Human Stress Response from the System Dynamics Point of View

Marek Susta[1,2], Gustav Bizik[2]

[1]Dept of Neurology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic
[2]Dept of Psychiatry, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

Abstract: This paper introduces system dynamics approach to the domain of psychiatric research. We have tried to develop a computer simulation model based on theoretical findings and facts known to clinicians and looked for an answer to the problem of different cortisol reactivity between major depression and PTSD patients with respect to trauma severity, length and proposed genetically based differences in hippocampal volume. Modeling PTSD and depression in one structure is to our knowledge the first attempt to grasp these widely spread disorders with substantial societal and clinical burden. Even though the current model structure is simplified, proposed approach has a powerful predicting potential in clinical practice and social policy. Model structure and model equations are in Appendices 1 and 2.

Keywords: System Dynamics, PTSD, Depression, HPA-axis

INTRODUCTION

Human mental activity is obviously resulting from complex, feedback driven, delayed and nonlinear system activity. Since the discovery of cybernetics and systems theory scientists are trying to understand the dynamics and in many cases the results show satisfactory "move forward" of our understanding. In Systems biology attention is being paid to molecular systems, psychiatrists and psychologists focus their attention to behavioral aspects of human activity but there is a strong call for integrating approaches(Tretter, 2010). A large number of articles have been written on the subject of stress and immune response interaction. Scientific teams work on particular parts of the HPA axis dynamics and publish their results in a number of ways. Hormone levels, intended systems maps, description of underlying dynamics presented in a form of static pictures. One of the methods available for studying dynamic systems is mathematical modeling. To study short-term and long-term stress response in humans, one has to deal with a great portion of nonlinearity, delays and interconnections among different "levels". These levels represent cellular, endocrine, humoral...and behavioral interconnected subsystems, which create unique human being that exhibits certain mental activity and interacts with his/her environment. While we can hardly aspire to model a human as a whole we have tried to address some issues in selected subsystems interaction in creating evaluable outcomes that help to understand stress response dynamics.

Human stress system and its essential component the hypothalamic-pituitary-adrenal (HPA) axis in particular (Figure 1) plays a major role in maintaining homeostasis within the human body. It is possible to distinguish two different functional modes of HPA activity. First of all, it serves as a structure performing metabolic function necessary for growth and development. The second function is related to stress response. When threat is perceived via signals from amygdala, the hypothalamus is stimulated to release corticotrophin releasing factor (CRF), which, in turn, activates the anterior pituitary producing adrenocorticotrophic hormone (ACTH). Subsequently, ACTH acts on the adrenal gland to release cortisol, main human stress hormone. Cortisol exerts various biological

effects on almost all body system, allowing adequate response through energy mobilization and effects on cognitive functions. Stress system activation is eventually terminated both by cessation of stressful condition and through negative feedback influence of increased cortisol levels on the hypothalamus and anterior pituitary with resulting decrease in CRF and ACTH levels, respectively(Cacioppo, Tassinary, & Berntson, 2000).

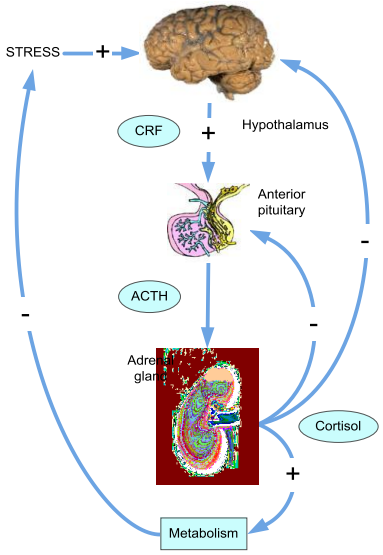

Figure 1 Hypothalamic-pituitary-adrenal axis scheme

Several brain structures are involved in activation (Figure 2), tuning and feedback termination of neuroendocrine stress response with prominent role played by amygdala, hippocampus and prefrontal cortex. Amygdala is believed to determine the emotional significance of external or internal stimuli and triggers the stress reaction. On the contrary, hippocampus and prefrontal cortex are thought to exert inhibitory effect over amygdalar and stress systems activation. Interestingly, during the ontogenesis, these structures seem to undergo important modification in structure and function according to programming effect of life events.

