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Neuroimunitní a endokrinní koreláty stresové odpovědi a disociace u afektivních poruch

Neuroimmune and endocrine correlates of stress response and dissociation in affective disorders

Disertační práce

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CONTENT

1. THEORETICAL INTRODUCTION AND REVIEW OF LITERATURE

1.1. INTRODUCTION

According to the Global Burden of Disease Study 2010, the last worldwide study of this nature up to date, mental disorders account for 7,4% of the total disease burden worldwide (indexed by disability-adjusted life years (DALY)) (Murray et al. 2012), but they are the leading cause of disability worldwide in terms of years lived with disability (YLDs). Not surprisingly, depression is the primary cause of disability caused by the whole group of mental disorders, contributing with 40.5% to total YLDs (Whiteford et al. 2013). Moreover, notwithstanding the fact that the global disease burden remain stable from 1990 (as compared to 2010), the relative importance of major depressive disorder increased considerably over past two decades (Murray et al. 2012).

As the data indicate, depression and other mental disorders are frequently chronic conditions with considerably increased rates of both somatic and psychiatric comorbidity, compared to non-psychiatric population (Buckley et al. 2009; De Hert et al. 2009a; Krishnan 2005). In addition to this, they tend to influence patients' life profoundly, decreasing the quality of life more than other chronic medical conditions (Bonicatto et al. 2001; Kuehner & Buerger 2005; Tarrier et al. 2007).

Contrasting with these alarming facts, the number of new molecular entities approved for psychiatric illnesses by U. S. Food and Drug Administration (FDA) has been declining in last decades (Kinch et al. 2014). Despite the efficacy of conventional psychopharmacological agents, a portion of treated patients continues to suffer from residual symptoms or remain resistant to treatment (Crown et al. 2002; Haro & Salvador-Carulla 2006; Rosenblat et al. 2014). As a result, a large body of research and clinical agenda in psychiatry and neurosciences focuses to further our understanding of pathophysiological mechanisms underlying mood disorders and other mental illnesses in order to improve the efficacy of current treatments and to identify new therapeutic agents.

According to current evidence, stress-related pathways have been directly involved in the pathophysiology of mood disorders, and other severe mental illnesses (SMI), especially bipolar disorder and schizophrenia (Gold et al. 2015; Juster et al. 2011). The mechanisms involved in the etiology of these disorders seem to be very complex, ranging from the neurodevelopmental changes, genetic vulnerability and neurological and behavioral alterations to various physiological dysregulations with a particular role of inflammation processes (Bizik et al. 2013; Rosenblat et al. 2014). Nevertheless,

these mechanisms refering to objective biological outcomes represent only one piece in the multidimensional construct of stress, which involves reciprocal interactions among inputs (such as environmental stressors and subjective psychological distress), and outputs (objective biological stress responses) (Levine 2005; Levine & Ursin 1991). Accordingly, the study of the effects and consequences of stress exposure requires an interdisciplinary approach, taking into account specific aspects of the "inputs", such as chronic stress and traumatic experiences (Teicher et al. 2003), and related psychological processes, with the crucial role of dissociation (Bob 2003a).

This chapter reviews some of the abovementioned neurobiological mechanisms possibly involved in stress-related pathways contributing to the development of depression and other SMI. Within an interdisciplinary perspective the main focus is put on processes of sensitization, which is conceptually related to the model of allostatic load (AL), and following processes on subjective psychological levels, related to defense mechanisms, especially dissociation and its consequences for the mental and physical health (somatoform dissociation).

1.2. NEUROBIOLOGY OF STRESS RESPONSE

The term stress refers to a real or interpreted threat to an individual's physiological and psychological integrity, provoking an adaptive biological and behavioral response (McEwen & Seeman 1999). In psychosocial context, situations that trigger the physiological stress response, have the following characteristics: novelty, unpredictability, threat to the ego/self, and/or lack of control (Dickerson & Kemeny 2004; Lupien et al. 2006; Mason 1968).

Stress system involves two main sub-systems: the autonomic nervous system (ANS) and neuroendocrine system (McEwen 1998a; Sapolsky et al. 2000). These two sub-systems respond with a different dynamics, but their activity is interrelated. The first observable response to a perceived and interpreted threat is represented by the activation of the *sympathetic–adrenal–medullary (SAM) axis*, releasing, within seconds, *catecholamines* (e.g., adrenalin) from the adrenal medulla. Follows activation of the *hypothalamic–pituitary–adrenal (HPA) axis*, resulting in release of *glucocorticoids (GCs)* from the adrenal cortex to the systemic circulation. This process includes three major steps, as illustrated in Figure 1.1. First, the hypothalamus activates the HPA axis by releasing *corticotrophin-releasing hormone (CRH).* CRH then passes through the hypothalamic-hypophyseal portal system and triggers the secretion of *adrenocorticotrophin hormone (ACTH)* from the anterior pituitary rich in blood capillaries. ACTH then travels viscerally to the adrenal cortex surrounding the kidneys where it binds to ACTH receptors and precipitates cellular activities in the zona fasticullata region, resulting in both release of GCs from the available pool, and

de novo biosysthesis of GCs (Sapolsky et al. 2000). The resulting surges in catecholamines and GCs have a pleiotropic regulatory effect on virtually all the biological systems in the body, permiting fight or flight responses to a threat.

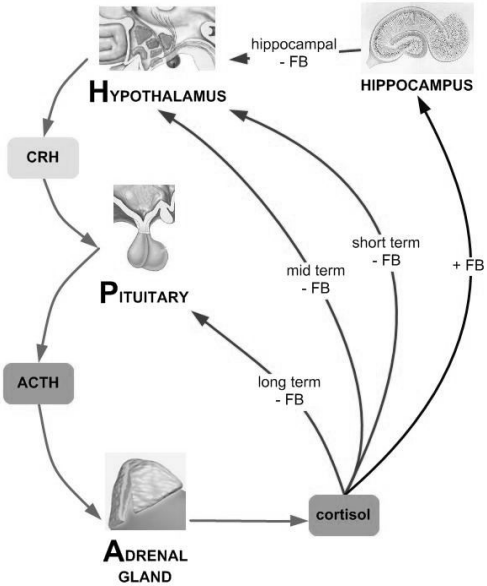

Figure 1.1. Overview of the HPA axis structures, main hormones included in the HPA axis activity and different types of regulatory feed-back loops. CRH-Corticotropin-Releasing Hormone; ACTH-AdrenoCorticoTropin Hormone; -FB-negative feed-back loop; +FB positive feed-back loop

It is important to note, that many brain areas has been studied in order to identify their contribution to triggering (detection of threat) and regulation (activation, sustaining and termination) of the stress response. In this context, three major brain structures has been found to play a particular role: (a) the *hippocampus* involved in negative feedback regulation of the HPA axis; (b) the *amygdala* responsible for fear conditioning and emotional processing with activating outputs to both autonomic and neuroendocrine regulatory systems; and (c) the *prefrontal cortex (PFC)* involved in

cognition and coping strategies and exerting a topdown control over subcortical structures (Gray & Bingaman 1996; McEwen 2004; McEwen et al. 1968; Reul & De Kloet 1985; Sánchez et al. 2000).

1.3. STRESS REACTIVITY AND STRESS-RELATED FINDINGS IN DEPRESSION AND OTHER MENTAL DISORDERS

Relationship between stress exposure and the pathogenesis of affective disorders and other SMI seems to involve several interrelated pathways. Their relative importance and their impact depend, among other factors, on the life phase, they are acting in, as will be discussed in the next chapter.

1.3.1. Life cycle model of stress

Brain regions central to HPA axis regulation, mentioned in the previous chapter, exhibit distinct neurodevelopmental patterns. Specifically, the hippocampus attains complete maturation first at age two, the prefrontal cortex (PFC) next between ages eight to fourteen, and finally the amygdala continues to grow slowly until the late 20s (Giedd et al. 1996; Yakovlev & Lecours 1967). The life cycle model of stress proposed by Lupien and colleagues (Lupien et al. 2009) postulates, that the exposure to adversity and chronic stress during critical periods may interfere with normal development of these brain regions. Consequently, the timing and the duration of stress exposure influence substancially subsequent individual vulnerability and resilience towards experiencing specific stress-related symptoms (Lupien et al. 2009).

Based on this model, regional volumes in conjunction to other biomarkers can be used to predict differential risk-profiles for specific psychopathologies in adulthood as well as to indicate potential moments in the lifespan when certain traumas might have occurred (Lupien et al. 2009). The rate of growth of these key brain regions depends on the developmental phases at which the stressors are experienced, which leads to differential effects on HPA axis functioning: (a) prenatal stress leads to *programming* effects, (b) postnatal stress leads to *differentiation* effects, (c) stress in adolescence leads to *potentiation/incubation* effects, and (d) stress in adulthood and aging is related to *maintenance/manifestation* effects (Lupien et al. 2009). The main outcomes are overviewed in Table 1.2.

In this context, it is important to mention, that adolescence is the most common period for the onset of any major psychiatric disorders (Kessler et al. 2005; Kessler et al. 1994). In order to reveal neurobiological mechanisms underlying this association, it

is essential to first chart normative ontogenetic trajectories for neural systems subserving cognitive and social abilities, motivational behavior, and stress reactivity.

Table 1.1. Differential effect of developmental phases at which stress is experienced on HPA axis functioning. GCs-Glucocorticoids; PTSD-Posttraumatic Stress Disorder.

	Prenatal stress	**Postnatal stress**	**Stress in adolescence**	**Stress in adulthood**	**Stress in aging**
Effect on HPA axis	programming effect	differentiation effect	potentiation / incubation effect	maintenance/ manifestation effect	
Outcome	↑ GCs	↑ GCs (maternal separation) ↓ GCs (severe trauma)	↑↑ GCs ↓↓ GCs	↑ GCs (depression) ↓ GCs (PTSD)	

The adolescent brain undergoes an important development in terms of structural (cortical grey matter and white matter changes, synaptic remodeling, myelination) and functional (spontaneous and task-related regional brain activity and neural connectivity) parameters, which are paralleled by the maturation of the neurotransmitter systems (Paus et al. 2008). Moreover, adolescence is characterized by substantial neuroendocrine changes in hypothalamic-pituitary-gonadal and -adrenal axes, with heightened basal and stress-induced activity of the latter (Lupien et al. 2009). As the majority of neuronal populations in the brain have receptors for adrenal and gonadal hormones, dynamic changes in the levels of these hormones may exert potent short- and long-term influences over brain activity and development (Paus et al. 2008) during different life periods (Perlman et al. 2007). Ongoing neural maturation, increased stress sensitivity, and novel social challenges during adolescence render the individual particularly vulnerable to the emergence of psychopathology.

Interestingly, in schizophrenia, but not in mood disorder, brain development seems to be compromised long before the first overt clinical symptoms (Murray et al. 2004). Longitudinal studies focusing on the clinical course of schizophrenia reveal a prodromal period of functional decline displayed as progressive behavioral and attentional problems (Corcoran et al. 2003; Miyamoto et al. 2003; Walker et al. 1996). These observations have led to the development of a "neural diathesis-stress" model suggesting a central role of the HPA axis in translating stress perception to a cascade

of neurobiological processes resulting eventually in an increase of dopamine signaling and related psychotic symptoms (Walker & Diforio 1997; Walker et al. 2008).

This explanatory framework was substantiated by the concept of behavioral sensitization (van Winkel et al. 2008a) postulating that mesolimbic dopaminergic deregulation develops progressively. This is reflected by not only by HPA axis overdrive, but also a synergistic endogenous sensitization of the dopamine neurocircuitry by previous activation(s) found in schizophrenic patients (Laruelle 2000). Consistently, experimental evidence has shown abnormally elevated striatal dopamine release in response to psychosocial stress in subjects who have experienced low maternal care (Pruessner et al. 2004). Consequently, cumulative exposure to psychosocial stress over critical developmental periods may enhance biobehavioral responses to subsequent stressors.

Overall, pathogenetic trajectories of SMI closely parallel HPA axis functioning that must inevitably influence neuromaturation and ultimately potentiate clinical symptoms during adolescence. An interaction between environmental stressors and endogenous enhancement of stress responsivity may induce HPA axis overactivation and mobilize sensitization mechanisms together with allostatic processes, as will be described in the chapter on allostatic load model (chapter 1.4.). In line with the life cycle model of stress, these results are also consistent with reports that earlier age of the onset of depression and other SMI is frequently associated with greater disorder severity and persistence, and poorer treatment outcomes (Kessler & Wang 2008).

1.3.2. Stress epidemiology

Chronic stress exposure contributes to the pathogenesis, maintenance of symptoms, and/or aggravation of comorbidities in mood and psychotic disorders. Indeed, a growing body of evidence suggests that the pathogenetic mechanisms, clinical stages, and symptoms of SMI are in part related to different stressor exposures during critical periods throughout the life cycle. Early-life environmental/biological/contextual factors in concert with genetic constitutions can have enduring effects by affecting brain development and susceptibility to psychopathologies.

Early adversities and traumas are related to a range of mental health problems in childhood (Spataro et al. 2004) and adulthood (Hyun et al. 2000; Janssen et al. 2004). Indeed, psychiatric patients who have experienced sexual or physical abuse have earlier first admissions, longer and more frequent hospitalizations, need more medication, have a higher rate of self-afflicted aggression, suicidal behavior, and have higher global symptom severity (Lange et al. 1995; Leverich et al. 2002; Mullen et al. 1993; Read 1998). Moreover, early adversities seem to render individuals more vulnerable to the onset of psychotic experiences, whereby adults who retrospectively

report having been abused as children are 10 times more severely distressed when first having psychotic experiences, compared to those who do not (Bak et al. 2005).

In contrast to early adversities which represent a risk for subsequent diagnosis of psychotic disorder, cross-sectional studies comparing the life histories of patients and age-matched controls have not provided consistent data sufficient to conclude that exposure to more frequent or severe psychosocial stressors triggers psychotic illnesses (Corcoran et al. 2003; Phillips et al. 2007). However, longitudinal studies provide evidence that aggregation of stressful life events precedes episodes of relapse and symptom exacerbation in schizophrenia (Corcoran et al. 2003). Moreover, patients with schizophrenia experience both negative and positive events as less controllable, handle them poorly, and perceive positive events as less desirable (Horan et al. 2005).

Importantly, patients with psychotic disorders experience increased stress reactivity that is not explained solely by their psychopathology itself (Myin-Germeys et al. 2001). For instance, a similar magnitude of stress reactivity is observed when assessing relatives of psychotic patients. These findings suggest that stress reactivity may represent a biobehavioral expression of inherited vulnerabilities towards psychiatric illnesses (Myin-Germeys et al. 2001). While a history of life events does not neccessarily increase the subjective distress that patients experience when faced with such difficulties, it does nevertheless appear to heighten their emotional sensitivity to environmental stressors (Myin-Germeys et al. 2003).

