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Final Activity Report

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Project coordinator name: Eric Vermetten, MD, PhD

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1. Publishable Final Activity Report

1.1 Project Execution

1.1.1 Project Coordinator

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1.1.2 Participants

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4. International Aid Network - IAN, Belgrade, Serbia and Montenegro
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The complete PBPTSD consortium in 2008

1.1.3 Summary of objectives, work performed and results achieved

General objective of this project was to contribute to understanding of the PTSD, its characteristics, subtypes, and risk factors in order to help improve its diagnosing and prevention. The study was designed to investigate the inner architecture of PTSD in terms of (some of the) supposedly relevant psychological, biochemical, endocrinological, genetic, physiological and anthropometric variables/parameters. More specifically, the scientific objectives were to explore the following:

1. Psychological parameters in PTSD:
    - basic personality traits (Big Five and behavioral disintegration)
    - memory performance, intelligence, and executive functions
    - overall psychiatric symptoms
2. Biological parameters in PTSD:
    - anthropometric status
    - metabolic status
    - HPA-axis function
    - endogenous opiate system
    - sleep status
3. Relations among the above mentioned biological and psychological parameters in health and PTSD

The results of the study are intended to be used for a. assessment of risk, b. providing brief assessment of PTSD symptomatology and c. improve the diagnosis of PTSD.

Realization of the cited objectives was enabled by investigations performed on five - two target (a, b) and three control (c-e) - groups of subjects:

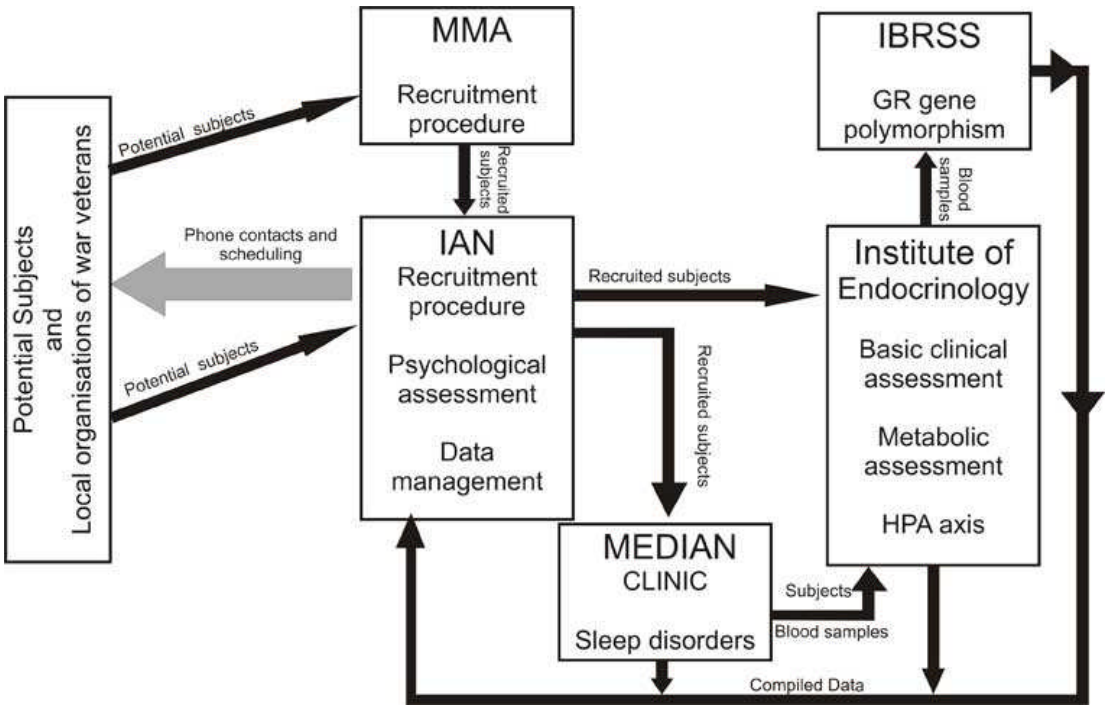
Group	Males	Females
a) PTSD patients	133	57
b) Subjects with PTSD in remission	66	123
c) Subjects with traumatic experiences without PTSD	102	105
d) Healthy controls from Western Balkans	99	95
e) Healthy controls from Western Europe	-/36	50/40
Total	436	470

The male subjects underwent simultaneous psychological and biological measurements (Serbia), while the female subjects (Croatia) participated only in psychological part of the study.