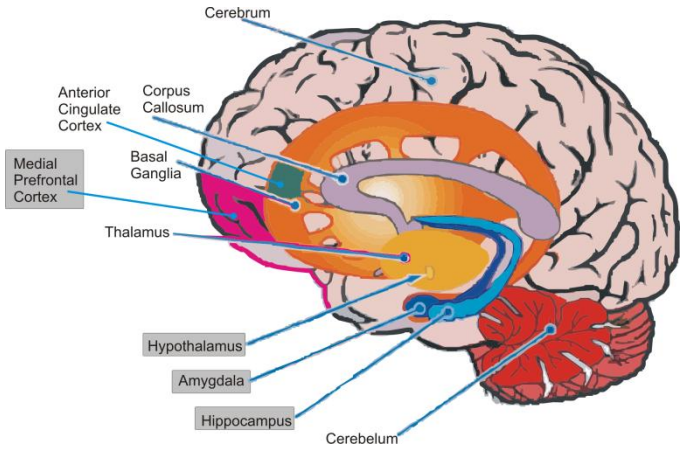

Figure 2 Key brain areas involved in stress response regulation (highlighted)

Growing number of evidence points to the essential role of chronic stress system over-activation in the development and maintenance of major psychiatric conditions. Together with genetic vulnerability, the potential of adverse life events exposure to program key brain structures of stress

system represent the core of the stress-vulnerability model of psychiatric disorders. In fact epidemiological studies have allowed to postulate important causal role of stress in the development of depressive disorder (Kendler, Karkowski, & Prescott, 1999). In PTSD, traumatic event is integral to the diagnosis.(Association, 1994)

We have tried to develop a computer simulation model based on these facts and looked for an answer to the problem of different cortisol levels between major depression and PTSD patients with respect to trauma severity, length and proposed genetically based differences in hippocampal volume as described in further text. The model is based on causal loop diagram (Figure 3) that clearly confirms feedback nature of the system.

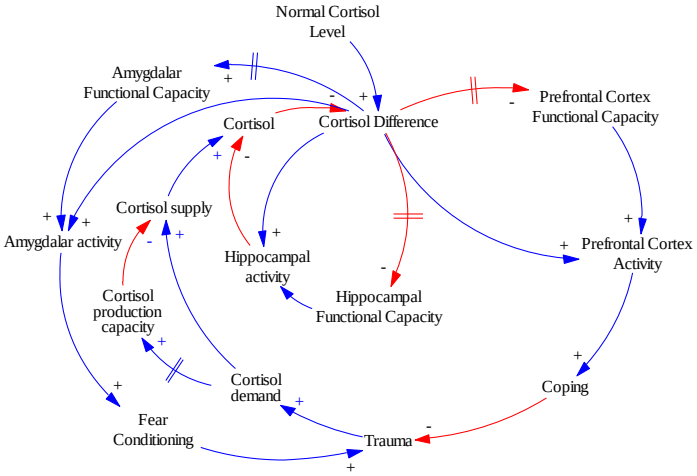

Figure 3 Causal loop diagram of the stress response dynamics

HPA axis activity is assessed either in basal (non-stressed) conditions or under pharmacological or non-pharmacological challenges. Several types of basal measurement are performed to assess HPA activity, among which cortisol level after awakening (during so called cortisol awakening response, reflective of stress reactivity(Edwards, Clow, Evans, & Hucklebridge, 2001; Schmidt-Reinwald et al., 1999)), in the afternoon and total 24h cortisol production (reflecting tonic activation of HPA axis). There are several pharmacological challenges that help to diagnose impaired feedback mechanism within HPA axis and pituitary sensitivity to CRF. In addition, non-pharmacological stress paradigm, such as cognitive stress or trauma reminders may reflect inter-individual differences in cognitive factors, coping capacities, deregulation of the negative feedback system and oversensitivity to CRH or ACTH (Lopez-Duran, Kovacs, & George, 2009).

Depressive patients

In depressive patients, neuroimaging analyses have revealed decrease in volume in hippocampi and in the right medial and inferior frontal gyrus, which were associated with both depressive psychopathology and worse executive performance(Bremner et al., 2002; Vasic, Walter, Hose, & Wolf, 2008). Even though several biologically distinguishable subtypes of depressive disorder have been proposed (related to childhood trauma vs. absence of childhood trauma(Heim, Mletzko, Purselle, Musselman, & Nemeroff, 2008; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008), chronic depression vs. acute episode(Watson et al., 2002), melancholic vs. atypical depression(Gold & Chrousos, 2002)), overall, (1) basal cortisol levels in depressive patients have been shown to be

increased compared to non-depressive controls(Knorr, Vinberg, Kessing, & Wetterslev, 2010) and (2) impaired feedback control of cortisol level have been consistently found.