The importance of stress exposure and stress reactivity in the development of schizophrenia is further evidenced by epidemiological studies linking schizophrenia and stressful environmental factors such as social disadvantage and social isolation (Morgan et al. 2008). Indeed, it has been estimated that around one-third of all schizophrenia incidence may be related to the factors directly related to urban environments (Krabbendam & van Os 2005). The risk of developing psychotic disorders is also higher in some immigrant ethnic groups compared to native-born individuals (Cantor-Graae & Selten 2005), and is even more pronounced if the area, where they live, has lower proportions of the same ethnic group (Boydell et al. 2001).

Likewise, data from populations with depression and other mood disorders provide similar findings, linking childhood adversities and negative life events to earlier onset, symptom recurrence, disease progression, and higher rates of co-morbid substance abuse (Post & Leverich 2006).

Notwithstanding, the directionality of this relationship has been questioned, as SMI can lead to downward social mobility and migration into lower socioeconomic neighborhoods as such conditions can limit employment.

In sum, mood disorders and schizofrenia are rooted in early adversities and are strongly influenced by lifelong distress; however, prospective research is needed in order to conclude whether socieconomic characteristics are causal or consequential of the disease course. It is therefore critical for scientist-practitioners to not only understand how biological antecedents like genetic endowments influences the

individual's response to its contextual environment, but also how the psychosocial context influences the biology of the brain at various moments throughout the lifespan. This is particularly the case in the context of extremely distressing episodes preceding and proceeding diagnosis.

1.3.3. Genetics and epigenetics

Genetic and epidemiological research confirms a substantial genetic component of mood disorders and schizofrenia (Abdolmaleky et al. 2005) with important overlap between these psychopathologies (Craddock et al. 2006). Many of the genetic polymorphisms that govern stress responsiveness also confer risk of developing depression and other SMI (cf. Table 1.2. for a detailed overview).
One of the most extensively studied genes in relation to the pathogenesis of SMI is the COMT gene, that encodes the catechol-o-methyltransferase. This gene contains two functionally significant variants based on a single nucleotide polymorphism (SNP) at position 158. The Val allele has been associated with reduced brain volume and impaired cognition in schizophrenia patients (Ohnishi et al. 2006) and in those at high risk of psychosis (McIntosh et al. 2007). Additionally, psychotic Val/Met genotype carriers experience more hallucinations after cannabis exposure in comparison to Met/Met carriers (Henquet et al. 2009). In the general population, the Val allele has been linked to a hypodopaminergic prefrontal state (Slifstein et al. 2008) and has been associated with more pronounced paranoid ideation and psychoticism in military recruits (Stefanis et al. 2007).

The role of the Val158Met polymorphism of COMT gene in stress reactivity and disease etiologies seems to be far more complex. In fact, the Met allele moderates sub-clinical affective and psychotic symptoms in unaffected first-degree relatives of schizophrenia patients (van Winkel et al. 2008b). Stress, in interaction with the Met allele, has been reported to worsen psychotic symptoms and negative affect in psychotic patients with cannabis misuse (van Winkel et al. 2008c). Moreover, the Met allele, in conjunction with early adversities, is a risk factor for the onset of both major depression and bipolar disorder (Mandelli et al. 2007) underscoring an important interaction between social context and genetic endowment. In the general population, Met allele carriers may be more vulnerable to negative affective states such as pain (Zubieta et al. 2003), react more strongly to psychosocial stress (Drabant et al. 2006; Smolka et al. 2005), be less extraverted and novelty seeking (Benjamin et al. 2000; Reuter & Hennig 2005; Stein et al. 2005; Tsai et al. 2004), and finally have an augmented propensity to be anxious (Enoch et al. 2003; Olsson et al. 2005; Stein et al. 2005).

Stein and coworkers (Stein et al. 2006) have proposed a "warrior versus worrier" model to integrate these data: under stressful conditions associated with increased

dopamine release, Val allele carriers may present an improved dopaminergic transmission and better performance associated with efficient processing of aversive stimuli, while Met allele carriers may have less regulated neurotransmission but experience a notable advantage in memory and attention tasks. Indeed, the sensitivity to threatening stimuli and cognitive impairments related to the Val allele may contribute to the formation of psychotic symptoms via different pathways (van Winkel et al. 2008b). This explanation is also consistent with the inverse relationship found between emotional reactions and neuropsychological performance in schizophrenics (Myin-Germeys et al. 2002).

Another vulnerability marker associated with depression, bipolar disorder and schizophrenia is the BDNF gene that encodes the brain derived neurotrophic factor (BDNF) protein. Preclinical evidence indicates that early adversity can influence BDNF expression in a long-lasting manner and can also influence neuronal maturation and plasticity in later life (Buckley et al. 2007). Two alleles (Val/Met) also exist for this gene at codon 66. In patients with mood disorders, homozygous (Val/Val) allele carriers experience better neuropsychological performance than genetically heterozygous patients (Val/Met) (Rybakowski et al. 2003). In schizophrenic patients, the Met allele has been associated with poorer verbal memory performance and visuospatial abilities as well as reduced temporal and occipital cortex volumes (Ho et al. 2006). In the general population, Met allele carriers have relative decreases in hippocampal volume (HV) compared to Val carriers independent of age and sex (Pezawas et al. 2004). Interestingly, a three-way interaction between BDNF, 5-hydroxytryptamine(serotonin)-transporter-linked polymorphic region (5-HTTLPR) genotypes and maltreatment history predicts depression, such that children carrying the Met allele for the BDNF gene and homozygous for the short allele of the 5-HTTLPR gene have the highest depression scores. This vulnerability was, however, only present in the maltreated children and mediated further by social support (Kaufman et al. 2006). Such complex interactions demonstrate the need to take multiple levels of factors into account when studying genetic vulnerabilities vis-à-vis the risk of developing depressive disorder.

While inconclusive, these findings collectively suggest that several candidate genes function as mediators and/or moderators of stress reactivity and risk of developing SMI. The polygenetics underlying such complex conditions as SMI pathophysiology in conjunction to pleiotropic functions (one gene effecting several phenotypes) of genes involved in stress reactivity (Abdolmaleky et al. 2005) prompts the need for continued research. Furthermore, research designed to reveal gene $(x\ gene)^n$ x environment (and early environment) interactions would provide relevant knowledge that could detect individuals at high risk for affective and psychotic disorders earlier on. Because epigenetic modifications on specific gene promoters can influence (both reduce and increase) gene expression (Meaney & Ferguson-Smith 2010), and because these modifications can last from the post-natal period to late adulthood (Zhang &

Meaney 2010), epigenetics may provide grounds for new investigative avenues. For example, groundbreaking work by Meaney and colleagues has demonstrated that early maternal care (licking and handling) in the rat induces epigenetic reprogramming of the CRH gene promoter, thus reducing CRH expression, which limits negative feedback on the HPA axis and leads to more stressful and aggressive animals in adulhood (Plotsky et al. 2005). In human medicine, the relevance of epigenetic mechanisms is illustrated by the finding of hypomethylated gene promoter of membrane-bound COMT in schizophrenia and bipolar patients compared to the controls (Abdolmaleky et al., 2006).

Studies documenting the genetic basis of HPA axis regulation are of particular interest, although they are scarce and, to our knowledge, have not targeted SMI populations. Specific CRH-Receptor1 (CRHR1) polymorphisms (Bradley et al. 2008) and their interactions with 5-HTTLPR polymorphisms (Ressler et al. 2010) have been shown to moderate the effects of child abuse. Likewise, interaction between CRHR1 gene polymorphisms and stressful life events also predict adolescent heavy alcohol use (Blomeyer et al. 2008). Additionally, several polymorphisms of the FKBP5 gene, encoding the FK506-binding-protein-5, have been reported to interact with severity of child abuse as a predictor of adult post traumatic stress disorder symptoms (Binder et al. 2008). These results suggest that the modulatory impact of different polymophisms of both CRHR1 and FKBP5 genes vis-à-vis stress exposure may have clinically relevant consequences that invariably increase risk for SMI as well.

Table 1.2. Some of the genes and their polymorhisms with a potential impact on stress reactivity and stress-related pathogenetic pathways. Hsp-heat shock protein; GR-Glucocorticoid Receptor; SNP-Single Nucleotid Polymorphisme.

Gene and Function	Polymorphism
Cathechol-O-methyl-transferase (COMT) ● Enzyme involved in catabolism of catecholamines (dopamine, noradrenalin) in postsynaptic sites. ● Concentrations are abundant in the prefrontal cortex and hippocampus (Harrison & Weinberger 2005).	● Codon 158 (Val158Met): Val allele carriers have significantly higher enzyme activity than Met allele (Chen et al. 2004b), which leads to decreased levels of cortical dopamine (Slifstein et al. 2008). ● Val allele is associated with reduced brain volume and impaired cognition in schizophrenic patients (Mata et al. 2006; Ohnishi et al. 2006) and in populations at high risk of psychosis (McIntosh et al. 2007). ● Psychotic Val allele carriers experience more hallucinations after cannabis exposure (Henquet et al. 2009). Val allele interacts with more pronounced paranoid ideation and psychoticism in military recruits (Stefanis et al. 2007). ● Met allele moderates subclinical psychotic and affective symptoms in unaffected first-degree relatives of

	schizophrenia patients (van Winkel et al. 2008b). ● Stress in interaction with Met allele worsens psychotic symptoms and negative affect in psychotic patients with cannabis misuse (van Winkel et al. 2008c). In conjunction with early adversities, Met allele is a risk factor for onset of both major depression and bipolar disorder (Mandelli et al. 2007). ● In general population, Met allele carriers are more vulnerable to negative affective states such as pain (Zubieta et al. 2003), react more strongly to psychosocial stress (Drabant et al. 2006; Smolka et al. 2005), are less extraverted (Benjamin et al. 2000; Reuter & Hennig 2005; Stein et al. 2005; Tsai et al. 2004) and have augmented propensity to be anxious (Enoch et al. 2003; Olsson et al. 2005; Stein et al. 2005).
Brain-derived neurotrophic factor (BDNF) ● Member of neurotrophin family of growth factors, involved in neuronal survival and differentiation, synaptic modeling, and neurotransmitter metabolism (Rybakowski 2008).	● Codon 66 (Val66Met): Met allele is associated with decreased HV in general population (Pezawas et al. 2004) and with poorer verbal memory performance and visuospatial abilities and reduced temporal and occipital cortex volume in schizophrenia patients (Ho et al. 2006). ● Met allele interacts with s/s genotype of 5-HTTLPR and children maltreatment in predicting depressive symptoms (Kaufman et al. 2006). ● Val/Val genotype is associated with better neuropsychological performance in bipolar patients compared to Val/Met genotype (Rybakowski et al. 2003).
Corticotropin-releasing hormone receptor 1 (CRHR1) ● Predominant CRH receptor in the brain (Hiroi et al. 2001) involved in affective regulation and arousal (Holsboer & Ising 2008).	● SNPs rs110402 and rs7209436: moderate the effect of child abuse on the risk for adult depressive symptoms (Carcaise-Edinboro & Bradley 2008). ● SNP rs1876831 interacts with exposure to stressful life events to predict heavy alcohol use in adolescents (Blomeyer et al. 2008). ● CRHR1 TCA haplotype interacts with s/s genotype of 5-HTTLPR and child abuse to predict depressive symptoms (Ressler et al. 2010).
FKBP5 ● Co-chaperone of hsp 90 (protein binding to GR), constitute a part of intracellular ultrashort negative feedback loop for GR activity (Vermeer et al. 2003) via regulation of hormone binding affinity	● SNPs rs9296158, rs3800373, rs1360780 and rs9470080 interact with severity of child abuse as a predictor of adult PTSD symptoms (Binder et al. 2008).

and nuclear translocation of GR (Denny et al. 2000; Wochnik et al. 2005).	

1.3.4. Neurological correlates

Consistently with the life cycle model of stress, brain structures involved in stress regulations exhibit structural and functional changes in patients with depression and other mental disorders. The changes seem to be most pronouced in schizophrenia patients, where volume reduction of the hippocampus, amygdala and PFC have been reported (Tamminga & Holcomb 2005). This atrophy has a functional significance; for example, reduced HV is related to cognitive deficits (Antonova et al. 2004). In addition, the frontal cortex is frequently hypofunctional, but not always (Tamminga & Holcomb 2005). Functional abnormalities have also been reported for both limbic structures (amygdala and hippocampus) at baseline (Tamminga et al. 1992) and under cognitive challenge tasks in which reduced hippocampal activation during memory retrieval is observed (Heckers et al. 1998). Twin studies (van Erp et al. 2004; van Haren et al. 2004) indicate that both genetic and environmental factors contribute to smaller hippocampi; however, environmental factors such as perinatal complications may have greater impact than genetic factors (McNeil et al. 2000). Lifestyles choices further exemplify the impact of environmental factors, as cannabis consumption, that represents a major risk factor for schizophrenia (Yucel et al. 2008), provokes structural hippocampal changes when chronically abused.

More specific analyse of neuroanatomical abnormalities in (i) high-risk individuals, (ii) first-episodes of schizophrenic symptoms, and (iii) individuals chronically afflicted by schizophrenia illustrate a dynamic progression of the illness. Respectively, this starts with: (i) grey matter reductions in distinct brain regions, progressing from the anterior cingulate cortex and amygdala, followed by insular cortex reductions; (ii) extending to fronto-striatal-temporal regions; and (iii) then affecting prefrontal and thalamic areas (Chan et al. 2009). This suggests progressive trajectories of neurological involvement in the development of schizophrenia.

Patients affected by major depressive disorder (MDD) have also been consistently shown to exhibit reduced volume of the hippocampus, amygdala and frontal cortex (Alves et al. 2014; Fakhoury 2015), together with altered neurocircuitry (Fakhoury 2015). Not surprisingly, these changes are associated with disease progression (Alves et al. 2014), although studies in pediatric patients with unipolar depression have shown that some changes, especially HV reduction, appear early in the course of depressive disorder (Serafini et al. 2014).

In individuals suffering from bipolar disorders, right PFC reduction is one of the most consistent findings (Monkul et al. 2005), with alterations in energetic metabolism in the frontal cortex (Frey et al. 2007). Moreover, postmortem histological studies in bipolar patients have found glial cell reductions (Ongur et al. 1998) and decreased number of pyramidal neurons in the PFC (Rajkowska et al. 2001). The amygdala is also larger in adult (Altshuler et al. 2000; Blumberg et al. 2005; DelBello et al. 2004; Vieta & Phillips 2007) and adolescent bipolar patients (Chen et al. 2004a). Consistently, evidence suggests amygdalar overactivation during acute mood episodes (Malhi et al. 2004; Yurgelun-Todd et al. 2000). In specific amygdala-related tasks, bipolar patients display a complex pattern of affective and cognitive processing dysfunctions that can persist even when remission is achieved (Harmer et al. 2002; Yurgelun-Todd et al. 2000).

In contrast with consistent volume reductions in the PFC and increases in the amygdala, it is unclear whether HV differs in individuals with bipolar disorders (Kapczinski et al. 2008; Velakoulis et al. 2006), although reduction has been reported early in the evolution of the illness (Brambilla et al. 2008) and in adolescence (Frazier et al. 2005a; Frazier et al. 2005b). Consistent with the life cycle model of stress, this structural reduction likely denotes developmental processes occurring before adolescence, a period when hippocampus maturation has been completed. Evidence also suggests that different psychopathologies (schizophrenic vs. affective disorders) correspond to different types of brain morphological impairments (Velakoulis et al. 2006). It is also likely that differences related to sex have confounded the data (Frazier et al. 2008).