Subjects that were recruited in Serbia mostly came from the Belgrade region. All subjects were hospitalized for three days for the acquisition of the parameters and were thus standardized. Biological measurements included variables related to hypothalamo-pituitary-adrenocortical (HPA) axis (including cortisol receptor and its gene polymorphism), anthropometry, body composition, lipid status, insulin resistance, and sleep and dream disturbances (nightmares). This included blood draws from an i.v. line on 13 time points (starting 2200h) with one hour intervals. All subjects received 0.5 mg dexamethasone at 2300h. Psychological and symptoms assessment were performed at discrete intervals and encompassed symptom The advantage of this study is that a large number of variables was measured on *one and the same* subject (on approx 400 male subjects - the whole set of biological and psychological variables), so that they can be cross-correlated. All data are collected in one database and are being analyzed by advanced statistical methods. The

database contains over 3600 variables, directly measured or derivedassessment, personality inventories, and life experiences.

Below is a routing of assessment in the Belgrade team. The lines represent the routing of the participants in the assessment or data acquisition phase through the various participating institutions.



In spite of the difficulties (mostly due to protocol development, and recruitment of subjects, to lesser extent to communication with the EC officers, and money deliverance that slowed down project dynamics), the main goals are almost fully attained: the intended scope of measurements is accomplished on the near to planned number of subjects. The entering and preparation of data is completed in Belgrade, Rijeka, Bari and Utrecht and we have started analyzing them. The database of Bari is not complete. The metabolic assessment in a healthy population of 50 males has not been completed; 50 females have been assessed on neuropsychological performance as planned. The database from Utrecht will be added after completion of data in the database. At the moment of writing this report the data of 76 subjects in Utrecht were completed.

The literature on PTSD research is vast and rapidly increasing (Vermetten and Bremner 2002a/b, Vermetten, 2008), but to date there are only a few studies that combine biological and psychological aspects of the disorder (Chung, Berger & Rudd, 2007; Olff, Langeland, & Gersons, 2005; Pole, 2007; Vermetten et al., 2003). Our multidisciplinary research design stemmed from the belief that such an approach can deepen the understanding of PTSD in a way not achievable by single disciplines. The choice of the variables to be measured was based on our professional experience with PTSD patients and/or scientific literature, yet was restricted by financial and technical possibilities. We preferred to include those measurements that either had resulted in contradictory findings in different studies (as, for example, the DST and glucocorticoid receptors characteristics in PTSD patients) or were not done

extensively, although hypothesized to be relevant for some aspects of PTSD (as, for example, the beta endorphin for traumatic memories, or insulin for metabolic changes). Our own original questionnaire (Delta, in review) on behavioral disintegration (Disintegration) was included and gave outstanding results that will be illustrated below.

Mastering different advanced statistical techniques enable us to examine the correlations between complex variables, i.e., linear combinations of the variables. Canonical discriminant analysis showed that Neuroticism from NEO-PI and Disintegration (as primary constituents of the first discriminative function in the personality space) discriminate, primarily, current PTSD patients from all other groups, thus composing the main component of our screening and risk batteries. This analysis also revealed that the level of general neurocognitive functioning is lower in both PTSD groups than in control groups (resilient and healthy). Further finding suggests that self-control and superior executive functioning define the individual resilience capacity in situations of extreme stressor exposure.

It seems that biological variables generally have larger intra-group variance, so it is more difficult to detect differences among groups. For example, a comprehensive set of measurements done on lymphocyte cortisol receptors did not show any inter-group differences. Although negative, this result is very significant because, due to the large sample on which it is obtained, adds considerable weight to the side with the same finding in the ongoing scientific debate. This debate involved several teams (and noteworthy material resources), but all those studies were done on far smaller samples.

No inter-group differences in mean cortisol values (obtained from 13 night measurements) could be seen in the same light (of huge intra group differences). But, analysis of low dose (0.5mg) dexamethasone suppression test data revealed that hypersuppression of cortisol is higher in PTSD patients (this result also confirms one side in the mentioned debate). Significant correlations of cortisol-related variables with personality variables are also found, but this line of analyses needs further, more detailed work.