PTSD patients

In PTSD patients, neuroimaging studies have reported increased amygdalar activation during symptomatic states and during the processing of trauma-unrelated affective information. Amygdalar responsivity has been positively correlated with symptom severity in PTSD. Conversely, medial prefrontal cortex volume has been found to be decreased in PTSD patients. Medial cortex activity have been reported to be decreased during symptomatic states and the performance of emotional cognitive tasks and negatively correlate with PTSD symptom severity(Shin et al., 2004; Shin, Rauch, & Pitman, 2006). Lastly, PTSD have been shown to be associated with hippocampal lesions(Bisson, 2007; Shin, et al., 2006), however it have been proposed that smaller hippocampal volume represents a vulnerability factor to the development of the disorder(Gilbertson et al., 2002).

Despite the fact, that differences exist between PTSD patients according to the sex and different types of experienced trauma, PTSD patients seem to exhibit (1) significantly lower basal cortisol levels compared to controls(Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007), (2) exaggerated cortisol response following non-pharmacological stress paradigm(de Kloet et al., 2006) and (3) enhanced feedback potential within the HPA axis(de Kloet, et al., 2006).

MODELING PROCESS

While building the model structure we kept in mind the principal question of the difference in dynamics in depressed and PTSD patients. These two diagnoses were so far described in terms of dynamics separately while we are trying to create only one structure that exhibits both kinds of behavior resulting from interaction between trauma exposure and hippocampal volume differences. The purpose of the model is to confirm that differences in trauma exposure in terms of severity and duration together with limited hippocampal functional capacity turns the system behavior in two different patterns – depressive or PTSD, respectively.

Key variables are depicted in (Figure 3) - Causal loop diagram. Detailed description of the dynamics and relationship is found in introduction of this paper.

There are two basic timelines when talking about the trauma. The first one is short-term immediate system response measured in minutes to hours that take into account circadian rhythmicity and other short-term physiological influences and simulation time is a week or so. The second possible approach looks at the person (system) from mid to long-term perspective where a simulation step is a day, week or even month and total simulation time is counted in years. We wanted to study long-term stress influence and that is why we came up with the second approach. Reference modes as well as dynamic hypotheses are described in detail in introduction, general shape of table functions were obtained from available literature and data obtained in our laboratory. Several parameters could not be extrapolated from results based on the current research strategies. In such cases, the parameters were estimated by experts.

RESULTS

The model was tested in three input modes (Table 1) that correspond to three subject types. All scenarios were set up with series of three consecutive "traumas", minimal in case of healthy control 5 (out of 100) to severe 80 in PTSD scenario. Scenarios differ also in trauma duration, from short-term 20 (in days) in PTSD and healthy controls to 150 in depression. The difference in predisposition to PTSD, described as lower hippocampal functional capacity was set to 80% (20 points of depletion) in prospective PTSD patients scenario, depressive and controls remained at full capacity. The simulation with 1 day step was run for 1000 steps with following results.

Table 1 Simulation setup - input parameters

	Depression		PTSD		Healthy Control	
	Intensity (0-100)	Duration (days)	Intensity (0-100)	Duration (days)	Intensity (0-100)	Duration (days)
Trauma 1	30	150	80	20	5	20
Trauma 2	15	60	5	20	5	20
Trauma 3	15	60	5	20	5	20
Hippocampal Depletion	0		20		0	

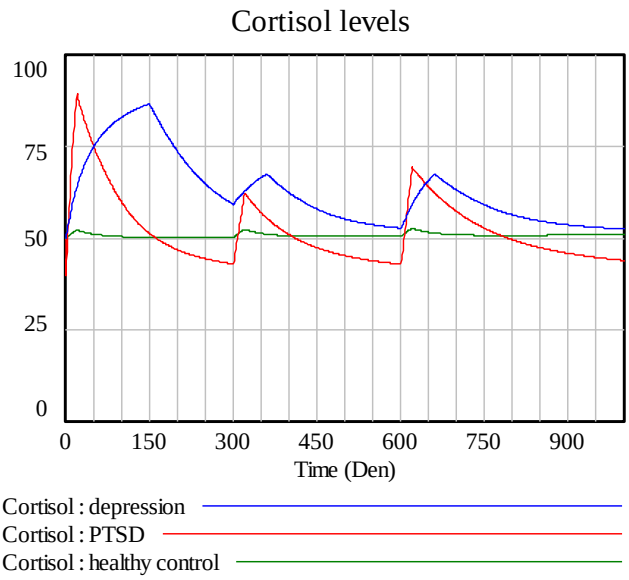

Figure 4 Simulated cortisol levels (correspond to 24hr cortisol production)