In sum, the most consistent evidence of brain morphological abnormalities are HV atrophy in schizophrenia and depression, and amygdala hypertrophy in bipolar disorder. Both abnormalities contribute to HPA axis over-reactivity; the former via impaired negative feedback, and the second via hyper-excitatory input to the hypothalamus.

1.3.5. Physiological dysregulations

1.3.5.1. HPA axis dysregulations

Increased basal HPA axis activity can be found across different pathological stages in mood disorders and schizophrenia. In depressed patients, basal hypercortisolemia is one of the best documented neuroendocrine changes, and it is probably caused by irregular basal hypersecretion of cortisol, associated with adrenal enlargement due to chronic sympathetic overactivation (Carroll et al. 2007; Carroll et al. 2012). Higher baseline cortisol levels have been also reported in drug-naive first-episode patients with schizophrenia (Muck-Seler et al. 2004; Walsh et al. 2005), as well as in medicated

(Gallagher et al. 2007; Ritsner et al. 2007) and in chronic schizophrenic patients (Yilmaz et al. 2007).

In addition, a dysfunctional diurnal pattern of cortisol secretion was reported in schizophrenic and mood disorders patients with elevations of afternoon cortisol levels (Gallagher et al. 2007; Linkowski et al. 1994). Furthermore, as drug abuse is a highly prevalent co-morbidity in SMI disorders, it is noteworthy that cortisol secretion is also stimulated by delta-9-tetrahydrocannabinol (THC), the active agent in cannabis (D'Souza et al. 2005), as well as by amphetamines (Munro et al. 2006; Oswald et al. 2005). Chronic consumption of these drugs may therefore contribute to dysregulations of the HPA axis.

In contrast to basal activity, findings focused on HPA reactivity assessed by dexamethasone suppression test (DST) in schizophrenic patients are less consistent, with reports of increased (Muck-Seler et al. 1999) and decreased reactivity (Ismail et al. 1998). Conversely, in depressed and bipolar patients, elevated reactivity has been consistently found (Gaudiano et al. 2009; Sher 2006). In bipolar disorder, this pattern persists regardless of the phase of the illness (Watson et al. 2004). Interestingly, the persistence of abnormal HPA axis reactivity has also been observed in a portion of patients in remission who are at higher risk of depressive relapse (Vieta et al. 1997).

Likewise, in SMI patients, expression of the glucocorticoid receptor (GR) messenger ribonucleic acid (mRNA) is reduced in brain regions involved in stress system regulation, specifically the amygdala (Perlman et al. 2004) and PFC (Xing et al. 2004). Abnormal distribution patterns of GR mRNA in other brain regions may also exist in patients with depression, bipolar disorder, and schizophrenia (Webster et al. 2002). Moreover, in bipolar patients, T-cell resistance to glucocorticoids (Knijff et al. 2006) and altered glucocorticoid-signaling cascades (Spiliotaki et al. 2006) have been documented. As proposed by Kapczinski and colleagues (Kapczinski et al. 2008), altered T-cell response might be an allostatic mediator between HPA axis overactivation and immune functioning in bipolar disorder (cf. chapter 1.4. for further discussion).

Cortisol also influences psychopathological manifestations in schizophrenia. Evidence suggests that cortisol levels in schizophrenic patients are related to both positive (Walder et al. 2000) and negative symptom severity (Goyal et al. 2004). Moreover, cortisol levels are inversely correlated to cognitive performance (Halari et al. 2004; Walder et al. 2000) in clinical populations.

One potential pathophysiological pathway linking cortisol release to schizophrenic symptoms is via its interference with dopamine functioning, which itself is prominently implicated in psychotic symptoms. In fact, cortisol secretion augments dopamine neurotransmission (Czyrak et al. 2003; Dallman et al. 2004; Marinelli et al. 2006; Moghaddam 2002; Pruessner et al. 2004) and the HPA axis and dopaminergic neurocircuitry appear to reciprocally activate each other (Walker et al. 2008). Consistently, higher cortisol responses to amphetamines are related to higher ratings

of positive drug effects, and greater dopamine release in normal individuals (Oswald et al. 2005).

1.3.5.2. Immune dysregulations

Different cytokines are also involved in stress-related etiopathogenic pathways in mental disorders (Kapczinski et al. 2008; McEwen 2003; Simon et al. 2008). This is due in part to their interactions with the neuroendocrine system and involvement in mood regulation (Irwin & Miller 2007). For example, individuals treated for metastatic cancer with interleukin-2 (IL-2) exhibit neuropsychiatric symptoms resembling the positive and negative symptoms of schizophrenia, including hallucinations, reality distortions, impaired cognition, and fatigue (Denicoff et al. 1987).

Individuals with schizophrenia have increased blood levels of IL-6, IL-1 receptor agonist (IL-1RA), soluble IL-2 receptor (sIL-2R) and decreased secretion of IL-2 by peripheral blood leukocytes (Potvin et al. 2008). In patients with mood disorders, elevations in IL-1 receptor (IL1-R), IL-2R, IL-4, IL-6, IL-8, and a decrease in IL-2 have been identified (Breunis et al. 2003; Kim et al. 2007; Liu et al. 2004; O'Brien et al. 2006; Ortiz-Domínguez et al. 2007; Tsai et al. 1999). Based on these results, it may be concluded that an ongoing "pro-inflammatory syndrome" is manifested by depressed, bipolar and schizophrenic patients (Table 1.3.). However, it is difficult to distinguish between the relative influence of pathophysiological mechanisms inherent to SMI and other factors that influence cytokines levels, such as adiposity and interactions with medications and other biomarkers (Bob et al. 2010a; Trayhurn & Wood 2004). It is interesting to note that pro-inflammatory states are often associated with enhanced cellular oxidative stress, which may be the primary biochemical effector underlying the process of neuronal death and neurodegeneration (Trushina & McMurray 2007).

Table 1.3. Overview of cytokines levels in mood disorders. Note: IL-1, IL-6, TNF-α are considered to be prominent pro-inflammatory cytokines while IL-4 and IL-10 act as anti-inflammatory cytokines.

Biomarker	Mania	Depression	Note	References
IL-1R	↑		Statistically higher in remitted patients	(Liu et al., 2004)
IL-2	↓	↓		(Ortiz-Dominguez et al., 2007)
IL-2R	↑	↑	Positively correlated to the severity of manic symptoms	(Tsai et al., 1999)(Breunis et al., 2003)
IL-4		↑		(Ortiz-Dominguez et al., 2007)
IL-6	↑	↑	Returned to baseline in response to stabilizers	(O'Brien et al., 2006; Kim et al., 2007; Ortiz-Dominguez et al., 2007)
IL-8	↑	↑		(O'Brien et al., 2006)
IL-10	=	=		(O'Brien et al., 2006)
TNF-α	↑	↑		(O'Brien et al., 2006; Kim et al., 2007; Ortiz-Dominguez et al., 2007)

1.3.5.3. Oxidative stress

Chronic stress and allostatic mechanisms (cf. chapter 1.4.) are believed to compromise the balance between reactive oxygen species production and antioxidant defenses, leading to oxidative stress that enhances cellular aging (Epel 2009). These processes occur in different SMI populations and in neurodegenerative diseases (Trushina & McMurray 2007). Studies among schizophrenic patients have found increased generation of reactive oxygen species (ROS), higher levels of lipid peroxidation and reduced antioxidant capacity in brain tissue (Dietrich-Muszalska & Olas 2009; Dietrich-Muszalska et al. 2005). Similar findings have been reported in patients with mood disorders (Andreazza et al. 2007; Ranjekar et al. 2003) along with a down-regulation of several antioxidant genes (Benes et al. 2006) across all mood states, suggesting that cellular oxidative stress is a component of these psychopathologies. Further to this point, the shortening rate of telomeres, which act as protective genomic caps at the end of chromosomes that gradually shorten as cell divisions happen, appears to be accelerated by oxidative stress and inflammation (Epel 2009).

Consistently, accelerated telomere shortening has been reported in leukocytes of bipolar patients (Simon et al. 2006) and decreased telomere content (a measure highly correlated with telomere length) has also been observed in blood leukocytes of newly diagnosed drug-naive schizophrenic patients (Fernandez-Egea et al. 2009). However, these findings in blood cells have not been confirmed in cerebellar gray matter by a study of psychiatric patients (Zou et al. 2010), perhaps because of the slow turnover of glial cells and the fact that neurons are post-mitotic cells. Epel and colleagues (Epel

2009) have postulated that psychological and metabolic processes associated with AL (cf. chapter on AL model (chapter 1.4.) for further information) may accelerate the rate of cellular aging. Therefore, the fact that telomere shortening seems to vary according the tissue type (Wang et al. 2005) could suggest that different cell types exhibit differential vulnerabilities to different allostatic mechanisms, and thus different aging rates.

1.3.6. Cognitive and behavioral impairments

Cognitive dysfunction appears to be consistent with structural and functional neuroimaging findings reviewed above that may relate to the exposure to trauma or sustained chronic stressors in different life periods. Across a range of neurocognitive domains (e.g., attention, working and long-term memory, verbal and visual learning, executive functioning, and social learning), schizophrenic patients demonstrate impairments (Fioravanti et al. 2005; Tamminga & Holcomb 2005). Cognitive impairments are however detectable even before the onset of the first psychotic episode (Walker et al. 1999) and often persist after psychotic symptoms are completely resolved (Szoke et al. 2008). The fact that cognitive deficits seem to be a better predictor of long-term outcome in schizophrenic patients than positive symptoms (Lublin et al. 2005) highlights the impact of altered neuropsychological functioning on patient's life course. Interestingly, neurocognitive impairments are associated with negative rather than positive symptoms, (Dominguez Mde et al. 2009) and have also been reported in non-psychotic first-degree relatives of schizophrenic patients (Park et al. 2004). This latter point raises the possibility that underlying genetic and/or social factors (family-related factors), or the interaction of both, are determinants of cognitive function.

In patients with mood disorders, neurocognitive impairments are frequent regardless of the disease phase: manic, depressed or in remission (Martinez-Aran et al. 2004; Robinson et al. 2006; Thompson et al. 2005). Cognitive impairments do, however, appear to be related to disease severity, illness duration, and the accumulation of manic episodes (Martinez-Aran et al. 2007). Unaffected relatives of adult bipolar patients also exhibit several neurocognitive abnormities (Antila et al. 2007) with similar findings reported in siblings of bipolar adolescents (Doyle et al. 2009). These findings underscore the importance of genetic/social factors in the development of cognitive impairment.

All neurobiological and psychopathological mechanisms described so far interact in complex ways to influence behavior. In the AL model, proposed in the next chapter (chapter 1.4.), the totality of regulatory systems across hierarchical levels interact in a dynamic and non-linear manner in response to actual or perceived stressors. From this perspective, lifestyle choices and behaviors of patients with SMI are "higher-order"

allostatic mechanisms deployed in reaction to surrounding environmental cues and individual perceptions, but they have the potent propensity of increasing AL levels even further. For instance, it has been proposed that changes in eating behaviors may be compensatory in nature – a form of "self-medication" – in conditions that are associated with chronic stress exposure that alter the brain reward system (Elman et al. 2006). For example, overeating may be a mechanism to dampen stress-induced negative affect. Depressed people who overeat show reductions in cerebrospinal CRH and catecholamine concentrations, which possibly counteracts the effects of stress (Dallman et al. 2003).

Furthermore, deficient reward pathways have been identified in both mood disorders (Abler et al. 2008; Satterthwaite et al. 2015) and schizophrenia (Elman et al. 2006). This may be due to abnormal motivational states referred to as aberrant salience attributions (Howes et al. 2009; Kapur 2003; Kapur et al. 2006) together with a lack of responsivity to normally rewarding stimuli (Gur et al. 2002; Paradiso et al. 2003) that might originate from altered mesolimbic dopaminergic circuitry in schizophrenic patients. Notably, this may explain the preference for highly salient cues, such as fast-foods and illicit substances (Elman et al. 2006). A similar mechanism has been proposed to mediate the vulnerability to addiction in schizophrenic patients.

Consistently, the rate of obesity, which represents a major risk factor for a range of chronic medical conditions (Sturm 2002), are substantially higher in SMI patients than in the general population (De Hert et al. 2009b). Although psychotropic medications explain a portion of weight gain in psychiatric populations, dietary habits remain an important contributing factor for obesity. SMI patients are reported to have diets rich in saturated fat (Brown et al. 1999), carbohydrates (Strassnig et al. 2003), scarce in fruits and vegetables (McCreadie 2003) further characterized by increased caloric intake due to overeating (Peet 2004). In addition, a nutrition rich in saturated fats and sugar are associated with worse clinical outcomes in schizophrenia (Peet 2004). It is interesting to note that high calorie diet, and particularly high-fat diet, may increase ROS production from mitochondria and lead to insulin resistance and other deleterious cellular metabolic consequences (Anderson et al. 2009; Wallace 2005).

Other behaviors that potentiate negative effects of sustained stress exposure in SMI patients include smoking, alcohol, and drug abuse, that can act as forms of self-medication secondary to psychopathological symptoms and medication side effects. The mechanisms underlying a greater propensity to develop substance abuse in schizophrenia is not completely understood, but mesolimbic dopamine-mediated reward regulation is clearly implicated (Chambers et al. 2001). Unfortunately, addictive behaviors worsen with stress and clinical instability in schizophrenic patients, who tend to over-evaluate immediate rewards and devaluate delayed punishments (Krystal et al. 2006). Of interest, data from animal research indicate that the regulation of addictive behaviors and the stress response share a common set of

genes (Fagen et al. 2007), suggesting a mechanistic coupling between stress reactivity and addiction.

Addictive behaviors are significant problems for SMI populations because of downstream clinical consequences. For example, smoking, which increases the incidence of lung diseases and cancer, reaches a prevalence of 50-80% in schizophrenic patients and 54-68% in bipolar patients, representing a 2-3 fold higher prevalence than in the general population (De Hert et al. 2009a). Similar prevalence of smoking has been reported in depressed patients as well (Luger et al. 2014). Lifetime incidence of substance misuse or dependence also exceeds the prevalence observed in the general population and all other axis I psychiatric diagnoses, and has been estimated to be as high as 47% in schizophrenia and 61% in bipolar disorder in the US (Regier et al. 1990). Alcohol represents the most commonly abused substance, followed by cannabis and cocaine (Mueser et al. 1992).

Other neurological systems involving cholinergic and dopaminergic neurotransmission may specifically be associated with the extremely high smoking rates observed in schizophrenic patients (Mobascher & Winterer 2008). Indeed, post-mortem studies in schizophrenic patients have found decreases in the number of nicotinic receptors in the hippocampus (Freedman et al. 1995). Moreover, evidence suggests that malfunction of the alpha 7 subunit of the nicotinic acetylcholine receptor is involved in the development of schizophrenia (Freedman et al. 2000). It is also known that this subunit contributes to nicotine's positive effects on memory function (Levin et al. 2006), positive impact on sensory gating (Adler et al. 1993), attention (Harris et al. 2004), and memory (Myers et al. 2004), collectively indicating that smoking may represent a way for schizophrenic patients to remediate cognitive disability (De Leon et al. 1995).