One of the objectives of the study was to use the findings as a basis for improving PTSD screening, diagnosing and risk factors assessing. This has been achieved by developing combined psycho-biological batteries and by improving psychological instruments for measuring PTSD:

a. Risk Assessment

As preliminary data-analyses suggested, the risk batteries should comprise measurements of personality traits and neurocognitive functioning. Although the design of our study does not unambiguously allow to ascribe the empirically found differences to predisposing factors, there is independent empirical evidence that emphasizes this conclusion (see e.g. Vasterling et al., 2006). Some prospective studies found neuroticism measured prior to trauma to be important predictor of PTSD after the trauma exposure (Engelhard, van den Hout & Kindt, 2003; Janssen, 1995; Knežević, Opačić, Savić & Priebe, 2005). Intelligence was found to be a predisposing factor for development of PTSD after traumatic exposure also (Macklin et al., 1998). Deficits of neurocognitive functioning were found not only among trauma survivors who developed PTSD in comparison to those who did not develop it, but also among their identical twins that not exposed to traumatic events, in comparison to the identical twins of those who did not develop PTSD (Gilbertson et al. 2006).

Having in mind the number and comprehensiveness of variables in our study, it would further contribute to a more precise definition of these factors, as well as to assessing their relative contribution to PTSD. Apart from Neuroticism, our study did reveal an independent important contribution of Disintegration in explaining variance in PTSD. Analysis of neurocogntive data pointed to the independent importance of intellectual factors and executive functions in understanding PTSD. Higher level of intelligence and memory functioning seemed to represent basic neurocognitive factors protecting against developing PTSD after the traumatic event, while superior executive functioning seems to reflect additional capacity for resilience. Precise composition of batteries for risk assessment will be a matter of further, more elaborated analyses of the data. More precise composition of the battery for risk assessment is outlined by preliminary results concerning personality/neurocognition and PTSD given in the section results from the workpackage Psychological Assessment.

b. Brief assessment of PTSD symptomatology

Brief assessment of PTSD symptomatology can be done by 22-items IES-R, a standard instrument for the assessment of posttraumatic symptomatology (Weiss & Marmar, 1997), followed by SRD-10, the 10-items instrument for measuring dissociative symptomatology (Knezevic & Jovic, 2004). IES-R is the most frequently used self-report instrument for the assessment of PTSD in the region of former Yugoslavia, so the norms for various types of vulnerable groups could be easily established. Apart from this, even the cut-off score on IES-R, which enables making tentative diagnosis of PTSD has been already established (Priebe, Ljubotina, Knežević**,** Frančisković, Kučukalić, & Schuetzwohl, 2007).

This study opens a new possibility for extracting the combination of a small number of symptoms that not only detect PTSD efficiently, but also help extract additional information about whether the person is prone to recover or to develop chronic PTSD. The list of symptoms is given in Table 1. This instrument is intended for use in primary health care for brief assessment of posttraumatic symptomatology. The additional ROC analysis will give opportunity to define the cut-off scores on this instrument that will enable detecting those with higher probability to develop PTSD, but also to detect those with higher probability to recover from PTSD. It might seem peculiar that the healthy control group is included in the analysis, knowing that this group is composed of subjects without a major traumatic experience (i.e. not having criterion A satisfied). However, since the whole population of Serbia was exposed at least to NATO bombing in 1999, some level of posttraumatic stress is expectable even among healthy controls.

In order to construct a brief measure, canonical discriminant function analysis was done on 90 symptoms from SCL-90 together with 22 symptoms from IES-R and 10 symptoms from DRS-10 scale.

Two canonical functions were significant in differentiating among the groups. Coefficient of canonical correlation for the first function was .77 (Wilks'$\Lambda = .36$, $\chi^2_{(36)=}$ 351.03, p<.001), for the second .32 (Wilks' $\Lambda = .88$, $\chi^2_{(22)} = 44.83$, p <.003). The first function explained 91.3% of the between-groups variance, while the second explained 7.4%.

The first function represents the overall proneness to developing PTSD after traumatic event. The second function reveals the proneness to recover from PTSD once the disorder was developed.

These twelve items enable to construct the three following measures:

1. *Overall proneness to PTSD* is obtained by summing the values on all twelve items and division of the sum by the number of items.

2. *Proneness to chronic PTSD* is obtained on the following way: (item3+item4+item5+item6-item10+item11+item12)/7.

3. *Proneness to recovery from PTSD* is obtained on the following way: (item2-item6+item7-item8+item9-item11)/6.

Table 4. Functions at Group Centroids

Group2	Function	
	1	2
1. CURRENT PTSD	1.517	-.189
2. PTSD IN REMISSION	.164	.546
3. RESILIENT	-.799	.239
4. HEALTHY CONTOL	-1.410	-.395

The evidence that the first function indicates the overall proneness to PTSD, and that the second indicates the set of symptoms of those who are prone to recover from PTSD or not to develop PTSD at all is given in Table 4. The correctness of the classification according to the proposed brief measure for PTSD assessment is given in Table 5.

