

# Course and prognosis of combat stress reaction/Croatian experience

Regional psychotrauma center Rijeka  
Prof.dr.sc.Tanja Frančišković



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*...that image of psychological disorganization doesn't fit, not even in it's lightest or the most extreme form, to any known syndrome ... For surely it is not a neurosis in it's common sense, and surly isn't just the state of fatigue... It can not adequately be described as anxiety or fear... If anything it is closer to the situational psychosis but the undergoing clinical course is completely different.  
(Bartemeier, 1946)*



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# Acute stress reaction -ICD-10 1992.

- Mixed and changing picture
- Initial state of "daze" with some constriction of the field of consciousness and narrowing of attention, inability to comprehend stimuli, and disorientation.
- Withdrawal from the surrounding situation or by agitation and over-activity
- Autonomic signs of panic anxiety (tachycardia, sweating, flushing)



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# Acute stress reaction -ICD-10 1992.

- Symptoms appear within minutes and disappear within two to three days (often within hours).
- Partial or complete amnesia for the episode may be present.
- Acute:
  - Crisis reaction / reaction to stress
  - Combat fatigue
  - Crisis state
  - Psychic shock



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# Z.Solomon: Combat stress reaction, 1994

- Anxiety
- Distancing
- Disorganization
- Loss of control
- Feeling of loneliness and vulnerability
- Guilt



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Year	PTSD after CSR	PTSD without CSR
1	59%	16%
2	56%	19%
3	43%	10%



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# Acute stress disorder DSM-IV, 1994.

- A. The person has been exposed to a traumatic event
- B. There are three (or more) dissociative symptoms:
  - a subjective sense of numbing, detachment, or absence of emotional responsiveness
  - a reduction in awareness of his or her surroundings (e.g., "being in a daze")
  - derealization
  - Depersonalization, dissociative amnesia
- C. The traumatic event is persistently reexperienced in at least one of the following ways:
  - recurrent images, thoughts, dreams, illusions, flashback episodes, or a sense of reliving the experience; or distress on exposure to reminders of the traumatic event.



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# Acute stress disorder DSM-IV, 1994.

- D. Marked avoidance of stimuli that arouse recollections of the trauma (e.g., thoughts, feelings, conversations, activities, places, people).
- E. Marked symptoms of anxiety or increased arousal (e.g., difficulty sleeping, irritability, poor concentration, hypervigilance, exaggerated startle response, motor restlessness).
- F. The disturbance causes clinically significant distress or impairment
- G. The disturbance lasts for a minimum of 2 days and a maximum of 4 weeks and occurs within 4 weeks of the traumatic event.



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# Frequency of PTSD diagnosis after experiencing an acute stress reaction after a year:

- After armed attack 83%
- After car crash 32%



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# Treatment doctrine for Acute combat stress reaction

- Proximity
- Immediacy
- Expectancy



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# AIM OF THE RESEARCH WAS TO DETERMINE:

- Course of ASR in the war conditions in Croatia and it's therapeutic implications
- Psychological consequences of ASR 10 years later
- Does the the treatment for ASR have a preventive effect for PTSD development
- Factors influencing development of PTSD



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# Material/Instruments

- Medical charts from 10.91. until 6.92. (1498 charts)
- 350 charts were selected according to inclusion criteria:
  - First psychiatric referral ever
  - Arriving straight from the war zone/front line



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# Analysis:

- Characteristics of clinical presentation
- Age
- Military division
- War service duration
- Diagnosis
- Treatment
- Number of medical exams
- Further treatment



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Average age  $30,7 \pm 6,3$  years

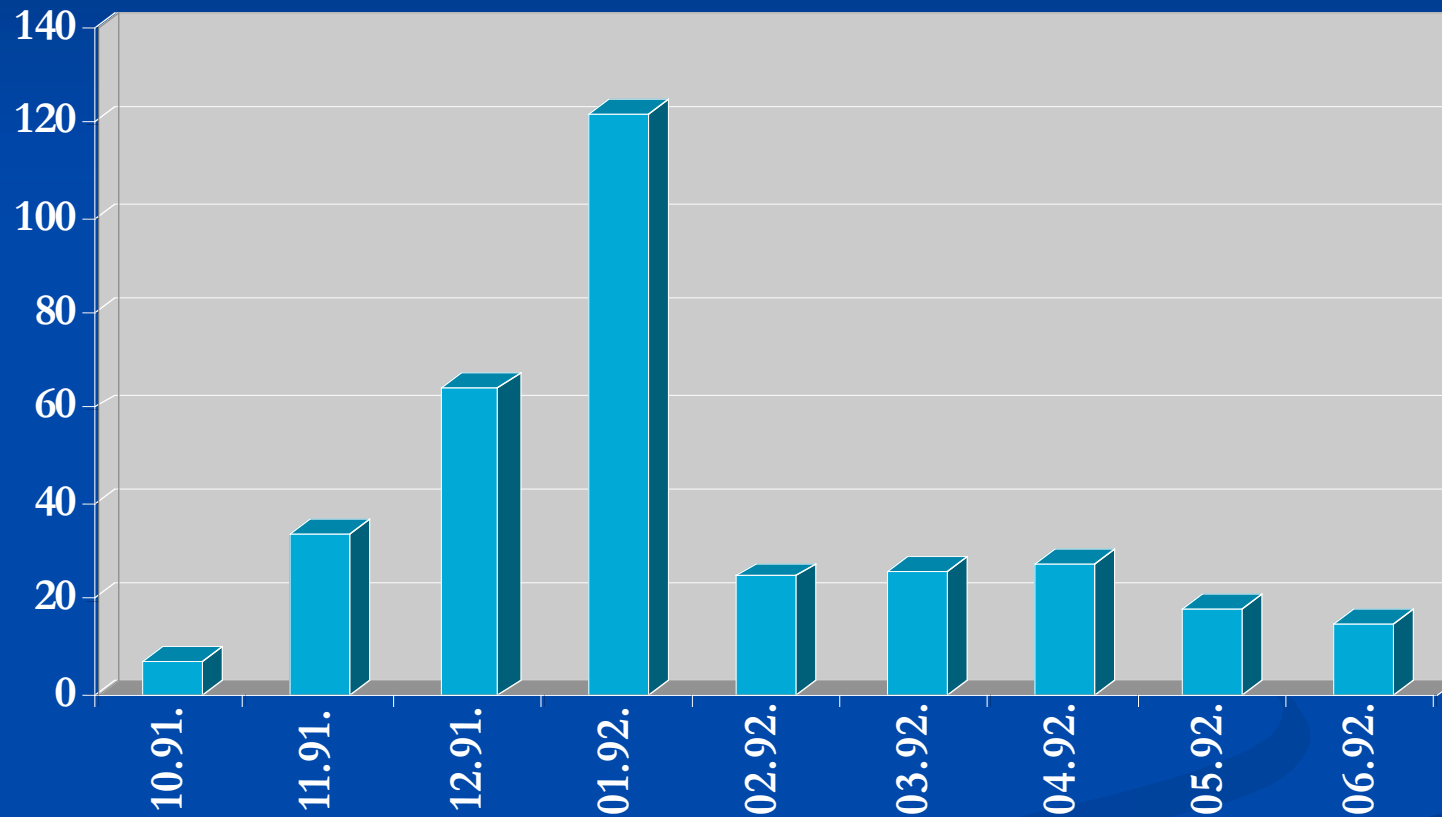


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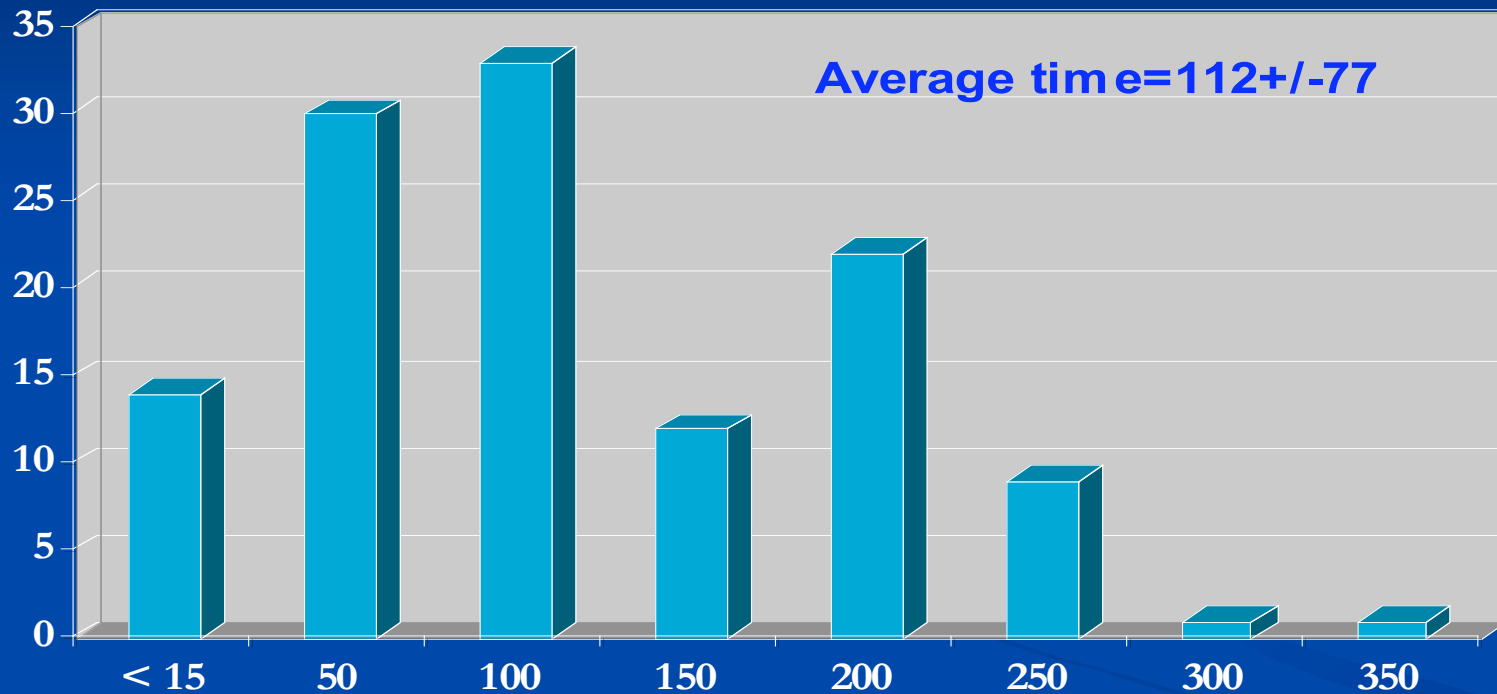
**Graph 1. Frequency of number of soldiers coming to the psychiatric clinic from Oct 91 until Jun 92.**



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## Graph 2. Time spent on the front line in days



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**Table 1. Number of patients according to clinical categories**

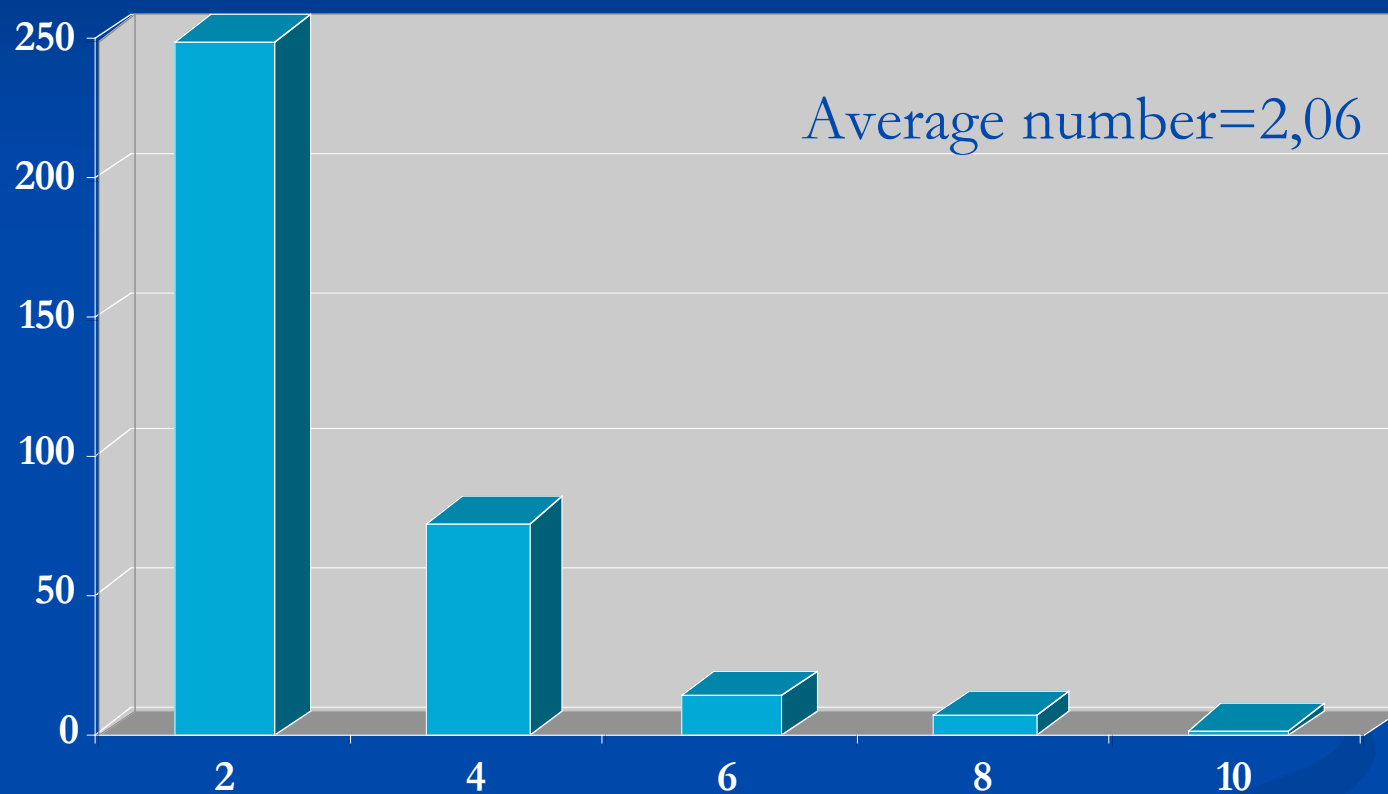
Diagnosis	N	%
ACUTE STRESS REACTION	206	58,8
COMBAT FATIGUE	104	29,7
PTSD ac.	34	9,7
Other	6	1,8
Total	350	100



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# Graph 3. Number of psychiatric visits by patient



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# Threatment interventions

- Support, counseling
- Multiple individual support
- “Group debriefing”
- Medicaments



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- 21% referred to group treatment
- 77,4% completed treatment during 1991 and 1992
- 70% contacted psychiatrist only once
- 7% recommended further treatment
- 4% still in treatment today