Nicotine has been shown to activate mesolimbic reward dopaminergic pathway in animal models (Pidoplichko et al. 1997) and this mechanism may contribute to alleviation of negative affective symptoms in depressed patients (Cardenas et al. 2002) and in schizophrenic patients (Goswami et al. 2004; Juckel et al. 2003). This supports the notion that smoking may be used for self-medication, further contributing to AL (cf. chapter 1.4.). Furthermore, because smoking has been shown to increase N-methyl-D-aspartic acid (NMDA) receptor-related gene expression in schizophrenic patients but not in healthy individuals (Mexal et al. 2005), it is possible that deficits in NMDA receptors (Pilowsky et al. 2006; Stone et al. 2007) contribute to higher smoking rates in these patients. Smoking byproducts might also interact by inducing drug metabolism, and thus reduce the doses of certain antipsychotic medications (Zevin & Benowitz 1999). In addition to biological factors, psychosocial vulnerability factors such as low levels of daily activity and boredom may also contribute to higher smoking rates in schizophrenic patients (Smith 1996; Todman 2003).

These findings indicate that SMI patients' cognitive and behavioral aspects must be taken into account in clinical and research settings alike as covariates that could

significantly influence the patient's symptomatologies, compliance, and vulnerable biological functioning that synergistically influence disease progressions. At the heart of these difficulties is the brain's command of stress hormones central to the AL model, substantiated in the following chapter.

1.4. ALLOSTATIC LOAD MODEL

The term *allostasis* was formulated to describe adaptive physiological responses organisms activate when homeostasis is disrupted (Sterling & Eyer 1988). Unlike homeostasis, where the body secures optimal functioning of the internal milieu through consistency of local feedback mechanisms (for exemple core body temperature, Ph level, electrolyte balance), allostatic processes alter metabolic functioning via optimal compensatory and anticipatory mechanisms responsive to environmental demands (for exemple autonomic nervous system arousal during acute stressors).

The allostatic concept conceptually implicates the whole brain and body rather than simple local feedback loops characteristic of homeostasis (Sterling 2004). For instance, if there was such thing as a homeostatic blood pressure set-point, our levels would invariably be at too low or too high to match resources to the needs of the situation. In this vein, Sterling and Eyer (Sterling & Eyer 1988) further postulated that age-related increases in blood pressure and differences between socio-economic strata could, within an allostatic framework, be viewed as physiological recalibrations to match the situational needs. The general basis of this biological phenomenon is therefore to direct compensatory mechanisms in bodily functions in order to promote adaptation to environmental changes.

The following three main limitations of traditional homeostatic theory are addressed by the concept of allostasis. First, homeostasis operates by shutting down overactive biological systems that function according to static set-points; however, these do not account for the process of dynamically matching needs to demands that recalibrate set-points to maximize the organism's resources (for exemple, increased blood pressure during strenuous physical activities). Secondly, when increased needs create an error signal, negative feedback mechanisms may try to correct the error ineptly (for exemple head-rush when rising too swiftly); note that neurological modulation and anticipation of physiological change can, however, shape behavior to specific needs (for exemple moving slowly to avoid a head-rush). Thirdly, and most notably for biomedicine, homeostatic models define health as a state in which all physiological parameters have normal values, while abnormal values are those out of range that warrant pharmaceutical intervention (for exemple hypertension).

In contrast, allostasis defines health as a state of responsiveness and optimal predictive fluctuation to adapt to the demands of the environment. Sterling and Eyer (Sterling & Eyer 1988) further argue that medical practices based on homeostatic definitions of health are in danger of iatrogenesis and polypharmacy, as treatment problems can arise when correcting one parameter causes other systems to become dysregulated, for exemple anti-hypertensive medications can dysregulate potassium, glucose, cholesterol, and uric acid levels (Sterling 2004). In sum, allostasis differs from homeostasis vis-à-vis its emphasis on dynamic set points, considerations of the brain's role in feedback regulation, and view of health as a whole mind-body adaptation to contexts (Schulkin 2003).

The physiological changes associated with chronic stress and/or traumatic experiences represent a potent manner whereby allostatic adaptation leads to pathogenic maladaptation(s). As described in the chapter on neurobiology of the stress response (chapter 1.2.), during acute stress, real or interpreted threats to homeostasis initiate the SAM axis release of catecholamines and the HPA axis secretion of GCs in order to mobilize energy that fuels adaptive fight-flight-freeze responses (Sapolsky et al. 2000). When chronically activated, allostatic mechanisms like adrenalin and cortisol become physiologically demanding - or an AL - that consequently increase one's susceptibility to disease (McEwen 1998a). AL is therefore defined as the physiological price of adaptation that organisms pay when allostasis is repeatedly activated during sustained periods (McEwen & Stellar 1993).

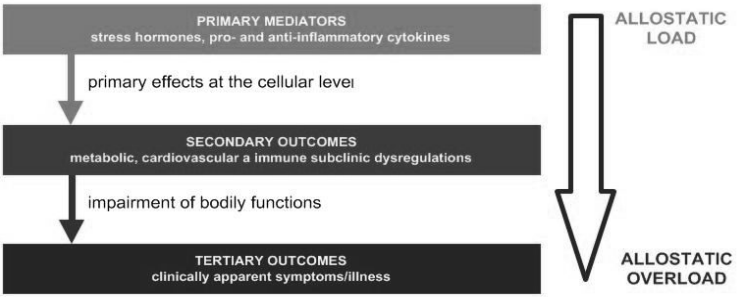

Figure 1.2. Three-steps sequence of physiological dysregulation, proposed by Mc Ewen (McEwen 1998a), translating the sustained activation of allostatic mechanisms into clinically apparent symptoms/illenesses. Hypercortisolism reported in depressed patients is a good exemple of a primary mediator that lead to increase of visciral adipous tissue (secondary outcome) being the risk factor for a set of metabolic abnormalities, including non insulin dependent diabetes and dyslipidaemias (tertiary outcomes) (Mann & Thakore 1999).

Multiple allostatic mediators function as part of a non-linear network that contribute to AL along a tripartite sequence of physiological dysregulation (McEwen 1998a; McEwen 1998b), illustrated in Figure 1.2. First, over-activation of allostasis mobilizes *primary mediators* such as stress hormones and pro- and anti-inflammatory cytokines that exert *primary effects* on cellular processes (McEwen 2003; McEwen 2006). Subsidiary systems in turn recalibrate their own activities to compensate for the over and/or under production of primary mediators. This leads to *secondary outcomes*, whereby metabolic, cardiovascular, and second-order immune biomarkers reach sub-clinical levels. AL becomes overloading when *tertiary outcomes* emerge with the manifestation of clinical endpoints such as cardiovascular disease, metabolic syndromes, mortality, etc.

In conclusion, AL model can be used as an explanatory framework for integrating trauma and stress-related effects documented on several levels: physiological dysregulation with central role of HPA axis overactivation and pro-inflammatory processes, neurological findings and cognitive and behavioral changes (Bizik et al. 2013; Juster et al. 2011). Primary mediators and secondary and tertiary outcomes interact in a non-linear manner, possibly implying processes known as sensitization (Bizik et al. 2013; Pruessner et al. 2004). In this context, complex psychological and physiological defence mechanisms, activated in response to trauma and/or chronic stress, act as "higher-order" allostatic processes. Dissociation as an important exemple of these mechanisms will be discussed in the next section.

1.5. DISSOCIATION

1.5.1. Definition

The term *dissociation* has been historically used to describe a wide variety of processes related to mental disintegration and intrapsychic conflict in various contexts (Holmes et al. 2005).

According to American Psychiatric Association it refers to a disruption of the usually integrated functions of consciousness, memory, identity or perception of the environment (American Psychiatric Association 1994).

More comprehensively, dissociation and its clinical assessment are characterised in the Standardized Clinical Interview for DSM-IV Dissociative Disorders (SCID-D) (Steinberg 1994), which defines five components of dissociation representing core features of disociative disorders: depersonalization, derealization, amnesia, identity confusion and identity alteration. *Depersonalization* refers to a feeling of detachment or enstrangement from one's self and includes "sensation of being an outside observer of one's body" together with "feeling like an automaton or as if (one) is living in a

dream" (American Psychiatric Association 1994). *Derealization* refers to "an alteration in the perception of one's surroundings so that a sense of reality of the external world is lost" (American Psychiatric Association 1994).

Table 1.4. Classifications of the dissociative disorders in DSM-IV (American Psychiatric Association 1994), DSM-5 (American Psychiatric Association 2013) and ICD-10 (WHO 1992). DSM-Diagnostic and Statistical Manual of Mental Disorders; ICD-International Classification of Diseases

DSM-IV	DSM-5	ICD-10
Dissociative amnesia	Depersonalization/Derealization disorder	Dissociative amnesia
Dissociative fugue	Dissociative amnesia	Dissociative fugue
Dissociative identity disorder	Dissociative identity disorder	Dissociative motor disorders
Depersonalization disorder	Other specified dissociative disorder	Dissociative convulsions
Dissociative disorder not otherwise specified	Unspecified dissociative disorder	Dissociative anaesthesia and sensory loss
		Dissociative stupor
		Trance and possession disorders
		Mixed dissociative (conversion) disorders
		Other dissociative (conversion) disorders
		Dissociative (conversion) disorder, unspecified

Table 1.4. shows a list of dissociation disorders emcompassed in most used diagnostic systems. Interestingly, *Posttraumatic stress disorder* (PTSD) is not categorized as a dissociative disorder in above-mentioned diagnostic systems, although dissociative symptoms represent a substantial part of the clinical picture (Ehlers & Clark 2000; Foa & Hearst-Ikeda 1996)

1.5.2. Epidemiology of dissociative symptoms

Dissociative symptoms has been described across a number of different psychiatric conditions, such as depressive disorder (Sedman & Reed 1963), bipolar and psychotic disorders (Coons 1996), obsessive-compulsive disorder (Simeon et al. 1997), eating disorders (Abraham & Beumont 1982), personality disorders (Coons 1996), panic disorder (Cassano et al. 1989; Marshall et al. 2000; Segui et al. 2000) and agoraphobia (Cassano et al. 1989). Mild forms of dissociative symptoms are also experienced quite frequently in non-clinical population, with high prevalence of depersonalization and derealization (Hunter et al. 2004).

1.5.3. Conceptual models of dissociation

Commonly, two different approaches can be identified in the conceptualization of the phenomenon of dissociation:

First approach describes dissociative phenomena as qualitatively similar, lying on a "dissociative continuum" and differering primarly by the degree in which they are expressed (Beahrs 1983; Kennerley 1996). This approach seems to reflects the common nature of dissociative experiences when non-pathological dissociation such as daydreaming or mild form of depersonalization/derealization, are takem into account (Holmes et al. 2005). Nevertheless, som authors argue, that it create considerable confusion (Allen 2001; Cardeña 1994; Frankel 1990)

On the other hand, the categorial approach postulates, that dissociative phenomena can be classified into distinct groups. This approach is supported by factor analytic studies of self-reports dissociative scales, such as Dissociation Experiences Scale (DES) (Darves-Bornoz et al. 1999; Ross et al. 1995; Stockdale et al. 2002), as well as by exprimental research using neuroimaging (Phillips et al. 2001), neurophysiological (Sierra et al. 2002) and other experimental procedures (Kuyk et al. 1999a; Simeon et al. 2003).

As a simplification, the table bellow (table 1.5.) shows some of the proposed two-factors models of dissociation. *Detachment* encompasses phenomena related to perturbated sense of one's body (out-of-body experiences), one's self or identity (depersonalization) or the external world (derealization) (Holmes et al. 2005) and several underlying mechanisms have been hypothesized, including lack of time code in memory (Ehlers & Clark 2000) and specific attentional disturbances (Conway & Pleydell-Pearce 2000). *Compartmentalisation* includes primarly conversion phenomena and somatoform symptoms, where "compartmentalized" processes escape volitional control and related physiological functions gain a certain degree of autonomy (Kihlstrom 1992).

1.5.4. Dissociation and traumatic stress

In agreement with historical tradition, Putnam in his studies of dissociative reaction states that the majority of dissociative disorders is induced by traumatic events (Putnam 1989; Putnam 1997). Analogically, other more recent studies indicate that dissociative disorders are primarly induced by a traumatic event (Bob 2008a; Brewin 2007; Sar & Ross 2006). It is however necessary to note, that other factors, such as brain insults, injury or other organic brain diseases may play a role in this process (Kihlstrom 2005; Spiegel 1997). Accordingly, ICD-10 acknowledges the organic

dissociation, induced by a variety of conditions affecting cerebral functions (Good 1993).

Table 1.5. Overview of proposed two-factors models of dissociation.

Two-factors models		References
Detachment	Compartmentalisation	(Allen 2001)
Dissociative-process symptoms	Compartmentalisation	(Putnam 1997)
Dissociation as an alteration in consciousness involving a disconnection from the self or the world	Dissociation as non-integrated mental modules or systems	(Cardeña 1994)
Depersonalization/derealization	Abnormal separation of material in memory	(Van Der Kolk & Fisler 1995)

Consistent with the life cycle model of stress (Lupien et al. 2009), most of traumatic experiences inducing dissociative symptoms or dissociative disorders relate to physical and/or sexual abuse in childhood, with subsequent development of symptoms often many years efter the exposure to traumatic experiences (Coons et al. 1989; Chu & Dill 1990; Teicher et al. 2006). Additionally, traumatic events related to serious accidents or natural disasters may trigger dissociative symptoms or dissociative disorders (Putnam 1997; Spiegel & Cardeña 1991).

In order to understand the underlying mechanims, it is relevant to mention, that exposure to a significant psychological stressor enhances memory for emotional aspects of the trauma-related event, and simultaneously disrupts memory for non-emotional aspects of the same event (Briere & Conte 1989; Kenardy et al. 2007; Payne et al. 2006). Similarly, individuals who are victims of a trauma are in many cases unable to register pain (for example during self-injury) and patients with dissociative disorders frequently report amnesia for self-injury (Saxe et al. 2002).

With regard to the type of traumatic exposure, not only physical and/or sexual abuse, or witnessing domestic violence, but also parental verbal aggression as a specific form of abuse may cause dissociation, symptoms of limbic irritability, depression and other psychiatric symptoms, as reported by Teicher and coworkers (Teicher et al. 2006).

Finally, a close relationship between symptoms of traumatic stress, dissociation, limbic irritability and depression has also been documented in depressive patients (Bob et al. 2010b). Depressed patients experiencing trauma-related symptoms exhibit significantly more severe symptoms of dissociation, depression and limbic irritability.