Table 5. Classification Results

GROUPS	Predicted Group Membership				Tot
	1	2	3	4	
1. CURRENT PTSD	100 (84,0)	6 (5,0)	12 (10,1)	1 (,8)	119
2. PTSD IN REM.	21 (34,4)	18 (29,5)	15 (24,6)	7 (11,5)	61
3. RESILIENT	12 (13,0)	11 (12,0)	33 (35,9)	36 (39,1)	92
4. HEALTHY CONT	5 (6,0)	3 (3,6)	17 (20,5)	58 (69,9)	83

In parentheses are the percentages of the total group numbers. 58.9% of original grouped cases correctly classified.

c. Improvement in diagnosing PTSD

This section will be a matter of more thorough analyses that will include the integration of empirical data from numerous previous studies done by the same research group. Current empirical evidence strongly emphasizes the role of disintegrative (dissociative) phenomena in PTSD, especially in the more severe forms of PTSD (Vermetten, Dorahy and Spiegel, 2007). Apart from psychological factors, the role of biological factors and their possible inclusion in diagnosing PTSD will be carefully analyzed and reported in scientific journals.

An important aspect of the dissemination strategy of the project is to make findings and implications of the study known to mental health care decision making bodies, including founders of treatment centers for patients suffering from PTSD and also to the users of services. In order to achieve these objectives, a brochure was written in non-scientific language which is aimed at non-professional stakeholders without medical or psychological knowledge of PSTD, as well as war veterans and

other persons affected by war. Consequently, collaboration has been established with several associations of ex-detainees, war veterans and persons disabled in war. The aim of the brochure is to improve treatment and rehabilitation of the patients, and also to improve access to treatment.

A plan is currently being developed to implement results of the study into community psychiatry of the Balkan countries by education and training of general practitioners (GP's), mental health professionals and paraprofessionals working with vulnerable groups.

1.1.4 Closing

Writing and publishing all papers that are resulting from this project will take us far in 2010, maybe even further towards 2011. In the meantime the consortium will convene at infrequent occasions to continue to analyse and publish and organize symposia to present the various parts of the studies. This will be with not budget, but the will to continue to use the momentum of the intellectual domain that we created with the results of the study.

A separate plan has been initiated to bring two other EU funded projects (STOP and CONNECT) together with PBPTSD and present the data in one symposium together. The consortium coordinators have started to reflect to this idea. The coordinator of PBPTSD will make an effort to try to accomplish this in the year 2010.

This report has one Annex, a plan for using and disseminating the knowledge as well as 14 appendices, with examples of workpackages and illustrations of reports.

2. Publishable results

2.1 List of publishable results of the project

1. Savić D, Knežević G, Damjanović S, Frančišković T, Matić G, Špirić Ž, Pierri G, Priebe S, Vermetten E. Psychobiology of PTSD: an international comprehensive study of PTSD. Psychiatry Today 2008; submitted.

   Abstract: Posttraumatic stress disorder (PTSD) is the most common war-related psychiatric disorder occurring among combat veterans and other people exposed to war-zone stress. In addition to health problems, this disorder causes numerous long-term socioeconomic damages. Current opinion is that the best results in PTSD understanding, diagnosis and treatment could be achieved by integrating psychological, biological and pharmacotherapeutical approaches.

   General objective of this project was to better understand the biological basis of psychophysical profiles of PTSD patients. The study focused on establishing multiple correlations of different PTSD subtypes with relevant psychological, biochemical, endocrinological, genetic, physiological and anthropometric parameters.

   The psychological and biological studies in this project were performed on five groups of subjects: a) PTSD patients, b) subjects with PTSD in remission, c) traumatized subjects without PTSD, d) healthy controls from Western Balkans, and e) healthy controls from Western Europe. All subjects in combined studies were male. The same psychological studies were performed on five analogous groups of female subjects. The traumatic experiences of the first three groups (of both genders) are war-related.

   The main psychological instruments that were used were personality inventories, disintegration questionnaire and neuropsychological tests. Biological measurements encompassed parameters related to hypothalamo-pituitary-adrenocortical axis (including cortisol receptor and its gene polymorphism), anthropometry, body composition, lipid status, insulin resistance, and sleep disturbances.