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# COMBAT FATIGUE

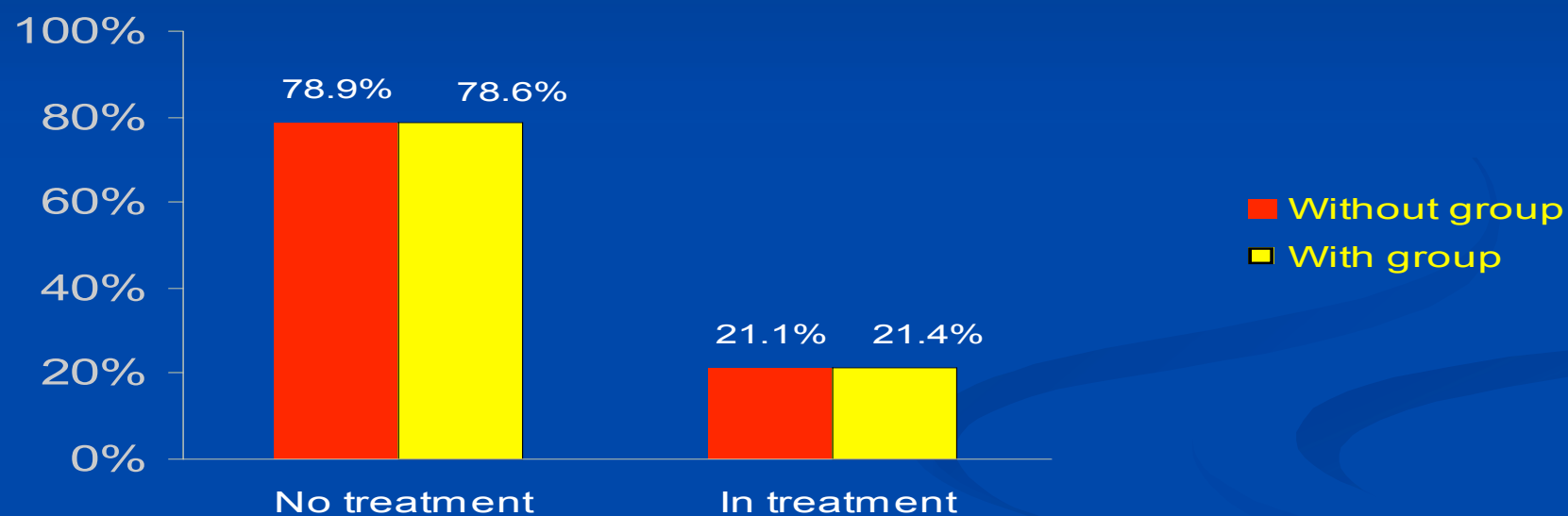
- Significantly longer stay in the front line comparing with other diagnoses (133:97)
- Different treatment needed
- **Specific clinical entity?**



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## Graph 4. Treatment status in present regarding past group treatment



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# Whether treatment is ongoing to present day does NOT depend on:

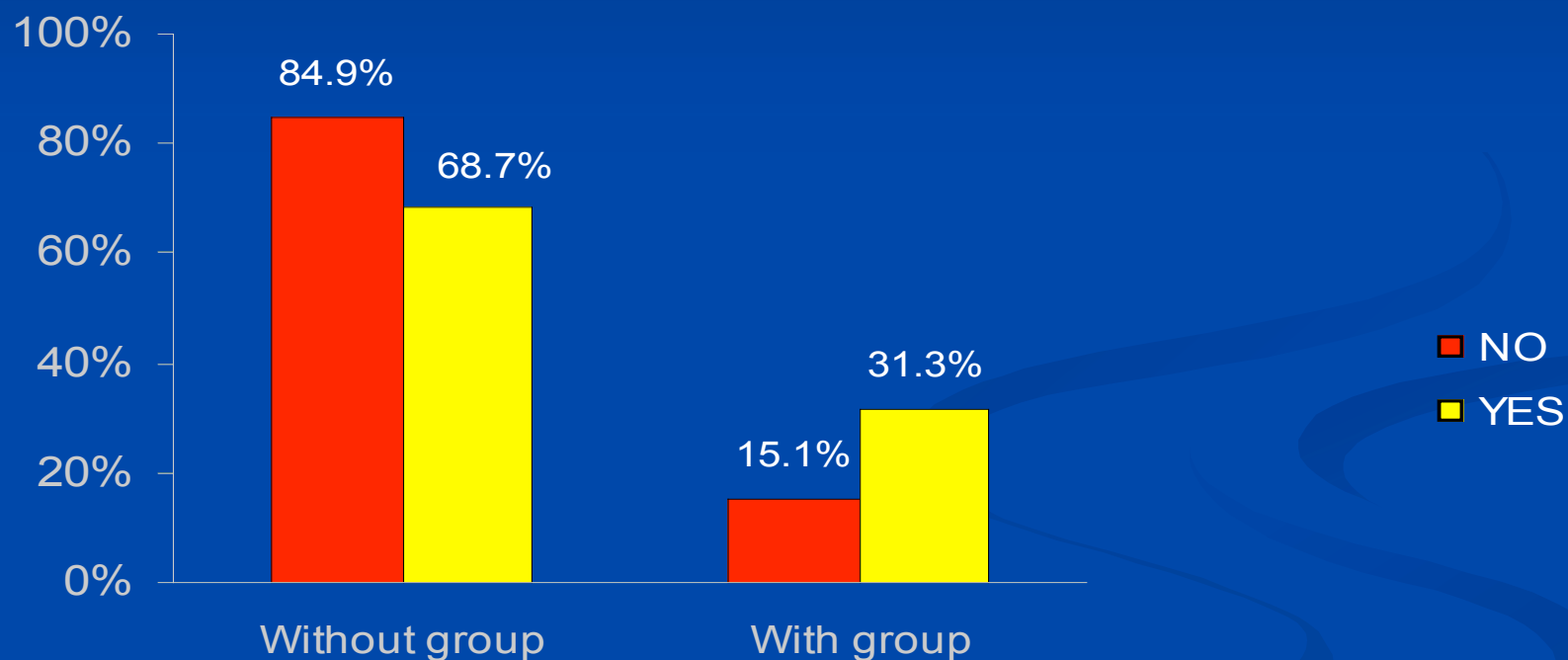
- Diagnosis
- Therapeutic intervention
- Duration of stay on the front line



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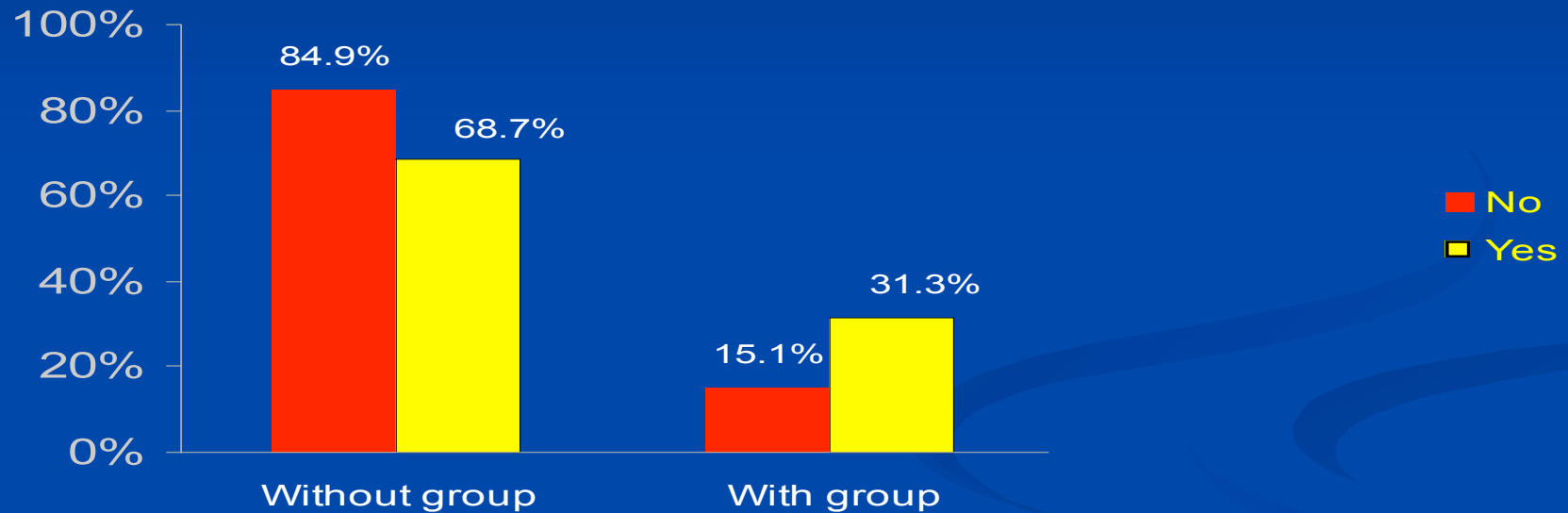
## Graph 5. Group regarding the end of therapy during 1991/1992



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# Graph 6. Ending therapy during 1991/1992 depending on group treatment



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350 participants were selected ten years later out of the database of soldiers who contacted psychiatrist due to acute psychological disorders in the period from 10.91. until 6.92.



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## OUT OF 350 PARTICIPANTS:

- 195 were not reachable
- 7 moved away
- 1 died in war
- 2 died of malign diseases
- 3 committed suicide
- 47 refused to participate
- **96 participated in the study (27,4)%**



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# Instruments

- General questionnaire
- MISS for combat related PTSP
- HTQ – Croatian version for war veterans
- STAI
- BDI
- COPE questionnaire



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# General sample characteristics

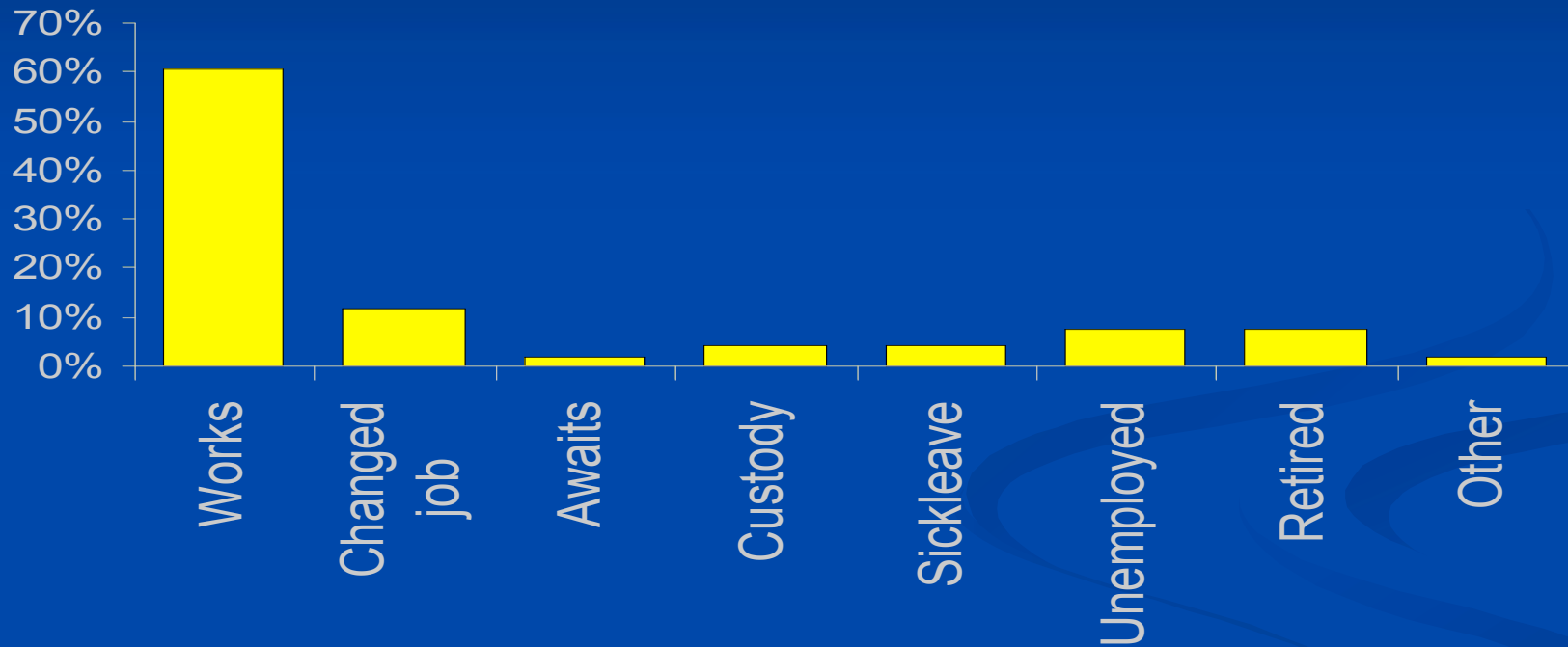
- Average age 38,6 years
- Average of secondary school education
- 42,6% volunteered soldiers
- 54,3% drafted soldiers
- Average of 6 months spent in the war



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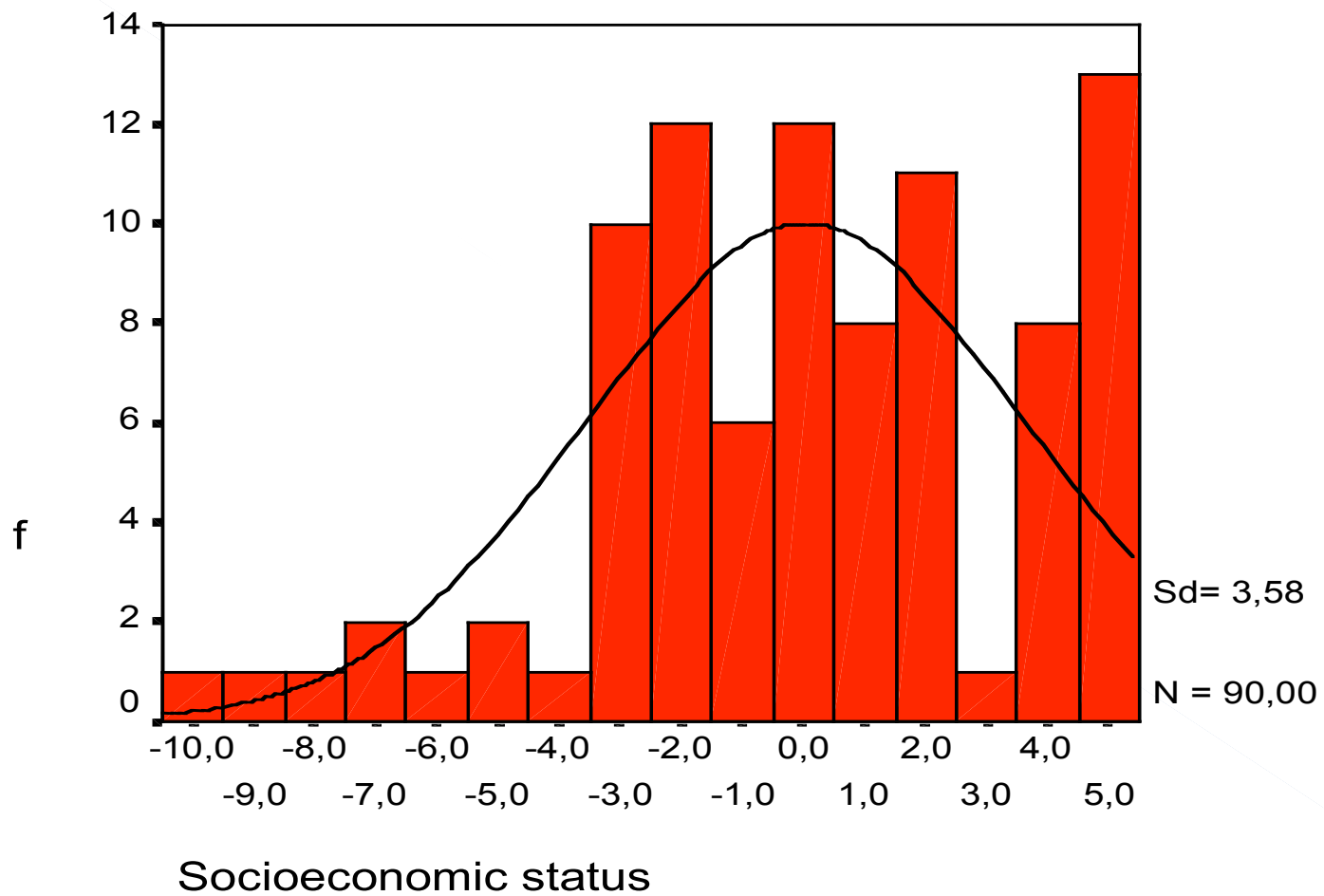
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# Graph 7. Work status