1.5.5. Psychic and somatoform dissociation and its assessment

Dissociation represents a special form of consciousness in which events that would be under normal conditions connected are divided from one another (Li and Spiegel, 1992). The subject usually fails to integrate specific contents, often related to trauma, into the consciousness (Bernstein & Putnam 1986). As a result, range of dissociative symptoms may develop, that could be phenomenologicaly divided into two groups: psychic and somatoform symptoms. Most commonly used psychometric tool to quantify psychic dissociative symptoms is represented by DES (Bernstein & Putnam 1986). It comprises three factors: depersonalization/derealization, amnesia and absorption (Goldberg 1999). It is important to note, that dissociative symptoms included in DES, are linked to both the detachment and the compartmentalization process, as described in chapter 1.5.3.
Somatoform dissociative symptoms include alterations in sensation of pain (analgesia), painful symptoms, perception alterations, motor inhibition or loss of motor control, kinesthetic anesthesia, gastrointestinal symptoms (Nijenhuis et al. 1996) and dissociative seizures (Brown & Trimble 2000; Kuyk et al. 1999b). These symptoms are primarly adressed by Somatoform Dissociation Questionnaire (SDQ), proposed by Nijenhuis and coworkers (Nijenhuis et al. 1996).

1.6. SOME IMPLICATIONS FOR FURTHER RESEARCH

As described in previous chapters, complex interaction between a subject, influenced by an individual psychological and genetic vulnerability and resilience to stress on one side, and traumatogenic factors, that operates within a particular social context on the other, may initiate a cascade of physiological and pathophysiological pathways, that leads over time to the development of various clinical symptoms and/or a mental disease. In this context, the concept of allostatic load represents an approximate description of the sensitization processes underlying the dynamic interplay between primary, secondary and tertiary mediators, that describe among other various levels of functional alterations of the neuroendocrine stress system and immune system. A purpose of this concept is to create systemic approaches using computational modelling that may help to understand various multidimensional factors that may play a role in the etiology of some mental diseases and their treatment.

An important factor in this multidimensional etiology is represented by dissociation, which is directly related to trauma exposure and neurobehavioral and psychological stress response. Further research focusing on dissociative processes might bring new insights into relationship between physiological regulations and

phenomena such as passive coping, somatoform symptoms and other, related to dissociation.

2. EMPIRICAL RESEARCH

Following the theoretical findings substantiated in previous chapters, this chapter will describe empirical research performed in two cohorts of inpatients with depressive disorder. The empirical studies aimed to examine the immune and endocrine responses to stress and their relationship to psychopathological symptoms focusing especially on symptoms of stress, dissociation and depression.

2.1. DISSOCIATIVE SYMPTOMS REFLECT LEVELS OF TUMOR NECROSIS FACTOR ALPHA (TNF-A) IN PATIENTS WITH UNIPOLAR DEPRESSION

2.1.1. Introduction

Advances in psychoneuroimmunological research suggest that the activation of pro-inflammatory mechanisms plays an important role in the pathophysiology of depression (Blume et al. 2011; Raison et al. 2006; Schiepers et al. 2005; Wichers & Maes 2002). Pro-inflammatory cytokines are substantially involved in this process and it has been proposed that, at least for a sub-group of depressed patients, they may represent a causal factor (Himmerich et al. 2008).

TNF-α, one of the prominent pro-inflammatory cytokines, has been studied largely in this context (Himmerich et al. 2008). It has been associated with the depressive disorder in a number of cross-sectional studies (Dowlati et al. 2010; Howren et al. 2009; Zorrilla et al. 2001), as well as one longitudinal study (van Zuiden et al. 2011). The research, however, has been extended beyond a simple association with depression; TNF-α has been related to different aspects of depressive symptomatology (Hauser et al. 2002; Kraus et al. 2003) and specific emotional and cognitive disturbances (Reichenberg et al. 2001). Moreover, TNF-α has been studied in relation to stress response and stressor-specific findings (García-Bueno et al. 2008) together with a moderating influence of depression (Weinstein et al. 2010), has been identified. However, association to specific trauma-related phenomena in depressed population, namely trauma-related and dissociative symptoms, has yet to be explored.

Based on these data, it was postulated that serum TNF-α levels, measured in depressed inpatients, would be related to both the depressive symptomatology and trauma-related and dissociative symptomatology.

2.1.2. Methods

2.1.2.1. Participants

In order to examine the above-mentioned hypothesis, assessment of basal serum TNF-α levels during rest conditions and psychometric measures were performed in 66 consecutive inpatients with unipolar depression. Extraction of blood samples and the administration of psychometric tools took place the same day. At the time of recruitment, participants were inpatients at the Department of Psychiatry at the First Faculty of Medicine in Prague. The assessments were performed within two weeks from the admission. Included were inpatients with the diagnosis of unipolar depressive disorder in relapse (i.e. patients with recurrent depression or single depressive episode; 296.30-296.34 and 296.20-296.24, respectively, according to DSM-IV diagnostic codes), without posttraumatic stress disorder (PTSD) and other comorbid diagnoses confirmed according to DSM IV criteria by clinical interview (American Psychiatric Association 1994).

In order to re-examine diagnosis and to exclude patients with PTSD or other comorbidities all patients were also screened using structured psychiatric interview M.I.N.I. version 5.0.0 (Sheehan et al. 1998). Patients' treatment at the time of recruitment was based only on antidepressant medication according to national guidelines (Raboch et al. 2006). Exclusion criteria were organic illnesses involving the central nervous system, psychotic disorders, PTSD, bipolar disorder, alcohol and/or drug abuse, any form of epilepsy and mental retardation, inflammatory, neuroendocrine and metabolic disorders, any hormonal or antipsychotic medication, methyldopa, prednisolone and cimetidine medication, electroconvulsive therapy or repetitive transcranial magnetic stimulation and pregnancy or lactation in women. All the patients gave written informed consent and the clinical study was approved by University ethical committee.

2.1.2.2. Psychometric meassures

For the assessment of depressive symptoms, Beck depression inventory BDI-II (Beck et al. 1996) was used. It represents a 21-items questionnaire for assessing depression (Cronbach's alpha 0.89, test-retest reliability after week 0.85). Subjects indicate the degree of their experience of depressive symptoms on 4-point Likert scale.

Psychic dissociative symptoms were assessed by Dissociative Experiences Scale (DES) (Bernstein & Putnam 1986). DES represents a 28 items self-reported questionnaire examining main dissociative phenomena such as absorption, amnesia, depersonalization, derealization, reality distortion, and others. Subjects indicate the degree of their experience on the a continuum from 0% to 100%. In the present study the Czech version of the DES was used, that similarly as original English version displays high reliability and internal consistency (Cronbach's alpha 0.92, test-retest reliability after week 0.91).

Somatoform dissociative symptoms were assessed using the 20-items self-reported Somatoform Dissociation Questionnaire (SDQ-20) (Nijenhuis et al. 1996). Somatoform dissociative symptoms represent alterations in sensations of pain (analgesia, kinesthetic anesthesia), alterations of perception, loss of motor control, gastrointestinal symptoms, etc. Subjects indicate the degree of their experience on a 5-point Likert scale. The Czech version of the SDQ-20 was used. It displays high reliability and internal consistency (Cronbach's alpha 0.91, test–retest reliability after week 0.90).

For investigation of traumatic symptoms, TSC-40 (Trauma Symptom Checklist) (Briere 1996) was used. TSC-40 is a self-reported 40-items questionnaire done on a 4-point Likert scale. TSC-40 evaluates trauma-related symptomatology in adults and assesses various aspects of posttraumatic stress and other symptom clusters found in traumatized individuals. The Czech version of the TSC-40 has high reliability and internal consistency (Cronbach's alpha 0.91, test-retest reliability after week 0.88).

Cf. Appendix (chapter 4) for the overview of all used psychometric tools.

2.1.2.3. Immunochemical measures

For biochemical assessment, blood samples of 5 ml volumes were collected in rest conditions according to common procedures at the time between 7.30 a.m. and 8 a.m. in the laboratory of Psychiatry department. The blood samples were carefully transferred (about 10 minutes) in icebox at the temperature of 4°C to the Central Laboratories of the Institute of Medical Biochemistry and Laboratory Diagnostics, 1st Faculty of Medicine, Charles University and General University Hospital in Prague where they were immediately centrifuged (4°C, 3000 rev., 10 minutes), pipetted into vials 2 x 0.5 ml each, and stored at – 20° C until the time of analysis. TNF-α serum levels were measured using a commercial immunoradiometric assay (IRMA) provided by DRG Instruments GmbH, Germany.

Principles of the TNF-α IRMA assay was based on coated-tube separation. The capture antibodies (Mabs1), were attached to the lower and inner surface of the plastic tube. Standards or samples added to the tubes at first showed low affinity for antibodies. The signal antibody labeled with ^{125}I, triggered the immunological reaction. After washing, the remaining radioactivity bound to the tube reflected the antigen concentration. Precision of the TNF-α IRMA corresponded to intrassay

coefficients of variation < 7.0 %. Sensitivity of the TNF-α concentration corresponding to the mean cpm + 2 standard deviations (SD) was 5 pg/ml.

2.1.2.4. Statistical methods

Statistical description of the studied population included means and standard deviation. In order to assess the relationship between TNF-α levels and psychometric measures, the Spearman rank correlation coefficients were determined. The Spearman rank correlation coefficient represent a robust nonparametric measure of correlation, resistant to the presence of outliers (Abdullah 1990).
All the methods of statistical evaluation were performed using the software package Statistica version 6. The statistical significance was presumed at P value <0.05.

2.1.3. Results

Table 2.1 presents the demographic and biometric characteristics of the studied population. Table 2.2 summarizes the drug treatment in the studied population.

Table 2.1. Demographic and biometric characteristics of the studied population.

	Depressed patients (n=66)
Male : Female	21 : 45
Age in years (mean +/-SD; min, max)	43.1 (+/- 7.3; min=18, max=60)
Education	
Elementary	5
Higher	50
University	11
BMI (mean +/-SD; min, max)	25.4 (+/-5.13; min=18, max=40.6)

The results indicate that TNF-α in the studied population is significantly correlated to DES (Spearman R=-0.42, p<0.01) (Figure 2.1.), SDQ-20 (Spearman R=-0.38, p<0.01) (Figure 2.2.) and TSC-40 (Spearman R=−0.41, p<0.01), but not to BDI-II (Table 2.3). These correlations show that TNF-α exhibits significant relationship to psychological and somatoform dissociation and the symptoms related to traumatic stress. Other

statistically significant correlations were also found between psychometric measures of depression, traumatic stress and dissociation (Table 2.3).

Table 2.2. Drug treatment in the studied population.

	Number of patients	Percentage of patients (%)	Dosage in mg (mean+/- SD; min, max)
Unmedicated	3	4.5	
Medicated			
1 antidepressant	48	72.7	
2 antidepressants	15	22.7	
Antidepressant treatment			
Amitriptyline	2	3	140
Dibenzepin	3	4.5	500 +/- 242.5; min=240, max=720
Trazodone	6	9.1	227 +/- 160.8; min=50, max=300
Moclobemide	1	1.5	900
Fluvoxamine	1	1.5	100
Fluoxetine	1	1.5	40
Sertraline	16	24.2	109 +/- 55.4; min=25, max=200
Citalopram	14	21.2	41 +/-10.7; min=20, max=60
Paroxetine	1	1.5	60
Escitalopram	6	9.1	19 +/-8.4; min=10, max=30
Venlafaxine	7	10.6	184 +/-71.9; min=150, max=300
Mirtazapine	17	25.8	43 +/-9; min=30, max=60
Milnacipran	3	4.5	167 +/-55.7; min=100, max=200

Table 2.3. Spearman correlations of TNF-α and results of psychometric measures. Note. *p < 0.05; **p < 0.01; BDI-II- Beck Depression Inventory; TSC-40- Trauma Symptom Checklist; DES- Dissociative Experiences scale; SDQ-20- Somatoform Dissociation Questionnaire

	TNF-α	BDI-II	TSC-40	DES
BDI-II	-0.04	–	–	–
TSC-40	-0.41**	0.43**	–	–
DES	-0.42**	0.29*	0.60**	–
SDQ-20	-0.38**	0.34**	0.68**	0.69**

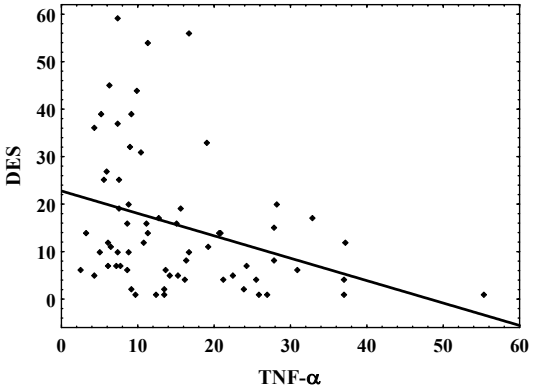

Figure 2.1. Dependency graph of TNF-α [pg/ml] and DES (Spearman R=-0.36, p<0.01).

Statistical comparison between men and women did not show significant differences in TNF-α or psychometric measures. No significant correlation was found between BMI and age and TNF-α and psychometric parameters.

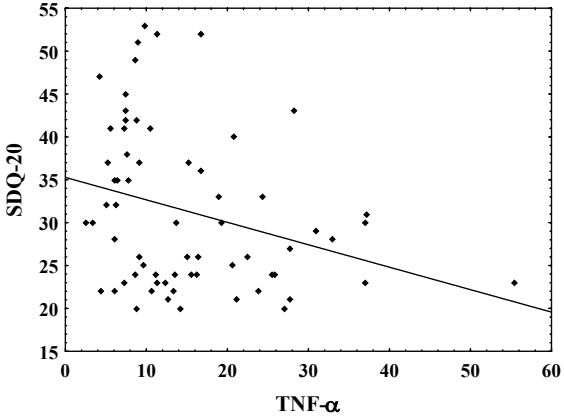

Figure 2.2. Dependency graph of TNF-α [pg/ml] and SDQ-20 (Spearman R=-0.30, p<0.05).

2.1.4. Discussion

In accordance with the hypothesis stated in the chapter 2.1.1., results of this study confirm a statistically significant relationship between TNF-α levels and the symptoms linked to chronic stressful experiences in depressed patients. However, the fact that the correlation is negative, is surprising and seems to be in contrast to both the theoretical framework and the previous research performed in our laboratory, focusing on interleukin 6 (IL-6), another pro-inflammatory cytokine. Moreover, unexpectedly, no significant relationship was revealed between TNF-α and depressive symptoms.

In order to understand the observed relationship between TNF-α and dissociative symptoms, studies on the HPA axis activation in depression appear relevant. Importantly, a negative correlation was found between cortisol and somatoform dissociation in a population of depressed patients (Bob et al. 2008b). On the other hand, TNF- α was reported to increase the HPA axis activity in depression (Himmerich et al. 2008). The present finding is in line with these results pointing to the fact, that somatoform dissociation may moderate the interplay between TNF-α and HPA axis activity in depression. Noteworthy, one of the previous work performed in our laboratory reported a positive correlation between IL-6 and somatoform dissociation (Bob et al. 2010a). Interestingly, taken together, both findings are consistent with the reported inhibition between TNF-α by IL-6 (Hirano et al. 1990) and they indicate that a

complex interaction between the two pro-inflammatory cytokines and their neurobiological effect may exist.