   After an advanced statistical analysis of the data, this study will yield new knowledge on relations between: a) basic psychological variables and PTSD, b) biological variables and PTSD, and c) biological and basic psychological variables in health and in PTSD. In addition, the foreseen benefits of the project include: d) development of combined psycho-biological batteries for PTSD screening, diagnosing and risk factors assessing, e) improvement of psychological instruments for measuring PTSD, f) implementation of new biological markers for PTSD, g) recommendation for the improvement of combined psycho- and pharmacotherapy of PTSD.

   Key words: PTSD/ multidisciplinary study.

2. Danka Savic, Goran Knezevic, Gordana Matic, Zeljko Spiric, Svetozar Damjanovic. Eric Vermetten, (presented as poster at the American College Neuropsychopharma-cology, 2008, paper in preparation)

Abstract: Background: There is a long belief that the behavior of the HPA/axis is correlated with the symptom profiles of psychiatric clusters eg depression or PTSD. Behavior of HPA axis can be well described by regulatory parameters such as the low dose (0,5 mg) dexamathasone suppression test (ldDST), but also by nocturnal variation, and the cortisol awakening response (CAR). We hypothesize that ldDST and the non pharmacological regulatory behavior is characterized by several mechanisms: psychopathology, personality/temperament, genetics and/or experience of life/war stress. Methods: These data are part of a larger study on the psychobiology of PTSD. We analysed data from 391 subjects in 4 groups current PTSD life time PTSD, trauma controls and healthy controls. All subjects recruited in Serbia, mostly Belgrade region. All subjects were hospitalized for three days for the acquisition of the parameters and were thus standardized. Blood was drawn from an i.v. line on 13 time points (starting 2200h) with one hour intervals. All subjects received 0.5 mg dexamethasone at 2300h. Psychological and symptoms assessment were performed (SCID, war and life stress, CAPS and personality assessment by NEO-PI) was performed during this period. In addition to the self assessment of the NEO, this instrument was also filled out for the subject by a significant other. Results: First we assessed ANOVA linear regression correlation of ldDST and CAPS score and did not find strong correlation, significant but low effect size. No correlation was found with personality, or stress scales. Data on ldDST were not distributed in linear way. Thus we redistributed dataset in quartiles and analyzed the upper and lower quartiles of ldDST ending up with 93 low and 92 upper quartiles, representing high and low suppressors. All subsequent analyses were performed both with ldDST based on ratio as well as absolute differences of pre/post ldDST. Discriminant analysis of upper and lower DST responders correlated significantly with NEO/SR, to confirm the stability of this we analysed the analysis on NEO report by others, and found same significant correlation. Both self-rating (SR) and ratings by a significant other showing correlation of impulsivity with behavior of HPA axis, in specific ldDST. Discriminant analysis with NEO showed the crucial importance of CONSC (negative) in the function (R = .53, Wilks Λ=.72, $\chi^2_{(30)}$=58.55, $p < 0.001$). To further validate this we looked at lower level dimensions of conscientiousness only. Discriminant analysis on lower level dimensions of CONSC was significant again both for difference ldDST, self-report NEOPIR, (R = .34, Wilks Λ=.89, $\chi^2_{(30)}$=22.58, $p < 0.001$), significant other NEOPR (R = .28, Wilks Λ=.92, $\chi^2_{(6)}$=15.27, $p < 0.018$) and ratio ldDST (self-report NEOPIR, R = .29, Wilks Λ=.92, $\chi^2_{(6)}$=16.56, $p < 0.011$, significant other NEOPR (R = .28, Wilks Λ=.92, $\chi^2_{(30)}$=15.62, $p < 0.016$). We also looked at the group with either current depression, life time depression and major depressive disorder (based on SCID items) and found similar relation with impulsivity on ldDST. To further validate this we analysed data on early morning rise (CAR), as well as nocturnal behavior. This time we divided the group into upper quartile and lower quartile of responders on CONSC showing a discriminant function significantly different in two groups when nocturnal regulation was taken into account. Same finding on CAR. Life stress was a factor that came up in discriminant analysis, neither any of the other personality scales, only paranoia and neuroticism in one of the sub analyses. Discussion: These data demonstrate that HPA axis behavior is correlated to the trait of CONSC, which is a personality trait that includes elements as self-discipline, carefulness, thoroughness, organization, deliberation and need for achievement. This is both for ldDST, CAR and well as nocturnal regulation. The long held belief that this HPA axis hold specificity for psychopathology may still be true but is attenuated by one of the trait factors. The implications need to be further thought through as

well as the mechanisms. Some first thoughts are in the domain of the failure to delay gratifications, i.e. failure of behavioral inhibition