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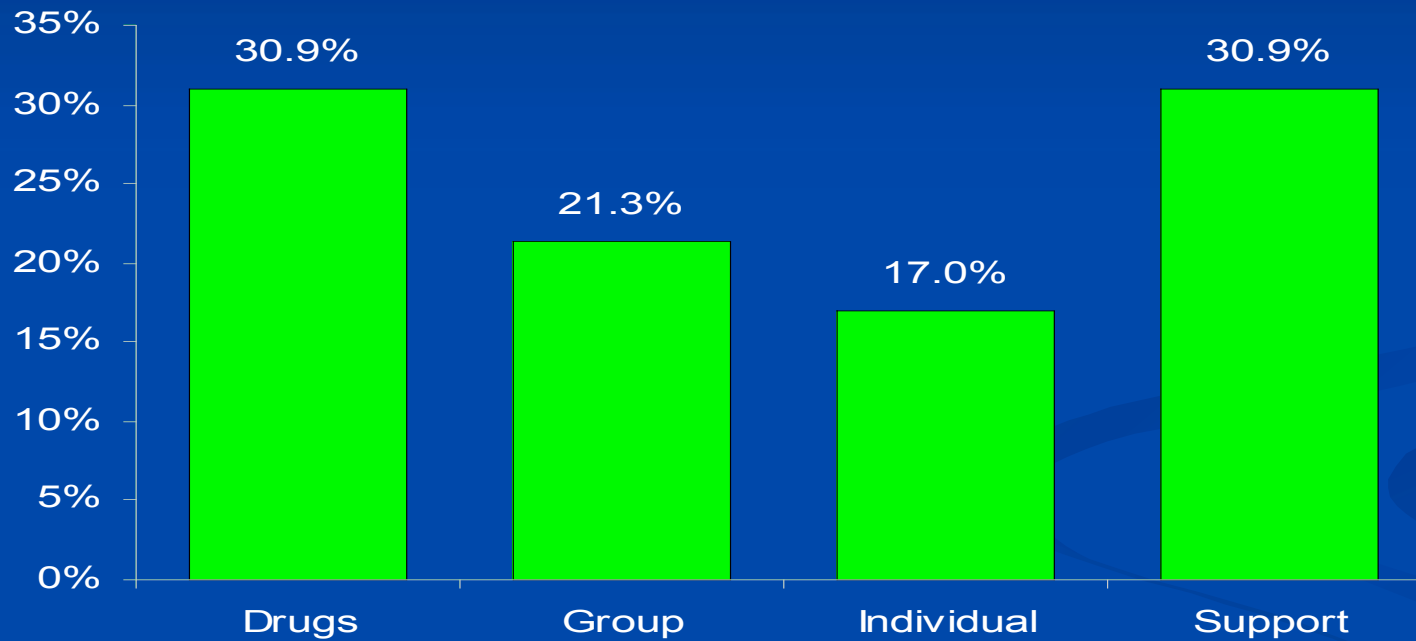
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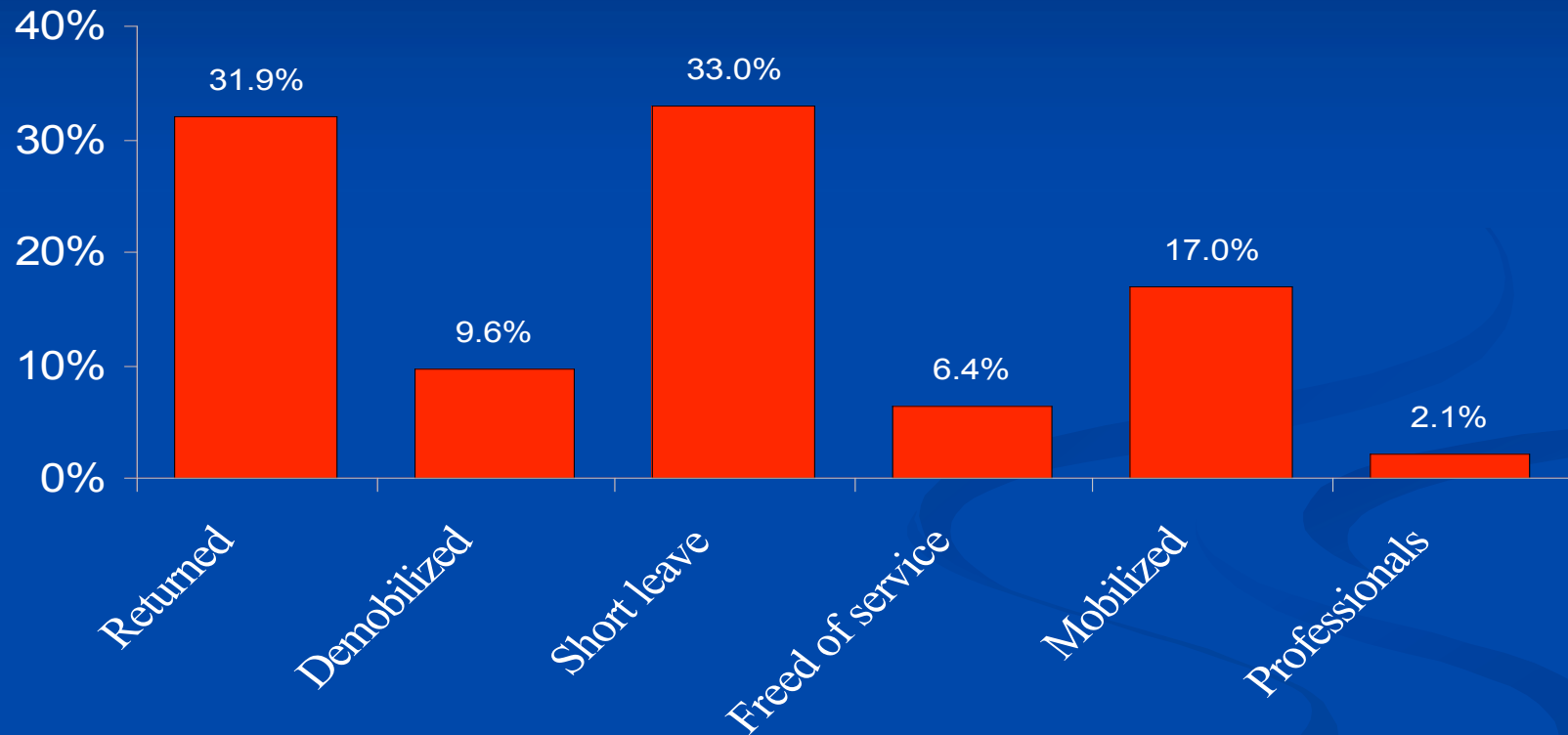
# Graph 8. Treatment



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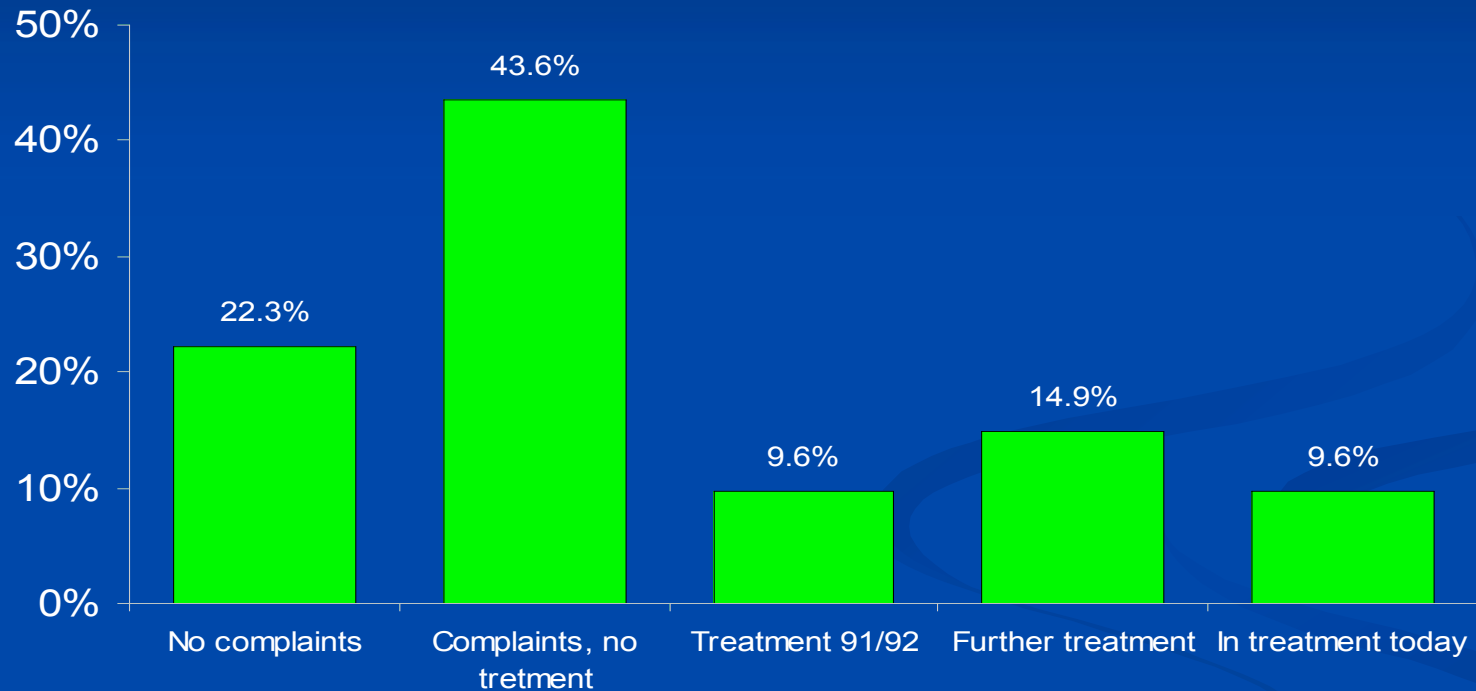
# Graph 9. Military status after treatment



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# Graph 10. Complaints and treatment today



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# HTQ results

Participants have experienced an average of 12 traumatic events



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# HTQ – posttraumatic symptoms (cut off score 1,5)

- Average score for
  - B symptoms - 0,8
  - C symptoms - 0,99
  - D symptoms – 1
- B, C and D symptoms highly correlate

# STAI results

- Average score –  $46,9 \pm 15$
- No PTSP group –  $41,8 \pm 11,84$
- PTSP group –  $62 \pm 13,14$
- **Control, mediterranean population – 40-47**



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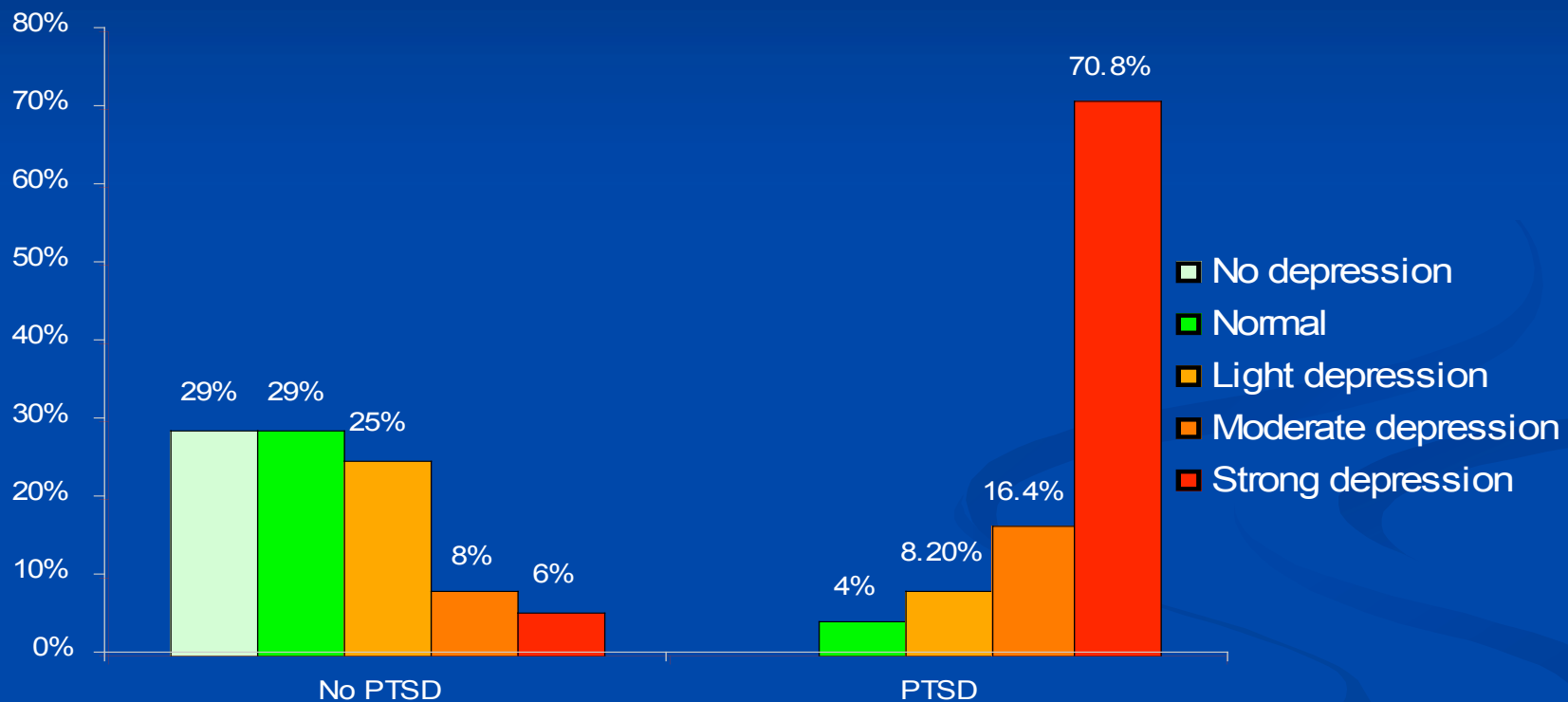
According to Mississippi  
questionnaire for combat related  
PTSD 26% participants have  
PTSD (cutt off score 107)



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# Graph 1, 1. Percentage of soldiers with and without PTSD by categories of depression



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# Coping strategies in groups with and without PTSD

Coping strategy	Group	M
Problem directed	No PTSD	1,96
	PTSD	2,07
Emotion directed	No PTSD	1,32
	PTSD	1,19
Avoidance	No PTSD	<b>1,15*</b>
	PTSD	<b>2,01*</b>



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# NO DIFFERENCES WERE FOUND AMONG GROUPS WITH AND WITHOUT PTSD ACCORDING TO:

- Age
- Education level
- Duration of stay in service
- Marital status
- Socioeconomic status
- Return to the war zone after having ASR
- Diagnosis in 1991. and 1992.



