distal factors contributing to the predisposition, including a family history of suicide, childhood adversity and the genetic background of the individual. The interaction between the genetic background and the environment in the form of stressful life events is known (Caspi et al., 2003). Secondly, there are developmental factors that mediate the effect of the distal factors to suicidal behavior. These are mainly personality traits as well as cognitive styles. Aggression, impulsivity, anxiety traits and deficits in decision making and problem solving are some mediating factors of importance (Hawton and van Heeringen, 2009; Turecki, 2014; Turecki and Brent, 2015). Finally, the proximal factors are responsible for triggering suicidal behavior. Studies of psychological autopsies highlight the importance

of psychopathology with more than 90% of suicide victims diagnosed with a psychiatric illness. Most commonly depression but also psychosis, alcohol and substance abuse as well as borderline personality disorder. The exposure to acute stress due to recent life events such as a psychosocial crisis, the availability of means to commit suicide, isolation and lack of social support may trigger the suicidal behavior (Turecki and Brent, 2015).

In Figure 1 the Stress Diathesis model of suicidal behavior.



1.2.1 Hypothalamic-Pituitary –Adrenal (HPA axis) and Serotonin

There has been extensive research on different biological systems that are thought to be involved in suicidal behavior (Mann, 2003; Oquendo et al., 2014; Turecki, 2014). The focus has been on the hypothalamic– pituitary–adrenal (HPA) axis as well as the monoamines, noradrenergic, dopaminergic and most importantly the serotonergic system.

The HPA axis is the central system of stress regulation that together with other neurobiological systems are responsible for homeostasis. Briefly, at the presence of a stressor, the corticotropin-releasing hormone (CRH) is released from the paraventricular nucleus of the hypothalamus. This subsequently triggers the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland. As a result glucocorticoids are produced by the adrenal cortex. The glucocorticoids have the ability to regulate the secretion of ACTH and CRH through inhibitory loops to achieve homeostasis. Glucocorticoids act by binding to the glucocorticoid receptor (GR) and the mineralocorticoid receptor (MR) that are scattered in different areas in the brain, including the hypothalamus and prefrontal cortex and regulate metabolism, the immune system as well as cognition (De Bellis and Zisk, 2014).

The dexamethasone suppression test (DST) has been used to test the function of the HPA axis (Carroll et al., 1968). In order to test the inhibition induced to cortisol production, a synthetic glucocorticoid, dexamethasone, is given. If the production of cortisol is not suppressed, as one would expect, then the individual is characterized as non-suppressor indicating a dysfunction of the HPA axis. The test has been broadly used in psychiatric research (Sher, 2006). According to a review by Coryell, completed suicide is associated with higher rates of DST non-suppressors, i.e., hyperactivity of the HPA axis (Coryell, 2012; Coryell and Schlessler, 2001; Jokinen et al., 2007; Jokinen et al., 2009). However, some other studies suggest a hypofunction of the HPA axis with Pfenning et al. (2005) reporting a lower adrenocorticotropin and cortisol response in the combined Dex/CRH test, especially in depressed patients with suicidal behavior (Pfenning et al., 2005). The HPA dysfunction has also been shown with increased CRH in the cerebrospinal fluid of suicide victims and with reduced sites in the frontal cortex for the binding of CRF in suicide victims (Arato et al., 1989; Nemeroff et al., 1988).

The other most profound/replicated neurobiological correlate of suicidal behavior has been with the hypofunction of the serotonin system, indicated by lower levels of 5-hydroxyindole acetic acid (5-HIAA), the main metabolite of serotonin, in the cerebrospinal fluid (Asberg et

al., 1976; Mann and Currier, 2010; Oquendo et al., 2014; van Heeringen and Mann, 2014). It is proposed that there is a deficiency in the transmission of serotonin and that changes reported in the literature such as increased number of serotonin binding sites in the ventral prefrontal cortex may indicate an attempt to compensate this deficiency (Arango et al., 1995; van Heeringen and Mann, 2014). Besides serotonin's effect on depression, the impact of this hypofunction of the serotonergic system on behavior is suggested as trait like aggression and impulsivity with impairment in inhibition that contributes to the vulnerability to committing suicide (Rosell and Siever, 2015; Turecki, 2014).

At the moment although the DST non-suppression may be seen as a long-term biologic predictor of suicide risk in some populations (Coryell and Schlessler, 2001; Jokinen et al., 2007; Jokinen et al., 2009; Jokinen and Nordstrom, 2008), the positive predictive value of the models used for prediction is still not acceptable. As suicide is a rather rare outcome, the construction of the prediction model is very important. Mann et al., in a prediction model for lethal outcome in suicide including both DST non suppression as well as low 5-HIAA showed a positive predictive value of 23% with 88% specificity and sensitivity 37.5%. Whereas, when either DST non suppression or low 5-HIAA were used in the model the positive predictive value was only 10% with 28% specificity and 87.5% sensitivity (Mann et al., 2006). However, in selected, well characterized populations of suicide attempters there might be a place for such prediction models (Jokinen et al., 2007). It is important to point out that the different biological systems are close related to each other and thus a number of different biomarkers would be more suitable to identify a "biosignature for suicide" and therefore the individuals who are at risk (Guintivano et al., 2014; Kaminsky et al., 2015; Niculescu et al., 2015; Oquendo et al., 2014).

Furthermore, the use of clinical predictors may help refining the prediction models in suicide. Two such important clinical predictors would be the suicide intent of the individual which is shown to be an important long term risk factor for suicide in suicide attempters and lifetime violent behavior (Freedenthal, 2008; Stefansson et al., 2010; Suominen et al., 2004).

1.2.2 Oxytocin

There is some evidence suggesting that other neuroendocrine systems may be involved in the neurobiology of suicidal behavior. Oxytocin is a neuropeptide implicated in social interaction and behaviors such as affiliation, trust, aggression and has an important role in early

attachment (Heinrichs et al., 2009; Insel, 2010; Neumann, 2009; Olf, 2012). Oxytocin is produced in the paraventricular and supraoptic nuclei in the hypothalamus and transferred in the posterior hypophysis where it is released. In the central nervous system, oxytocin has its effects in the hypothalamus, cortical, brainstem, olfactory areas and amygdala and is implicated in depression, anxiety, autism, fear and resilience to stress (Heinrichs et al., 2009; Pierrehumbert et al., 2010; Veening et al., 2010). Oxytocin is important in stress regulation and interacts with the HPA axis in an inhibitory manner (Neumann et al., 2000; Petersson et al., 1999; Windle et al., 2004; Windle et al., 1997).

As oxytocin is both involved in the stress response and has major effects on social behavior it is reasonable to assume a role in suicidal behavior. Indeed, there is some evidence that Oxytocin is involved in suicide. Lee et al. (2009) reported that CSF oxytocin was inversely correlated with life history of aggression, a known risk factor for suicide (Lee et al., 2009). Interestingly through an exploratory analysis, lower levels of CSF Oxytocin were found in suicide attempters compared to patients with no history of suicidal behavior (Lee et al., 2009).

1.2.3 Dehydroepiandrosterone sulphate (DHEA-S)

DHEA-S is one of the most abundant circulating steroids in humans, and its secretion is regulated by adrenocorticotrophic hormone, which also regulates the secretion of cortisol. Together with DHEA they are synthesized both in the brain and in the adrenals. Unlike DHEA, DHEA-S exhibits little circadian rhythmicity due to its very long half-life.

Both DHEA and DHEA-S have been implicated in different psychiatric conditions such as depression, post-traumatic stress syndrome, and schizophrenia. DHEA-S can modulate several neurobiological systems including catecholamines and glutamate, implicated in the neurobiology of depression; it has anti-glucocorticoid and neuroprotective effects. DHEA-S is important in stress regulation and together with cortisol is taken into account in the allostatic load, a measurement of the negative physiological effect of stress over time (Maninger et al., 2009). Their ratio (cortisol/DHEA-S) might be a sensitive measure of the allostatic load. Moreover, Morgan et al., (2004 and 2009) in experimental studies of submitting individuals under stress reported the positive role of DHEA-S in coping under stress conditions (Morgan et al., 2009; Morgan et al., 2004). DHEA-S is also considered a marker for psychophysiological well-being (Maninger et al., 2009).

Even though DHEA-S is investigated in depression and elevated cortisol/DHEAS ratios has been proposed to be a state marker of depressive illness, (Maninger et al., 2009) there are very few studies of the relationship of DHEA-S and suicidal behavior. A study of Butterfield et al., (2005) reported that male veterans with PTSD and suicide attempt had higher plasma DHEA levels compared to patients with no suicide attempt (Butterfield et al., 2005).

It is important to mention that most of the studies of biological systems in suicide may have been confounded by other factors such as current psychopathology with depressive symptoms, symptoms of post traumatic syndrome, anxiety as well as exposure to childhood adversity. All the above mentioned possible confounders have been reported to affect the HPA axis independently of suicide behavior and especially the effects of childhood trauma are independent of psychopathology in general. Early life adversity has longstanding effects in adulthood through alternations of biological systems (Heim et al., 2008b).

1.3 HYPERSEXUAL DISORDER

Sexuality is a central part of human behavior and the most essential in an evolutionary aspect. Psychiatric disorders may have effects on sexuality and sexual symptoms are included in their diagnostic criteria such as depression, bipolar disorder and personality disorders (DSM 5). Some aspects of risky sexual behavior such as the infrequent use of condom and the early onset of sexual behavior are even related with increased suicidality (Mota et al., 2010).

Hypersexual disorder has been described previously in the literature with different names reflecting different models such as sexual addiction, compulsive sexual behavior, sexual impulsive behavior and sexual lust dysregulation (Bancroft et al., 2009; Garcia and Thibaut, 2010; Kafka, 2010).

Hypersexual Disorder (HD) is conceptualized as a nonparaphilic sexual desire disorder with an impulsivity component integrating various pathophysiological perspectives such as sexual desire deregulation, sexual addiction, impulsivity and compulsivity and was proposed as a diagnosis to be included in the DSM 5 (Kafka, 2010). Furthermore, hypersexual behavior is proposed to be a maladaptive response to dysphoric affective states as well as life stressors (Kafka, 2010).

Hypersexual disorder includes repetitive and intense preoccupation of the patient with sexual behavior, urges and fantasies that are difficult to control resulting in negative consequences

and significant impairment and/or distress for the individual in different areas such as social contacts and work (Kafka, 2010). The negative consequences might be isolation, depressive and anxiety symptoms, unwanted pregnancies and sexual transmitted diseases. Långström and Hanson (2006) reported also that individuals with hypersexuality had more negative health indicators as well as life problems (Langstrom and Hanson, 2006). Examples of hypersexual behavior include masturbation, use of pornography, sex with consenting adults and sexual activities related to the use of internet (Kafka, 2010).

There is still no full consensus on the conceptualization of the hypersexual disorder and there was a debate when proposed for inclusion as a diagnosis in the DSM-5 (Kafka and Krueger, 2011; Moser, 2011). Finally, it was not included in the DSM-5, although the proposed criteria showed high validity and reliability at the field study (Reid et al., 2012). Kafka has also addressed the criticism against the exclusion of hypersexual disorder (Kafka, 2014; Kafka and Krueger, 2011).

Although there have been problems with methodology as there was no consensus regarding hypersexual disorder, the literature indicates that hypersexual behavior affects 3-6% of the population (Kafka, 2010; Langstrom and Hanson, 2006). Långström and Hanson, (2006), in a population based study reported that 12% of men and 7% of women could be classified as hypersexual although that did not necessarily classified them as having hypersexual disorder.

There are high rates of comorbidity between hypersexual disorder and other psychiatric conditions. The most common are depression and anxiety such as social phobia but also substance abuse and ADHD (Kafka, 2010). Schultz et al., (2014) reviewing the literature reported positive moderate correlation between symptoms of depression and hypersexual behavior (Schultz et al., 2014).

1.3.1 Biological systems in hypersexual disorder

Even though human sexuality is very strongly related to cultural factors, biological systems offer the matrix to understand sexual behavior. Central mechanisms including the limbic system, neuroendocrine control as well as the inhibition from the frontal lobe regulate the human sexual behavior (Goldey and van Anders, 2012; Ragan and Martin, 2000). The sexual response is controlled by monoamines noradrenaline, dopamine, serotonin as well as acetylcholine, neuropeptides, glutamate and GABA (Bancroft, 2002; Saleh and Berlin, 2003).

Bancroft (2002) suggests a model with both excitatory and inhibitory factors in the brain, where the sexual response is based on the balance between them.

Although HPA axis dysregulation has been reported in a number of psychiatric populations most commonly with the use of the dexamethasone suppression test (DST) (Sher, 2006), the relationship between stress and sexual behavior is not clear. Some studies on the HPA axis proposed a negative effect on sexual behavior while others indicate a facilitative effect (Goldey and van Anders, 2012). The existing research has focused on alternations of the stress system as a direct effect of sexual behavior. Exton et al. reported unchanged plasma cortisol levels in individuals watching a film that would induce sexual arousal and during sexual arousal and orgasm (Exton et al., 2001; Exton et al., 2000). Additionally, sexual arousal but not sexual thoughts during an imagined social situation exercise were positively related to salivary cortisol at baseline (Goldey and van Anders, 2012).

The HPA axis besides being a central part of the stress system, also interacts directly with the Hypothalamus Pituitary Gonadal (HPG) axis and thus controls the secretion of steroid hormones such as testosterone and estradiol (Cunningham et al., 2012). Both testosterone and estradiol have a very important role in sexual drive and behavior but their exact role is far from clarified (Cunningham et al., 2012; Saleh and Berlin, 2003). Other androgens that have the ability to transform to testosterone and estradiol as well as DHEA-S that is related to feelings of wellbeing may be relevant to male sexuality.

Other hormones may be also related to sexual behavior. Prolactin is proposed to have an inhibitory effect on sexual behavior through the inhibition of dopaminergic activity (Bancroft, 2005) and oxytocin with its key role in affiliative behavior, childbirth and reproduction may be implicated in sexual behavior by both central and peripheral mechanisms.