Key words: PTSD, personality, impulsivity, cortisol, conscientiousness

3. Comorbidity of PTSD with other mental and behavioral disorders.

Abstract: It is already known that patients with a lifetime history of PTSD have a high rate of comorbidity with substance abuse, depressive disorders and anxiety disorders. Using special questionnaire on sociodemographic data and SCID we assessed the existence of other psychiatric disorders, and behavioral characteristics such as frequency of smoking, alcohol consumption, eating habits, etc., in patients with current and lifetime PTSD, combat veterans without PTSD and in healthy controls. In addition we examined correlation of psychiatric comorbidity with neuropsychological and personality measures.

Key words: PTSD/ war trauma/ comorbidity/ mental disorders/ behavioral disorders/ substance abuse

4. Posttraumatic stress disorder and physical comorbidity.

Abstract: Patients with PTSD are high users of healthcare. It has been noticed that patients with a lifetime history of PTSD have a high rate of hypertension, cardiovascular diseases and gastrointestinal disorders. All participants in the study (patients with current and lifetime PTSD, combat veterans without PTSD and healthy controls) were hospitalized and medically examined for existence of somatic complaints and/or medical disease. Relationship of biological measures (anthropometric, metabolic and endocrinological) and subjective and objective physical health was examined.

Key words: PTSD/ war trauma/ comorbidity/ physical health/ somatic complaints/

5. The role of intelligence, neuropsychological measures and personality in PTSD.

Abstract: In this paper the relevance of three broad areas of psychological measurement for the understanding of PTSD is evaluated. Our preliminary results indicated the crucial importance of personality, moderate relevance of intelligence and, comparatively to it, small significance of neuropsychological measures. Theoretical and practical consequences of these findings will be discussed.

Key words: personality traits/ intelligence/ neuropsychological measures/ PTSD

6. Neuroticism is not the only personality trait having strong relationship with PTSD: Disintegration is equally important.

Abstract: In this paper the importance of the trait called disintegration of regulative function for the understanding of PTSD will be demonstrated. Our preliminary analyses showed that disintegration is a variable having the highest (together with neuroticism) discriminative potential for differentiating among study groups. Theoretical and practical consequences of this result will be discussed.

Key words: personality traits/ big five/ neuroticism/ disintegration/ PTSD

7. Cortisol and memory functions.

Abstract: In this paper the potential role of cortisol/glucocorticoid receptor in declarative memory functions will be evaluated. Measures of basic cortisol level,

12-hours cortisol curves, the number and hormone-binding affinity of the glucocorticoid receptor, as well as dexamethasone suppression will be related to the measures of verbal and visual declarative memory. Theoretical and practical consequences of the results will be discussed.

Key words: Declarative memory/ basic cortisol level/ 12-hours cortisol curves/ glucocorticoid receptor binding properties/ dexamethasone suppression test/ PTSD/ WMS-III/ SRT

8. PTSD subtypes.

Abstract: In this paper potential subtypes of patients with PTSD (acute or life-time) will be investigated. Formation of subgroups will be based on personality/neuropsychological/intelligence measures. The obtained clusters will be evaluated at socio-demographic variables, psychiatric symptoms, and biological measures (anthropometric, metabolic and endocrinological). The consequences of this newly established subtypes on the understanding of PTSD clinical picture will be discussed.

Key words: personality traits/ intelligence/ neuropsychological measures/ PTSD subtypes

9. Cortisol and receptors in personality.

Abstract: Hypothalamo-pituitary-adrenal (HPA) axis is the system of immediate stress response, with cortisol as its final product. The interval of normal basic cortisol levels is relatively wide. Empirical findings indicate that individuals with higher values of basal (free) cortisol have stressful experiences. This cortisol level depends on the quantity excreted and on the portion that is bonded to its receptors. On the other hand, it is known that individuals with higher scores on NEO-PI R personality trait Neuroticism are more vulnerable (have lower threshold for stress response). The hypothesis we are testing in this study is that there are correlations among basal cortisol level, receptor concentrations and the score on Neuroticism.