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# WITH AND WITHOUT PTSD GROUPS DIFFER SIGNIFICANTLY REGARDING:

- Current working status (more unemployed)
- Contacting psychiatrist and being in treatment



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# CONCLUSIONS:

Group debriefing proved to be a successful therapeutic method in:

- fast recovery from ASR
- faster return to the battlefield
- prevention of immediate cronification of complaints



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## CONCLUSIONS:

- ASR 10 years later is not a predictor of PTSD development
- The strongest predictor of PTSD is number of traumatic experiences



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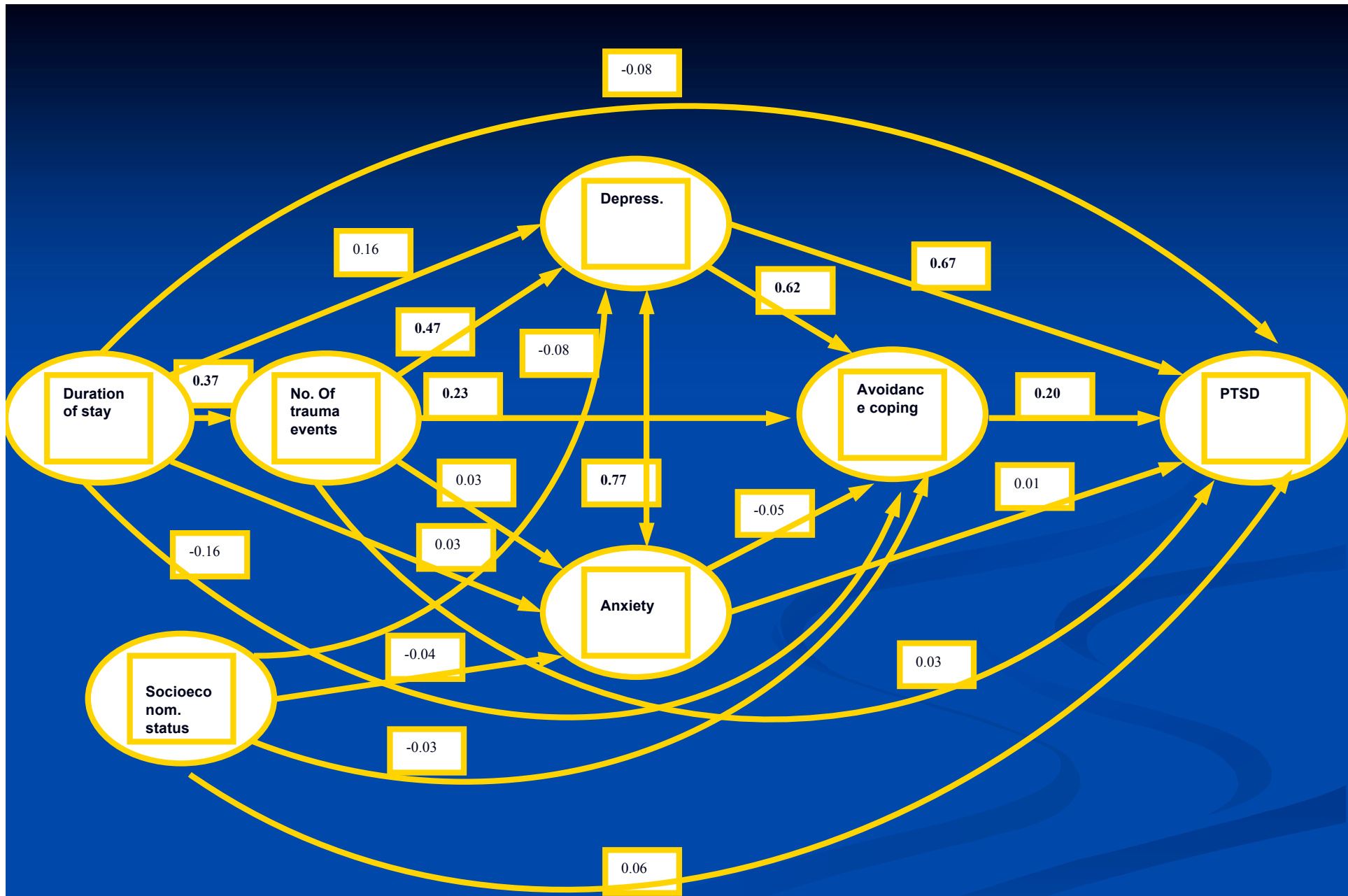
# CONCLUSIONS:

- Trauma influences the PTSD development by contributing to the development of depression and somatizations which with use of avoidance as a coping strategy lead to PTSD



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# CONCLUSIONS:

- Clinical manifestations of ASR during Croatian war are in concordance with experiences from other wars
- Clinical manifestations are characterized by polymorph symptoms with anxiety being the dominant ones



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# CONCLUSIONS:

- **Combat fatigue might be a separate diagnostic entity**



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# CONCLUSIONS:

- Suicide rate in this group was 1,9%

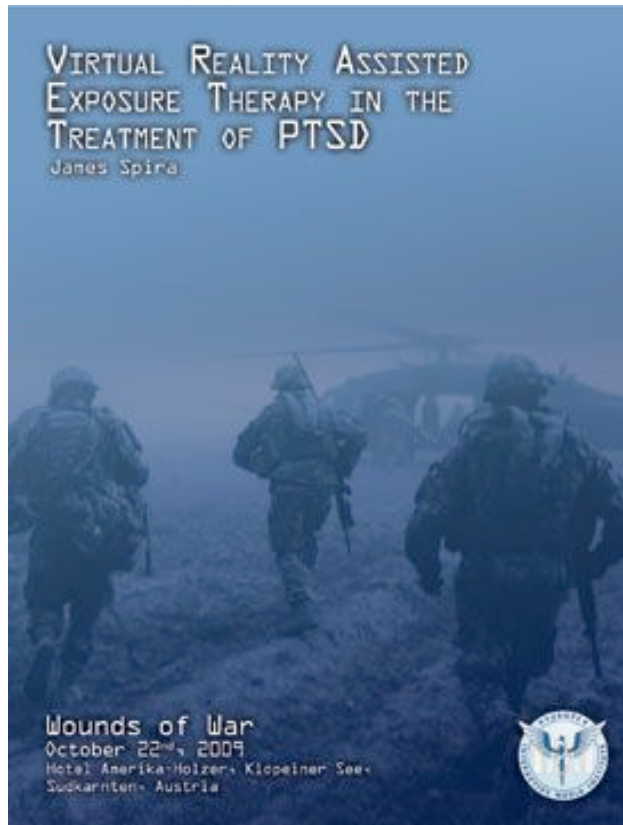


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# “Coping with Posttraumatic Stress Disorder...

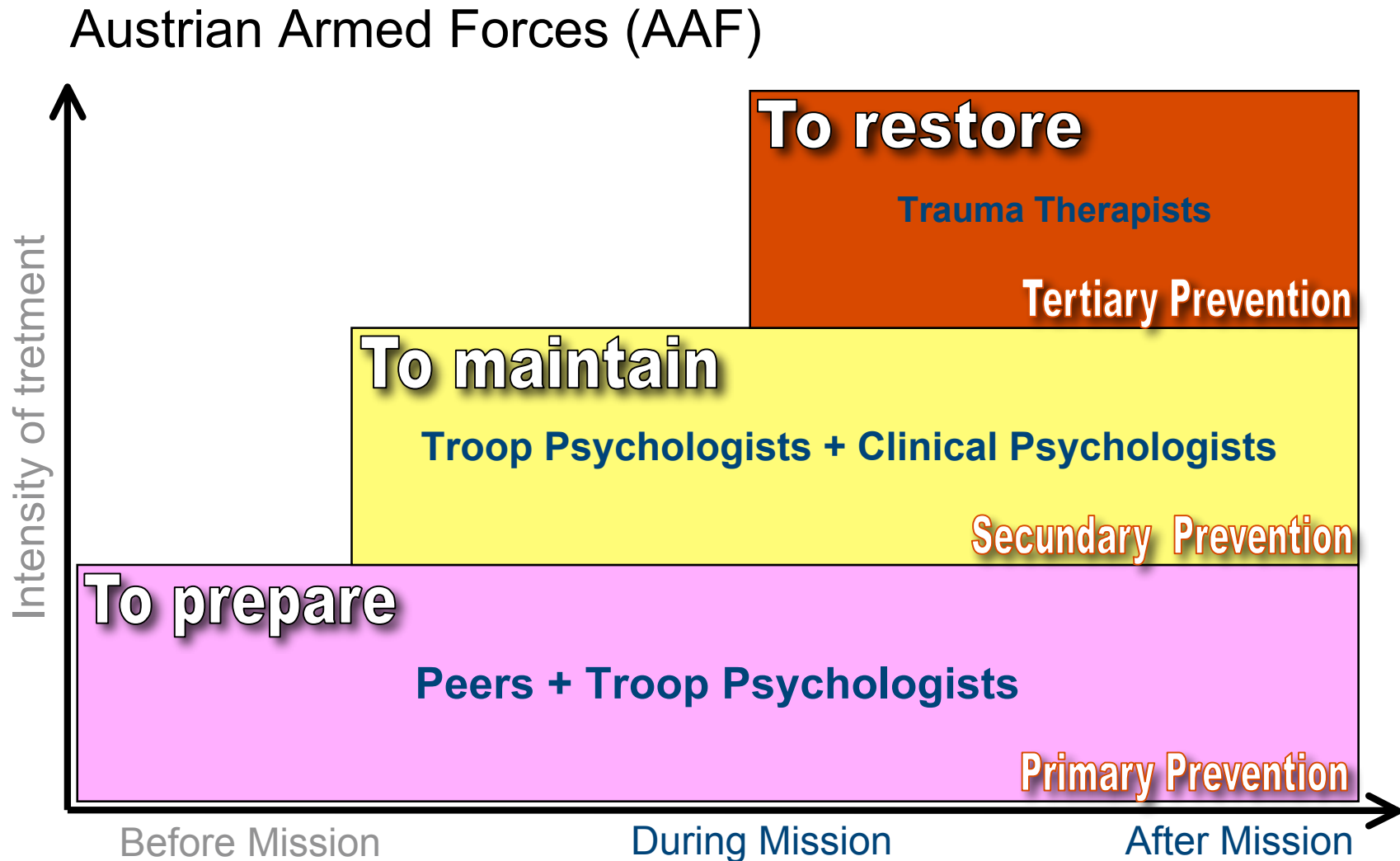


BG Thomas STARLINGER  
[Thomas.Starlinger@A1.net](mailto:Thomas.Starlinger@A1.net)

... Commander's view”



# “Coping with Posttraumatic Stress Disorder...



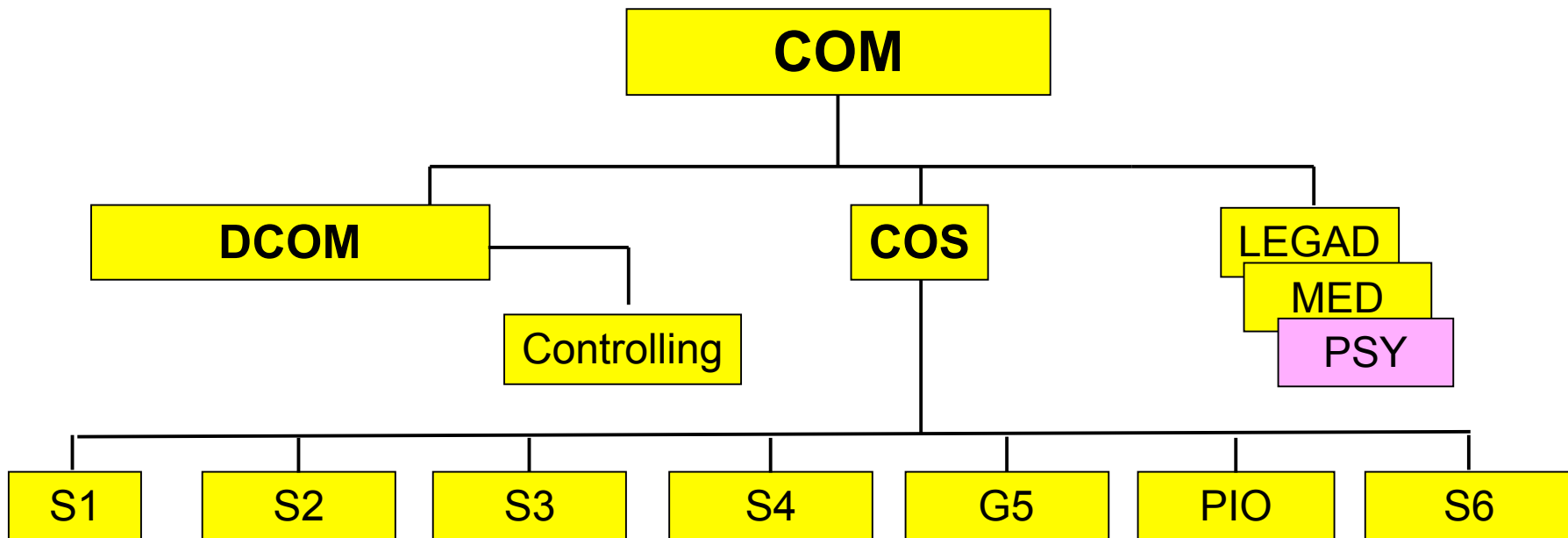
# “Coping with Posttraumatic Stress Disorder...

## Psychological Care Concept / AAF

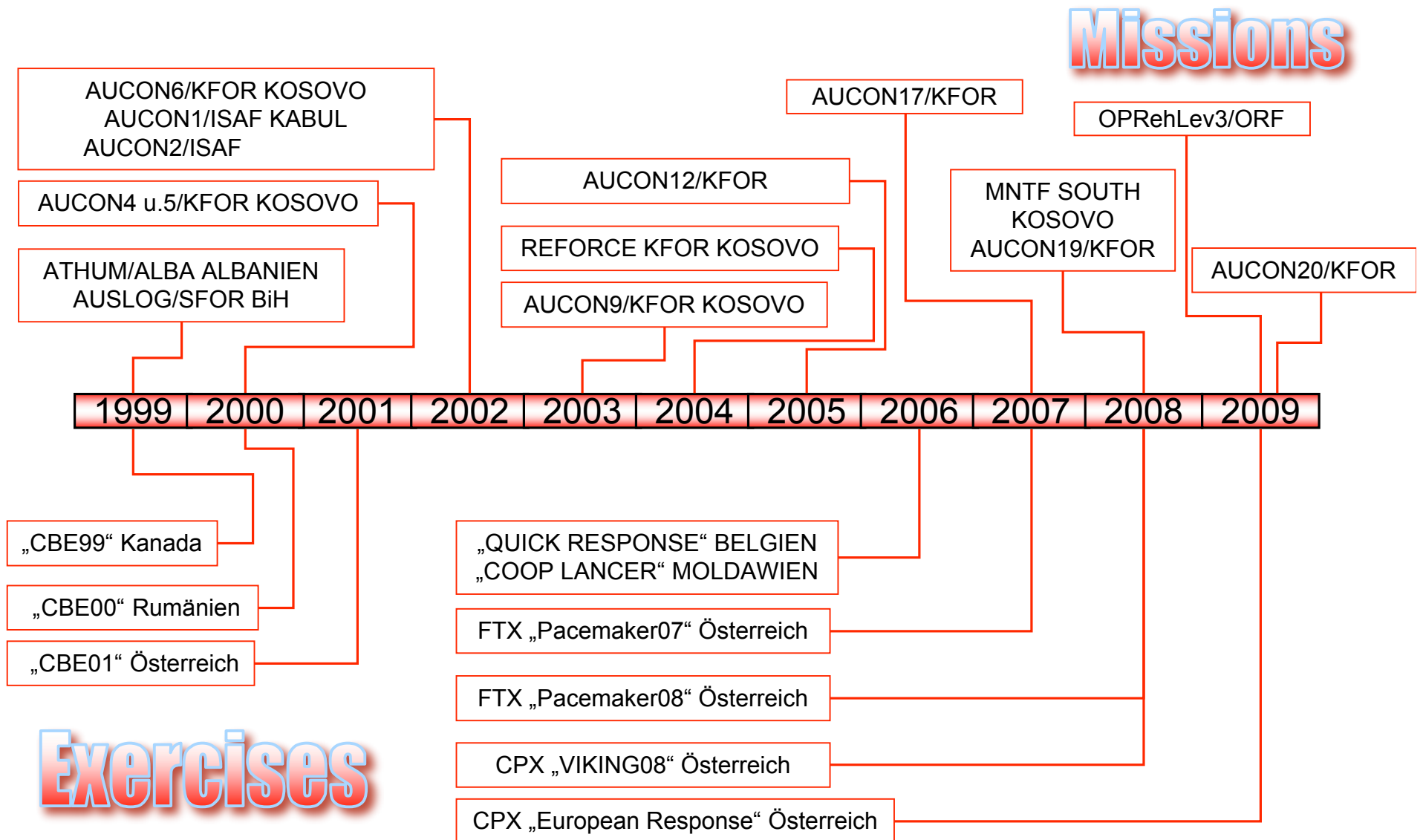
- **Before Mission**
  - Psychological Check + Selection → Capacity, Motivation, Attitude
  - Education + Training → Stress factors, Signals of PTSD, How to cope with stress ...
- **During Mission**
  - Psychological Care (Soldiers + Families at home)
- **After Mission**
  - Screening / PTSD
  - Reintegration seminar
  - Evaluation of mission
  - Care / Trauma Centre (INNSBRUCK)

# “Coping with Posttraumatic Stress Disorder...”

## HQ 7<sup>th</sup> InfBde

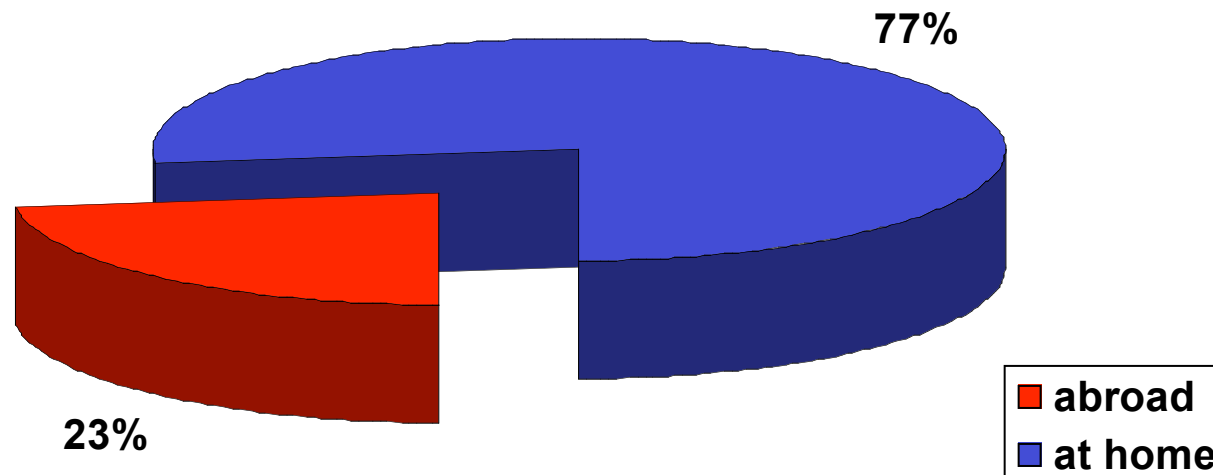


# “Coping with Posttraumatic Stress Disorder...



# “Coping with Posttraumatic Stress Disorder...

**23% of the professionals / 7<sup>th</sup> InfBde  
in missions abroad**



# “Coping with Posttraumatic Stress Disorder...

- PTSD starts already with accidents during EXERCISES
- 07 Oct 2009, 120mm Howitzer M-109, Grenade explodes inside tank: 1 dead, 1 heavily wounded, 3 uninjured !!
  - ↳ KIT / Psychologist started their work at same time as Medical Emergency Teams
  - ↳ All soldiers **gratefully** used the offered psychological support

# “Coping with Posttraumatic Stress Disorder...

- Own Experience / Missions Abroad
  - ↳ 1991 / Tajikistan: Ambushes by Mujahidins to Russian Forces ↩  
↗ Retaliation to Civil Population  
... NO psychological treatment at all !
  - ↳ 2009 / KOSOVO: shooting incidents between soldiers ...  
Psychologists from very beginning on the scene !!