Regarding hypersexual disorder, very little is known about the neurobiology behind this disorder and especially about the role of neuroendocrine systems. In a sample of healthy young adults, Harrison et al. reported increased salivary cortisol reactivity as a response to a psychological stressor (imagined social situation exercise) in individuals with risky sexual behavior (Harrison et al., 2014). These mixed results on the role of HPA axis and other neuroendocrine systems in human sexuality remain to be clarified and particularly in deviant expressions of human sexuality such as in hypersexual disorder. It is also important to notice that possible confounders, when evaluating neuroendocrine systems, such as the exposure to childhood adversity should be taken under consideration.

1.4 EARLY ADVERSITY AND PSYCHOPATHOLOGY

It is important to mention that the exposure to childhood adversity, emotional and physical abuse and neglect has been shown to increase both the risk for psychopathology in adulthood and suicide (Brodsky and Stanley, 2008; Jokinen et al., 2010; Teicher and Samson, 2013; van Heeringen and Mann, 2014). Childhood adversity is also related to adversity in adult life, increasing the risk for revictimization (Widom et al., 2008).

The relationship between childhood trauma and hypersexual behavior is very important with Långström and Hanson reporting that individuals with hypersexuality were more often coming from adverse family backgrounds (Langstrom and Hanson, 2006). In addition, childhood adversity is suggested as a mediator of increased risk for the development of risky sexual behavior and especially sexual abuse is suggested to be directly linked to hypersexuality (Aaron, 2012; Wilson and Widom, 2008). The younger the age of the victim when sexually abused and male gender were suggested to lead to hypersexual behavior (Aaron, 2012).

The mechanism through childhood adversity increases risk for psychopathology in adult life is suggested to be via the long standing effects and alternation of the neurobiological systems that occurs due to the exposure to childhood adversity (De Bellis and Zisk, 2014; Lupien et al., 2009; Turecki, 2014; Turecki et al., 2012; van Heeringen and Mann, 2014). These alternations have functional consequences in adult life as the homeostasis of the neurobiological systems is dysregulated. De bellis and Zisk present twelve different mechanisms in how childhood adversity affects the HPA axis but also other neurobiological systems that are involved such as the serotonin and the oxytocin system. Individual differences, the gender, the timing of the trauma, duration and severity as well as genetic, epigenetic and social factors are important in the development of the effects of the trauma on the biological systems and psychopathology (De Bellis and Zisk, 2014).

The most common finding when investigating adults with childhood adversity is low levels of cortisol (De Bellis and Zisk, 2014; Heim et al., 2001). Contrary, Heim et al., showed increased cortisol and ACTH responses at the dexamethasone/CRF test in depressed men with a history of childhood abuse compared to healthy controls and depressed men without a history of childhood abuse (Heim et al., 2008a). This is not necessarily contradicting as different mechanisms may be in place (De Bellis and Zisk, 2014).

Regarding suicide there is increasing evidence of the biological effects of childhood adversity leading to vulnerability to suicide (Heim et al., 2008b; Turecki, 2014; Turecki et al., 2012). The main effect is proposed to be through a dysregulation of the HPA axis and the regulation of neurotrophic factors such as the brain derived neurotrophic factor (BDNF) through genetic and epigenetic mechanisms (Turecki et al., 2014).

But also steroids such as DHEA-S that are in close relation with glucocorticoids are related to childhood adversity. Kellner et al., when investigating patients with post-traumatic stress disorder and exposure to childhood abuse found increased plasma levels of DHEA and DHEA-S in the group exposed to childhood abuse (Kellner et al., 2010). On the other hand, Pico Alfonso et al., measuring salivary DHEA did not find a significant difference in DHEA levels in women exposure to childhood abuse (Pico-Alfonso et al., 2004). A decreased plasma cortisol/DHEA(S) ratio has also been reported in patients with post-traumatic stress disorder and exposure to childhood abuse (Kellner et al., 2010; Yehuda et al., 2006) and Yehuda et al., proposed that DHEA-S promotes resilience and thus has a protective role in childhood trauma (Yehuda and Flory, 2007). DHEA-S has been mainly measured in saliva or in plasma during most studies and only a few studies in psychiatric patients have measurements in the cerebrospinal fluid (Kancheva et al., 2011).

The oxytocin system is also closely related to early adversity related psychopathology (De Bellis and Zisk, 2014). Heim et al., found lower CSF Oxytocin concentrations in women with a history of childhood abuse compared with women without childhood abuse (Heim et al., 2009). Similarly, in healthy men plasma oxytocin levels were negatively associated with early life adverse experiences (Opacka-Juffry and Mohiyeddini, 2012) and likewise Bertsch et al., found a negative correlation between plasma oxytocin levels and childhood trauma when investigating women with borderline personality disorder (Bertsch et al., 2013). On the other hand, Pierrehumbert et al., reported that abused women had higher baseline oxytocin levels and premature suppression of oxytocin in a study using the Trier Social Stress Test, an experimental psychosocial challenge (Pierrehumbert et al., 2010). In the same line, Seltzer et al., reported high levels of oxytocin secretion only in girls with a history of childhood abuse that underwent the Trier Social Stress Test for children while there was no difference in boys (Seltzer et al., 2014). Furthermore, Thompson et al., showed an interaction between high early adversity and the oxytocin transporter rs2254298 polymorphism in predicting anxiety and depressive symptoms in a group of adolescent girls (Thompson et al., 2011).

2 AIMS

2.1 OVERALL AIMS

The aim of this thesis was to investigate different neuroendocrine systems with focus on the HPA axis, Oxytocin and DHEAS in suicide attempters and in patients with Hypersexual Disorder. These neuroendocrine systems were investigated in relation to exposure to childhood adversity and interpersonal violence as well as different aspects of psychopathology such as suicide intent, depressive symptoms and hypersexual behavior.

The specific research aims were as follows:

2.2 STUDY I

To investigate CSF and plasma Oxytocin levels in suicide attempters and healthy volunteers. Another aim was to assess the relationship between CSF and plasma Oxytocin levels, suicide intent and lifetime expressed interpersonal violence in suicide attempters. The final aim was to assess whether CSF and plasma oxytocin would predict subsequent suicide in suicide attempters.

2.3 STUDY II

To investigate CSF levels of 5-Hydroxyindoleacetic acid (5-HIAA) and CSF and plasma levels of cortisol and DHEAS in suicide attempters and healthy volunteers. Another aim was to investigate the relationship between neuroendocrine measurements and childhood adversity in suicide attempters. The final aim was to investigate whether CSF cortisol, 5-HIAA or DHEAS levels would predict subsequent suicide.

2.4 STUDY III

To assess the association between CSF and plasma Oxytocin levels and lifetime trauma history (exposure to interpersonal violence as a child, as an adult or during both periods) in suicide attempters. Another aim was to assess the relationship between CSF and plasma oxytocin and childhood emotional climate.

2.5 STUDY IV

To investigate the function of the HPA axis in hypersexual disorder and assess the relationship of neuroendocrine measurements to childhood adversity and hypersexual behavior.

3 METHODS

3.1 STUDY SETTINGS

Studies I, II and III: Patients who were admitted after a suicide attempt at the psychiatric wards at the Karolinska University Hospital and accepted to participate in a study of biological and psychological risk factors for suicidal behavior. Healthy volunteers were also recruited as a control group.

Study IV: Patients with hypersexual behavior seeking medical and/or psychotherapeutic treatment at the Center for Andrology and Sexual Medicine (CASM), at the Karolinska University Hospital were invited to participate in a study of biological markers for hypersexual behavior. Healthy volunteers were also recruited as a control group.

3.2 PARTICIPANTS IN THE SUICIDE ATTEMPTERS COHORT (STUDIES I-III)

Suicide attempters

Studies I-III are based on a cohort of suicide attempters that were included between the years 1988 and 1991. The sample of twenty eight (28) suicide attempters includes eighteen (18) men, and ten (10) women. The mean age of the men was 44 years, range 23-65 years, standard deviation (SD) = 14.6 while the women had a mean age of 41 years, range 26-66 years, standard deviation (SD) = 12.3. All suicide attempters were medication free.

The inclusion criteria of this cohort were a recent suicide attempt and the age of 18 years or older. The suicide attempt was defined as any nonfatal, self-injurious behavior with at least some intent to die. The exclusion criteria included schizophrenia spectrum psychosis, intravenous drug abuse, or circumstances where informed consent could not be obtained.

All the suicide attempters were interviewed by trained psychiatrists using the SCID I research version interview to establish psychiatric diagnoses according to DSM-III (American Psychiatric Association 3rd edition). The SCID II interview was used to assess Axis II diagnoses.

The criteria by Träskman et al. were used to assess whether the suicide attempt was considered violent. According to these criteria the use of all violent methods (e.g., firearm, hanging, jumping from a high place, car exhaust) classify as a violent suicide attempt whereas suicide attempts involving drug overdose or superficial phlebotomy are classified as non-violent. According to these criteria, five patients (18%) had used a violent suicide attempt method (Traskman et al., 1981).

Ninety-three per cent of the patients (n=26) had at least one current Axis I or Axis II psychiatric diagnosis. Eight (n=8) patients had more than one Axis I diagnosis. Among Axis II diagnoses, two thirds of the patients fulfilled criteria for a personality disorder and one patient was diagnosed with an organic personality syndrome. Table 1 shows Axis I and Axis II diagnoses.

Table 1. Psychiatric diagnoses in suicide attempters

DSM III Axis 1 diagnosis	Number of suicide attempters	DSM III Axis 2 diagnosis	Number of suicide attempters
Mood disorders	13	Paranoid	2
Bipolar disorder	1	Schizoid	1
Alcohol abuse	6	Dependent	1
Alcohol addiction	3	Passive-aggressive	1
Adjustment disorder	3	Borderline	6
Anxiety disorder	6	Antisocial	2
Organic personality syndrome	1	Avoidant	2
Anorexia nervosa	1	Mixed	1
No axis 1 diagnosis	4	No axis 2 diagnosis	8
Not assessed	0	Not assessed	4

Healthy Volunteers

Nineteen (19) healthy volunteers including twelve (12) men and seven (7) women were recruited as a control group. The healthy volunteers were screened with the SCID interview by a trained psychiatrist in order to exclude previous or current psychiatric or medical conditions. The healthy volunteers had a mean age of 30 years (range: 23-48).

3.3 PARTICIPANTS IN THE HYPERSEXUAL DISORDER COHORT (STUDY IV)

Patients with hypersexual disorder

Sixty seven (n= 67) male patients with hypersexual disorder, (mean age 39.2 years, range 19-65) were included between the years 2013 and 2014 at the Center for Andrology and Sexual Medicine, (CASM), which is a multidisciplinary center for diagnostics and treatment of patients with sexual dysfunctions. The recruitment of the patients was through advertising in media as well as referrals to the Center for Andrology and Sexual Medicine.

The inclusion criteria were a diagnosis of hypersexual disorder, available contact information and the age of 18 years or older. The exclusion criteria were current psychotic illness, current alcohol or drug abuse, other psychiatric disorder that would require immediate treatment such as major depression with high suicidal risk and serious physical illness such as severe hepatic or renal disease.

The patients were after initial contact with the study coordinators asked to log into a web based platform, leave their preliminary informed consent to participate in the study, and complete their personal information as well as the self-rated questionnaires. Subsequently, all patients were evaluated in a face to face interview by a trained psychiatrist and a psychologist using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to establish psychiatric diagnoses and the diagnosis of hypersexual disorder. Eligible patients gave their final written informed consent and were included in the study. Seven (n=7) patients had more than one diagnosis and five (n=5) had more than one anxiety diagnosis. Table 2 shows the diagnoses and characteristics of the patients with hypersexual disorder.

Table 2. Diagnoses and characteristics of the patients with hypersexual disorder.

Diagnosis and characteristics	Number of patients
Depression	n=11, 16.4%
Anxiety	n=12, 17.9%
Social Phobia	n=8
Panic syndrome	n=4
Obsessive compulsive disorder	n=2
Generalized Anxiety Disorder	n=2
Post-Traumatic Stress Syndrome	n=1
Diagnosis (other)	n= 1, (ADHD)
History of Suicide attempt	n=8, 11.9%
Antidepressants	n=11, 16.4%

Healthy volunteers

Forty male healthy volunteers (n=40) were recruited from the Karolinska Trial Alliance (KTA) database. KTA was founded by a collaboration of Stockholm County Council and the Karolinska Institutet and functions as a Clinical Research Center at Karolinska University Hospital. The first phase included a telephone pre-screening when the volunteers gave their informed consent. To be included, healthy volunteers should have been physically healthy with no serious illnesses, no previous or ongoing psychiatric illness and no first degree relatives with schizophrenia, bipolar disorder or completed suicide. Finally they should not have been exposed to serious trauma such as assault and natural disasters that required treatment or caused disability.

The healthy volunteers followed the same procedure as the patients with HD, after initial contact with the study coordinators they were asked to log into the Web based platform, leave their preliminary informed consent to participate in the study, and complete their personal information as well as the self-rated questionnaires. Individuals who screened positive for pedophilic disorder were excluded from the study. Written informed consent was given before the baseline blood samples were taken. One individual was excluded, due to medical illness that was withheld in the pre-screening but was evident from the laboratory results. The total number of healthy volunteers was thirty nine (n = 39). An effort was made to match the group of healthy volunteers to our patients with HD regarding age. Possible seasonal variations were minimized by matching time of blood sampling to either spring or fall. The mean age of the healthy volunteers was 37.5 years (range 21-62).

3.4 ASSESSMENT OF CHILDHOOD ADVERSITY, EXPOSURE AND EXPRESSED INTERPERSONAL VIOLENCE IN CHILDHOOD AND ADULT LIFE IN SUICIDE ATTEMPTERS

Study I-III:

Karolinska Interpersonal Violence Scale (KIVS) contains four subscales assessing expressed violent behavior as well as exposure to violence in childhood (between 6 and 14 years of age) and during adult life (15 years or older) (Jokinen et al., 2010). The ratings are based on a semi structured interview and the items were scored 0-5. Interviews and ratings were performed by trained clinicians. Revictimization was defined as having both ratings above the mean and the sum score 6 or above.