Similarly, the negative correlation between TNF-α and trauma-related symptoms is in an apparent contradiction with the theoretical framework. Notably, acute stress condition are associated with the increase of TNF-α in depressed patients (Pepys & Hirschfield 2003). Nevertheless, when focusing specifically on chronic stress condition, the result corresponds to the work by Bartolomucci and colleagues (Bartolomucci et al. 2003) who observed that chronic psychosocial stress down-regulated TNF-α mRNA levels in striatum and hippocampus.

Finally, as stated previously, it was unexpected to find no relevant association between TNF-α and depressive symptoms. Mean serum TNF-α level for the whole group (25,4 pg/ml +/- 5.1SD) appears higher than the TNF-α serum values reported in healthy volunteers (1-10 pg/ml) (Dowlati et al. 2010). Nevertheless, TNF-α assessment was not performed in healthy controls in our study and only a single self-reported test was used to assess the depressive symptoms (BDI-II). Therefore, it is not possible to decide, if the lack of correlation between TNF-α and depressive symptoms is due to low TNF-α levels in depressed group, a low sensitivity of psychometric instrument or another reason.

The present study has several limitations. First, since the scope of the study was to describe the nature of the relationship between TFN-α and specific psychometric characteristics in depressive disorder, no healthy or other control group was included into the analysis. The interpretation of the findings is therefore limited to this clinical condition. Second, the main focus on trauma-related psychopathology determined largely the choice of psychometric test, preferring reliable and widely used self-reported tests such as DES, SDQ-20 and TSC-40. As a result, the findings may be set in the context with the large body of research performed using these instruments while further interpretation must be done with precaution, taking into account the limitation imposed by self-reported nature of the testing. This precaution is even more relevant for the interpretation of the results related to depressive symptoms, as already mentioned. Third, while the recruitment of participants led to a quite naturalist clinical cohort, the characteristics of the studied group (inpatients, heterogeneous antidepressant treatment) limit the findings. In particular, the effect of antidepressant treatment may vary considerably between different substances and therapeutic regimens (Brustolim et al. 2006; Janssen et al. 2010; Kraus et al. 2002). Larger clinical group and a longitudinal study design is needed to address this issue. Last, the study is limited to only one of a large group of pro-inflammatory cytokines. In order to have a complex insight into the role of immune processes in emotional regulation and the development of affective disorders, other pro- and anti- inflammatory cytokines together with stress axis activity have to be explored (García-Bueno et al. 2008; Schiepers et al. 2005).

All together, TNF-α has been intensively studied as one of the prominent candidates in the cytokine model of depression and as a primary allostatic mediator. The role of TNF-α within depressive disorder seems, however, rather complex; specific emotional and stress system regulations may play an important role. The findings of this study reveal a tiny piece in this puzzle, encouraging further efforts to describe more in details the interplay of TNF-α regulations and chronic stress and dissociative processes in the development and clinical manifestation of depression.

2.2. DISSOCIATIVE SYMPTOMS AND NEUROENDOCRINE DYSREGULATION IN DEPRESSION

2.2.1. Introduction

As mentioned in the chapter on dissociation (chapter 1.5.), dissociation is traditionally attributed to trauma and other psychological stressors that are linked to dissociated traumatic memories (Bob 2003a; Bob 2007a; Kihlstrom 2005; Spiegel 1997); nevertheless brain injury or other organic brain disease may play a role in this process (Kihlstrom 2005; Spiegel 1997).

On the psychological level, dissociation encompasses phenomena such as memory losses, fragmentation of knowledge of the self and experience of the external world, splitting of emotional and cognitive aspects of experiences, numbing of affect, psychological escape from unpleasant stimuli, trance-like states, increased suggestibility and greater hypnotizability (Bob 2007a; Bob 2007b; Ellenberger 1970; Hall & Powell 2000; Putnam 1997). In addition to this, somatic components of dissociation have been suggested to play an important role in the long-term adaptation to traumatic experience, resulting in a lack of integration of somatoform components of experience, reactions, and functions (Nijenhuis 2000; Nijenhuis et al. 1996). Physiological reactions to traumatic stress include disturbances of self-regulatory systems such as HPA axis leading to hyperarousal, tachycardia or other symptoms of ANS instability (Bob et al. 2007c; Newport & Nemeroff 2000; Teicher et al. 2003). HPA axis activity has a profoud effect on the overall neuroendocrine balance, energetic metabolism, neuroimmunomodulation and disturbances of memory processes during stress reaction (Bob et al. 2008b; Bob et al. 2007d; Esch & Stefano 2005; Jasova et al. 2007; Kellner & Yehuda 1999; Mason et al. 2001; Newport & Nemeroff 2000; Payne et al. 2006b; Plotsky et al. 1998; Stefano & Esch 2007; Teicher et al. 2003; van West & Maes 2007). In accordance with the life cycle model of stress

(chapter 1.3.1.), current neurodevelopmental research suggests, that the most prominent disturbances of HPA axis are related to traumatic events such as childhood abuse or neglect in the first years of life and have often long-term impact on emotional, behavioral, cognitive, social and physiological functions (Newport & Nemeroff 2000; Teicher et al. 2003; van West & Maes 2007). Considering that traumatic stress is typically associated with dissociation, HPA axis functioning in relationship with dissociative symptoms is of interest, as supported by a few recent studies focusing to the neuroendocrinology of dissociation (Bob et al. 2007e; Carvalho Fernando et al. 2012; Giesbrecht et al. 2007; Simeon et al. 2001; Simeon et al. 2007a; Simeon et al. 2007b).

To our knowledge and according to PubMed search, there are six studies examining HPA axis reactivity to psychosocial stress as a function of dissociative symptoms (Bob et al. 2007e; Carvalho Fernando et al. 2012; Giesbrecht et al. 2007; Simeon et al. 2001; Simeon et al. 2007a; Simeon et al. 2007b). These studies examined dissociation-related dysregulation in clinical population with dissociative disorders and borderline personality disorder. The aim of the following study was to examine stress-related disturbances of HPA axis functioning indexed by basal cortisol and prolactin, and to assess their relationship with psychic and somatoform dissociative symptoms, trauma-related symptoms, and depressive symptoms in patients with depressive disorder.

2.2.2. Methods

2.2.2.1. Participants

For empirical examination of suggested hypothesis, assessment of basal serum prolactin and cortisol levels during rest conditions were performed in 40 consecutive inpatients with unipolar depression. The patients were at the time of recruitment treated at the university hospital, Psychiatry department and the clinical assessments were performed within 14 days from the admission. The patients were diagnosed with the unipolar depressive disorder (i.e. patients with recurrent depression or depressive period) in relapse according to DSM IV criteria (American Psychiatric Association 1994).

With the purpose to re-examine diagnosis and exclude PTSD or other comorbidities all the patients were also screened using structured psychiatric interview M.I.N.I. version 5.0.0. (Sheehan et al. 1998). The patients were treated only by SSRI antidepressants in usual recommended doses according psychiatric

guidelines. Exclusion criteria were organic illnesses involving the central nervous system, psychotic disorders, PTSD, bipolar disorder, alcohol and/or drug abuse, any form of epilepsy and mental retardation (IQ Raven higher than 90), neuroendocrine and metabolic disorders, any hormonal or antipsychotic medication, triclic antidepressant, methyldopa, prednisolone and cimetidine medication, ECT or rTMS therapy and pregnancy or lactation in women. The patients were 10 males and 30 females in average age 43.47±12.21 (age range 30-60) predominantly with high-school education, non-smokers with adequate nutritional status and body mass index (17-29). All the patients gave written informed consent and the clinical study was approved by university ethical committee.

2.2.2.2. Psychometric measures

Czech versions of following psychometric tools were used in the study: DES, SDQ-20, TSC-40 and BDI-II. Cf. chapter 2.1.2.2. for further description. Cf. Appendix (chapter 4) for the overview of all used psychometric tools.

2.2.2.3. Neuroendocrine measures

For biochemical assessment, blood samples of 5 ml volumes were collected in rest conditions according to common procedures at the time from 7:30 to 8 a.m. in laboratory of Psychiatry department. The blood samples were then transferred in iceboxes at the temperature of 4°C to university biochemical department and immediately centrifuged at the temperature of 4°C. After that prolactin and cortisol serum levels have been assessed in biochemical laboratory according to common analytical procedures.

Prolactin and cortisol serum levels were assessed by chemiluminiscent immunoassay (CLIA) using analysator ADVIA (Centaur Bayer). The intra- and interassay coefficients of variance were 2.9 and 12.2%.

2.2.2.4. Statistical methods

Statistical analysis of the results of serum prolactin and cortisol levels, and psychometric measures included common methods of descriptive and inferential statistics. For quantitative description means, standard deviations and multiple and simple regression for the study of the relationship between several independent or predictor variables and a dependent or criterion variable the methods of simple or multiple regression were used. For description of functional relationship between psychometric measures Pearson product-moment correlation for independent

samples were used. All the methods of statistical evaluation were performed using the software package Statistica version 6.

2.2.3. Results

Results of the present study confirm relationship between HPA axis reactivity and psychosocial stressors leading to dissociative symptoms in the depressive patients. Data show that prolactin and cortisol as indices of HPA axis functioning manifest significant relationship to dissociative symptoms. The main result is represented by a highly significant correlation obtained by simple regression between psychic dissociative symptoms measured by DES and serum prolactin (R=0.55, p=0.00027, F=16.11) (Figure 2.3.). Significant correlation was also found between somatoform dissociative symptoms measured by SDQ-20 and serum cortisol (R=-0.38, p=0.015, F=6.39) (Figure 2.4.).

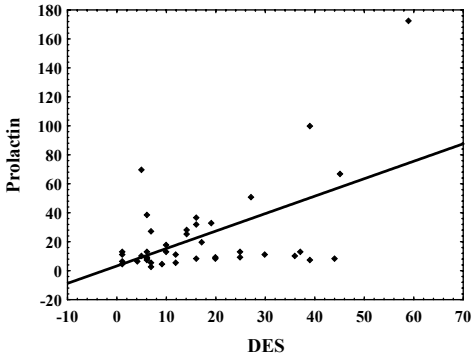

Figure 2.3. Dependency graph between DES and prolactin serum levels [µg/l] (r=0.55, p=0.00027).

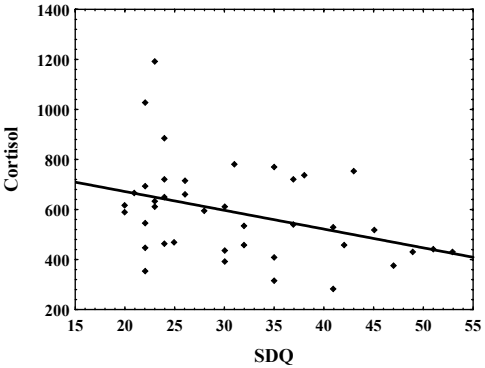

Figure 2.4. Dependency graph between SDQ-20 and cortisol serum levels [nmol/l] (r=-0.38, p=0.015).

Other correlations assessed by simple regression among prolactin, cortisol and psychometric measures were not statistically significant (Table 2.4). Significant relationships are also indicated by Pearson product-moment correlations for psychometric measures of dissociation, symptoms of traumatic stress and depressive symptoms (Table 2.4).

Table 2.4. Pearson product-moment correlations (r), correlations coefficients obtained by simple regression (R) and p-values of the statistical tests.

	DES	SDQ-20	TSC-40	BDI-II
Prolactin	R=0.55, p=0.00027	R=0.14, p=0.19	R=0.30, p=0.06	R=0.20, p=0.11
Cortisol	R=-0.07, p=0.33	R=-0.38, p=0.015	R=-0.19, p=0.24	R=0.12, p=0.33
DES	1	r=0.65, p=0.000003	r=0.49, p=0.001	r=0.34, p=0.016
SDQ-20	r=0.65, p=0.000003	1	r=0.63, p=0.00001	r=0.52, p=0.0003
TSC-40	r=0.49, p=0.001	r=0.63, p=0.00001	1	r=0.72, p=0.0000001

Coefficient of multiple determination R=0.62 obtained by multiple regression is highly statistically significant for prolactin as linear function of independent variables DES and SDQ-20, i.e. prolactin=f(DES,SDQ-20); F=11.34, p=0.00014, df=2.37, R-square=0.38, standard error of estimate is 25.62.

Coefficient of multiple determination R=0.45 obtained by multiple regression is statistically significant also for cortisol as linear function of independent variables DES and SDQ-20, i.e. cortisol=f(DES,SDQ-20); F=4.67, p=0.015, df=2.37, R-square=0.201, standard error of estimate is 172.46.

Hypoprolactinemia or hypocortisolemia was not present in any of the patients. On the other hand hyperprolactinemia (higher than 30 μg/l) was found in 9 patients (1 man) and hypercortisolemia (higher than 620 nmol/l) in 15 patients (1 man). Simultaneous occurrence of hyperprolactinemia and hypercortisolemia was found in 5 women.

2.2.4. Discussion

In line with the previous studies (Bob et al. 2007e; Carvalho Fernando et al. 2012; Giesbrecht et al. 2007; Simeon et al. 2001; Simeon et al. 2007a; Simeon et al. 2007b), reported results point to a relationship between HPA axis reactivity and dissociative symptoms.

The correlation between DES and serum prolactin (R=0.55, p=0.00027) is in agreement with findings of other cross-sectional and longitudinal studies, showing that both increased or decreased prolactin levels have been related to psychological stressors (Sonino et al. 2004; Theorell 1992; Uhart et al. 2006). Specifically, stressful experiences resulting in passive coping behavior are associated with increased plasma prolactin levels whereas stress situations associated with active coping are associated with unchanged or decreased levels (Theorell 1992). Theorell (Theorell 1992) reported a bimodal prolactin secretion in response to stress, i.e. it increased in subjects that experienced passive helplessness, whereas it decreased in conjunction with increased anxiety and active coping. In contrast to acute (phasic) emotional states associated with decreased prolactin (Codispoti et al. 2003; Olff et al. 2006), Theorell focused his research on chronic (tonic) stress condition (Codispoti et al. 2003; Theorell 1992). Considering that prolactin regulation is directly interrelated with the dopaminergic activity, he proposed that increased prolactin levels may play a role in the preservation of vital functions during withdrawal (Theorell 1992). Animal studies further support this line of reasonning, as increased prolactin levels have been found in submissive subjects, and decreased levels in dominant subjects (Henry et al. 1986).

Dissociation could be interpreted as a parallel process to animal defensive and recuperative states activated by severe threat. Empirical data and clinical observations suggest that there are similarities between freezing and concomitant development of analgesia in threatened animals (Nijenhuis et al. 1998). These primary defense strategies involve the parasympathetic nervous system and lead to passive coping strategies such as withdrawal or disengagement, and the immobility response (Schore 2001; Schore 1994). Emotions typically associated with parasympathetic functions

have a negative valence, such as shame, disgust, hopelessness, and despair (Schore 2001; Schore 1994). Dissociation represents a corresponding form of human response to inescapable threat and stress, with the same defensive tendency toward passive and avoidant coping that emerge as hopelessness, learned helplessness, social and emotional withdrawal and disengagement (Nijenhuis et al. 1998; van der Kolk et al. 1985). In this context, correlation between prolactin and DES found in the present study is supportive of the idea, that there is a close relationship between prolactin and dissociation as a typical form of passive coping behavior related to withdrawal and disengagement related to chronic stress conditions.