# “Coping with Posttraumatic Stress Disorder...

- Very much appreciated ....
  - ↳ Open exchange of information & experience between nations
    - Post incident treatment → “Invisible wounds of war”
    - Prevention → How soldier could be prepared, so they don't develop PTSD
  - ↳ What are the symptoms & consequences associated with PTSD ?



# “Coping with Posttraumatic Stress Disorder...

- Wish you lots of success in ....
  - ↳ Understanding what programs are already in place for detection, assessment, prevention, and treatment
  - ↳ Critically assessing the existing knowledge
  - ↳ Formulating a more common set of best practices + guidelines, which can be implemented in all armies for the sake of our soldiers

# “Coping with Posttraumatic Stress Disorder...

*“The most important thing we can do for service members who have been in combat is to help them understand that the earlier that they get help when they need it, the better off they’ll be!”*

Dr. Charles W. Hoge (US, Walter Reed Army Institute of Research)



... Commander’s view”



**DEFENSE CENTERS OF EXCELLENCE**  
For Psychological Health & Traumatic Brain Injury



# The Emergence of Total Fitness in the United States Department of Defense: A Necessary Focus for Sustaining the Human System in the New Era of Full Spectrum Operations

Major Todd M Yosick  
Chief, Operational Resilience Division  
Defense Centers Of Excellence For Psychological Health and Traumatic Brain Injury  
United States of America



25 OCT 09

# A New Era

**“If we’ve learned nothing else these past 8 years, it should be that the lines between strategic, operational, and tactical are blurred beyond distinction.”**

**Admiral Michael G. Mullen**

*United States Chairman of the Joint Chiefs Of Staff*

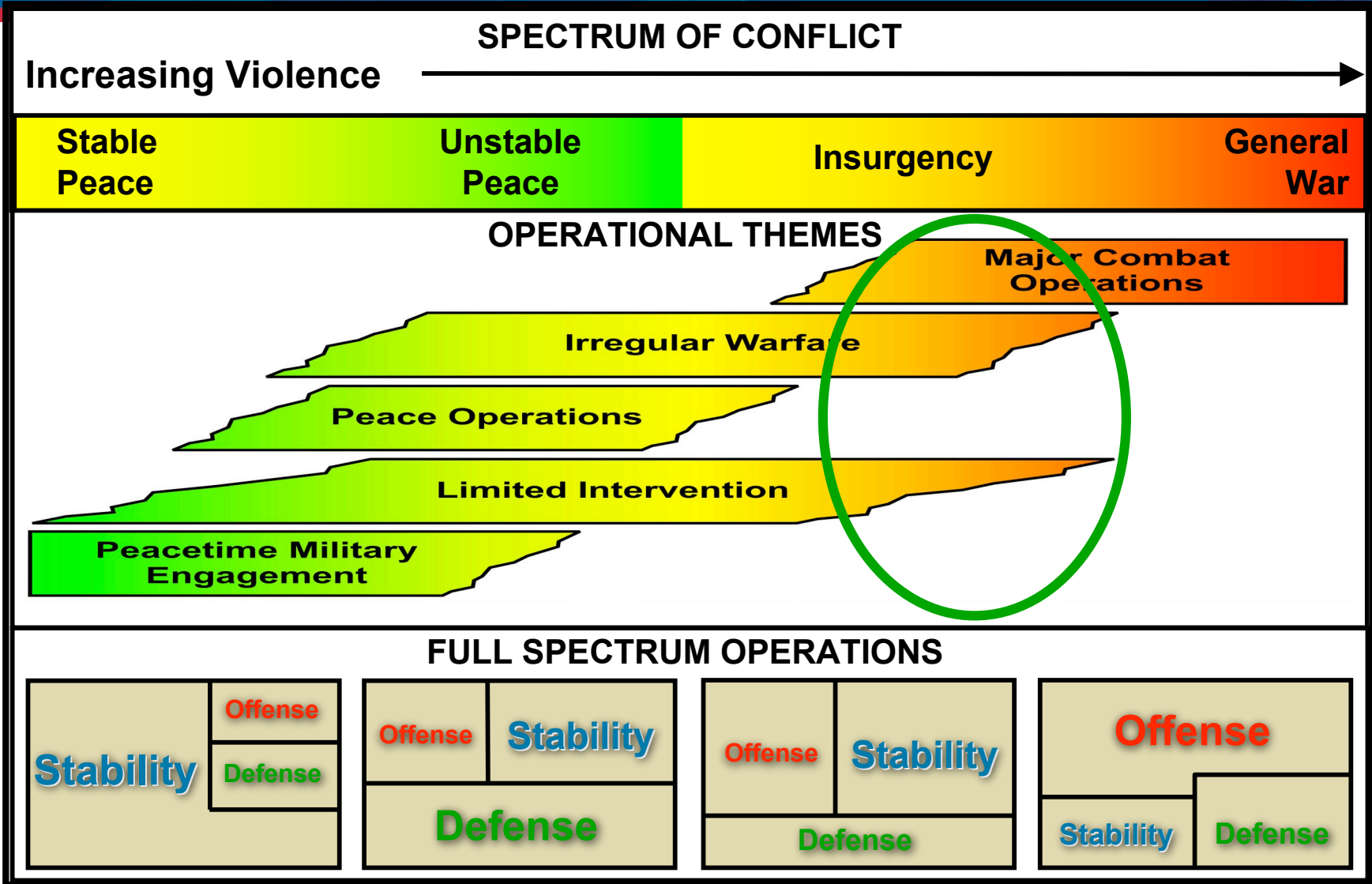
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For Psychological Health & Traumatic Brain Injury

2

# Full Spectrum Operations





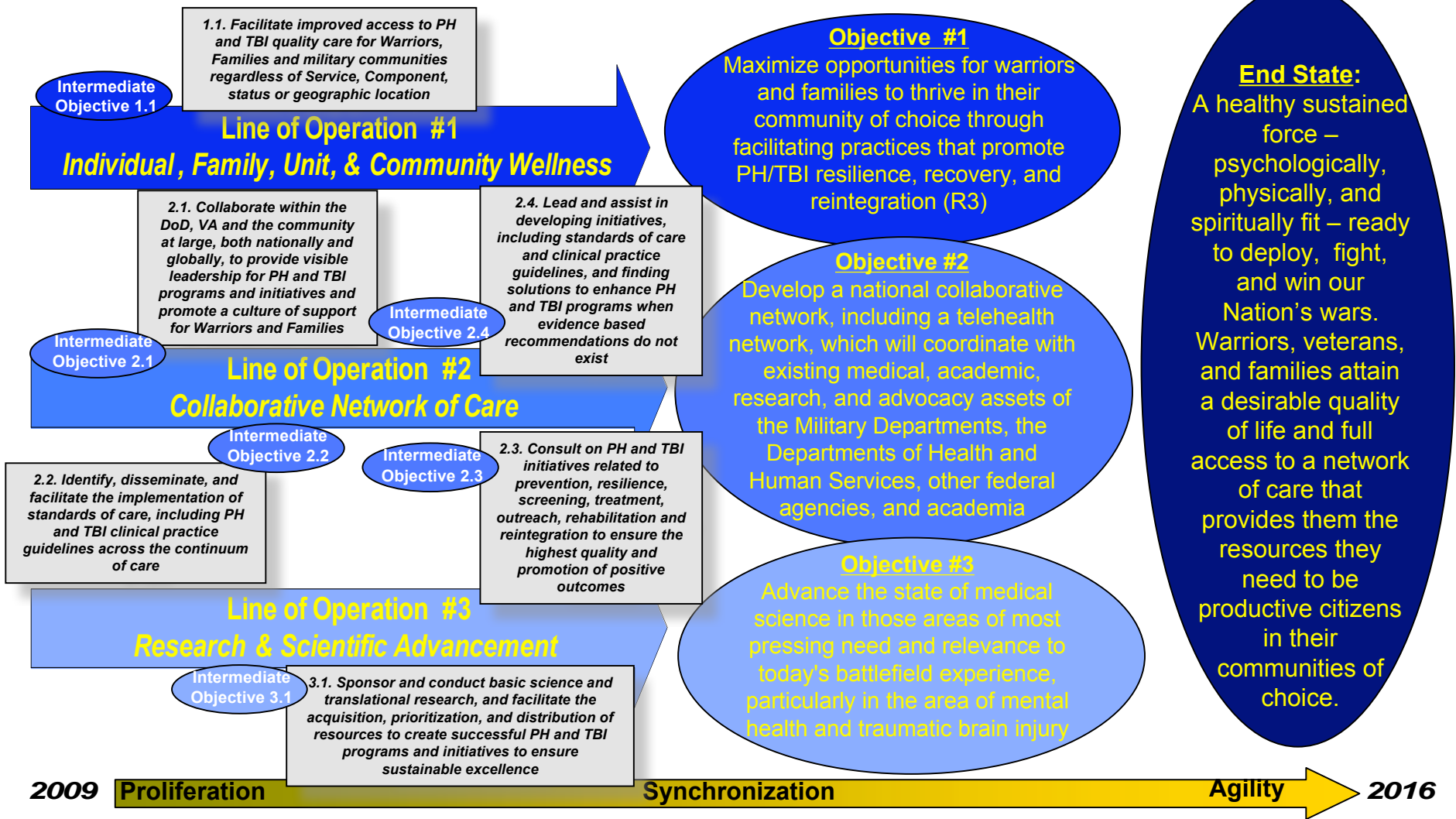
# Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury

**Vision:** Lead the nation in resilience, recovery, and reintegration for warriors and their families in all areas related to PH and TBI

**Mission:** DCoE assesses, validates, oversees, identifies, and facilitates prevention, resilience, screening, treatment, outreach, rehabilitation, and reintegration programs for PH and TBI to ensure the United States Department of Defense meets the needs of the nation's warriors, families, and military communities



# DCoE Lines of Operation



# A Resilient Spirit

# ON PATROL

UNTIL EVERY ONE COMES HOME | THE MAGAZINE OF THE USO | VOLUME ONE | NUMBER 2 | SUMMER 2009

ATTENTION  
TO ALL WHO ENTER HERE

IF YOU ARE COMING INTO THIS ROOM WITH SORROW OR TO FEEL SORRY FOR MY WOUNDS, GO ELSEWHERE. The wounds I received, I got in a job I love, doing it for people I love, supporting the freedom of a country I deeply love. I am incredibly tough and will make a full recovery. What is full? That is the absolute utmost physically my body has the ability to recover. Then I will push that about 20% further through sheer mental tenacity. This room you are about to enter is a room of fun, optimism, and intense rapid regrowth. If you are not prepared for that. Go ELSEWHERE.

# SPECIAL OPS ISSUE



# Total Fitness Initiative

- Optimizes the different components of the human dimension
- Far “left of the boom” approach to primary prevention
- Emphasizes comprehensive integration of holistic process
- Supports human performance initiatives



# The Body

- Element often overlooked is physical endurance of the human body
  - Fitness requirements of line infantry Soldiers in the U.S. Army are more rigorous than those for Vietnam-era Special Forces troops
  - As advancements in weaponry accelerate, so does gear protecting service members
- Physicality and weaponry are no longer the sole factors for operational success alone...the human dimension has emerged



# The Mind

- Greek and Roman civilizations placed unparalleled attention on fitness for both men and women
  - Sheer strength behind crude weapons was the most important factor to survivability
  - “Mens sano in corpore sano,” healthy mind and healthy body
- The full spectrum transition
  - Warriors today are expected to adjust from combatants to ambassadors of good will in short order



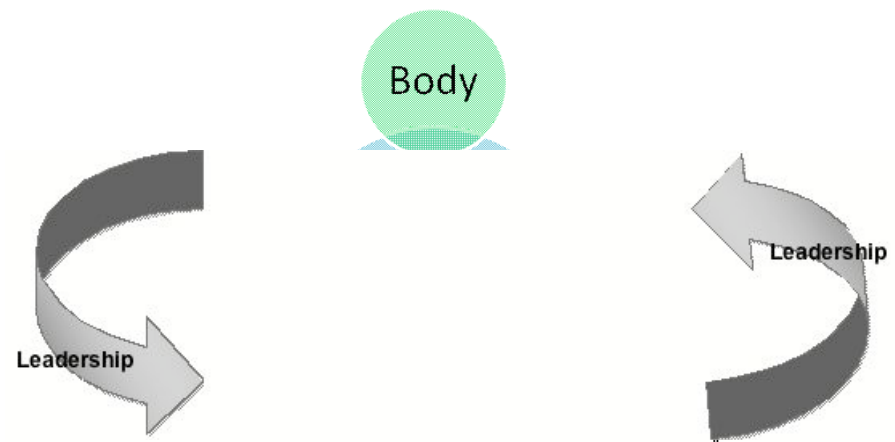
# The Spirit

- **Military basic tenant of spirituality**
  - Army “Army Strong”
  - Navy “Honor, Courage, and Commitment”
  - Marine Corps “Semper Fidelis” or “always faithful”
  - Air Force “Integrity first, Service before Self, and Excellence in all we do”



# Leadership; The Necessary Element

- The conventional military leader mindset must adjust to an era of full spectrum operations
- Leadership training must include both performance enhancement and health promotion
- Importance for training focus to leaders at all levels



# Training Leadership

*“Commitment of top leaders and managers means that the program will be highly regarded, aligned with strategy, and focused on the right issues.”*

*-Josh Bersin, President and Chief Executive Officer of Bersin and Associates*

## Best Practices for Leadership Development:

1. Maintain strong executive engagement
2. Define tailored leadership competencies
3. Align with business strategy
4. Target all levels of leadership