Study III:

Childhood emotional climate factor of the Socialization subscale from the Karolinska Scales of Personality (KSP) was used to assess childhood emotional climate. The Socialization subscale consists of 20 items, with emphasis on negative childhood experiences, poor school and family adjustment, and general dissatisfaction. Eight of the items reflect negative childhood emotional climate, 4 items reflect childhood adjustment problems and 8 items assess feelings of resentment and victimization (Svanborg et al., 1999).

3.5 ASSESSMENT OF DEPRESSION SEVERITY IN SUICIDE ATTEMPTERS (STUDIES I-III)

Montgomery-Åsberg Depression Rating Scale (MADRS): It was used to assess the severity of depression. It consists of 10 items based on a clinical interview evaluating apparent sadness, reported sadness, inner tension, sleep, appetite, concentration, lassitude, inability to feel, pessimistic and suicidal thoughts. Total scores range 0-60 points (Montgomery and Asberg, 1979).

3.6 ASSESSMENT OF SUICIDE INTENT OF THE SUICIDE ATTEMPTERS (STUDY I)

Suicide intent was measured with two different instruments. Beck's Suicide Intent Scale (SIS), was the first instrument with 15-items and is designed to examine the factual aspects of the suicide attempt. These are the patient's thoughts and feelings as well as the circumstances at the time of the suicide attempt (Beck, 1974). Individual responses are coded on a 0-2 scale and the total SIS range is between 0-30 reflecting low to high suicide intent. A factor analysis of SIS (Mieczkowski et al., 1993) defined the components of suicide intent and the planning subscale (items 1-7, 15) was used separately in the analysis.

The second instrument was the Freeman scale (Freeman, 1974) that takes into account the type and quantity of drugs used or the extent of self-injury inflicted. A high score on the scale indicates 'low reversibility of suicidal method' (i.e. serious attempt) and a low score indicates 'high reversibility' (i.e. non-serious attempt). The Freeman scale includes a second part rating the likelihood that someone would interrupt the attempt (Freeman interruption probability). Individual responses are coded on a 1-5 scale and the total Freeman range is between 2 and 10.

3.7 MEASUREMENTS OF BIOMARKERS IN THE SUICIDE COHORT (STUDIES I-III)

Shortly after the suicide attempt at approximately 8 am, after fasting in bed since midnight, blood samples (10 ml) were collected in tubes containing heparin (10 IU ml⁻¹) and were centrifuged. The plasma was removed and frozen at -80 °C.

Fifteen minutes after the blood samples were collected lumbar punctures were performed in a standardized manner between 8 and 9 am. Twelve (12) ml CSF was withdrawn with the participant in the sitting position and the needle being inserted between lumbar vertebrae IV and V. CSF was immediately centrifuged and aliquoted in six 2 ml samples and stored at -80 °C. All biochemical analyses were contemporaneous with the clinical protocol.

3.7.1 CORTISOL and DHEAS

The concentrations of cortisol and DHEAS in plasma and CSF were measured according to radioimmunoassay (RIA) methods (Hedman et al., 1989). The antisera for DHEA were prepared in our laboratory. The methods were validated for the assay of sulphoconjugated steroids as earlier described (Hedman et al., 1989). The intra- and inter assay coefficients of variation never exceeded 10% and 20% respectively.

3.7.2 5-HIAA

CSF 5-HIAA was analyzed by using mass fragmentography (GC–MS) according to methods developed by Bertilsson. The coefficient of variation of the analytical method is less than 5% (Bertilsson, 1981).

3.7.3 OXYTOCIN

The concentration of oxytocin in plasma and CSF was measured with specific radio-immunoassay (RIA) using the antibody KA19 (Milab, Malmo, Sweden). The limit of oxytocin detection was 2 fmol/mL and the intra- and inter-assay coefficients of variation were 11.2 and 13%, respectively (Stock and Uvnas-Moberg, 1985; Uvnas-Moberg et al., 1993).

3.8 MORTALITY IN THE SUICIDE ATTEMPTERS COHORT (STUDY I-II)

All the patients were linked to the Cause of Death register, maintained by the National Board of Health and Welfare in Sweden (<http://www.socialstyrelsen.se>) by using the unique personal identification number. The cause of Death register is based on information from the death certificates. Six patients (two women and four men) had committed suicide before April 2011; suicides were ascertained from the death certificates. The follow up time ranged between 20 and 22 years.

3.9 ASSESSMENTS IN THE HYPERSEXUAL DISORDER COHORT (STUDY IV)

3.9.1 PSYCHIATRIC DIAGNOSES

The diagnostic process was based on a clinical interview by a trained psychiatrist and psychologist. The Mini-International Neuropsychiatric Interview (MINI 6.0), a validated, structured diagnostic clinical interview for assessing psychopathology along the Axis I (Sheehan et al., 1998), was used during the interview.

3.9.2 DIAGNOSIS OF HYPERSEXUAL DISORDER

The diagnosis of hypersexual disorder was defined according to the criteria proposed during the revision of DSM 5 by Kafka (2010). These criteria include:

A. Over a period of time of at least six months, recurrent and intense sexual fantasies, sexual urges, or sexual behaviors in association 4 or more of the following 5 A criteria:

A1. Time consumed by sexual fantasies, urges or behaviors repetitively interferes with other important (non-sexual) goals, activities and obligations.

A2. Repetitively engaging in sexual fantasies, urges or behaviors in response to dysphoric mood states (e.g., anxiety, depression, boredom, irritability).

A3. Repetitively engaging in sexual fantasies, urges or behaviors in response to stressful life events.

A4. Repetitive but unsuccessful efforts to control or significantly reduce these sexual fantasies, urges or behaviors.

A5. Repetitively engaging in sexual behaviors while disregarding the risk for physical or emotional harm to self or others.

B. There is clinically significant personal distress or impairment in social, occupational or other important areas of functioning associated with the frequency and intensity of these sexual fantasies, urges or behaviors.

C. These sexual fantasies, urges or behaviors are not due to the direct physiological effect exogenous substance (e.g., a drug of abuse or medication).

Specify if: masturbation, pornography, sexual behavior with consenting adults, cybersex, telephone sex, strip clubs, other.

3.9.3 ASSESSMENTS OF HYPERSEXUAL BEHAVIOR, DEPRESSION SEVERITY AND CHILDHOOD ADVERSITY

The following self-rated scales were administrated by the Web based platform:

Hypersexual disorder screening inventory (HDSI):

It is consisted of 7 items that follow the criteria (5A and 2B criteria) of hypersexual disorder. These are graded 0-4, from “never true” to “almost always true” during the past 6 months. The total score ranges from 0 to 28. In order to be diagnosed with Hypersexual Disorder a minimum score of 3 is required on 4 out of 5 A-criteria, and 3 or 4 points on a minimum of 1 B-criteria is required with minimum total score of 15 (www.dsm5.org).

Sexual Compulsivity Scale (SCS):

It consists of 10 statements about sexually compulsive behavior, sexual preoccupations, and sexually intrusive thoughts that respondents are called to endorse agreement with. Agreement is on 4-point scale (1 “not at all like me” to 4 “very much like me”) with total score range 10-40. <18 is classified as not sexually compulsive, 18-23 as mild sexual compulsivity, 24–29 as moderate and >30 as sexually compulsive. SCS was first developed for the assessment of high-risk sexual behaviors (Kalichman and Rompa, 1995).

Hypersexual Disorder: Current Assessment Scale (HD:CAS):

It contains seven questions with the first one (A1) asking for the type as well as the number of sexual behaviors reported (including masturbation, pornography, sex with consenting adults, cybersex, telephone sex, strip clubs, and other sexual behaviors). The remaining six questions (A2-A7) quantify these symptoms during the most recent 2-week time frame thus assessing the current state of hypersexual behavior. Each question (A2-A7) is rated in a 5 point intensity scale (0-4) with total scores from 0 to 24 points. HD:CAS is considered to be the dimensional measurement of hypersexual behavior.

Montgomery-Åsberg Depression Rating Scale Self rating (MADRS-S):

It was used to assess the severity of depression (Svanborg and Asberg, 2001). The rating scale includes nine questions on depressive symptoms, rated from 0 to 6 points, with total scored 0–54.

Childhood Trauma Questionnaire (CTQ):

CTQ is a psychometric instrument for the assessment of childhood trauma. It is consisted by five subscales, measuring Emotional Abuse (EA), Physical Abuse (PA), Sexual Abuse (SA), Emotional Neglect (EN) and Physical Neglect (PN). Each subscale consists of 5 items and gets scores between 5 and 25 and classifies maltreatment as none, low, moderate and severe. The CTQ is completed with 3 items that constitute the minimization/denial scale used to identify individuals who may be underreporting traumatic events. Thus the total CTQ includes 28 items (Bernstein and Fink, 1998).

3.10 MEASUREMENTS OF CORTISOL AND ACTH IN THE HYPERSEXUAL DISORDER COHORT

Blood sampling for patients and healthy volunteers were performed all year round in order to have subject and volunteer samples equally distributed between spring and fall. All blood samples were taken at approximately 8 am. The analyses were performed directly after sampling at the laboratory of the Karolinska University Hospital using a chemiluminescence immunoassay with sensitivity for ACTH of 0.5 pmol/l, (normal range 1.6–13.9 pmol/l) and sensitivity for Cortisol 15 nmol/l (normal range 200–800nmol/l). Inter assay and intra assay coefficients of variation were 1.3% and 1.5% for Cortisol and 0.6% and 3.5% for ACTH.

3.11 DEXAMETHASONE SUPPRESSION TEST IN HYPERSEXUAL DISORDER

After the baseline plasma samples of ACTH and Cortisol were gathered, all patients with HD and healthy volunteers underwent a low dose dexamethasone suppression test. 0.5 mg of dexamethasone was administrated orally at 23:00 h the same day as the baseline sample was taken. Post dexamethasone suppression test blood samples were collected the next day at approximately at 08:00 h, using the same method as for baseline Cortisol. A plasma Cortisol level of 138 nmol/l (=5 g/dl) or higher in the morning sample after dexamethasone administration classified as non-suppressed.

3.12 STATISTICAL ANALYSES

Initial analyses were carried out to evaluate skewness and kurtosis of the distributions in with Shapiro-Wilks test (studies I, III and IV) or with Kolmogorov test (study II). In study I data for CSF and plasma oxytocin were transformed into normal distribution using the natural logarithms before statistical analysis.

As the healthy volunteers were younger than patients, the group comparison of oxytocin levels (study I) was adjusted for age using linear regression. In study II as DHEA-S levels decline strongly with age, while cortisol levels increase modestly (o Hartaigh et al., 2012), all group comparisons of hormone values were adjusted for age using linear regression. Group differences were assessed with Anova (study II), Wilcoxon test (study II and III), the Kruskal-Wallis' test (study IV) and t-test (study III, IV) in continuous variables. Fisher's exact test was used for cross tabulations of categorical variables (study II) and to detect group differences between patients and healthy volunteers, in the rates of cortisol non-suppression after dexamethasone challenge (study IV).

In study II as comorbid substance abuse diagnosis and depression severity showed a trend for significant correlation with CSF and plasma cortisol levels and CSF 5-HIAA levels, group comparisons between patients and healthy volunteers were also adjusted for diagnosis of major depression and comorbid diagnosis of substance abuse. CSF or plasma DHEAS did not differ significantly between patients with and without diagnosis of major depression or substance abuse (p values between 0.49 and 0.92), and therefore the group comparisons were adjusted only for age. Men and women were assessed separately adjusting the group differences between male suicide attempters and male healthy volunteers as well as female suicide attempters and female healthy volunteers as above.

Correlation analyses were used to determine associations between the clinical ratings and biologic variables. Tests of non-parametric or parametric correlations were performed using Spearman rho (study I,II, III,IV) or Pearson's r (I,II,IV). Post-hoc power analysis indicated that only large effect sizes could be detected. The effect sizes were calculated using Cohen's d (Cohen, 1992).

From the results of the correlational analyses, standard regression analyses were conducted. In study I, standard regression analysis was conducted to determine whether CSF oxytocin could be predicted by suicide intent and lifetime violent behavior corrected for age and

gender. In study II, standard regression analysis was conducted to determine whether CSF cortisol/DHEAS ratio could be predicted by exposure to violence as a child corrected for age, gender and depression severity. Median split subgrouping for further analysis of CSF 5-HIAA and CSF cortisol levels in suicide victims and survivors was applied. In study IV, standard regression analysis was conducted to determine whether DST non-suppression and plasma ACTH could be predicted by the diagnosis of hypersexual disorder adjusted for childhood trauma. All statistical tests were two-tailed. An ad hoc receiver-operating characteristic (ROC) analysis was used to find optimal threshold for DST cortisol level to predict hypersexual disorder diagnosis. ROC table and curve were created to establish the optimal cut-off value and ROC area under the curve (AUC) was determined as a measure of the diagnostic execution according to the methods of Hanley and McNeil.

The p value was set at <0.05. The Statistical Package JMP VI software, SAS Institute Inc., Cary, NC, USA was used for all statistical analyses.

3.13 ETHICAL CONSIDERATIONS

Studies I-III: The Regional Ethical Review Board in Stockholm approved the study protocols (Dnrs: 88—216; 91—96; 2010/3:4) and the participants gave their written informed consent to the study. The suicide attempters are in a high risk for subsequent suicide and especially in this cohort with high levels of psychopathology. Thus research of such vulnerable groups is of high importance as it may lead to gain knowledge that hopefully leads to a better understanding of the mechanisms behind suicide which is one of the leading causes of mortality in the world.