The correlation between SDQ-20 and serum cortisol (R=-0.38, p=0.015) might have an analogical, though reciprocal meaning. This finding is in agreement with the results of other studies showing that chronic stress exposure is associated with decreased cortisol levels, which is related to defense mechanisms (Mason et al. 2001; Van Der Hart et al. 2005). As was the case in prolactin, both human and animal studies indicate, that cortisol levels reflect not only emotional arousal but also active defensive or antiarousal intrapsychic mechanisms, conceptualized in psychological perspective as a balance between opposing intrapsychic forces. In other words, engagement that represent active emotional response is associated with high cortisol levels, and disengagement (e.g. avoidance, withdrawal or denial) related to passive defense with low cortisol levels (Mason et al. 2001). These findings suggest that the cortisol decrease related to somatoform dissociation reflects typical vulnerability to mental stress exposure that emerges as disengagement.

Additionally, the relationship between SDQ-20 and basal serum cortisol (R=-0.38, p=0.015) related to chronic stress conditions found in the present study appears to be in agreement with similar result described by Simeon et al. (Simeon et al. 2007b), i.e. a negative correlation between DES and plasma cortisol level (r=-0.32, p=0.03) during stress stimulation in patients with dissociative disorders, as there is a high correlation between DES and SDQ-20 (r=0.65, p=0.000003) (Nijenhuis 2000).

3. CONCLUSIONS

Current knowledge of the relationship between stress and etiopatogenesis of mood disorders aggregate a large body of biomedical and psychosocial research. Among many areas in this context, the study of dissociation has a potential to further our understanding of how trauma and chronic stress exposure lead to the development of different psychopathology and somatic symptoms. Specifically, as documented by the results reported in the previous chapter, dissociation may be involved in neuroimmune and neuroendocrine response to stress in mood disorder.
Three findings seem to be of particular interest:

(1) TNF-α, that has been intensively studied as one of the prominent candidates in the cytokine model of depression, was found to be negatively correlated with both psychic and somatoform dissociative symptoms and trauma-related symptoms in patients with depression. Furthermore, no significant correlation was discovered with the severity of depressive symptoms. These findings are rather surprising, as theoretical model would expect an opposite relationship. Possible explanations are discussed in the chapter 2.1.4., and although no theoretical or clinical conclusions can be taken at this point, the findings encourage to further efforts to describe more in details the interplay of TNF-α regulations, chronic stress and dissociative processes in the development and clinical manifestation of depression.
(2) Prolactin was found to be (possitively) correlated with psychic dissociative symptoms in the studied cohort of depressed patients. Interestingly, no significant correlation was revealed between prolactin level and neither trauma-related symptoms or severity of depressive symptoms. As proposed in the chapter 2.2.4, prolactin (patho)physiology and psychic dissociative mechanism may represent interelated processes in the complex regulation of passive coping behavior, at least in depressed patients.
(3) Cortisol, the primary stress hormone in humans, was found to be negatively correlated with somatoform dissociation in the same cohort of patients. As was the case in analyses including prolactin, no significat correlation was discovered between cortisol level and neither trauma-related symptoms or severity of depressive symptoms. Based on this finding, it could be suggested, that low level of cortisol is in relation with active defensive or antiarousal intrapsychic processes, such as avoidance, withdrawal and denial.

To our knowledge and according to a PubMed search (1985 to present, with following serch terms: dissociation, dissociative, tumor necrosis factor, tnf, prolactin, cortisol), these findings contribute to a so far restricted research area (no study examing immune/cytokine reactivity to stress as a function of dissociation, 6 studies examining HPA axis reactivity to stress in relation to dissociation (Bob et al. 2007e; Carvalho Fernando et al. 2012; Giesbrecht et al. 2007; Simeon et al. 2001; Simeon et al. 2007a; Simeon et al. 2007b). Their interpretation need to be careful, due to several limitations described in correspondings chapters (chapter 2.1.4., chapter 2.2.4.). Newertheles, the results justify future efforts to carry out further research in this area using longitudinal design and larger cohorts of patients.

4. APPENDIX – USED PSYCHOMETRIC MEASURES

The psychometric measures used in the studies described in the chapter Empirical research were presented to the patients with the following layout.

Vliv stresu na lidské zdraví

Jméno a příjmení:

Rodinný stav:

Věk:

Zaměstnání:

Vzdělání:

Tělesná výška v cm:

Tělesná hmotnost v kg:

Kuřák: ANO NE (zakroužkovat)

Pokud ano: počet vykouřených cigaret denně:

Kouření bezprostředně před odběry: ANO NE (zakroužkovat)

Pro pacientky:
Menopauza: ANO NE (zakroužkovat)
Pokud ne: kolikátý den od prvního dne poslední menstruace:

V případě zájmu o sdělení klinicky významných výsledků, uveďte prosím, koho informovat (Vás, praktického lékaře, psychiatra + kontaktní adresa, nebo telefonické spojení):

Je důležité, abyste vyplnil(a) níže uvedené otázky tak, jak to skutečně cítíte. Tím pomůžete sobě i druhým.

DES (Dissociative experiences scale)

Pokyny:
Tento dotazník obsahuje 28 otázek, jež se týkají zkušeností, které se mohou vyskytovat ve vašem každodenním životě. Zajímá nás, jak často se Vám tyto události stávají. Je však důležité, aby Vaše odpovědi ukázaly, jak často tyto zkušenosti prožíváte, aniž jste pod vlivem alkoholu nebo drog. K tomu, abyste mohli odpovědět na otázku, je nutné, abyste vyjádřili odpovídající stupeň zkušenosti vyjádřené v otázce ve vztahu k sobě a vyznačili jej vertikální čarou na příslušném místě, jak je ukázáno na příkladu.

Příklad:
0% |————————————/————————————|100%

1. Někteří lidé mají zkušenost, že si při řízení auta náhle uvědomí, že si nemohou vzpomenout na to, co se událo v průběhu celého výletu nebo jeho části. Vyznačte čarou, v jakém procentu času se to stává Vám.
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2. Někteří lidé občas shledají, že si při poslechu něčí řeči náhle uvědomí, že neslyšeli část nebo vůbec nic z toho, co bylo řečeno. Vyznačte čarou, v jakém procentu času se to stává Vám.
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3. Někteří lidé mají zkušenost v tom, že shledají sebe sama na nějakém místě a nevědí, jak se tam dostali . Vyznačte čarou, v jakém procentu času se to stává
0% |————————————————————————————————————|100%

4. Někteří lidé mají zkušenost s tím, že naleznou sebe sama oblečené v oděvu a nevzpomínají si, že se oblékali. Vyznačte čarou, v jakém procentu času se to stává Vám.
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5. Někteří lidé mají zkušenost, že naleznou nové věci mezi těmi jež vlastní a nemohou si vzpomenout, že je kupovali. Vyznačte čarou, v jakém procentu času se to stává Vám.
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6. Někteří lidé občas shledají, že se setkají s lidmi, které neznají a kteří je nazývají jiným jménem a trvají na tom, že se spolu již setkali. Vyznačte čarou, v jakém procentu času se to stává Vám.

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7. Někteří lidé mají občas zkušenost, že cítí, jakoby stáli vedle někoho, nebo hledíce na sebe sama něco dělají a vidí sebe sama, jakoby hleděli na jinou osobu. Vyznačte čarou, v jakém procentu času se to stává Vám.
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8. Někteří lidé říkají, že občas nepoznávají přátele nebo členy rodiny. Vyznačte čarou, v jakém procentu času se to stává Vám.
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9. Někteří lidé někdy shledají, že si nevzpomínají na důležité události ve svém životě [například svatba, promoce, maturita a podobně]. Vyznačte čarou, v jakém procentu času se to stává Vám.
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10. Někteří lidé mají zkušenost s tím, že jsou obviňováni ze lhaní, aniž by lhali. Vyznačte čarou, v jakém procentu času se to stává Vám.
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11. Někteří lidé mají zkušenost, že hledí do zrcadla a nepoznávají sami sebe. Vyznačte čarou, v jakém procentu času se to stává Vám.
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12. Někteří lidé mají občas zkušenost s tím, že cítí, že jiní lidé, věci nebo svět kolem nich nejsou reálné. Vyznačte čarou, v jakém procentu času se to stává Vám.
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13. Někteří lidé mají občas zkušenost s tím, že cítí, jakoby jim jejich tělo nenáleželo. Vyznačte čarou, v jakém procentu času se to stává Vám.
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14. Někteří lidé mají zkušenost, že si občas vzpomenou na nějakou minulou událost, tak živě, že cítí, jakoby tuto událost znovu prožili. Vyznačte čarou, v jakém procentu času se to stává Vám.
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15. Někteří lidé mají zkušenost s tím, že si nejsou jisti, zda události, na něž si vzpomínají, se opravdu staly, nebo si je jen vysnili. Vyznačte čarou, v jakém procentu času se to stává Vám.
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16. Někteří lidé mají zkušenost s tím, že se octnou na známém místě, které jim připadá zvláštní a neznámé.
Vyznačte čarou, v jakém procentu času se to stává Vám.
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17. Některým lidem se stává, že když hledí na televizi nebo film, jsou tak pohlceni příběhem, že si nejsou vědomi ostatních událostí kolem nich. Vyznačte čarou, v jakém procentu času se to stává Vám.
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18. Některým lidem se občas stává, že jsou tak pohlceni fantazií nebo denním snem, že pociťují, jakoby se jim to opravdu stalo. Vyznačte čarou, v jakém procentu času se to stává Vám.
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19. Některým lidem se stává, že jsou občas schopni ignorovat bolest. Vyznačte čarou, v jakém procentu času se to stává Vám.
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20. Některým lidem se stává, že občas sedí a upřeně hledí před sebe, o ničem nepřemýšlí a nejsou si vědomi uplynulého času. Vyznačte čarou, v jakém procentu času se to stává Vám.
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21. Některým lidem se občas stává, že když jsou sami, hovoří nahlas sami se sebou.
Vyznačte čarou, v jakém procentu času se to stává Vám.
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22. Někteří lidé shledávají, že v některé situaci jednají tak odlišně ve srovnání s jinou, že se cítí téměř tak, jakoby byli dvěma různými lidmi. Vyznačte čarou, v jakém procentu času se to stává Vám.
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23. Některým lidem se občas stává, že v některých situacích jsou schopni vykonávat věci, které jsou pro ně obvykle obtížné s úžasnou lehkostí a spontaneitou [například sport, práce, sociální situace]. Vyznačte čarou, v jakém procentu času se to stává Vám.
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24. Někteří lidé si občas nemohou vzpomenout, zda-li něco udělali, neboť mají jen myšlenku o tom, že tu věc udělali [například nevědí, zda-li poslali dopis, nebo si jen myslí, že jej poslali]. Vyznačte čarou, v jakém procentu času se to stává Vám.
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25. Někteří lidé někdy shledají, že udělali věci, na něž si nemohou vzpomenout, že je dělali. Vyznačte čarou, v jakém procentu času se to stává Vám.
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26. Někteří lidé občas naleznou zápisky, kresby, nebo poznámky, mezi těmi jež jim náleží, které museli sami učinit, ale nemohou si vzpomenout kdy. Vyznačte čarou, v jakém procentu času se to stává Vám.
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27. Některým lidem se občas stává, že slyší hlasy uvnitř své hlavy, které jim říkají, co mají dělat, nebo komentují to, co dělají. Vyznačte čarou, v jakém procentu času se to stává Vám
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28. Někteří lidé občas pociťují, jako když hledí na svět skrze mlhu, takže lidé a objekty se jim jeví být vzdálenými a nejasnými. Vyznačte čarou, v jakém procentu času se to stává Vám.
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SDQ-20 (Somatoform dissociation questionnary)

Odpověď znázorněte na škále od 1 [neodpovídá to mým zkušenostem a pocitům] do 5 [velmi dobře odpovídá]. Občas se mi stává [že]:

Jakoby moje tělo nebo jeho část zmizela.	1	2	3	4	5
Jsem na chvíli paralyzován[a].	1	2	3	4	5
Nemohu mluvit [nebo pouze s velkým úsilím], nebo mohu pouze šeptat.	1	2	3	4	5
Moje tělo nebo jeho část je necitlivá vůči bolesti.	1	2	3	4	5
Zažívám bolest v průběhu močení.	1	2	3	4	5
Na chvíli nemohu vidět [jako bych byl[a] slepý[á].	1	2	3	4	5
Mám potíže při močení.	1	2	3	4	5
Nemohu na chvíli slyšet [jako bych byl[a] hluchý[á].	1	2	3	4	5
Slyším zvuky zblízka, jakoby přicházely zdaleka.	1	2	3	4	5
Na chvíli zůstanu strnule stát.	1	2	3	4	5
Nemám rýmu a k tomu mám buď mnohem lepší nebo horší čich než je tomu obvykle.	1	2	3	4	5
Cítím bolest v genitálu [zvláště po sexuálním styku].	1	2	3	4	5
Mám záchvat, který se podobá epileptickému.	1	2	3	4	5
Jsou mi nepříjemné vůně, jež mám obvykle rád[a].	1	2	3	4	5

Jsou mi nepříjemné chutě, jež mám obvykle rád[a]

[pro ženy, mimo průběh těhotenství nebo menstruace].	1	2	3	4	5
Vidím věci kolem mne jinak než je tomu obvykle [Například, jako když hledím skrze nějaký tunel, nebo vidím pouze část nějakého objektu].	1	2	3	4	5
Nemohu spát v průběhu noci až do jejího konce, ale přesto zůstávám velmi aktivní během dne.	1	2	3	4	5
Nemohu polykat, nebo jen s velkým úsilím.	1	2	3	4	5
Lidé a věci vypadají větší, než jaké ve skutečnosti jsou.	1	2	3	4	5
Mé tělo, nebo jeho část, vnímám jako znecitlivělou.	1	2	3	4	5

BDI-II (Beck depression inventory)

Zakroužkujte v každé skupině jeden výrok, který nejlépe vystihuje, jak se cítíte **během posledních 14 dnů včetně dneška.**

1. Smutek
0 Nejsem smutný[á].
1 Většinou jsem smutný[á].
2 Pořád jsem smutný[á].
3 Jsem tak smutný[á], že se to nedá vydržet.

2. Pesimismus
0 O svou budoucnost nemám obavy.
1 O svou budoucnost se obávám více než dříve.
2 Myslím, že se mi nebude dařit.
3 Moje budoucnost je beznadějná a bude ještě horší.

3. Minulá selhání
0 Nemám dojem, že selhávám.
1 Selhal[a] jsem častěji než bych měl[a].
2 Když se dívám do minulosti vidím spoustu selhání.
3 Jako člověk jsem úplně selhal[a].