**5. Apply a comprehensive learning approach**

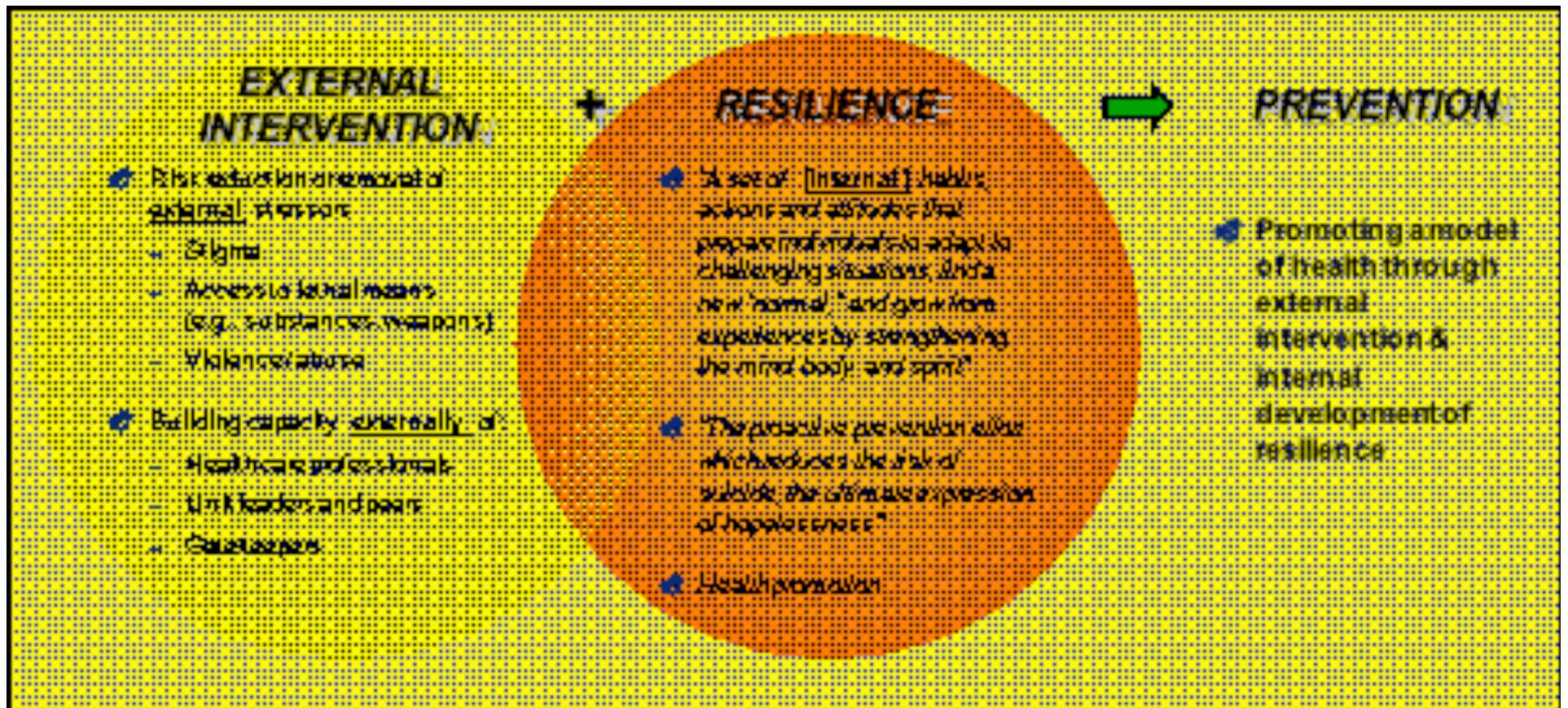
6. Build a sustainable leadership pipeline

From Bersin, Josh, “Six Best Practices for Leadership Development”, *Leadership Excellence* April 2008





# Great Leadership and Support (external intervention) and Total Fitness (resilience) Equals a Healthier Force





# Resilience Promoting Factors

## By Levels of the Human Dimension

Physical	Psychological	Social	Spiritual
<ul style="list-style-type: none"> <li>• Healthy sleep</li> <li>• Nutrition/Hydration</li> <li>• Exercise/Physical readiness</li> <li>• Energy management</li> <li>• Environmental management</li> <li>• Personalized optimization</li> </ul>	<ul style="list-style-type: none"> <li>• Adaptive flexibility/Planning</li> <li>• Problem solving</li> <li>• Coping/Stress control</li> <li>• Self-regulation (e.g., substance use, meditation)</li> <li>• Psychological fitness</li> <li>• Emotional intelligence</li> </ul>	<ul style="list-style-type: none"> <li>• Service support</li> <li>• Utilization</li> <li>• Quality leadership</li> <li>• Relationship support</li> <li>• Trust in others</li> <li>• Healthy medical environment</li> <li>• External support resources</li> <li>• Social organizations</li> <li>• Community involvement</li> <li>• Communication</li> <li>• Family cohesion</li> <li>• Education/Accredited</li> <li>• Financial health</li> <li>• Culture of support/meaningful</li> </ul>	<ul style="list-style-type: none"> <li>• Positive affectivity</li> <li>• Post-traumatic growth</li> <li>• Purpose/meaning</li> <li>• Faith-based support</li> <li>• Service/faith</li> <li>• Trust in self</li> <li>• Self-awareness</li> <li>• Forgiveness</li> <li>• Altruism</li> <li>• Ethics</li> <li>• Spiritual direction</li> </ul>





# Human System Sustainment in Full Spectrum Operations

- **It is really easy to do something once or twice with great success...it is much more difficult to sustain it**
- **The way ahead is not a marathon...it is a continual series of sprints which must be supported with uncompromised periods of recovery**
- **The paradigm of building on existing strengths in your warriors, families, units, and communities is low hanging fruit**



# Proteomics and PTSD



**Dragica Kozarić-Kovačić<sup>a</sup>, Krešimir Pavelić<sup>c</sup>, Vanda Filipac<sup>a</sup>, Mario Cindrić<sup>b</sup>, Sandra Kraljević-Pavelić<sup>c</sup>**

*<sup>a</sup>University Hospital Dubrava, Referral Centre for the Stress Related Disorders of the Ministry of Health of the Republic of Croatia, Department of Psychiatry*

*<sup>b</sup>Ruđer Bošković Institute, Division of Molecular Medicine, Center for Proteomics and Mass Spectrometry*

*<sup>c</sup>University of Rijeka, Division of Biotechnology*

Klopeiner See, Südkärnten, Austria

October 18-21, 2009

# PTSD



- Post-traumatic stress disorder (PTSD) is a severe, chronic and disabling anxiety disorder occurring following an extreme traumatic event. Defining symptoms of this disorder include persistent re-experiencing of the traumatic event, followed by persistent avoidance of stimuli associated with trauma, numbing of general responsiveness and persistent symptoms of increased arousal, which are present for more than a month and cause significant distress or impairment in social, occupational or other important areas of functioning (APA, 1994)



# PTSD – an important public health issue

- Epidemiological data: PTSD is a highly prevalent disorder and thereby an important public mental health problem
- The lifetime prevalence of PTSD is about 7.8% (about 10% for women and 5% for men) (Kessler et al., 1995)
- Our clinical studies have shown high prevalence of PTSD in Croatian war veterans (Kozaric-Kovacic, Kocijan-Hercigonja, 2001)
- In 2007 PTSD was responsible for 13.6% of all hospitalizations for mental disorders in Croatia and was in the second place among all mental disorders as a cause of hospitalization in men (data from the Croatian Institute for Public Health)

# PTSD - uncertainties

- Difficult diagnosis – it mostly relies on the symptoms as reported by the patient, difficult differential diagnosis, frequent comorbidities
- “Secondary gain” issues - particularly important in forensic psychiatric evaluations
- The etiology of PTSD is still largely unknown
- The effect of pharmacotherapy has so far been unsatisfactory (Kozaric-Kovacic, 2008; National Institute for Clinical Excellence, 2005).
- Considering objective difficulties in diagnosing PTSD it is necessary to develop more objective diagnostic methods, which would include newer scientific findings about the possible etiology of the disorder.

# Endophenotypes

- Endophenotypes – quantifiable measures that may have the ability to reduce the heterogeneity inherent in psychiatric disorder
- May be neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological in nature
- E.g. in schizophrenia endophenotypes may include working memory deficits, impairments in prepulse inhibition and smooth pursuit eye movement abnormalities
- In PTSD – e.g. platelet MAO activity, increased startle response
- They remain undiagnostic at this stage

# PTSD - biomarkers

- Biomarker – “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention” (NIH Biomarker Definitions Working Group, 2001)
- Types of biomarkers (Zhang et al., 2009)
  - Type 0 biomarker – a marker of the natural history of a disease (correlates longitudinally with known clinical indices)
  - Type 1 – captures the effects of a therapeutic intervention in accordance with its mechanism of action
  - Type 2 – intended to substitute for a clinical end point; expected to predict clinical benefit on the basis of epidemiological, therapeutic, pathophysiological, or other scientific evidence
  - Risk marker – can be measured quantitatively in the subject at risk, can be used to identify cohorts for prevention

# PTSD - biomarkers

- PTSD biomarkers – indicators of PTSD traits (risk marker), disease state (preclinical or clinical) or disease rate (progression)
- Benefit – to enhance the ability of the clinician to optimally diagnose and manage the patient with PTSD, to help identify specific therapeutic target and to use it preventatively (determination of risk)
- Needs to be acceptable to PTSD patients and easy-to-use for clinicians
- Strategy to develop biomarkers – 3 steps: screening, analytical validation and clinical validation
- Several candidates identified by screening approaches, few have been validated



# Biomarkers for PTSD (Zhang et al. 2009)

T-cell phenotypes	Lemieux et al. (2008)
Assumptions	Rosen and Lilienfeld (2008)
ESR, WCC, and cortisol/DHEA-sulfate ratio	Boscarino (2008)
Endothelial dysfunction in plasma	Von Kaenel ((2008)
Serum interleukin-2 and interleukin-8 levels	Song et al. (2007)
Platelet serotonin concentration	Kovacic et al. (2008), Pivac et al. (2006), Mueck- Seler et al. (2003), Spivak et al. (1999)
Platelet MAO-B activity	Pivac et al. (2007)
Circulating cortisol levels	Meewisse et al. (2007), Ehlert et al. (2001), Heber et al. (2002), Glover and Poland (2002), Yehuda et al. (2002)
Glucocorticoid receptor expression in lymphocyte	Gotovac et al. (2003)
WFS1 gene	Kesner et al.(2009)
Platelet CD63 expression, leukocyte CD63 expression, platelet CD63 expression, leukocyte CD63 expression, selectin concentration	Vidovic et al. (2007)
GABA plasma levels	Vaiva et al. (2006)
S-100B and neuron-specific enolase	Sojka et al. (2006)
NPY expression	Dutton et al. (2006)
Myelin basic protein	Wang et al. (2004)
CRP and serum amyloid A	Soendergaard et al. (2004)
Urinary dopamine	Glover et al. (2002)
Thyroid hormone	Garrison and Breeding (2003)
Neopterin	Atmaca et al. (2002)
Plasma and CSF interleukin-6 concentration	Barker et al. (2001), Maes et al. (1999)
REM latency	Reist et al. (1995), Kauffman et al. (1987)
Average heart rate responses to a series of sudden, loud-tone presentations	Ptiman et al. (2006), Bryant et al. (2007)
Mixed lateral preference and parental left-handedness	Chemtob and Taylor (2003)
Startle responses	Milde et al. (2003)

# Proteomics in psychiatric research

- Proteomics – the study of protein expression and function on a genome-wide scale (high-throughput, multidisciplinary and technology-driven science, providing global characterization of different levels of protein changes - localization, interaction and post-translational modifications)
- Ideal to characterize cellular and molecular mechanisms of psychiatric disorders and correlate altered behaviour with biological processes occurring at the proteome level
- ‘Psychoproteomics’ – integral proteomics approach dedicated to studying proteomic changes in the field of psychiatric disorders (Kobeissy et al, 2008)
- Apart from elucidation of etiology proteomics can be used to identify therapeutic targets and develop diagnostic tests

# Proteomics and biomarkers

- Comparing qualitative and quantitative protein expression data in healthy and diseased states it is possible to find biomarkers for various psychiatric disorders using the differential display technology
- Growing number of studies are showing qualitative and quantitative changes in brain, CSF and peripheral tissue proteins in neurodegenerative and some psychiatric disorders, such as schizophrenia, bipolar disorder, depression and autism (Pennington et al., 2008; Huang et al, 2008; Corbett et al., 2007; Prabakaran et al, 2007; Wan et al, 2007 and 2006; Novikova et al, 2006, Clark et al, 2006;Fonteh et al, 2006; Brunner et al, 2005; Lopez et al, 2005)
- Some studies further suggest the potential for using peripheral tissue (e.g. leukocytes) to monitor pharmacological action in neurodegenerative diseases (Mhyre et al., 2008)

# Proteomics and biomarkers

- Proteomic analysis of the CSF revealed alterations in suicide attempters (Brunner et al., 2005)
- Animal studies:
  - glyoxalase-I was identified as a protein marker for trait anxiety in mice (Kroemer et al, 2005)- potential biomarker of genetic predisposition to anxiety and depression-like behaviour
  - protein changes following sleep deprivation in mice (Pawlyk et al, 2007; Basheer et al, 2005)
  - repeatedly traumatized rats (during adolescence and adulthood) showed extensive changes in brain proteins (Uys et al, 2008)

# Proteomic analysis of serum in PTSD – pilot study

- **Aim:** to show differential display of proteomic profile in serum of persons with PTSD and healthy controls
- **Methods:** subjects – 3 persons with PTSD and 3 healthy controls – participating in a larger database at the Referral Centre for Stress Related Disorders, University Hospital Dubrava (3 groups of participants- exposed to war trauma with PTSD, exposed to war trauma without PTSD, not exposed to war trauma without PTSD)
- All male - tried to be matched for age, duration and type of traumatic experience, medication, lack of physical illness, substance abuse or psychiatric comorbidities
- Diagnosis (ICD-10)– made by psychiatrist - clinical interview, MINI, CAPS

# Proteomic analysis of serum in PTSD – pilot study

	PTSD			Controls		
Age	42	42	41	37	38	40
PTSD present	YES	YES	YES	NO	NO	NO
CAPS score	47	60	91	n/a	n/a	n/a
Medication	SSRI	SSRI	SSRI	Nil	Nil	Nil

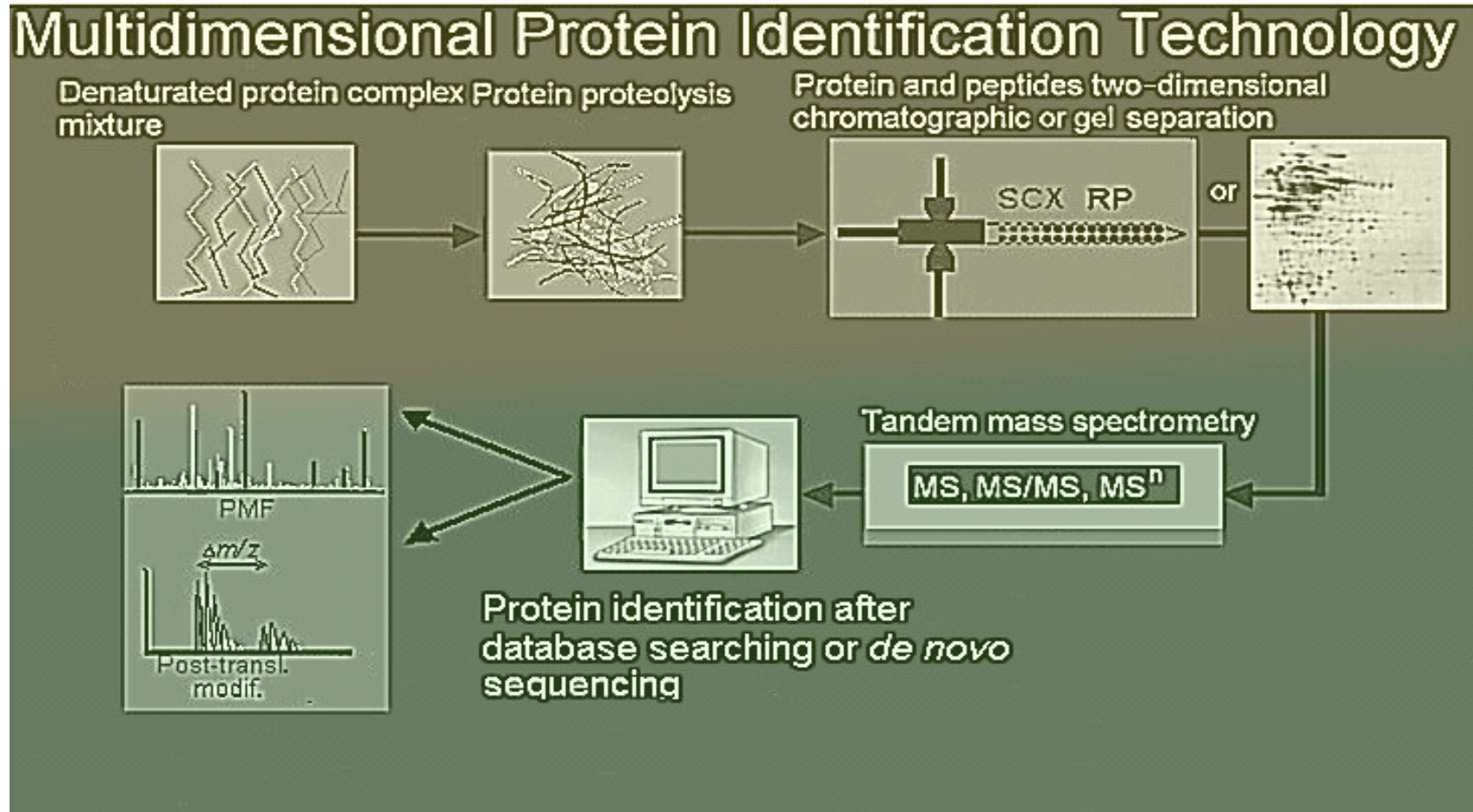
# Proteomic analysis of serum in PTSD – pilot study