Studies IV: The study protocols were approved by the Regional Ethical Review Board in Stockholm (Dnrs:2013/1335-31/2) and the participants gave their written informed consent to the study. Hypersexual disorder is accompanied with suffering, adverse consequences and possible neurobiological alterations in patients with hypersexual disorder were at the time of project planning unknown. The knowledge that derives from this research has the potential to contribute significantly to the understanding of this disorder.

The relationship of the potential biomarkers to childhood adversity may give insight to biological mechanisms that contribute to psychopathology as the outcome. Consequently, the

study of this relationship becomes of high importance as childhood adversity is a great target for prevention both at the individual level and from policy makers.

4 RESULTS

4.1 CLINICAL RATINGS IN SUICIDE ATTEMPTERS AND IN HYPERSEXUAL DISORDER

4.1.1 Depression severity, Suicide intent, Interpersonal Violence and Revictimization in suicide attempters

Clinical ratings of suicide attempters are presented in Table 3.

Table 3. Clinical ratings of depression severity, suicide intent, expressed and exposed interpersonal violence and revictimization in suicide attempters

Ratings	Mean	Median	S.D.	Range
MADRS (N=27)	20.7	19	10.3	4-38
KIVS, Expressed violent behaviour lifetime (N=24)	2.9	2.5	2	0-7
KIVS, Exposure to violence as a child (N=24)	2.5	2.5	1.6	0-5
KIVS, Exposure to violence as an adult (N=24)	1.9	2	1.6	0-5
KIVS, Revictimized, Exposure to violence (N=8)	7.8	8	1.4	6-9
KIVS, Non-Revictimized, Exposure lifetime (N=15)	2.7	3	1.5	0-5
Childhood emotional climate (revictimized) (N=8)	16.1	16	3.7	10-21
Childhood emotional climate (non-revictimized) (N=15)	22.5	24	5.7	11-29
SIS (N=23)	17.9	18	5	8-27
Planning SIS (N=23)	8.4	9	3.6	3-16
Freeman reversibility of the suicide attempt method (N=25)	2.8	3	1	1-5
Freeman probability of intervention (isolation) (N=25)	3.2	3	1.1	1-5
Freeman total (N=25)	6	6	1.6	2-9

There was a significant correlation between the exposure to interpersonal violence as a child and exposure as an adult ($\rho=0.58, p=0.004$). Childhood emotional climate showed a significant negative correlation with KIVS exposure to interpersonal violence as a child and exposure as an adult ratings ($\rho=-0.63, p=0.005$; $\rho=-0.64, p=0.004$). The correlation between KIVS exposure to violence as a child and depression severity measured with MADRS was non-significant ($r=0.09, n=22, p=0.7$).

Revictimization

Eight suicide attempters (5 women and 3 men, mean age = 42 years) were characterized as revictimized and 15 as non-revictimized (3 women and 12 men, mean age = 43 years). Total lifetime trauma exposure in revictimized suicide attempters was significantly higher compared to non-revictimized suicide attempters ($F\text{-ratio}=63.1, p<0.0001$). Figure 2. Childhood emotional climate scores were significantly lower in revictimized suicide attempters compared to non-revictimized suicide attempters ($p=0.02$).

There was no difference in depression severity (MADRS) or in comorbidity with personality disorder or substance abuse between revictimized and with non-revictimized patients ($p\text{-values } 0.47\text{--}0.84$).

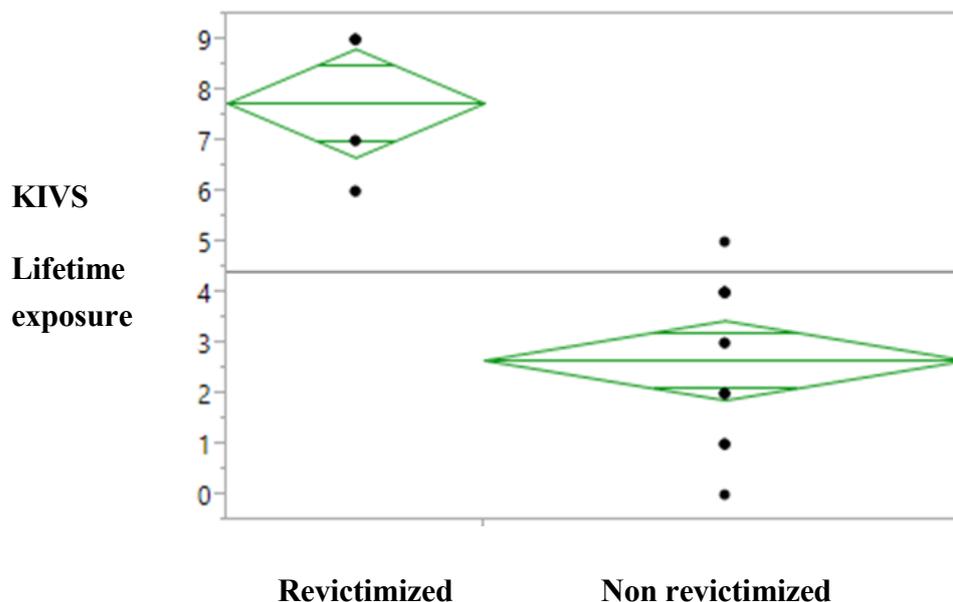


Figure 2. KIVS lifetime exposure in revictimized and non revictimized suicide attempters

4.1.2 Clinical characteristics and ratings of depressive symptoms, childhood adversity and hypersexuality in study IV of hypersexual disorder

Characteristics of study participants are presented in Table 4.

Table 4. Characteristics and clinical ratings of study participants in study IV-Hypersexual disorder

		Patients	Healthy Volunteers N=39	Statistics (<i>t-test</i> , Kruskal Wallis), p value
Age (years)	Mean	39.2	37.5	<i>p</i> =0.45
	Range	19-65	21-62	
	Std	11.5	11.9	
HDSI	Mean	19.6	1.6	<i>p</i> <0.001
	Range	6-28	0-9	
	Std	5.7	2.2	
SCS	Mean	27.8	11.1	<i>p</i> <0.001
	Range	12-39	10-14	
	Std	6.9	1.2	
HD:CAS	Mean	10.3	0.38	<i>p</i> <0.001
	Range	1-22	0-4	
	Std	5.4	0.88	
MADRS	Mean	18.9	2.4	<i>p</i> <0.001
	Range	1-50	0-12	
	Std	9.7	2.9	
CTQ Total (n=65)	Mean	39.95	32.53	<i>p</i> <0.001
	Range	25-80	25-70	
	Std	11.48	8.75	
CTQ Emotional Abuse	Mean	8.1	6.2	<i>p</i> =0.0003
	Range	5-18	5-16	
	Std	3.1	2,4	
CTQ Physical Abuse	Mean	6.5	5.4	<i>p</i> =0.0084
	Range	5-19	5-9	
	Std	2.8	1.1	
CTQ Sexual Abuse	Mean	5.8	5.1	<i>p</i> =0.0079
	Range	5-16	5-7	
	Std	2.1	0.3	
CTQ Emotional Neglect	Mean	12.0	9.4	<i>p</i> =0.0011
	Range	5-25	5-24	
	Std	4.5	4.1	
CTQ Physical Neglect	Mean	7.5	6.4	<i>p</i> =0.0017
	Range	5-17	5-16	
	Std	2.5	2.5	
CTQ Minimization/Denial	Mean	8.5	10.6	<i>p</i> =0.0004
	Range	3-15	3-15	
	Std	3.0	2.7	

The SCS scores showed a significant positive correlation with HD:CAS scores ($\rho = 0.5$, $p < 0.0001$).

There was a significant positive correlation between depression severity measured with MADRS-S and ratings of hypersexual behavior (SCS, HD:CAS), ($p = 0.0026$; $p = 0.0036$). There was also a significant positive correlation between HD:CAS and CTQ ($\rho=0.28$, $p = 0.025$).

The correlations between CTQ with SCS and MADRS-S scores were not significant ($p = 0.76$; $p = 0.49$).

4.2 NEUROENDOCRINE MEASUREMENTS IN SUICIDE ATTEMPTERS

4.2.1 CSF and plasma Oxytocin levels

The mean CSF and plasma oxytocin levels are presented in Table 5.

CSF oxytocin levels in suicide attempters showed a trend to be lower compared to healthy volunteers adjusted for age, (t ratio = -1.81, $p = 0.077$, Cohen's $d = 0.59$, 95% CI = -0.03-1.21), Figure 3.

CSF and plasma oxytocin levels did not differ significantly between male and female suicide attempters ($p = 0.38$; $p = 0.35$) or between male and female healthy volunteers ($p = 0.57$; $p = 0.13$).

Table 5. CSF and plasma oxytocin levels in suicide attempters and healthy volunteers

CSF Oxytocin (fmol/mL)				
	Mean	Median	SD	Range
All patients, (N=24)	11.7	11	3.9	6-22
Healthy volunteers (N=18)	19.2	13	15.1	5-54

Plasma Oxytocin (fmol/mL)				
	Mean	Median	SD	Range
All patients,(N=24)	6.2	5	3.2	2-15
Healthy volunteers, (N=19)	4.9	4	3.8	1-16

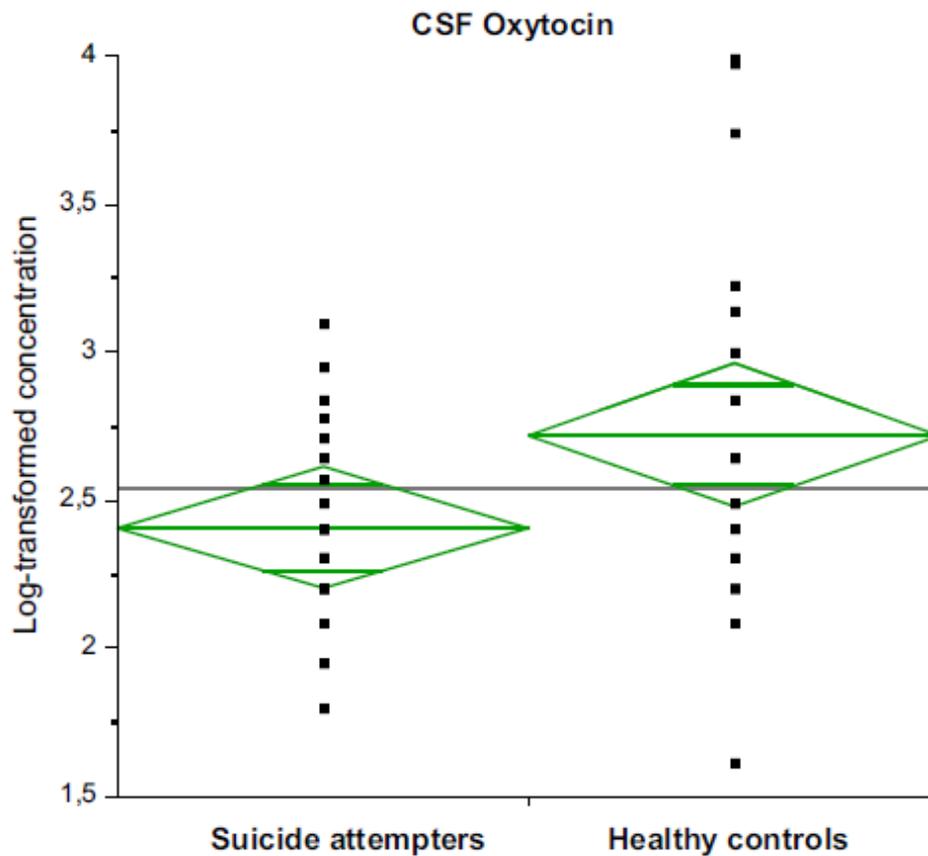


Figure 3. CSF oxytocin levels in suicide attempters and healthy volunteers

4.2.2 CSF and plasma Cortisol and DHEAS levels

CSF and plasma cortisol and DHEA-S levels in patients and in healthy volunteers as well as unadjusted and adjusted group comparisons are shown in Table 6. CSF and plasma cortisol levels were higher in suicide attempters compared to healthy volunteers adjusted for age, major depression diagnosis and comorbid substance misuse diagnosis (t ratio=2.8, p=0.009; t ratio=2.8, p=0.007), Figure 4.

CSF DHEA-S levels did not differ significantly between suicide attempters and healthy volunteers (t ratio=0.9, p=0.4). Broken down by gender, male suicide attempters had

significantly higher CSF DHEA-S levels compared to male healthy volunteers adjusted for age (t ratio=2.2, p=0.04).

A sensitivity analysis was performed due to the age difference between the groups by removing male patients within the age range not represented in controls. There was a significant difference in mean CSF DHEA-S levels between male patients (Mean±SD) (12.9±3.7 nmol/l, n=6) and male controls (8.4±2.6 nmol/l, n=12), p=0.009, Figure 5.

CSF DHEA-S levels did not differ significantly between female suicide attempters (Mean±SD) (7.2±3.9 nmol/l, n=10) and female healthy volunteers (Mean±SD) (9.2±3.5 nmol/l, n=6) (t ratio=-0.74, p=0.47, age adjusted).