Cortisol

The output shows clear differences in HPA axis activity (Figure 4). One of the markers is a level of stress hormone cortisol. In depressed patients it grows slowly in response to mild but long lasting trauma, and then seeks new (higher) stable level, responds to following traumas of low intensity but long duration and stays higher than in healthy controls. In PTSD patients the cortisol level increase is enormous in response to initial severe trauma (eventually limited by total secretion capacity), then drops below the normal level due to enhanced negative feedback influence and re-urge upon repeated experience in enhanced manner as a result of stress sensitization. Healthy control reacts to

low traumatization by slight short-term increase in cortisol level without long-lasting changes in acting brain areas.

Functional capacity of Prefrontal Cortex

As previously stated, healthy control does not exhibit changes in brain structures, prefrontal cortex functional capacity (Figure 5) in response to low trauma remains unchanged. Prefrontal cortex functional capacity in PTSD is not as substantial as in depression, based on proposed cortisol neurotoxic hypothesis chronic high cortisol levels cause more damage to the tissue than lower than normal levels. The behavior of the system therefore also confirms the hypothesis.

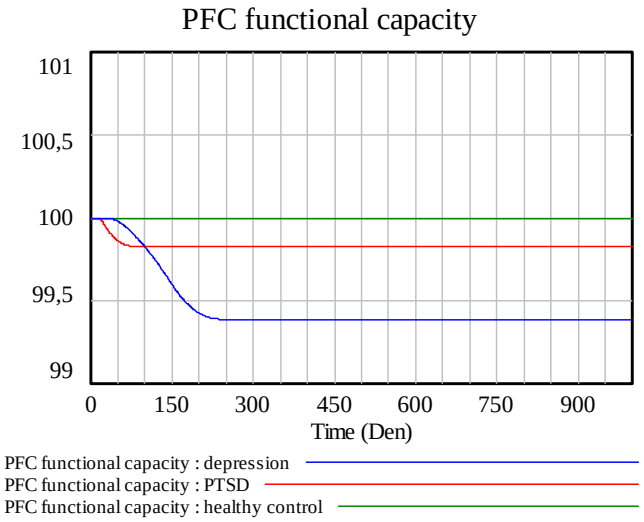

Figure 5 Prefrontal cortex functional capacity (index)

Amygdalar Functional Capacity

Amygdalar functional capacity (Figure 6) in healthy controls also remains intact, but undergoes changes due to lasting higher cortisol levels both in depressive and PTSD patients. Unlike prefrontal cortex (together with hippocampal tissue – not reported here), amygdala responds to chronic cortisol over-activation by hypertrophy (increase in volume) reflecting enhanced traumatic memory and the rate of stress sensitization. According to clinical experience, this pattern is more pronounced in PTSD patients than in depression.

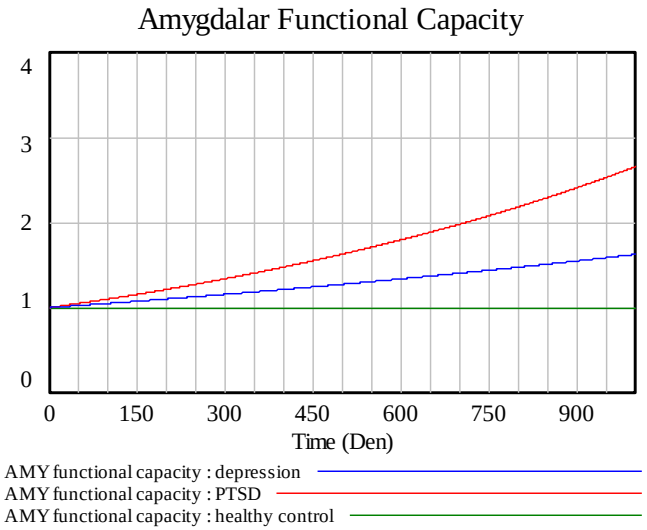

Figure 6 Amygdalar Functional Capacity (index)

CONCLUSION

Presented results show that interdisciplinary approach connecting system dynamics, physiology and psychiatry could bring fruitful outcome. Modeling PTSD and depression in one structure is to our knowledge the first attempt to grasp these widely spread disorders with substantial societal and clinical burden. Two important points are of a special importance.