## Method: (2D gel electrophoresis and MALDI-TOF MS)

- Serum samples were initially frozen at -80 °C
- After defreezing, serum samples were precipitated in acetone, and after centrifuge dissolved in resolvatation buffer with the addition of the nuclease mixture and protease inhibitors
- 600 µg of sedimented proteins were dissolved in in 0.5 ml of resolvatation buffer and the solution applied to 17cm of the IPG strip with pH area 3-10 NL
- Second dimension of the 2-D gel electrophoresis was made on 12% polyacrylamide gels
- In the initial analysis 2-D gels were stained with the colloid Coomassie stain, then unstained and restained with silver
- Proteomic analysis was done with the use of VersaDoc Imaging Systems 4000 device (Bio-Rad, Hercules, SAD)
- Quantitative and qualitative analysis of the developed gels was made with *PDQuest* 2-D Analysis Software
- Mass spectrometry - MALDI-TOF/TOF analysis, comparison with the protein databases (NCBI, SwissPROT etc.)

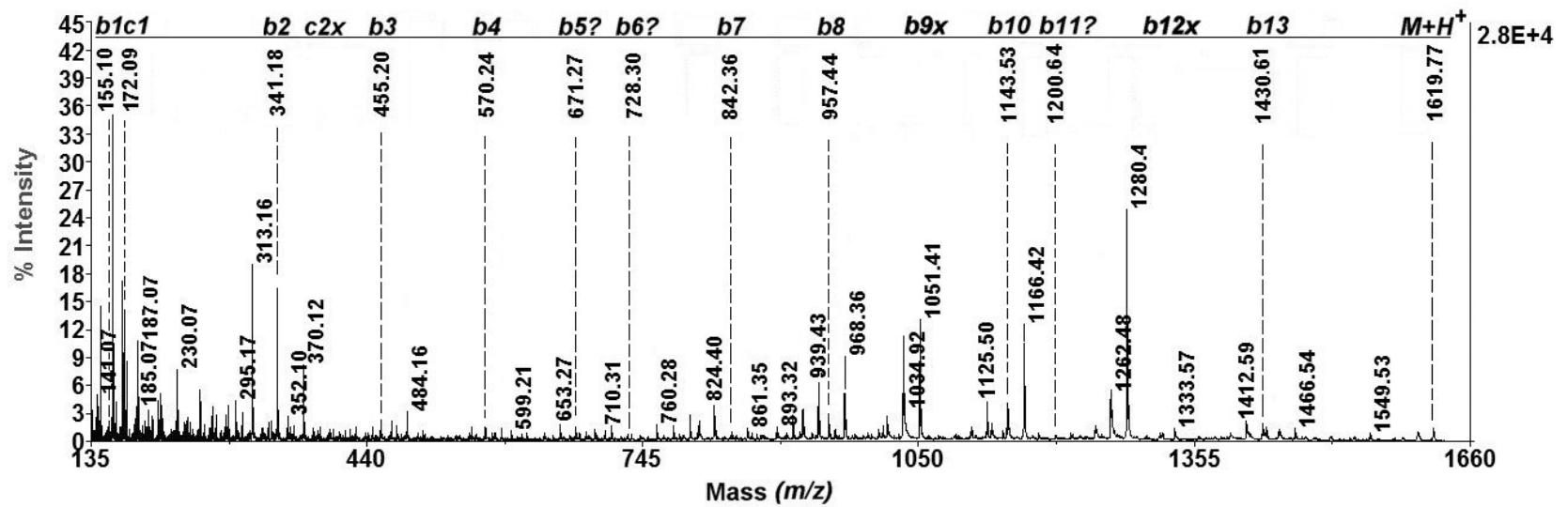


# Proteomic analysis of serum in PTSD – pilot study

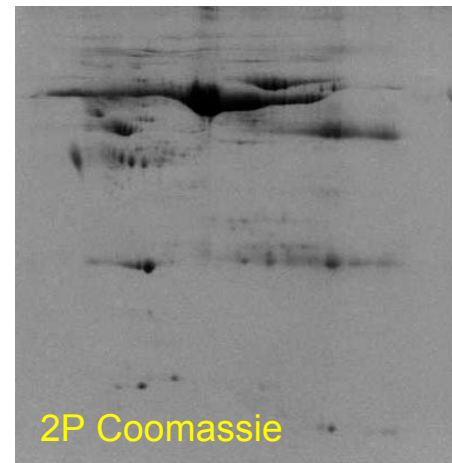
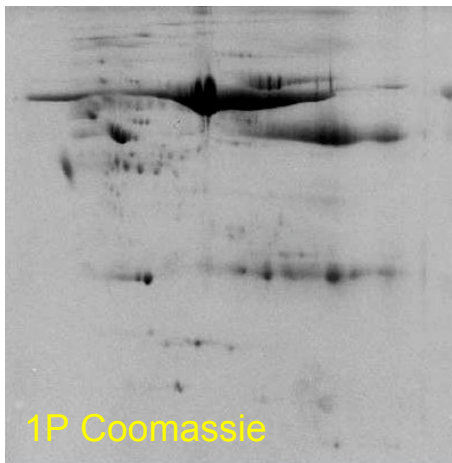
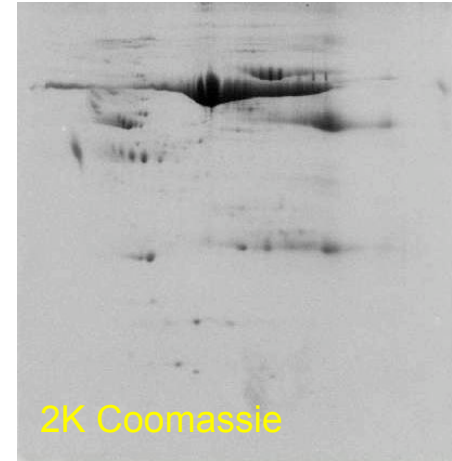
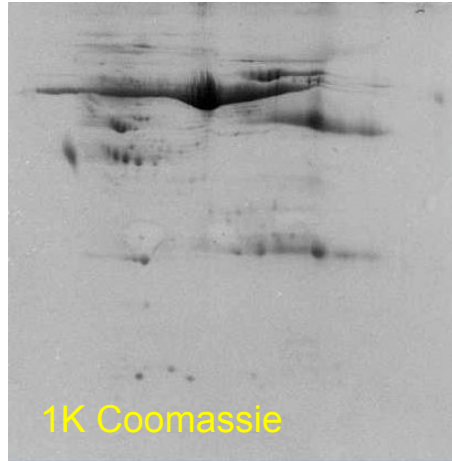




# Proteomic analysis of serum in PTSD – pilot study



# Proteomic analysis of serum in PTSD – pilot study - Results



# Proteomic analysis of serum in PTSD – pilot study



- **Results:**
- There were more than 122 qualitatively and 22 quantitatively differentially expressed proteins
- Further identification of these proteins is currently under way

# Proteomic analysis of serum in PTSD – pilot study - conclusions

- 1st such study in patients with PTSD
- This study was made in order to direct a wider analysis of a larger sample (>50) of subjects with PTSD
- The selected group of proteins found in 2-D gel differential display will be used in further studies for identification of the biomarker(s) through the use of MS technology and protein databases search
- Continuation of this study on a larger number of subjects and linking the results with those from the previous biomarker research in PTSD and other psychiatric disorders, as well as animal models, could lead the way towards development of the specific diagnostic tests in PTSD (based on biomarkers), help in clarification of the disorder's etiology and guide further development of specific pharmacotherapy



# Genes-by-environment interaction and PTSD

Vsevolod A. Rozanov  
Odessa National Mechnikov University  
Human Ecological Health (NGO)  
Odessa, Ukraine













# Odessa Mechnikov University

- ONU is a classical university since 1863 named after Ilya Mechnikov, second Russian Nobel Prize winner (1908) in biology and medicine
- Today has a variety of departments (including Institute of Post-Diploma Education) and more than 15000 students



# Behavioral genetics and genomics

- From main question: What is the differential role of genes and environment in behavior, trait or disorder (nature or nurture) to
- Main question: How genes interact with the environmental stimuli in the individual development and what it means for further life (due to molecular genomics)



# Genes-environment correlation and interaction

- How certain genotypes can influence the way how individuals self-select themselves into certain environments (passive, reactive and active correlation)
- How genotypes can moderate the effects of situations and circumstances (interactive predispositions – J. Tabery,

# Complexity of genetic basis of behavior



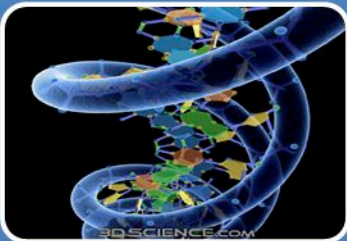
## Phenotype

- Behaviors, traits or disorders



## Endophenotypes

- Thousands of biological mechanisms)



## Genotype

- (about 20000 genes)



# PTSD – a unique situation

- PTSD is unique among other disorders – it requires a potentially traumatic event
- But not all who experienced stressful events develop PTSD
- Why some individuals are more likely than others to develop the disorder in the face of similar levels of trauma exposure?

# To what extent PTSD is based on genes?

- Early family studies – genetic component exists
- Later veterans twin studies – genetic contribution is about 30%
- Civilian twin studies – genetic component within 15%

# Main lessons learnt from early studies

- Genetic factors also influence exposure
- Genetic influences explain a substantial part of the vulnerability
- Genetic influences in PTSD overlap with those for other mental disorders (depression, anxiety disorders, addictions, suicidality)

# What genes are involved?

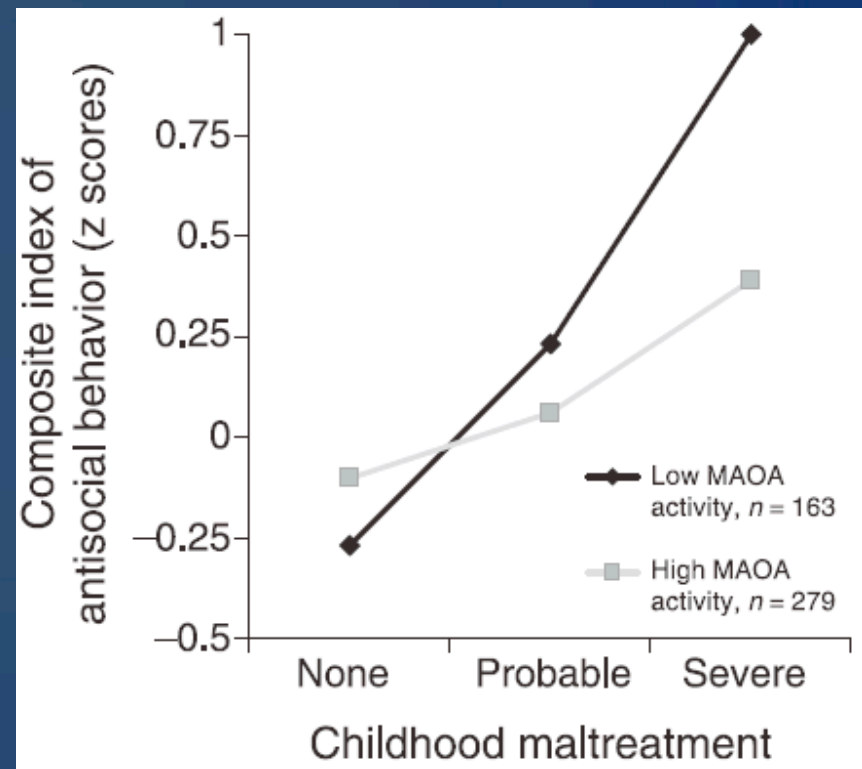
- Association studies – genes of the dopaminergic system of the brain (fear conditioning) – involvement of the D2 dopamine receptor gene (DRD2) and dopamine transporter gene SLC6A3. These results were not replicated.

# What genes are involved (2)?

- Association studies – key candidate genes of the serotonin system (5-HTT), HPA axis, i.e. glucocorticoid receptor (GR), GABA system (GABRB), apolipoprotein system (APOE2), brain-derived neurotrophic factor (BDNF) and neuropeptide Y (NPY). Most of these genes are involved in many disorders, including depression, alcoholism and suicide. Studies have produced not very **convincing results.**

# Important examples of GxE

- Caspi et al. (2000) found that low MAOA activity allele carriers show higher antisocial behavior as teenagers if they were abused in childhood



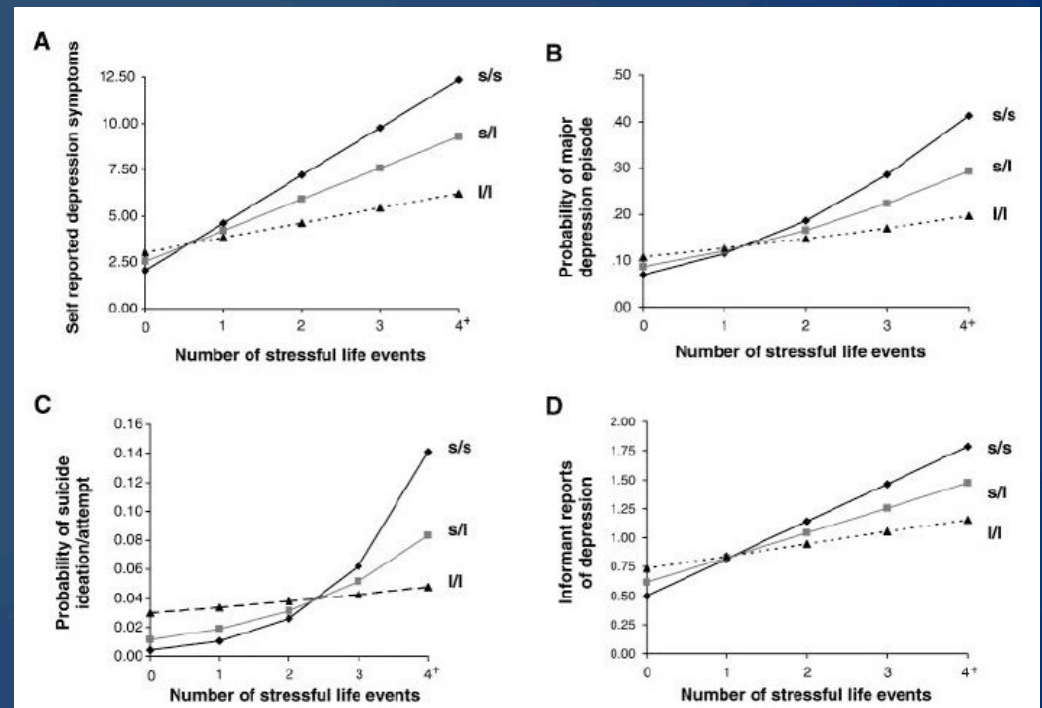


# Important examples of GxE

- Later the same authors (2003) have shown that individuals with one or two short alleles of the 5-HTT serotonin transporter gene (5-HTTLPR) become depressed more often after stressful events in childhood than individuals with two