Key words: HPA-axis/ glucocorticoid receptors/ NEO-PI R/ Neuroticism

10. PTSD anthropometry.

Abstract: It has been shown that patients with PTSD may suffer from abdominal obesity which is known to promote classical and global cardio-metabolic risk (CMR) factors. We assessed the frequency of smoking, diabetes, hypertension, hyperlipidemia and obesity, among patients with PTSD and in healthy controls. In addition we examined anthropometric parameters and body composition in relation to CMR factors. The preliminary data suggest that patients with PTSD have increased frequency of abdominal obesity which is associated with increased risk for cardiovascular disease.

Key wards: post-traumatic-stress-disorder/ cardio-metabolic risk factors/ waist to hip ratio/ body composition

11. Catabolic and anabolic hormonal effects in patients with PTSD.

Abstract: While the body weight may vary, constant flux of glucose toward brain has to be maintained. Glucose allocation is dependent on hypothalamo-pituitary-adrenal axis (HPA) activity. In patients with PTSD set point of HPA axis activity is set to a novel position after traumatic experience. This is associated with misbalance between catabolic and anabolic hormonal activity. We measured cortisol, insulin, IGF-1, testosterone and thyroid hormones

concentrations. Initial analysis of our results revealed significant differences in basal testosterone and insulin levels between control subjects and patients with traumatic experience.

Key wards: PTSD/ cortisol/ insulin/ IGF-1/ testosterone

12. Glucocorticoid receptor expression and binding activity in lymphocytes of traumatized war veterans with and without PTSD.

    Abstract: In this study GR functional properties, such as the number of receptor sites per cell (B_{max}) and their affinity for the hormone (K_D), are determined in PBMCs of healthy men (N=95) and traumatized war veterans with PTSD (N=123 actual + 64 life-time), or without PTSD (N=117). These data are correlated with the level of the GR protein in the lymphocytes assessed by a quantitative Western blot approach, as well as with the rate of the GR gene transcription measured by a real-time PCR method. The amounts of heat shock proteins Hsp90 and Hsp70, which are known to chaperone the receptor throughout its life span influencing its hormone binding activity, were also determined. The results comprise a consistent set of data showing that neither war trauma nor PTSD pathophysiology are associated with statistically significant alterations in the number of functional GR molecules and their affinity for the hormone, in the level of GR, Hsp90 and Hsp70 proteins, or in the level of GR mRNA in PBMCs. Therefore, variations in the level of expression and functional properties of GR do not seem to underlie PTSD and/or trauma–related alterations in HPA axis sensitivity to glucocorticoids, in the cases where these alterations are confirmed. Alternatively, it might appear that, in spite of generally accepted opinion, PBMCs should not be used as a reliable neural probes, at least when GR expression and functional modulation are concerned.

    Key words: PTSD/ war trauma/ glucocorticoid receptor (GR)/ Hsp90/ Hsp70/ human peripheral blood mononuclear cells (PBMCs)

13. Relevance of corticosteroid receptors level and functional status for HPA axis activity in PTSD.

    Abstract: Based on rather limited and inconsistent literature data it is believed that PTSD is associated with hypocortisolemia that results from increased responsiveness of hypothalamo-pituitary-adrenocortical (HPA) axis to cortisol. The hypersensitivity of the HPA axis is supposed to be a consequence of an increased number of glucocorticoid receptor (GR) molecules in the hypothalamus and/or pituitary. Noteworthy, the data on GR binding properties, except those from the rare post-mortem studies, derive from measurements on readily available human cells – peripheral blood mononuclear cells (PBMCs). In this study GR functional properties, such as the number of receptor sites per cell (B_{max}) and their affinity for the hormone (K_D), the level of the GR protein and the rate of the GR gene transcription were determined in PBMCs of healthy men and traumatized war veterans with and without PTSD. Besides, the basal level of cortisol, as well as its level after oral administration of dexamethasone (DST test) were determined in blood plasma of the same subjects. This paper will contribute to clarification of the relationship between alterations in HPA axis activity, on one hand, and GR binding activity and expression, on the other, in PBMCs of traumatized combat veterans with or without PTSD.

    Key words: PTSD/ war trauma/ glucocorticoid receptor (GR) binding properties/ human peripheral blood mononuclear cells (PBMCs)/ basal cortisol level/ dexamethasone suppression test (DST)

2.2. List of other titles of work in progress

1. A new self-report instrument for PTSD.
2. High conscientiousness and executive superiority is the most protective factor discriminating between resilient and non-resilient people.
3. The role of insulin resistance and leptin levels in prolonged activation of HPA axis in men with PTSD.
4. Does cleavage of POMC differ in people with and without PTSD?
5. Sensitivity of HPA axis and the development of PTSD in men.
6. Sensitivity of HPA axis, metabolic syndrome and obesity in PTSD.
7. GR polymorphism in the etiology of PTSD subtypes.
8. Sleep fragmentation in PTSD.
9. Dream analysis in PTSD.
10. A combined psycho-biological battery for PTSD assessment.
11. PTSD: a psychological study in Croatian women.