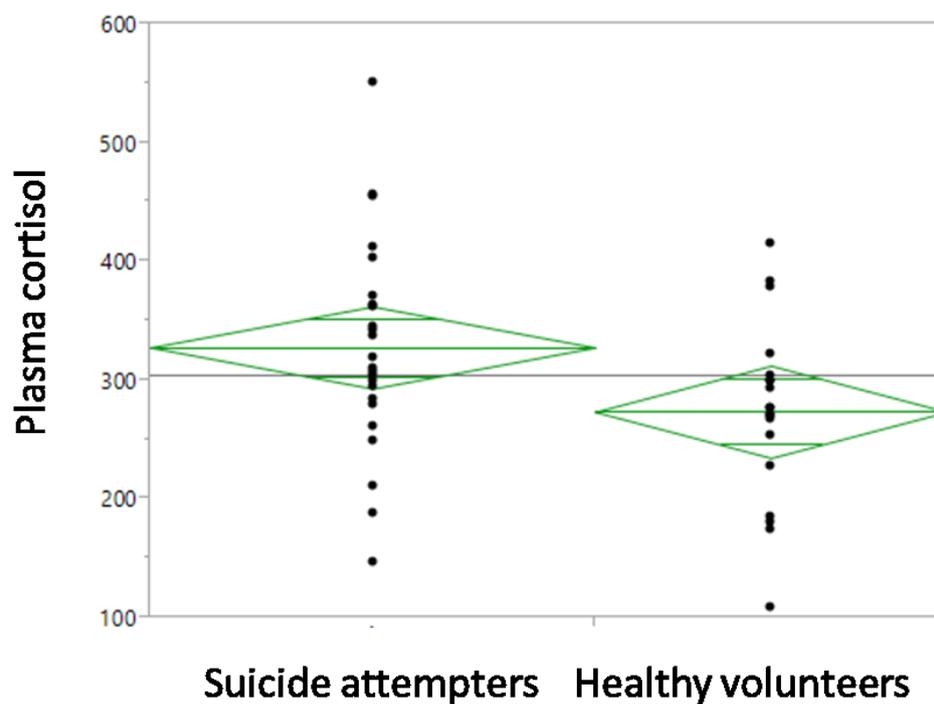


Figure 4. Plasma cortisol levels in suicide attempters and healthy volunteers

Table 6. CSF 5-HIAA, CSF and plasma cortisol and DHEAS levels (nmol/l) in suicide attempters and healthy volunteers

Endocrine measure	Suicide attempters				Healthy volunteers				Statistics p-value unadjusted (adjusted)
	Mean	Median	SD	Range	Mean	Median	SD	Range	
CSF cortisol (n=24; n=18)	20.8	18.5	8.1	11-40	14.6	15	3.4	4-19	Z=-2.1 ^a , p=0.04, (p=0.009*)
Plasma cortisol (n=24; n=19)	327.5	315	89.4	148-551	273.4	277	76.1	109-416	F ratio=4.4, p=0.04, (p=0.007*)
CSF DHEAS (n=24; n=18)	8.1	8.1	4.5	1.8-17.8	8.7	8.4	2.9	3.9-13.7	F ratio=0.3, p=0.6, (p=0.4*)
Plasma DHEAS (n=24; n=19)	3939	3978	1952	780-8000	4918	4587	1063	3760-7767	Z=2.1 ^a , p=0.04, (p=0.7)
CSF cortisol DHEAS ratio	3.8	3.1	3.0	0.8-13.6	1.9	1.8	0.9	0.5-3.8	F ratio=6.1, p=0.02, (p=0.3)
Plasma cortisol DHEAS ratio	0.1	0.08	0.1	0.04-0.6	0.06	0.06	0.02	0.03-0.1	Z=-3.2 ^a , p=0.001, (p=0.7)
CSF 5-HIAA (n=26; n=17)	86.5	84.6	28	47.8-161	97.8	88.4	41.4	25.8-183	F ratio=1.1, p=0.3, (p=0.1*)

a Univariate test methods one way Anova, Wilcoxon test.

*Group comparison adjusted for age, comorbid substance abuse and diagnosis of major depression. All other comparisons adjusted for age.

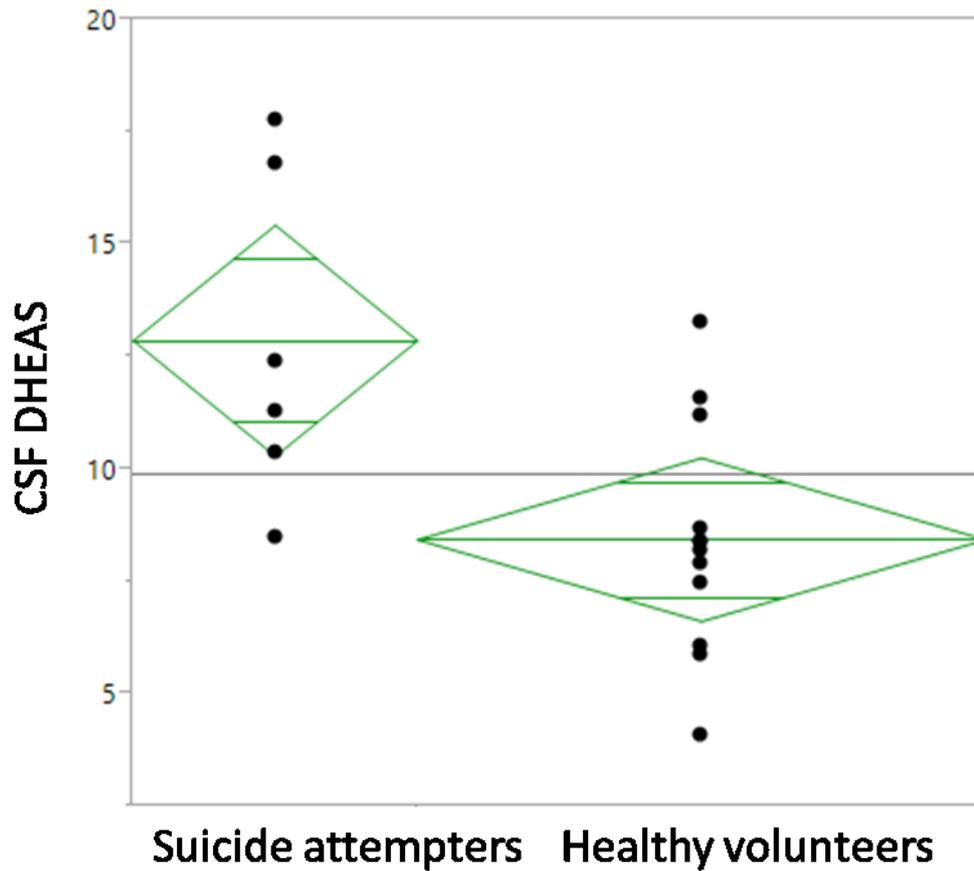


Figure 5. CSF DHEAS levels in male suicide attempters and male healthy volunteers (sensitivity analysis)

4.2.3 CSF 5-HIAA levels

Suicide attempters tended to have lower CSF 5-HIAA levels compared to healthy volunteers adjusted for age (t ratio=-1.5, $p=0.1$). Broken down by gender only female suicide attempters had significantly lower CSF 5-HIAA levels compared to female healthy volunteers adjusted for age, comorbid depression diagnosis and substance abuse (t ratio=-3.2, $p=0.009$).

CSF 5-HIAA showed a trend for correlation with CSF cortisol levels in suicide attempters ($r=0.40$, $n=24$, $p=0.05$) and a significant positive correlation with CSF cortisol/DHEAS ratio ($\rho=0.55$, $p=0.04$) in male suicide attempters,

4.3 NEUROENDOCRINE MEASUREMENTS IN HYPERSEXUAL DISORDER

4.3.1 Dexamethasone suppression test

Baseline cortisol and ACTH levels did not differ between patients and healthy volunteers. The dexamethasone non-suppression status was significantly more common in patients with hypersexual disorder with 18 of 67 (26.9%) classified as non-suppressors whereas 4 of 39 (10.3%) healthy volunteers were classified as non-suppressors ($p = 0.049$, Fisher's exact test, two-tailed). There was no significant difference in age, use of antidepressants, or depression severity between non-suppressors and suppressors in patients with hypersexual disorder.

DST Cortisol levels showed a trend to be higher in patients compared to healthy controls ($p = 0.096$). A ROC analysis, estimated the optimal threshold level for the non-suppressor status of DST cortisol concentration at 8 a.m., for prediction of the diagnosis of hypersexual disorder, to be higher than ($=5\mu\text{g/dl}$), namely $7.3\ \mu\text{g/dl}$ (sensitivity 19.4 %, specificity 100%, AUC = 0.60; Chi square DST cortisol = 4.92, $p = 0.027$).

Patients with hypersexual disorder had significantly higher DST ACTH compared to healthy volunteers ($p = 0.001$), Figure 6.

Models from regression analyses to determine whether DST non-suppression status could be predicted by the diagnosis of hypersexual disorder adjusted for childhood trauma and for frequency of hypersexual behavior during the last two weeks and whether plasma DST ACTH could be predicted by the diagnosis of hypersexual disorder adjusted for childhood trauma were significant, (Chi square = 11.83, $p = 0.0080$; adjusted RSq = 0.13, $p = 0.0003$). Tables 7 and 8.

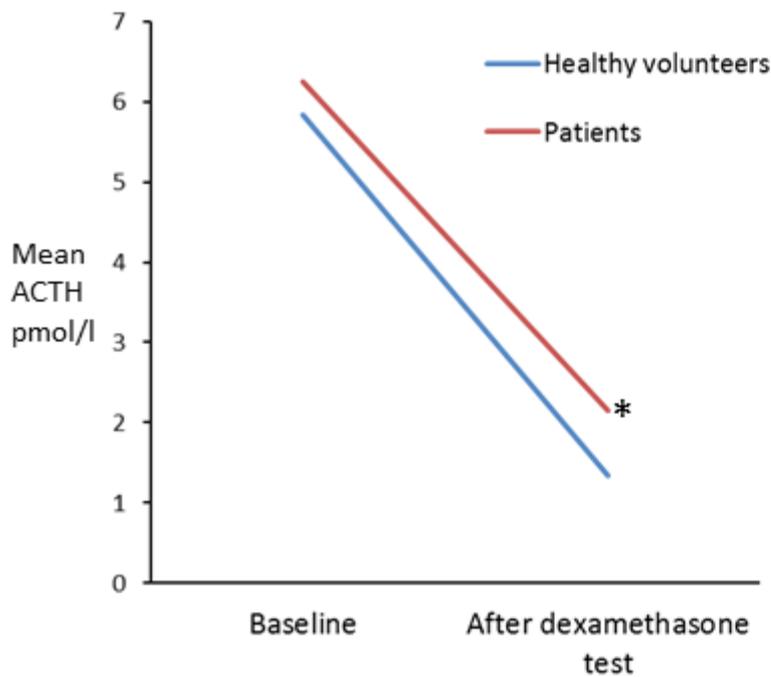


Figure 6. Mean post-dexamethasone plasma ACTH concentrations in male patients with hypersexual disorder and in male healthy volunteers.*p-value = 0.0011.

Table 7. Logistic regression analysis of predictors to dexamethasone non suppression status in study participants

	chi square	<i>p</i> value
Hypersexual disorder	9.90	0.0016
Childhood trauma (CTQ)	1.53	0.22
HD:CAS	3.65	0.056

Table 8. Regression analysis of correlates to post dexamethasone suppression test ACTH levels in men with hypersexual disorder.

	t ratio	<i>p</i> value
Hypersexual disorder	3.74	0.0003
Childhood trauma (CTQ)	-3.03	0.0031

4.4 NEUROENDOCRINE MEASUREMENTS AND CLINICAL RATINGS

4.4.1 CSF and plasma oxytocin and suicide intent

Correlations between CSF oxytocin and the Suicide Intent Scale, Planning subscale and Freeman scales in suicide attempters broken down by gender are presented in Table 9 and Figure 7.

Table 9. Correlations (Pearson's r or Spearman's ρ) between CSF oxytocin and the Suicide Intent Scale, Planning subscale and Freeman scales in suicide attempters

	Suicide Intent	Planning subscale	Freeman probability of intervention	Freeman total
CSF Oxytocin	-0.37*	-0.48**	-0.40*	-0.18
	<i>-0.87***</i>	<i>-0.78***</i>	<i>-0.58**</i>	<i>-0.23</i>
	0.06	-0.28	-0.15	-0.05

*** $p < 0.01$

** $p < 0.05$

* $p < 0.1$

Bold: all suicide attempters

Men

Women

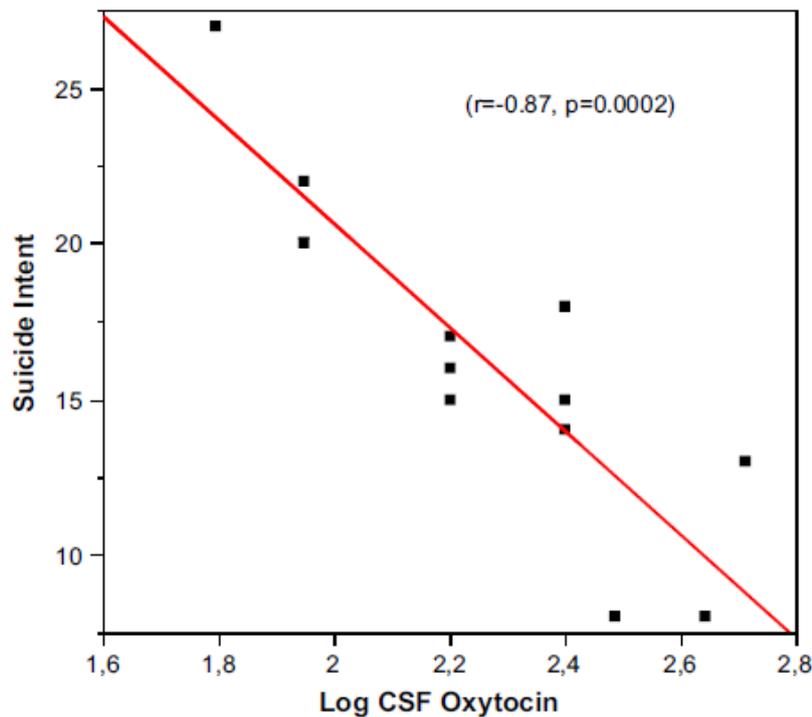


Figure 7. Suicide intent (SIS score) and CSF Oxytocin in male suicide attempters

A regression model for predicting CSF oxytocin was significant (RSq adj = 0.52, DF = 4, n = 20, p = 0.0042.), Table 10.