First, clinicians were so far unable to simulate mentally long-term behavior of both examined disorders. Everyone knew that some structures are impaired and negative feedbacks are compromised one way or the other, but no one was able to simulate overall behavior of all those interconnected components. That prevented clinicians and researchers from formulating global hypothesis.

Second, even though the current model structure is simplified, proposed approach has a powerful predicting potential. Further development of the model promises chance to predict clinically relevant states of the patient far beyond timeframe available today. This then allows more precise planning of a community care, medical interventions, relapse risk assessment, etc.

References

Association, A. P. (1994). *DSM IV, Diagnostic and Statistical Manual of Mental Disorders*. Washington DC: American Psychiatric Association.

Bisson, J. I. (2007). Post-traumatic stress disorder. *BMJ, 334*(7597), 789-793.

Bremner, J. D., Vythilingam, M., Vermetten, E., Nazeer, A., Adil, J., Khan, S., et al. (2002). Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry, 51*(4), 273-279.

Cacioppo, J. T., Tassinary, L. G., & Berntson, G. G. (2000). *Handbook of psychophysiology* (2nd ed. / edited by John T. Cacioppo, Louis G. Tassinary, Gary G. Berntson. ed.). Cambridge: Cambridge University Press.

de Kloet, C. S., Vermetten, E., Geuze, E., Kavelaars, A., Heijnen, C. J., & Westenberg, H. G. (2006). Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *J Psychiatr Res, 40*(6), 550-567.

Edwards, S., Clow, A., Evans, P., & Hucklebridge, F. (2001). Exploration of the awakening cortisol response in relation to diurnal cortisol secretory activity. *Life Sci, 68*(18), 2093-2103.

Gilbertson, M. W., Shenton, M. E., Ciszewski, A., Kasai, K., Lasko, N. B., Orr, S. P., et al. (2002). Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci, 5*(11), 1242-1247.

Gold, P. W., & Chrousos, G. P. (2002). Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states. *Mol Psychiatry, 7*(3), 254-275.

Heim, C., Mletzko, T., Purselle, D., Musselman, D. L., & Nemeroff, C. B. (2008). The dexamethasone/corticotropin-releasing factor test in men with major depression: role of childhood trauma. *Biol Psychiatry, 63*(4), 398-405.

Heim, C., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2008). The link between childhood trauma and depression: insights from HPA axis studies in humans. *Psychoneuroendocrinology, 33*(6), 693-710.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *Am J Psychiatry, 156*(6), 837-841.

Knorr, U., Vinberg, M., Kessing, L. V., & Wetterslev, J. (2010). Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis. *Psychoneuroendocrinology, 35*(9), 1275-1286.

Lopez-Duran, N. L., Kovacs, M., & George, C. J. (2009). Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents: a meta-analysis. *Psychoneuroendocrinology, 34*(9), 1272-1283.

Meewisse, M. L., Reitsma, J. B., de Vries, G. J., Gersons, B. P., & Olff, M. (2007). Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *Br J Psychiatry, 191*, 387-392.

Schmidt-Reinwald, A., Pruessner, J. C., Hellhammer, D. H., Federenko, I., Rohleder, N., Schurmeyer, T. H., et al. (1999). The cortisol response to awakening in relation to different challenge tests and a 12-hour cortisol rhythm. *Life Sci, 64*(18), 1653-1660.

Shin, L. M., Orr, S. P., Carson, M. A., Rauch, S. L., Macklin, M. L., Lasko, N. B., et al. (2004). Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. *Arch Gen Psychiatry, 61*(2), 168-176.

Shin, L. M., Rauch, S. L., & Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Ann N Y Acad Sci, 1071*, 67-79.

Tretter, F. (2010). *Systems biology in psychiatric research : from high-throughput data to mathematical modeling*. Weinheim: Wiley-VCH.

Vasic, N., Walter, H., Hose, A., & Wolf, R. C. (2008). Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. *J Affect Disord, 109*(1-2), 107-116.

Watson, S., Gallagher, P., Del-Estal, D., Hearn, A., Ferrier, I. N., & Young, A. H. (2002). Hypothalamic-pituitary-adrenal axis function in patients with chronic depression. *Psychol Med, 32*(6), 1021-1028.