4. Ztráta radosti
0 Raduji se stejně jako dříve.
1 Neraduji se stejně jako dříve
2 Téměř nemám potěšení s věcí, které jsem měl[a] rád[a].
3 Vůbec nemám potěšení s věcí, které jsem měl[a] rád[a].

5. Pocit viny
0 Nemívám nijak zvlášť pocity viny.
1 Cítím vinu za řadu věcí, které jsem udělal[a] nebo měl[a] udělat.
2 Mívám často pocity viny.
3 Pořád mám pocity viny.

6. Pocit potrestání
0 Nemyslím, že mě život trestá.
1 Myslím, že by mě život mohl potrestat.
2 Očekávám trest.
3 Myslím, že jsem životem trestán[a].

7. Znechucení ze sebe sama
0 Myslím si o sobě pořád to samé.
1 Ztratil[a] jsem důvěru v sebe sama.
2 Jsem ze sebe zklamaný[á].
3 Sám[a] sebou jsem znechucen[a].

8. Sebekritika
0 Nekritizuji nebo neobviňuji sebe sama více než obvykle.
1 Jsem sám[a] k sobě více kritický[á] než dříve.
2 Kritizuji se za všechny své chyby.
3 Obviňuji se za všechno špatné co se přihodí.

9. Sebevražedné myšlenky nebo přání
0 Nepřemýšlím o tom, že bych se zabil[a].
1 Mám myšlenky o sebevraždě, ale neudělal[a] bych to.
2 Chtěl[a] bych se zabít.
3 Kdybych měl[a] možnost se zabít, tak bych se zabil[a].

10. Plačtivost
0 Nepláču více než dříve.
1 Pláču více než dříve.
2 Pláču kvůli každé maličkosti.
3 Je mi do pláče, ale nejsem toho schopen[na]

11. Agitovanost
0 Nejsem více neklidný[á] nebo napjatý[á] než obvykle.
1 Cítím se více neklidný[á] nebo napjatý[á] než obvykle.
2 Jsem tak neklidný[á] nebo rozrušený[á], že je těžké to vydržet.
3 Jsem tak neklidný[á] nebo rozrušený[á], že nemohu zůstat v nečinnosti.

12. Ztráta zájmu
0 O jiné lidi nebo věci jsem zájem neztratil[a].
1 Méně se zajímám o jiné lidi nebo věci.
2 Mnohem méně se zajímám o jiné lidi nebo věci.
3 Je těžké se zajímat o cokoliv.

13. Nerozhodnost
0 Rozhoduji se stejně dobře jako dříve.
1 Rozhodovat se je obtížnější, než obvykle.
2 Rozhoduji se mnohem obtížněji než dříve.
3 Mám problém udělat jakékoliv rozhodnut

14. Pocit bezcennosti
0 Necítím se bezcenný[á]
1 Nemyslím, že mám pro lidi stejnou cenu jako jsem míval[a].
2 Ve srovnání s jinými lidmi se cítím více bezcenný[á].
3 Cítím se úplně bezcenný[á].

15. Ztráta energie
0 Mám stejně energie jako vždy.
1 Mám méně energie než jsem míval[a].
2 Nemám dost energie, abych toho hodně udělal[a].
3 Vůbec na nic nemám energii.

16. Změna spánku
0 Nevšiml[a] jsem si žádných změn u svého spánku.
1a Spím trochu více než obvykle.
1b Spím trochu méně než obvykle.
2a Spím mnohem více než obvykle.
2b Spím mnohem méně než obvykle.
3a Většinu dne prospím.
3b Probouzím se o jednu až dvě hodiny dříve a už nemohu usnout.

17. Podrážděnost
0 Nejsem podrážděný[á] více než obvykle.
1 Jsem více podrážděný[á] než obvykle.
2 Jsem mnohem více podrážděný[á] než obvykle.
3 Bývám pořád podrážděný[á].

18. Změny chuti k jídlu
0 Necítím žádné změny v chuti k jídlu.
1a Mám trochu menší chuť k jídlu než obvykle.
1b Mám trochu větší chuť k jídlu než obvykle.
2a Mám mnohem menší chuť k jídlu než obvykle.
2b Mám mnohem větší chuť k jídlu než obvykle.
3a Vůbec nemám chuť k jídlu.
3b Jíst mohu pořád.

19. Koncentrace
0 Mohu se soustředit jako vždycky.
1 Nejsem schopný[á] se soustředit jako obvykle.
2 Je těžké se na cokoliv delší dobu soustředit.
3 Nejsem schopný[á] se soustředit na nic.

20. Únava

0 Nejsem unavený[á] více než obvykle.
1 Unavím se snadněji než obvykle.
2 Jsem příliš unavený[á], než abych dělal[a] tolik věcí, jako jsem dělával[a].
3 Jsem tak unavený[á], že nedokážu dělat skoro nic.

21. Ztráta zájmu o sex

0 V současnosti jsem nezaznamenal[a] změnu zájmu o sex.
1 Mám menší zájem o sex než obvykle.
2 Mám nyní mnohem menší zájem o sex.
3 Úplně jsem ztratil[a] zájem o sex.

TSC-40 (Trauma symptoms cheklist)

Jak často jste zažil[a] každou z následujících položek v posledních dvou měsících?

	Nikdy			Často
1. Bolesti hlavy.	0	1	2	3
2. Nespavost [problém s usnutím].	0	1	2	3
3. Ztráta váhy [bez diety].	0	1	2	3
4. Žaludeční problémy.	0	1	2	3
5. Sexuální problémy.	0	1	2	3
6. Pocit izolovanosti od ostatních.	0	1	2	3
7."Retrospektivy" [náhlé, živé zneklidňující vzpomínky].	0	1	2	3
8. Neklidný spánek.	0	1	2	3
9. Snížený zájem o sex.	0	1	2	3
10. Záchvaty úzkosti.	0	1	2	3
11. Zvýšený sexuální zájem.	0	1	2	3
12. Pocit osamělosti.	0	1	2	3
13. Noční můry.	0	1	2	3
14. "Úlety" [úniky ve vaší mysli].	0	1	2	3
15. Smutek.	0	1	2	3
16. Závrať.	0	1	2	3
17. Nespokojenost se sexuálním životem.	0	1	2	3
18. Obtížná kontrola nálady.	0	1	2	3
19. Probouzení se brzy ráno a nemožnost opět usnout.	0	1	2	3
20. Nekontrolovatelný pláč.	0	1	2	3
21. Strach z mužů.	0	1	2	3
22. Rána bez pocitů odpočinku.	0	1	2	3
23. Máte sex, který Vás netěší.	0	1	2	3
24. Potíže ve vycházení s druhými.	0	1	2	3
25. Problémy s pamětí.	0	1	2	3
26. Zájem o sebepoškozování.	0	1	2	3
27. Strach ze žen.	0	1	2	3
28. Probouzení o půlnoci.	0	1	2	3
29. Špatné myšlenky nebo pocity v průběhu sexu.	0	1	2	3
30. Odchody někam.	0	1	2	3
31. Pocity, že věci jsou "nereálné".	0	1	2	3
32. Nadbytečné nebo příliš časté mytí.	0	1	2	3
33. Pocity ponížení.	0	1	2	3
34. Trvalé pocity napětí.	0	1	2	3
35. Zmatenost pokud jde o pocity související se sexualitou.	0	1	2	3

36. Přání fyzicky poškozovat druhé.	0	1	2	3
37. Pocity viny.	0	1	2	3
38. Pocity, že nejste vždy ve vašem těle.	0	1	2	3
39. Máte potíže s dýcháním.	0	1	2	3
40. Sexuální pocity tam, kde si je nepřejete mít.	0	1	2	3

5. LIST OF ORIGINAL PUBLICATIONS

publications *in extenso* in relationship to the subject of dissertation

a) with IF

Bizik G., Bob P., Raboch J., Pavlat J., Uhrova J., Benakova H., Zima T., Dissociative symptoms reflect levels of TNF alpha in patients with unipolar depression. Neuropsychiatric disease and treatment. 2014; 10, 675-679. IF = 1,809

Bizik G., Juster R. P., Picard M.,Nijjar R., Tourjman V., McEwen B. S.,Lupien S. J., Allostatic load as a tool for monitoring physiological dysregulations and comorbidities in patients afflicted by severe mental illnesses, Harvard Review Of Psychiatry. 2013; 21(6), 296-313. IF = 3,046

Juster R P, Bizik G, Picard M, Arsenault-Lappierre G, Sindi S, Trepanier L, Marin M F, Wan N, Sekerovic Z, Lord C, Fiocco A J, Plusquellec P, McEwen B S, Lupien S., A transdisciplinary perspective of chronic stress in relation to psychopathology. Development and Psychopathology. 2011; 23, 725-776. IF = 4,4

Bob P, Fedor-Freybergh P, Jasova D, Bizik G, Susta M, Pavlat J, Zima T, Benakova H, Raboch J. Dissociative symptoms and neuroendocrine dysregulation in depression. Med Sci Monit. 2008; 14(10), 499-504. IF = 1,699

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b) without IF

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6. ABBREVIATIONS

ACTH – AdrenoCorticoTropic Hormone
AL – Allostatic Load
ANS - Autonomic Nervous System
BDI-II - Beck Depression Inventory-II
BDNF – Brain Derived Neurotrophic Factor
BMI - Body Mass Index
CLIA - ChemiLuminiscent ImmunoAssay
COMT – Catechol-O-MethylTransferase
CRH - Corticotropin-Releasing Hormone
CRHR - Corticotropin-Releasing Hormone Receptor
DALY - Disability-Adjusted Life Years
DES – Dissociative Experiences Scale
DSM – Diagnostic and Statistical Manual of Mental Disorders
DST - Dexamethsone Suppression Test
ECT – ElectroConvulsive Therapy
FDA – Food and Drug Administration
FKBP – FK506 Binding Protein
GCs – GlucoCorticoids
GR – Glucocorticoid Receptor
HPA axis - Hypothalamic-Pituitary-Adrenal axis
Hsp – heat shock protein
HV – Hippocampal Volume
ICD – Internation Classification of Diseases
IL – Interleukine
IRMA - ImmunoRadioMetric assay
MINI - Mini International Neuropsychiatric Interview
MDD - Major Depresive Disorder
mRNA – messenger RiboNucleic Acid
NMDA – N-Methyl-D-Aspartate Acid
PFC - Prefrontal Cortex
PTSD - Postraumatic Stress Disorder
ROS - Reactive Oxygen Species
rTMS – repetitive Transcranial Magnetic Stimulation
SAM axis - Sympatho-Adrenal-Medullary axis
SDQ-20 – Somatoform Dissociation Questionnaire
SMI – Severe Mental Illnesses
SNP – Single Nucleotid Polymorphism
THC - delta-9-TetraHydroCannabinol

TNF – Tumor Necrosis Factor
TSC-40 – Trauma Symptom Checklist - 40
YLDs - Years Lived with Disability
5-HTTLPR – 5-Hydroxy-Triptamine(Serotonin)-Transporter-Linked Promotor Region

7. SUMMARY

Depression and other mental disorders are the leading cause of disability worldwide and their burden has increased considerably over past decades. However, advances in psychopharmacology of psychiatric disorders are not in measure with this negativ trend. As a result, a large body of research in psychiatry and neurosciences tries to further our understanding of pathophysiological mechanisms underlying mood disorders and other mental illnesses in order to improve the efficacy of current treatments and to identify new therapeutic agents. According to current evidence, stress-related pathways and inflammation processes are directly involved in the development of depressive disorder and several other psychiatric conditions. The study of the effects and consequences of stress exposure requires an interdisciplinary approach, taking into account specific aspects of the "inputs", such as chronic stress and traumatic experiences, and related psychological processes, with the crucial role of dissociation.

Following these theoretical findings, the empirical research performed in two cohorts of inpatients with depressive disorder focused on immune and endocrine responses to stress and their relationship to psychopathological symptoms, specifically trauma-related symptoms, psychic and somatoform dissociation and depressive symptoms.

The main findings of the empirical research shows that TNF-α, that has been intensively studied as one of the major candidates in the cytokine model of depression, is related to both psychic and somatoform dissociative symptoms and trama-related symptoms. This finding suggests that TNF-α regulation and dissociation could be interrelated in the complex response to stress.

Other main results of this study indicate that prolactin is associated with psychic dissociative symptoms, supporting the findings of previous research, pointing to the relationship between prolactin regulation and passive coping behaviour. Finally, cortisol has been found to be related to somatoform dissociation, suggesting that low level of cortisol could be associated with active defensive or antiarousal intrapsychic processes, such as avoidance, withdrawal and denial.

Although no clinical conclusions can be taken at this point, the findings encourage further efforts to describe more in details the interplay between TNF-α, prolactin and cortisol regulations, chronic stress and dissociative processes in the development and clinical manifestation of depression.

8. SOUHRN

Deprese a některá další psychiatrická onemocnění představují ve světovém měřítku jednu z hlavních příčin pracovní neschopnosti, jejichž vliv navíc v průběhu několika desetiletí významnou měrou narůstá a to navzdory významným pokrokům v psychofarmakologii. V důsledku toho je výzkum v psychiatrii a v neurovědách značnou měrou zaměřen na hlubší porozumění patofyziologickým mechanismů deprese a dalších psychických poruch s cílem zlepšit účinnost léčby. Podle stávajících poznatků stres a imunitní procesy hrají významnou roli v patofyziologii afektivních poruch a některých dalších psychických onemocnění. Tento interdisciplinární výzkum vlivů a následků stresu zahrnuje celou řadu aspektů jako například chronický stres nebo traumatické zkušenosti v nichž významnou úlohu má proces disociace.

V návaznosti na tyto poznatky byl v této studii realizován empirický výzkum zahrnující dva vzorky pacientů s depresivní poruchou, který byl zaměřen na vztahy imunitních a endokrinních odpovědí na stres v souvislosti s psychopatologickými symptomy a to především se zaměřením na symptomy vztahující se k traumatickému stresu, psychickým a somatoformním disociativním symptomům a také k symptomům deprese jako takové. Hlavní výsledky tohoto empirického výzkumu ukazují na to, že TNF-α, který je jedním z hlavních faktorů v patogenezi depresivní poruchy podle tzv. cytokinového modelu deprese, vykazuje velmi významný vztah k symptomům psychické a somatoformní disociace a také k symptomům vztahujícím se k traumatickému stresu. Tento poznatek ukazuje na významnou roli TNF-α ve vztahu k disociativním procesům.

Další z hlavních výsledků této studie ukazuje na významný vztah psychických disociativních symptomů a prolaktinu v souladu s dosavadními poznatky, které poukazují na souvislosti mezi zvýšenou hladinou prolaktinu a pasivní odpovědí na stres. Další výsledky této studie také ukazují, že somatoformní disociace, která je také formou pasivní odpovědi na stres vykazuje souvislost se snížením hladiny kortizolu.

Ačkoliv z těchto získaných poznatků nelze zatím vyvozovat klinicky aplikovatelné závěry, výsledky této studie dokládají nové poznatky, které ukazují na významnou úlohu TNF-α, prolaktinu a kortizolu v patogenezi deprese a disociativních procesů.

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