Table 10. Regression analysis with suicide intent and violent behavior as predictors for CSF oxytocin levels in suicide attempters

	t ratio	p value
Suicide Intent	-3.33	0.0046
KIVS lifetime violent behaviour	-1.79	0.094
Age	-0.36	0.72
Gender (Woman)	2.68	0.017

CSF Oxytocin did not correlate with plasma oxytocin significantly. Plasma oxytocin was significantly correlated with the planning subscale of SIS in the whole group of suicide attempters and with both Freeman interruption probability and the planning subscale of SIS only in male suicide attempters when broken by gender ($r = -0.44$, $p = 0.048$; $r = -0.29$, $p = 0.18$; $r = -0.58$, $p = 0.029$).

4.4.2 HPA axis and hypersexual behavior

Both the Sexual compulsivity scale scores and HD:CAS scores showed a significant negative correlation with baseline cortisol plasma levels ($r = -0.25, p = 0.041$; $\rho = -0.31, p = 0.012$) HD:CAS scores correlated also negatively with DST cortisol ($\rho = -0.33, p = 0.0071$), Figure 8.

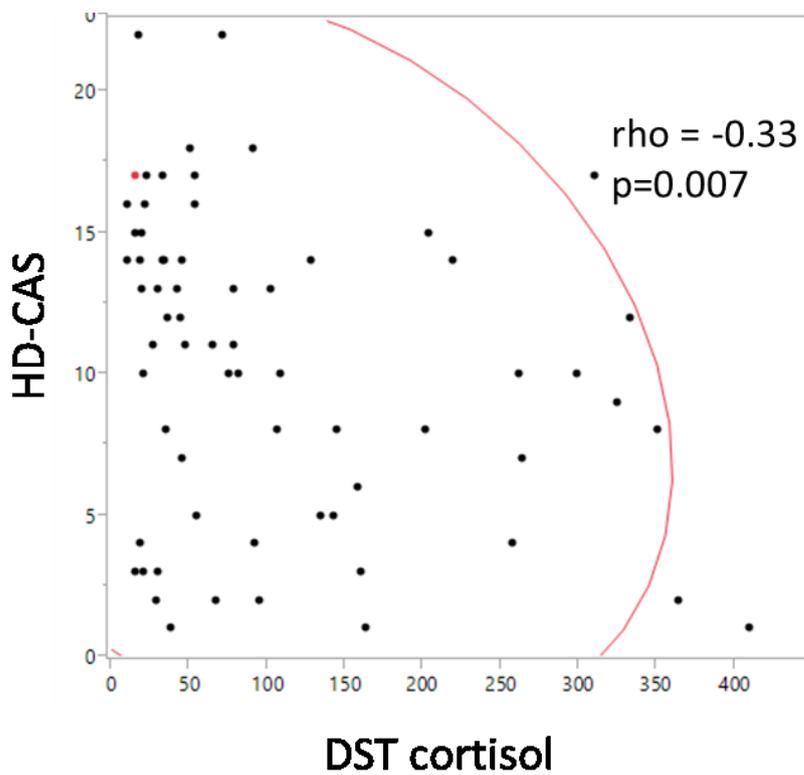


Figure 8. Hypersexual behavior (HD:CAS) and DST cortisol levels in male patients with hypersexual disorder

4.4.3 Childhood adversity-Revictimization, Depression and Neuroendocrine measurements

Oxytocin- Cortisol and DHEAS in Suicide attempters

CSF and plasma oxytocin did not show a significant correlation with exposure scores to interpersonal violence as a child and as an adult ($\rho=0.16$, $p=0.49$; $\rho=0.04$, $p=0.85$), ($\rho=-0.23$, $p=0.31$; $\rho=-0.30$, $p=0.18$)

Revictimized suicide attempters had significantly lower plasma oxytocin levels compared to non revictimized suicide attempters ($p=0.046$) whereas the CSF oxytocin levels did not differ significantly between the two groups ($p=0.85$), Figure 9.

Exposure to interpersonal violence as a child showed a trend for negative correlation with CSF cortisol/DHEAS ratio ($\rho=-0.39$, $n=21$, $p=0.08$). Lower CSF cortisol/DHEAS ratio was associated with higher exposure to interpersonal violence as a child adjusted for age, gender and severity of depression in the regression model.

Lifetime violent behavior showed a trend to negative correlation with CSF oxytocin ($r=-0.38$, $n=22$, $p=0.084$). CSF oxytocin showed this trend for negative correlation with lifetime violent behavior only in women suicide attempters ($r=-0.64$, $n=9$, $p=0.065$).

Depression severity measured with MADRS showed a trend for positive correlation with CSF cortisol ($r=0.35$, $p=0.1$) and a significant positive correlation with CSF cortisol only in male suicide attempters ($r=0.69$, $p=0.009$).

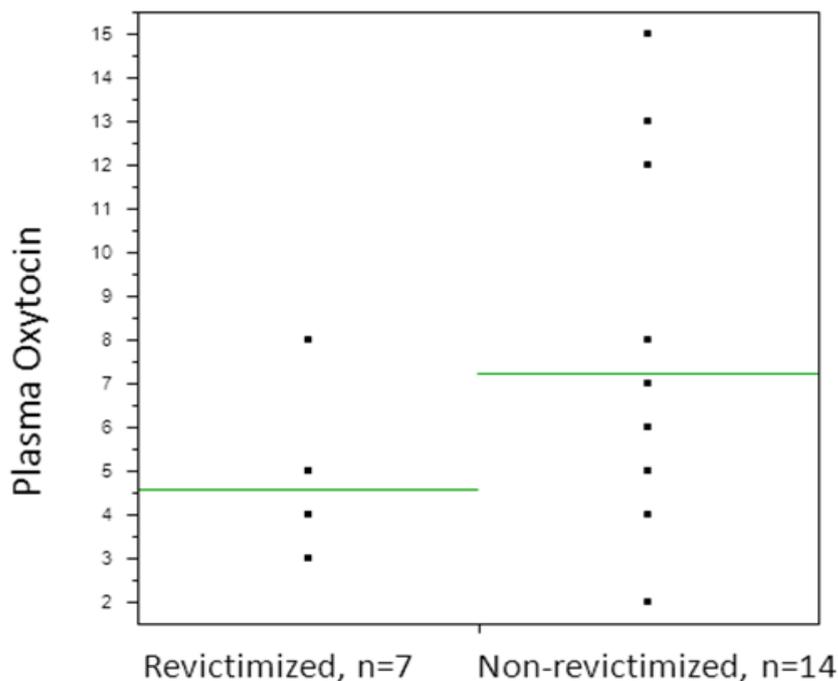


Figure 9. Mean plasma oxytocin levels in revictimized and non-revictimized suicide attempters

Hypersexual disorder

In the patients with hypersexual disorder, exposure to childhood trauma measured with CTQ showed a significant negative correlation with DST ACTH ($\rho = -0.28$, $p = 0.02$) and a trend for negative correlation with DST Cortisol ($\rho = -0.21$, $p = 0.09$), Figure 10.

The correlations between all HPA axis measures and depression severity measured with MADRS were non-significant ($p = 0.9$; $p = 0.7$; $p = 0.8$; $p = 0.7$).

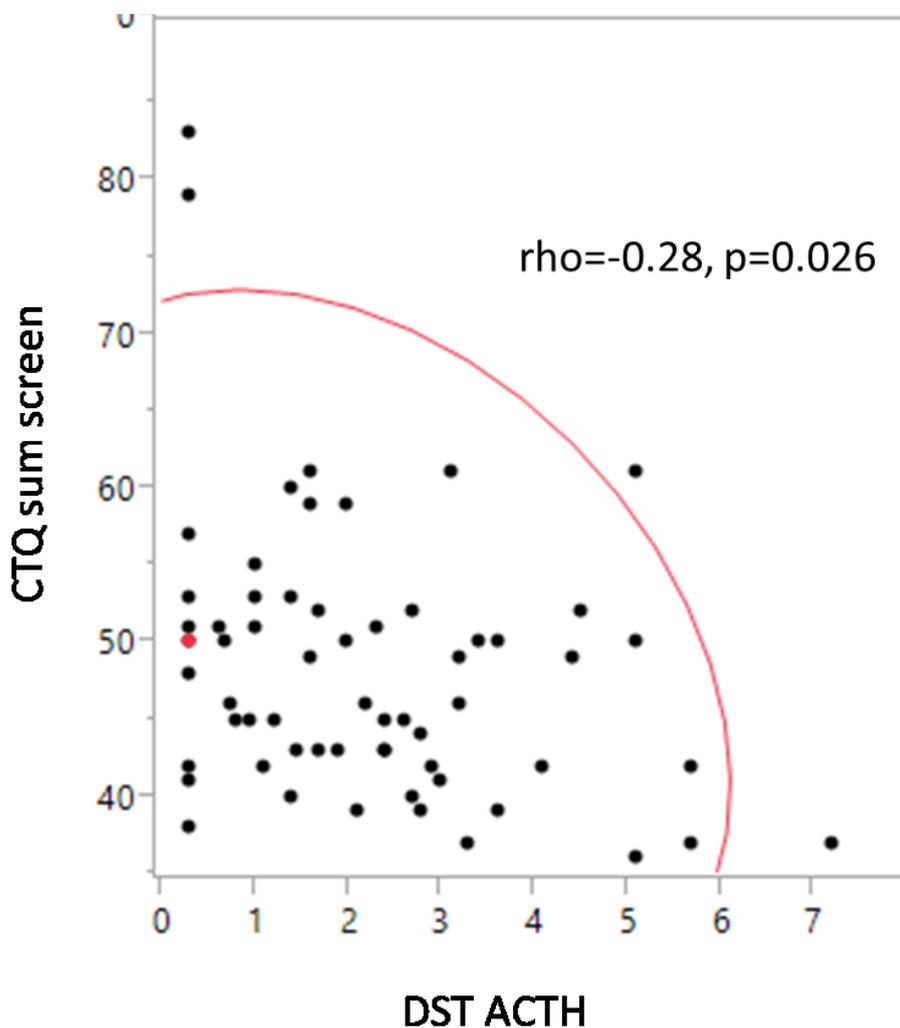


Figure 10. Exposure to childhood trauma (CTQ) and DST ACTH in hypersexual disorder

4.5 COMPLETED SUICIDE

There were six suicides (21.4%) during the follow-up time: 2 women and 4 men.

SIS and KIVS scores did not differ significantly between suicides and survivors ($p = 0.45$; $p = 0.53$).

Five of six suicide victims had CSF 5-HIAA level below the median ($p=0.08$, Fisher exact one sided). Four of five suicide victims had CSF cortisol level above the median ($p=0.16$, Fisher exact one sided). Figure 11.

CSF cortisol was significantly higher in suicide victims with high exposure to interpersonal violence as a child (scores from 4 to 5) compared to suicide victims with low exposure to interpersonal violence as a child (scores from 0 to 2), ($p=0.003$).

There was no significant difference in CSF and plasma oxytocin, CSF DHEA-S levels, and CSF cortisol/DHEAS ratio between suicides and survivors ($p = 0.32$; $p = 0.49$; $p=0.47$; $p=0.9$), Figure. 12 shows CSF oxytocin levels in suicide victims and survivors.

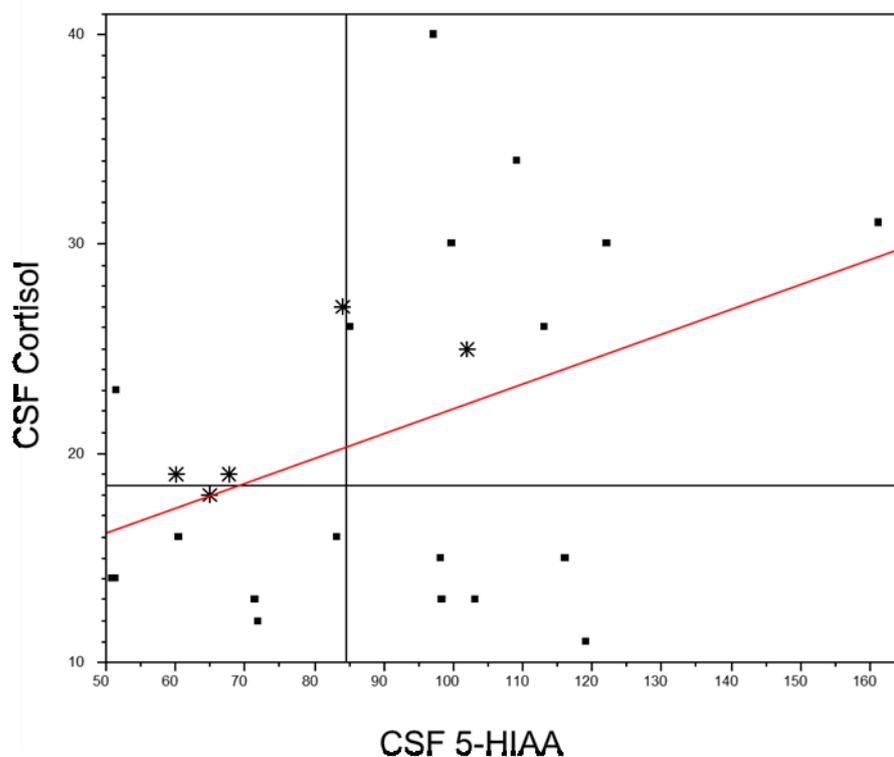


Figure 11. Correlation between CSF 5-HIAA and CSF cortisol with median split lines. Suicide victims marked with stars.