Coping strategies and posttraumatic response among women with war trauma.

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4. Tables 1-3

4.1 Table 1.

Means and standard deviations on neurocognitive measures

	PTSD		PTSD IN REMISSION		RESILIENT		HEALTHY CONTROL	
	M	SD	M	SD	M	SD	M	SD
IES11 I tried not to think about it	2.98	.883	2.38	1.186	1.78	1.459	1.24	1.367
IES15 I had trouble falling asleep	3.29	.783	2.23	1.283	1.46	1.440	.65	1.098
IES18 I had trouble concentrating	2.97	.920	1.97	1.224	1.16	1.207	.60	1.047
IES20 I had dreams about it	2.87	1.049	1.79	1.318	1.16	1.295	.48	.832
IES23 I feel completely empty and numbed	2.78	.903	1.84	1.157	1.18	1.249	.54	.954
IES31 Sometimes it happens to me to go out without putting on some piece of my clothes	1.97	1.262	1.11	1.185	.55	.843	.33	.734
scl18 Feeling that most people cannot be trusted	2.75	1.106	2.36	1.225	1.74	1.221	1.12	1.120
scl28 Feeling blocked in getting things done	2.51	1.049	1.41	1.070	1.00	1.119	.82	.965
scl42 Soreness of you muscles	2.32	1.112	1.92	1.269	1.14	1.210	.60	.910
scl67 Having urges to break or smash things	1.70	1.393	.98	1.162	.54	.965	.47	.888
scl75 Feeling nervous when you are left alone	2.28	1.200	1.33	1.044	.72	.856	.46	.668
scl86 Thoughts and images of a frightening nature	2.45	1.260	1.44	1.218	.55	.942	.36	.835

4.2 Table 2.

Tests of Equality of Group Means

	Wilks' Lambda	F	df1	df2	Sig.
IES11 I tried not to think about it	.758	37.288	3	351	.000
IES15 I had trouble falling asleep	.548	96.444	3	351	.000
IES18 I had trouble concentrating	.563	90.748	3	351	.000
IES20 I had dreams about it	.587	82.250	3	351	.000
IES23 I feel completely empty and numbed	.588	82.106	3	351	.000
IES31 Sometimes it happens to me to go out without putting on some piece of my clothes	.696	51.047	3	351	.000
scl18 Feeling that most people cannot be trusted	.766	35.718	3	351	.000
scl28 Feeling blocked in getting things done	.679	55.234	3	351	.000
scl42 Soreness of you muscles	.725	44.472	3	351	.000
scl67 Having urges to break or smash things	.821	25.549	3	351	.000
scl75 Feeling nervous when you are left alone	.624	70.404	3	351	.000
scl86 Thoughts and images of a frightening nature	.595	79.524	3	351	.000

4.3 Table 3.

Structure of the Discriminant Functions

	Standardized Canonical Discriminant Function Coefficients		Correlations between variables and Discriminant Function	
	1	2	1	2
1. IES11 I tried not to think about it	.10	.09	**.47**	.21
2. IES15 I had trouble falling asleep	.11	**.28**	**.76**	**.24**
3. IES18 I had trouble concentrating	**.16**	.00	**.74**	.10
4. IES20 I had dreams about it	**.25**	.00	**.70**	.11
5. IES23 I feel completely empty and numbed	**.14**	.05	**.70**	.16
6. IES31 Sometimes it happens to me to go out without putting on some piece of my clothes	**.21**	**-.31**	**.55**	**-.13**
7. scl18 Feeling that most people cannot be trusted	.05	**.55**	**.45**	**.39**
8. scl28 Feeling blocked in getting things done	.10	**-.82**	**.57**	**-.34**
9. scl42 Soreness of you muscles	-.06	**.81**	**.51**	**.37**
10. scl67 Having urges to break or smash things	**-.23**	.00	**.39**	-.19
11. scl75 Feeling nervous when you are left alone	**.24**	**-.29**	**.65**	**-.16**
12. scl86 Thoughts and images of a frightening nature	**.37**	-.18	**.69**	-.15