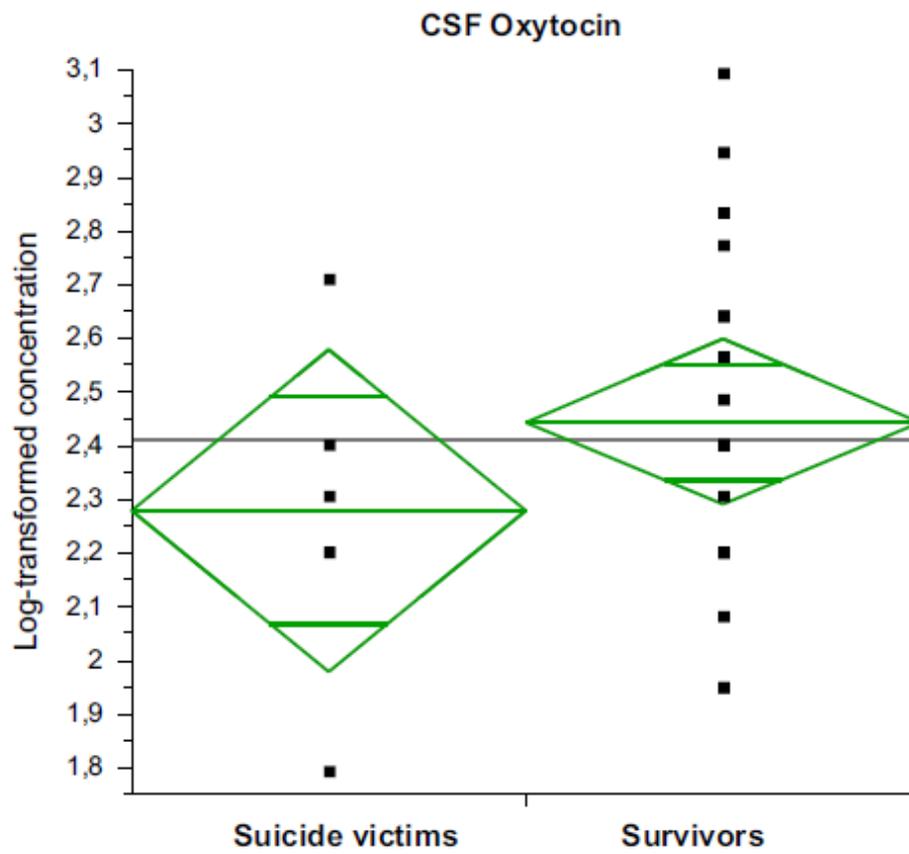


Figure 12. CSF oxytocin levels in suicide victims and survivors.

5 DISCUSSION

5.1 THE ROLE OF OXYTOCIN IN SUICIDE ATTEMPTERS

To begin with, although there was no significant difference in CSF and plasma oxytocin levels between suicide attempters and healthy volunteers, there was a trend for lower CSF levels in suicide attempters group compared to healthy volunteers. Moreover, both low CSF and plasma oxytocin were associated with a stronger intent to die in male suicide attempters. The activity of oxytocin in the brain is measured with CSF levels, that do not necessarily correlate with plasma levels as the dendritic and terminal secretion of oxytocin may not be always coordinated and depends on the stimulus (Altemus et al., 2004; Landgraf and Neumann, 2004). In our study, although CSF and plasma oxytocin levels did not show a correlation, they both negatively correlated with suicide intent. The inverse relationship between oxytocin and suicide intent was shown with two different rating scales measuring suicide intent. This negative correlation between oxytocin levels and suicide intent was more obvious with the planning subscale of the Suicide Intent Scale, reaching significance level in the whole group of suicide attempters. Only one study, Lee et al. investigated oxytocin's relation in suicide behavior and reported lower levels of CSF oxytocin in four suicide attempters compared to 36 non-attempters with personality disorder (Lee et al., 2009).

But what are the suicide intent scales measuring and how can their relationship with oxytocin be understood? The planning subscale of Beck Suicide Intent Scale includes the factual aspects and circumstances of suicide behavior such as the degree of premeditation and preparation for attempt, leaving a suicide note, the timing and isolation with precautions against intervention as well as acting to gain help during the attempt and the final acts in anticipation of death. Similarly, the Freeman interruption probability scale measures how likely is the event of rescue that depends directly on the circumstances of the suicide attempt, explicitly the degree of isolation.

Known risk factors for suicide include lack of social support, isolation (Heikkinen et al., 1994) and oxytocin has a key role in prosocial behavior, affiliative behavior and attachment (Heinrichs et al., 2009). Oxytocin is also important in processing social stimuli and social memory as well as social decision making in social contexts (Macdonald and Macdonald, 2010). In the present cohort of suicide patients scored high in SIS with mean score almost 18. Although the predictive value of a rare event such as suicide is low, in a review on suicide

intent scale, the authors report a positive predictive value of 22.5% with a cut-off score of 19 (Freedenthal, 2008). This indicates that this sample of suicide attempters had a serious intent to die rather than the suicide attempt being a way to get attention and help. The lower oxytocin in the suicide attempters might reflect a deficit in prosocial behavior leading to an impaired social support network that increases the risk for suicide behavior.

Oxytocin might be related with suicide behavior in other ways. It has been suggested that suicide attempters have “cognitive rigidity” (Neuringer, 1964) as well as deficits in decision making when making choices under uncertainty (Jollant et al., 2010; Turecki and Brent, 2015). Even healthy first degree relatives to suicide completers may exhibit impairment in decision making (Hoehne et al., 2015). Oxytocin is implicated in stress regulation, regulates stress in relation to social interaction and has an inhibitory effect on the HPA axis (Heinrichs et al., 2003; Neumann, 2009). In animal studies, intracerebral administration of oxytocin increases cognitive flexibility and the impaired social behavior in oxytocin receptor null mice (Sala et al., 2011).

Yrigollen et al. reported that a number of genes associated with the oxytocin system and affiliative behavior are associated with autism spectrum disorders (Yrigollen et al., 2008) and Hollander et al., reported that infusions of oxytocin can reduce repetitive behavior in adults with autistic traits and Asperger syndrome (Hollander et al., 2003). Neumann et al., reported that oxytocin inhibits the stress-induced activity of the HPA axis responsiveness (Neumann, 2002). Thus the oxytocin system might be related to suicide behavior through social factors as well as stress regulation and cognitive deficits such as in decision making.

Although in the same direction, no significant correlation of suicide intent and oxytocin was observed in women. This lack of association might be due to confounding factors that were not taken into consideration, namely the effects of estrogen on oxytocin levels as a result of the normal variation of their menstrual cycle. It might also be that gender difference regarding the role of oxytocin make men more vulnerable to a possible dysfunction of the oxytocin system.

Oxytocin is also related to aggression and is shown that mice with knockout of the oxytocin gene or receptor have more aggression and altered social behavior (DeVries et al., 1997; Ragnauth et al., 2005; Takayanagi et al., 2005; Winslow et al., 2000; Winslow et al., 2003). Moreover, exogenous intracerebral administration of oxytocin in oxytocin receptor null mice causes a reduction in their aggressive behavior (Sala et al., 2011). In humans, the administration of intranasal oxytocin regulates defensive aggression toward out-groups

among humans and increases in-group trust and cooperation among humans (De Dreu et al., 2010). Oxytocin was also reported to reduce stress reactivity when administered to patients with borderline personality disorder (Simeon et al., 2011). However, the effects of oxytocin seem to depend on the context and underlying psychopathology. Bartz et al., reported that patients with borderline personality disorder with chronic interpersonal insecurities when administered intranasal oxytocin showed less trust and less cooperative responses (Bartz et al., 2011).

Lee et al., reported for the first time in humans that life history of aggression was negatively correlated with CSF oxytocin (Lee et al., 2009). In the same study, it was also first reported an inverse relationship between CSF Oxytocin levels and a history of suicidal behavior. In the same line, in the female suicide attempters, we reported a trend for negative correlation between CSF oxytocin and lifetime expressed violent behavior and in the regression analysis for predicting CSF oxytocin (corrected for age and gender) suicide intent was a significant predictor whereas lifetime expressed violent behavior remained at the trend level.

As already been discussed, childhood trauma has an impact and long lasting effects on the different neurobiological systems (De Bellis and Zisk, 2014). We did not find the expected negative correlation between oxytocin levels and childhood trauma as it was previously reported in the literature (Bertsch et al., 2013; Heim et al., 2009; Opacka-Juffry and Mohiyeddini, 2012). As only large effects of the exposure to childhood trauma on oxytocin levels could be shown because of sample size limitations, these negative finding may be a type II error. There are also importance differences in the sample characteristics between different studies. Heim et al., as well as Opacka-Juffry and Mohiyeddini reported the inverse correlation in samples of volunteers while our sample consisted of suicide attempters with high levels of psychopathology including comorbidity. Different instruments in measuring childhood trauma were used that may also account for this discrepancy as our measurement with KIVS does not focus on emotional abuse and neglect that has been strongly associated with oxytocin.

Moreover, the revictimized group that had the highest sum of exposure to violence and trauma had lower levels of plasma oxytocin compared to non revictimized suicide attempters. Additionally, as childhood emotional climate scores were lower in the revictimized group and the revictimized were not more depressed than non revictimized, the revictimization status seems to be related more to childhood adversity than the present state. It might be so that the revictimized group had a major impact on the oxytocin system that we were able to detect and the subsequent dysfunction with lower oxytocin levels leads

to revictimization (Heim et al., 2009). Being a victim of violence in childhood is associated with higher risk for revictimization in adult life (Widom et al., 2008). This was also present in our group with reported positive correlations between exposure to violence as a child and exposure to violence in adulthood.

However, not all studies report lower oxytocin in relation to childhood adversity. Pierrehumbert et al., reported higher levels of oxytocin in maltreated women and young girls (Pierrehumbert et al., 2010). Although there are contradicting results, there is consensus regarding the possible effect of both genetic and epigenetic factors on the oxytocin system (De Bellis and Zisk, 2014; Herpertz and Bertsch, 2015; Seltzer et al., 2014). Genetic factors such as the oxytocin transporter rs2254298 polymorphism were reported to interact with early adversity and predict anxiety and depressive symptoms (Thompson et al., 2011). Cicchetti et al., reported a three way interaction between maltreatment X gender X Genetic variants of the OXTR genotype in predicting borderline symptomatology (Cicchetti et al., 2014). Bradley et al., reported an interaction between the oxytocin receptor gene polymorphism OXTR rs53576 and a positive family environment in predicting resilient coping and positive affect (Bradley et al., 2013). Finally, Herpertz and Bertsch proposed a model for the pathophysiology of borderline personality disorder in which oxytocin has a central role affecting among others the social approach behavior and affect regulation (Herpertz and Bertsch, 2015).

5.2 THE ROLE OF CORTISOL AND SEROTONIN

Cortisol in both CSF and plasma was significantly higher in suicide attempters compared to healthy volunteers. This is in line with the literature suggesting a hyperactivity of the HPA axis often shown with DST non suppression. This is most commonly found in suicide victims with Coryell and Schlessler reporting that DST non suppression status increases the risk for suicide 14 times compared to suppressors (Coryell and Schlessler, 2001). In suicide attempters the hyperactivity of HPA axis is not that profound and literature has shown mixed results (Coryell, 2012). A recent meta-analysis of cortisol levels reported an age depended effect of cortisol with the association shown in younger patients (O'Connor et al., 2016). Depression can be a confounding factor and in our sample depression severity tended to correlate with CSF cortisol levels and correlated significantly only in men. However, mood disorder diagnoses did not have effect on the results concerning the group

comparisons of CSF cortisol. The literature suggests a deregulation of HPA axis in depression with higher cortisol levels (Swaab et al., 2005). The deregulation is from an overactive HPA axis with increased ACTH secretion and hypercortisolemia, especially in depression with melancholic and psychotic features (Carroll et al., 2007; Mann and Currier, 2007).

Only female suicide attempters had lower CSF 5-HIAA levels compared to female healthy volunteers. Low 5-HIAA in the CSF is the most replicated biomarker for suicide (Rosell and Siever, 2015; Turecki, 2014) but mostly reported in men. The question of trait or state of the low 5-HIAA in suicide has been ongoing (Asberg et al., 1986). Serotonin dysfunction has been related to both traits of anxiety, impulsivity and aggression and at the same time to depression (Mann and Currier, 2007).

5.3 THE ROLE OF DHEA-S IN SUICIDE ATTEMPTERS

There was no significant difference between CSF and plasma DHEA-S levels in the whole group of suicide attempters compared to healthy volunteers. When gender and age taken into account, as DHEA-S levels are declining with increasing age, we found that only male suicide attempters had higher CSF DHEA-S levels compared to male healthy volunteers. This finding is not related with depression severity or comorbidity with mood disorder and substance abuse. Additionally, the most common finding in depression is decreased DHEA-S (Maninger et al., 2009). DHEA-S has not been investigated in suicide and only one study in male veterans with PTSD reported increased DHEA plasma levels in the veterans with a previous suicide attempt compared with those without a history of suicide attempt (Butterfield et al., 2005). How can the higher DHEA-S levels interpreted in suicide?

The higher DHEA-S levels can be understood as an adaptive and compensatory mechanism as an effect of childhood adversity. DHEA-S is implicated in stress regulation and the ratio with cortisol (cortisol/DHEA-S) in the estimation of the allostatic load (Maninger et al., 2009). This ratio is proposed as a sensitive measure of the allostatic load. The role of DHEA-S is suggested to be protective, promoting resilience in stress and childhood trauma (Yehuda and Flory, 2007). DHEA-S has been shown to promote coping even in experimental stress conditions (Morgan et al., 2009; Morgan et al., 2004).

Indeed, higher exposure to interpersonal violence as a child adjusted for age, gender and severity of depression was related with lower CSF cortisol/DHEA-S ratio in suicide attempters. Other studies also found lower plasma cortisol/DHEA-S ratio in PTSD patients with a history of childhood abuse (Kellner et al., 2010; Yehuda et al., 2006). Low cortisol levels are usually found in adults that were exposed to childhood adversity (Heim et al., 2001), together with high DHEA-S levels as compensation, can stand for the low ratio in suicide attempters exposed to childhood trauma.

An alternative explanation of the higher levels of DHEA-S can be found in aggressive and violent behavior that is a known risk factor for suicide (Jokinen et al., 2010). Although the role of DHEA-S is not clear yet in aggression there is some preliminary findings such as the fact that higher DHEA-S levels were reported in male adolescents with conduct disorder (Maninger et al., 2009; van Goozen et al., 1998). Furthermore, congenital adrenal hyperplasia, prenatal androgen exposure of the brain alters personality characteristics of aggression in a gender specific manner (Mathews et al., 2009).

Although, the exact actions of DHEA-S are yet to be revealed, DHEA-S increases neurogenesis via brain-derived neurotrophic factor (BDNF), is a non-competitive antagonist on the GABAA receptors and acts on NMDA and sigma-1 receptors (Maninger et al., 2009).

5.4 SUICIDE RISK AND PREDICTION

From the 28 suicide attempters, 6 (21.4%) died from a subsequent suicide during the mean follow up time of more than 20 years. This indicates that this was a clinical sample of very high suicide risk equivalent to the risk suicide attempters with severe coexistent psychiatric disorder (Tidemalm et al., 2008).

We confirmed previous findings of the hyperactivity HPA axis and suicide risk as four of five suicide victims had CSF cortisol level above the median (Jokinen et al., 2007). Specifically, suicide victims with high exposure to interpersonal violence as a child had higher CSF cortisol levels compared to suicide victims with low exposure.

This is in line with previous research on gene X environment interaction. Although the results from environment gene interaction studies have not been consistent, mainly due to methodological issues, there are some promising results by revealing specific interactions (Mandelli and Serretti, 2013). Roy et al. found an interaction effect increasing the risk for

suicide attempt, between exposure to childhood adversity and the FKBP5, a gene related to stress by moderating the activation of the glucocorticoid receptor (Roy et al., 2010). In the same line, Guillaume et al. reported an environment (childhood adversity in the form of sexual abuse and emotional neglect) X gene (CRH receptors gene) interaction on decision-making in suicide attempters (Guillaume et al., 2013). But beyond the genetic control of the FKBP5 gene, Zannas et al., proposes also epigenetic regulation of glucocorticoid-responsive genomic sites leading to FKBP5 disinhibition and stress related disorders (Zannas et al., 2016).

Results on epigenetic regulation have been already reported. Mc Gowan et al., in a post mortem study found epigenetic changes, increased methylation in a neuron-specific glucocorticoid receptor (NR3C1) promoter and lower levels of hippocampal glucocorticoid receptor expression in suicide victims with a history of childhood abuse compared to suicide victims without a history of child abuse (McGowan et al., 2009). Additionally, Labonte et al., reported site-specific DNA methylation alterations at the hippocampal glucocorticoid receptor promoter in abused suicide victims supporting that childhood adversity induces long lasting effects (Labonte et al., 2012). Moreover, in a study investigating DNA methylation levels genome-wide, reported that increased methylation of the Kit ligand gene was a mediator of the effect of childhood trauma resulting in lower cortisol reactivity in healthy individuals who underwent the Trier Social Stress Test (Houtepen et al., 2016).

Regarding the serotonin system, its main metabolite 5-HIAA in CSF was below the median in five out of six suicide victims. This is well documented finding in the literature that confirms the deregulation of the serotonin system in suicide. CSF 5-HIAA has been suggested as a suicide risk factor in the short term together with DST non suppression in the long term (Jokinen et al., 2009; Nordstrom et al., 1994; Samuelsson et al., 2006). Neither oxytocin nor DHEA-S was associated with completed suicide.

It is important to notice that there were correlations between the neuroendocrine biomarkers. CSF 5-HIAA showed a trend for positive correlation with CSF cortisol in suicide attempters and correlated positively with CSF cortisol/DHEAS ratio in male suicide attempters. Previous research suggests that although the serotonergic system and HPA axis interact and are influenced by genetic and epigenetic factors they are considered as independent predictors of suicide behavior (Jokinen et al., 2008; Jokinen et al., 2009). A bidirectional interaction is also proposed between the serotonergic system and DHEA-S through modulation of the CRH and ACTH release by hypothalamic 5-HT_{1A} receptor and GABA_A receptor-mediated regulation (Gartside et al., 2010; Moser et al., 2010).

The current predictive models for suicide are not effective in clinical praxis and the “biosignature for suicide” remains to be found (Oquendo et al., 2014). New biological pathways and research methodologies are applied and Sokolowski et al., proposed suicide behavior as one meta-system based on physical protein interaction, the interactome addressing the neurobiology of suicidal behavior as system imbalances (Sokolowski et al., 2015). The combination of both genetic as well as clinical assessments has shown promising results in the prediction of suicidal behavior (Niculescu et al., 2015).

5.5 HPA AXIS IN HYPERSEXUAL DISORDER

This thesis includes the first study investigating the HPA axis in male patients with hypersexual disorder reporting a dysregulation of the HPA axis shown with significantly more prevalent DST non-suppression status and higher DST ACTH plasma levels compared to healthy controls. These results were neither an effect of depressive symptoms nor childhood adversity suggesting a hyperactive HPA axis in male patients with hypersexual disorder and DST non-suppression status was predicted by the diagnosis of hypersexual disorder even when adjusted for childhood trauma and for hypersexual behavior during the last two weeks.

A hyperactive HPA axis in hypersexual disorder could be understood from the addiction model perspective. The definition of hypersexual disorder includes aspects of addiction such as that the person is “repetitively engaging in sexual fantasies, urges or behaviors in response to dysphoric mood states” such as anxiety and depression that may well correspond to craving and that there are “repetitive but unsuccessful efforts to control or significantly reduce these sexual fantasies, urges or behaviors” as well as “repetitively engaging in sexual behaviors while disregarding the risk for physical or emotional harm to self or others” (Kafka, 2010). According to the addiction model, the chronic use of substances induces increased levels of ACTH, thus a hyperactive HPA axis, with the corticotropin-releasing factor (CRF) facilitating craving by increasing negative affects during drug withdrawal. Thus, craving is a response to the allostatic load (Kakko et al., 2008; Koob et al., 2014). Likewise, in hypersexual disorder, patients with a hyperactive HPA axis and increased ACTH maintain their “addictive” sexual behavior to avoid the negative affective state that occurs with withdrawal. Supporting the addiction model, a recent fMRI study in individuals with problematic hypersexual behavior reported significantly increased sexual desire as well as

changed activation in the prefrontal cortex and subcortical areas compared to controls suggesting an altered neural circuitry mediating cue-induced desire for sexual behavior analogous to substance and behavioral addiction (Seok and Sohn, 2015).

Additionally, ratings of recent hypersexual severity (HD:CAS) showed a significant negative correlation with DST cortisol levels and both hypersexual rating scores (SCS, HD:CAS) were inversely related to baseline cortisol plasma levels. The interpretations of results becomes difficult as the effect of stress and HPA axis on sexual behavior is not well understood with contradicting results (Goldey and van Anders, 2012). In some studies of healthy volunteers plasma cortisol levels did not change during sexual arousal and orgasm (Exton et al., 2001; Exton et al., 2000) while in others cortisol was positively related to sexual arousal (Goldey and van Anders, 2012). When investigating individuals with risky sexual behavior, Harrison et al., reported higher salivary cortisol reactivity to the imagined social situation exercise and proposed that childhood adversity might have been related to the results as they could not control for it (Harrison et al., 2014).

In our study, patients scored higher in childhood trauma than healthy controls and in the same levels with other male clinical samples in Sweden (Gerdner and Allgulander, 2009). An inverse correlation between childhood trauma scores and DST ACTH was also reported. Being hyper suppressor of cortisol and ACTH after the DST was also reported in women with depression and a history of abuse in childhood (Newport et al., 2004). Contrary, Heim et al., reported increased cortisol and ACTH levels in the dexamethasone/CRF test in depressed men with childhood abuse compared to healthy controls as well as depressed men without a history of childhood abuse (Heim et al., 2008a). Differences in the degree of traumatization might account for this difference and the effects of childhood trauma on neurobiological systems with genetic and epigenetic regulation that have already been discussed, apply in this case also. Childhood adversity was positively related with the severity of hypersexual symptoms (HD:CAS). This is in the same line with studies reporting childhood adversity and especially sexual abuse as a risk factor for developing risky sexual behavior and sexual hyperactivity (Aaron, 2012; Wilson and Widom, 2008).

The hypersexual patients had also more depressive symptoms but did not have an effect on the HPA axis, as already mentioned, it is depression with melancholic and psychotic features that usually affects the HPA axis (Mann and Currier, 2007).

Hypersexual behavior scores (SCS, HD:CAS) were positively related to depression scores (MADRS-S) and in line with previous studies reporting positive correlation between

depressive symptoms and hypersexual behavior (Schultz et al., 2014). Hypersexual behavior is considered a response to dysphoric emotional states including anxiety and depressive symptoms (Kafka, 2010).

Strengths and limitations

The major strengths of the studies on suicide attempters (I-III) is the unique sample of suicide attempters with simultaneous measurement of different neuroendocrine biomarkers in both CSF and plasma such as cortisol, oxytocin, DHEA-S and 5-HIAA. The suicide attempters group was well characterized with structured diagnostics and evaluation of multiple psychometric scales such as MADRS for depression severity and the assessment of the suicide intent with two different clinical ratings. The assessment of exposure to interpersonal violence was both in childhood and in adulthood thus assessing revictimization status. These data together with the long follow up through the death registry, of more than 20 years, make this material extremely valuable.

The limitations should also mentioned, mainly the small sample size that is a limitation for generalizing the results as well as the lack of an age matched group of healthy volunteers. Due to the small sample size of the suicide attempters cohort (n=28) the question of statistical power to detect group differences arises. Therefore, false negative results that may occur may be from the lack of power to detect differences at the statistically significant level rather than being true negative results. Keeping that in mind, negative results were interpreted with extra caution.

Additionally, the small sample is a limitation to use corrective analyses for multiple testing such as the Bonferroni to counteract possible false positive results. The risk would be great to dismiss false negative results as they would not reach the statistical level after applying Bonferroni correction analysis. In order to minimize these problems, all the analyses performed were hypothesis driven based on the literature and not exploratory analyses. It is also important to mention that the cohort of suicide attempters is a unique, rare sample of well characterized patients with CSF sampling that is very difficult to collect.

Another issue is the mismatch regarding age between suicide attempters and healthy volunteers. As neuroendocrine measurements are affected by age efforts were made to adjust for age in the analyses and when necessary sensitivity analyses were performed to verify

some results. Especially, the number of females was very small and no information was acquired regarding their menstrual cycle or use of hormonal preparations. Additionally, due to some missing data in some measurements the sample size was smaller.

The strengths of the study on hypersexual disorder (study IV) are the well characterized group of male patients with hypersexual disorder, the presence of an aged matched control group of healthy volunteers both with a structured interview and the use of rating scales that enabled us to control for possible confounders such as childhood adversity and depressive symptoms. The limitations include the self-report of childhood adversity, not controlling for dexamethasone plasma levels at the DST and as this is the first study reporting HPA axis deregulation in males with hypersexual disorder, the results needs replication in independent samples.

Although there was a follow up of the suicide attempters the assessment of neuroendocrine biomarkers was in a cross-sectional design as in hypersexual disorder and this prevents us from drawing casual conclusions.

6 CONCLUSIONS

In conclusion, this thesis is a compilation of neuroendocrine studies in suicide attempters and in hypersexual disorder. Focus was on oxytocin, DHEA-S and the HPA axis as well as aspects such as suicide intent, lifetime violent behavior, exposure to childhood trauma and revictimization. Suicide attempters showed a trend for lower CSF oxytocin levels compared to healthy volunteers, CSF oxytocin was significantly negatively related to suicide intent and showed a trend for negative correlation with lifetime violent behavior. Revictimized suicide attempters had lower plasma oxytocin and more negative childhood emotional climate compared to non revictimized suicide attempters. Violence, trauma and suicide intent are risk factors for suicide and oxytocin by modulating prosocial behaviors might thus be protective in individuals with high suicide risk.

Higher CSF and plasma cortisol levels were also present in suicide attempters compared to healthy volunteers, whereas CSF DHEA-S levels were higher in male suicide attempters and CSF 5-HIAA levels lower in female suicide attempters respectively. The role of DHEA-S in suicidal behavior is proposed to be through the effects of childhood trauma and its implication to the allostatic load while other possible mechanisms cannot be excluded.

In suicide prediction, suicide victims tended to have low CSF 5-HIAA and high CSF cortisol and suicide victims that were abused in childhood had higher CSF cortisol compared to suicide victims with low exposure to interpersonal violence as a child. The first study investigating HPA axis in hypersexual disorder shows hyperactivity with non-suppression after the dexamethasone suppression test and higher DST ACTH in male patients with hypersexual disorder compared to controls. Early life adversity, more prevalent in men with hypersexual disorder, was also related to HPA axis measures. However, diagnosis of hypersexual disorder was independently associated with hyperactive HPA axis, which fits well in neurobiology of addiction models. The results underlie the important role of biological systems such as the serotonergic system and HPA axis in the neurobiology of suicide and the preliminary results on oxytocin and DHEA-S calls for further investigation. The effect of childhood trauma on biological systems should be further studied in well-defined clinical settings and taken into consideration when investigating neurobiological systems. Finally, there is an increasing need for both biomarkers and prevention in both suicide and hypersexual disorder and childhood trauma and adversity is a possible target for prevention.

7 FUTURE DIRECTIONS

This thesis includes neuroendocrine studies in suicide attempters and in hypersexual disorder. The preliminary results on Oxytocin and DHEA-S are promising and these systems should be investigated also in hypersexual disorder. We have already approval from Regional Ethical Review Board in Stockholm (Dnrs:2013/1335-31/2) to conduct a broader study in hypersexual disorder including analysis of DHEA-S, testosterone and Oxytocin. Genetic as well as epigenetic analyses are planned in the near future. There is also an ongoing treatment study with cognitive behavioral therapy for patients with hypersexual disorder. Assessments of possible neuroendocrine biomarkers as well as dexamethasone suppression test was performed before and after the intervention and the results remain to be analyzed. Regarding suicide attempters, genetic as well as epigenetic analyses will be conducted. These studies in hypersexual disorder and suicidal behavior have the potential to contribute significantly to the development of new knowledge that might lead to clinical implications.

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