November 09  
long alleles

"Wounds of War PTSD Seminar" America Holzer  
Hotel



# What is known about GxE in PTSD?

- 5-HTTLPR and stressful life events interact to predict endocrine stress reactivity in a non-clinical sample (N. Alexander et al., 2009)
- Low expression (s) variant of the 5-HTTLPR increased risk of post-hurricane PTSD only under the condition of high hurricane exposure and low social support (D. Kilpatrick et al., 2007)

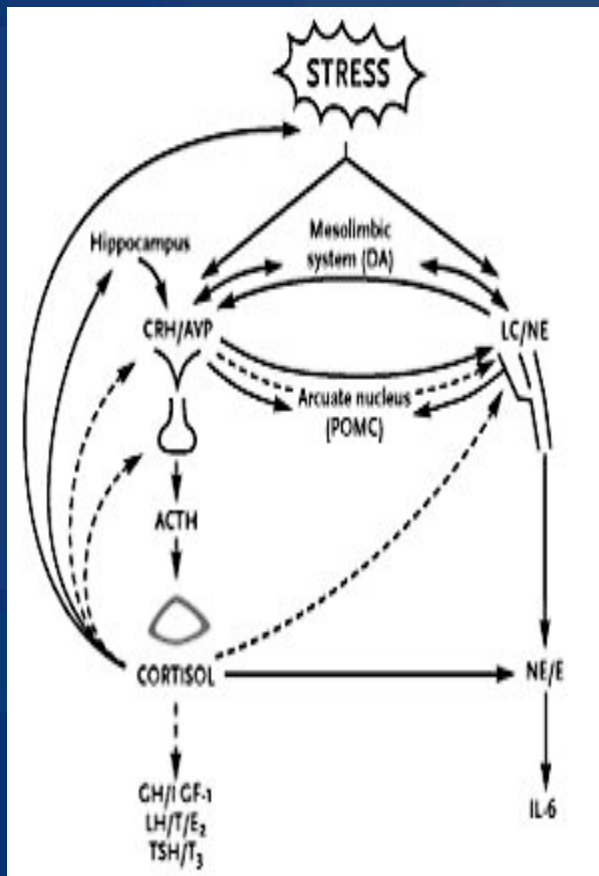
# Most recent results

- An additive gene-environment interaction with the high expression  $L_A$  allele of 5-HTTLPR and frequent trauma in PTSD was found (H.J. Grabe et al., 2009)
- Traumatic event is much more likely to result in PTSD in adults who experienced trauma in childhood and who bear variant of the gene FKBP5 and if trauma involved physical or sexual abuse (E.B. Binder et al., 2008)

# FKBP5 and PTSD

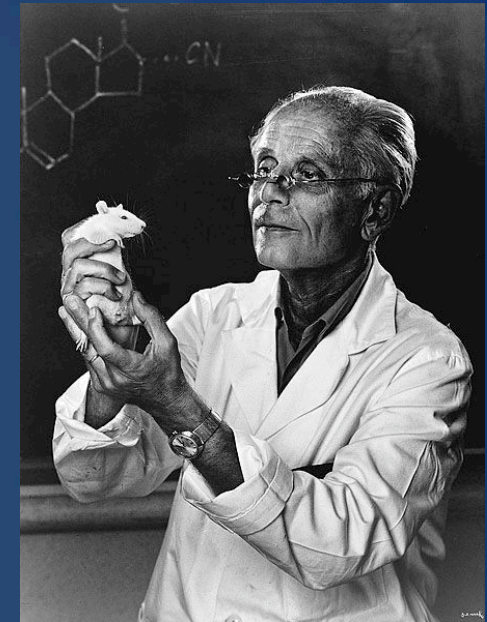
- 765 afro-Americans who addressed for help in a hospital were genotyped
- Combination of early childhood abuse and variant of stress-related gene FKBP5 predicted PTSD if individual is exposed to further stresses
- FKBP5 is a member of immunophilin protein family, which interacts functionally with mature corticoid receptor hetero-

# Stress in modern understanding



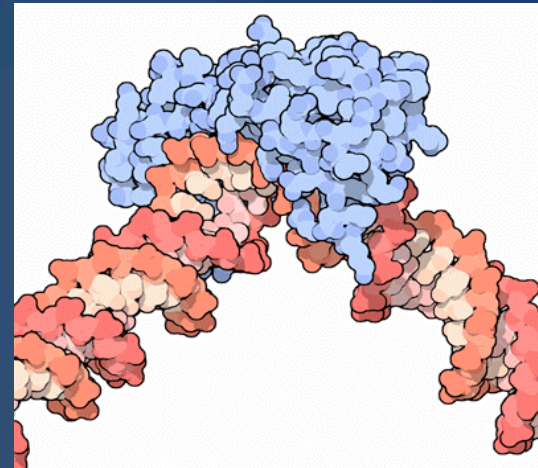
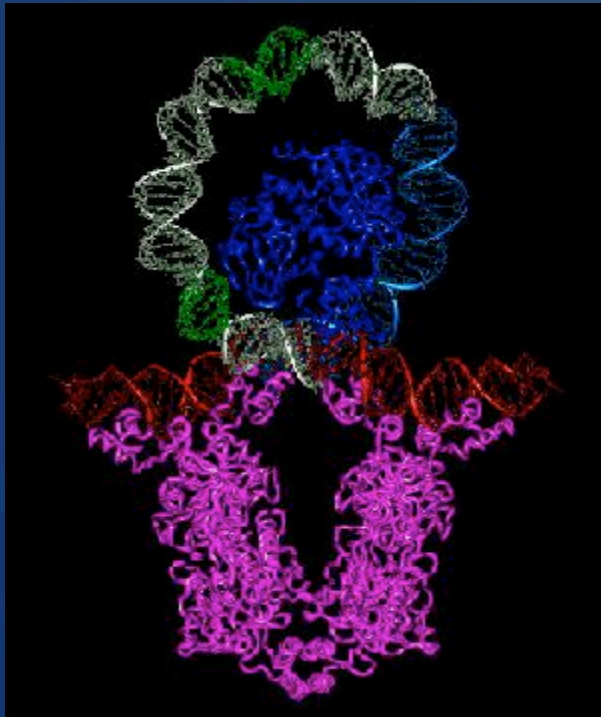
Main actors:  
**CRH**  
**ACTH**  
**Cortisol**

But also many others:  
arginine vasopressin,  
proopiomelanocortin-  
derived alpha-MSH,  
catecholamines,  
thyroid hormones,  
somatotropin, etc.



Recent decade is  
characterized by great  
number of scientific  
publication within the topic  
“stress and genes  
functioning”

# Cortisol-receptor complex as transcription factor





# Stress can have long-lasting effect

- Moderate stresses and normal responsiveness of the stress system gives a sense of well-being while severe stresses may impair growth and development
- Prenatal life, infancy, childhood and adolescence are critical periods characterized by increased vulnerability to stressors

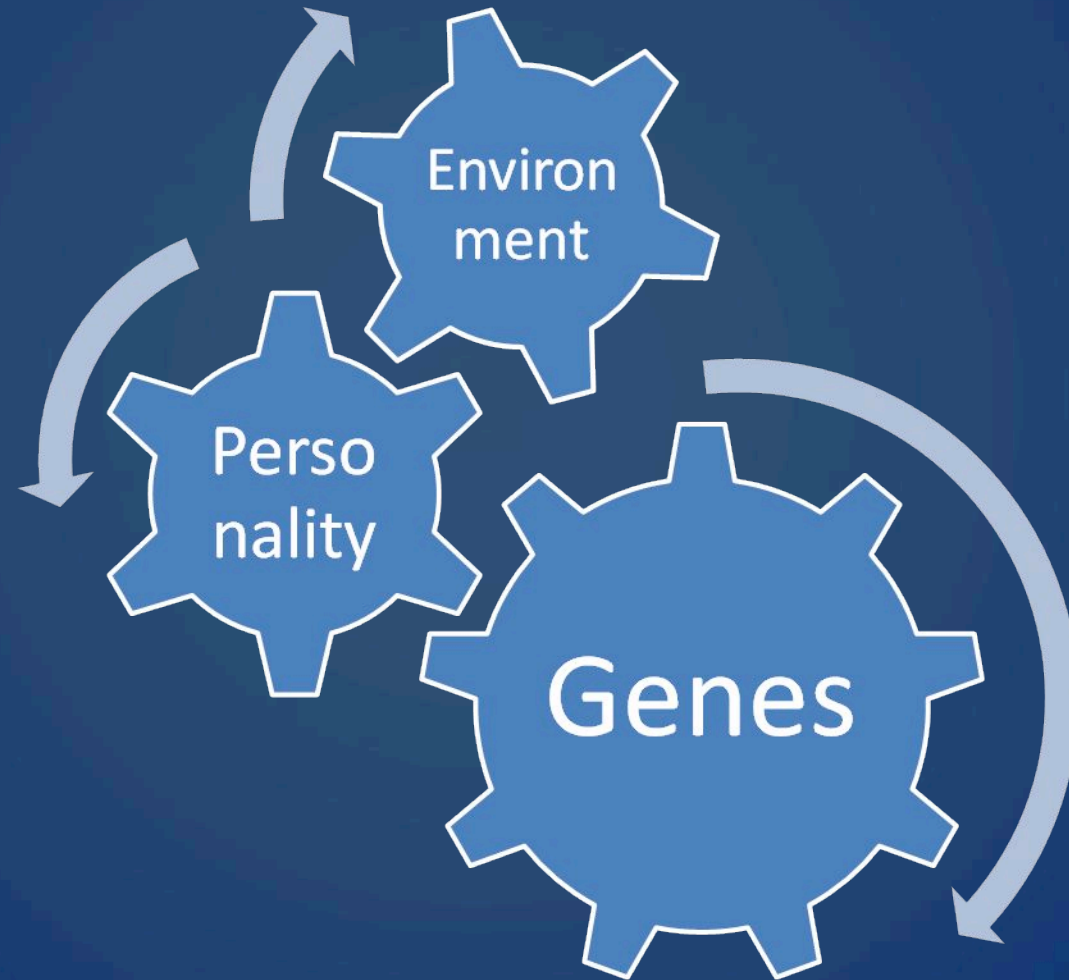
# Early life trauma consequences



# Stress effects throughout life

- Multiple and chronic stress - poor mental health in general
- Prenatal – negative programming effects on hippocampus, frontal cortex, amygdala – anxiety, phobias, cognitive deficits, personality
- Childhood – mainly hippocampus impaired – bad coping skills, poor school performance, self-agression
- Adolescents – frontal cortex – decisions, personality
- Older age – neurogenesis inhibition – secondary cognitive deficits

# How genes interact with stresses?



# Interactions, interactions, etc.

- Personality x PTSD
- Early adversity x PTSD
- Current adversity x PTSD
- Early adversity x current adversity
- Genes x environment
- Culture x genes
- Genes x environment x development, etc.  
(Kendler, 2009)

# Abuse and good parenting differentially affect genes

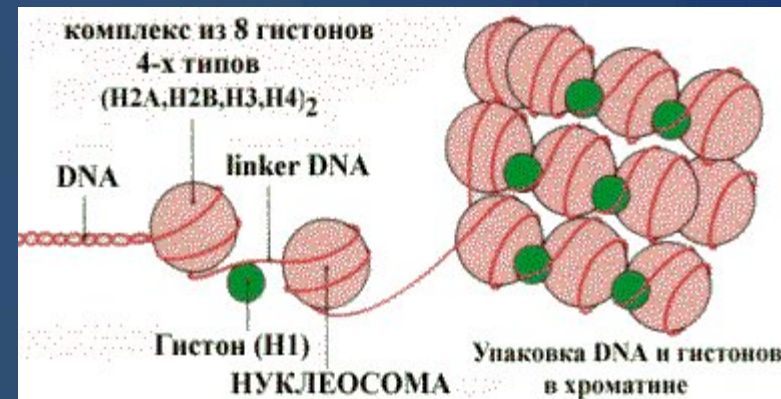
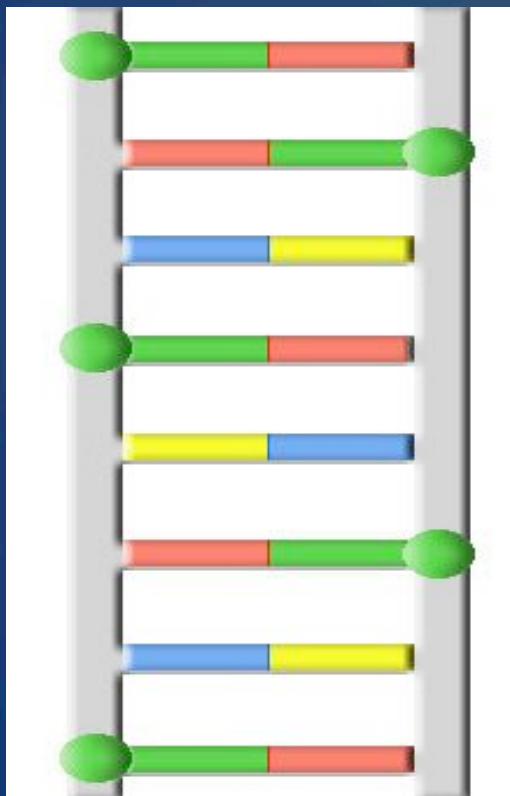
- Maternal care influences HPA function in the rat through epigenetic programming of glucocorticoid receptor expression (M.Meaney et al, 2004).
- Neuron-specific glucocorticoid receptor (*NR3C1*) promoter mRNA was lower in postmortem hippocamps obtained from suicide victims with a history of childhood abuse as compared with suicide victims with no childhood abuse or control (P. McGowan et al., 2009)



# Epigenetics – what it means in PTSD

- Epigenome is an interface between static inherited genome and changing environment (M. Szyf, 2007)
- Even though the genes we inherit from our parents remain with us throughout our lives, epigenetic changes such as DNA methylation can shape their effects on us
- Epigenetic changes can be environmentally triggered and markedly affect development and behaviour (including adult life)

# Cytosine methylation and histones acetylation



# Summing up - more questions

- What are the possibilities for early detection of vulnerability?
  - Combination of early abuse assessment
  - Parental style evaluation and
  - Genotyping
- Are there perspectives for early intervention?
- What about resilience? Genes?

# Resilience

- Recent research has begun to identify the environmental, genetic, epigenetic and neural mechanisms that underlie resilience
- Adaptive changes in neural circuits involving numerous neurotransmitter and molecular pathways.
- Regulate reward, fear, emotion reactivity and social behavior, which together mediate successful coping with stress (A. Feder et al., 2009).

# Instead of conclusion - threats

- Not to fall into naïve genetic determinism (“genes for criminality, genes for PTSD, etc.)
- Not to forget about spirituality (meditation can cause biological effects in the brain)
- Adversities can also be helpful (“altruism born of suffering” and prosocial behavior following adverse life events, J.R.Vollhardt, 2009)

Thank you for your attention !

[rozanov@te.net.ua](mailto:rozanov@te.net.ua)  
[www.humeco.org.ua](http://www.humeco.org.ua)





Christian Paping



Willem-Paul Brinkman (PhD)



Charles van der Mast (PhD)

# An explorative study into a tele-delivered multi-patient virtual reality exposure therapy system

Section Man-Machine Interaction, Delft University of Technology

The Netherlands



*This workshop  
is supported by:*

The NATO Science for Peace  
and Security Programme



# Overview

- Background
- Scenario-based investigation
- Controlled lab experiment
- Conclusion and discussion

# 1.

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*Background*

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# Current situation

*One Patient – One Therapist*

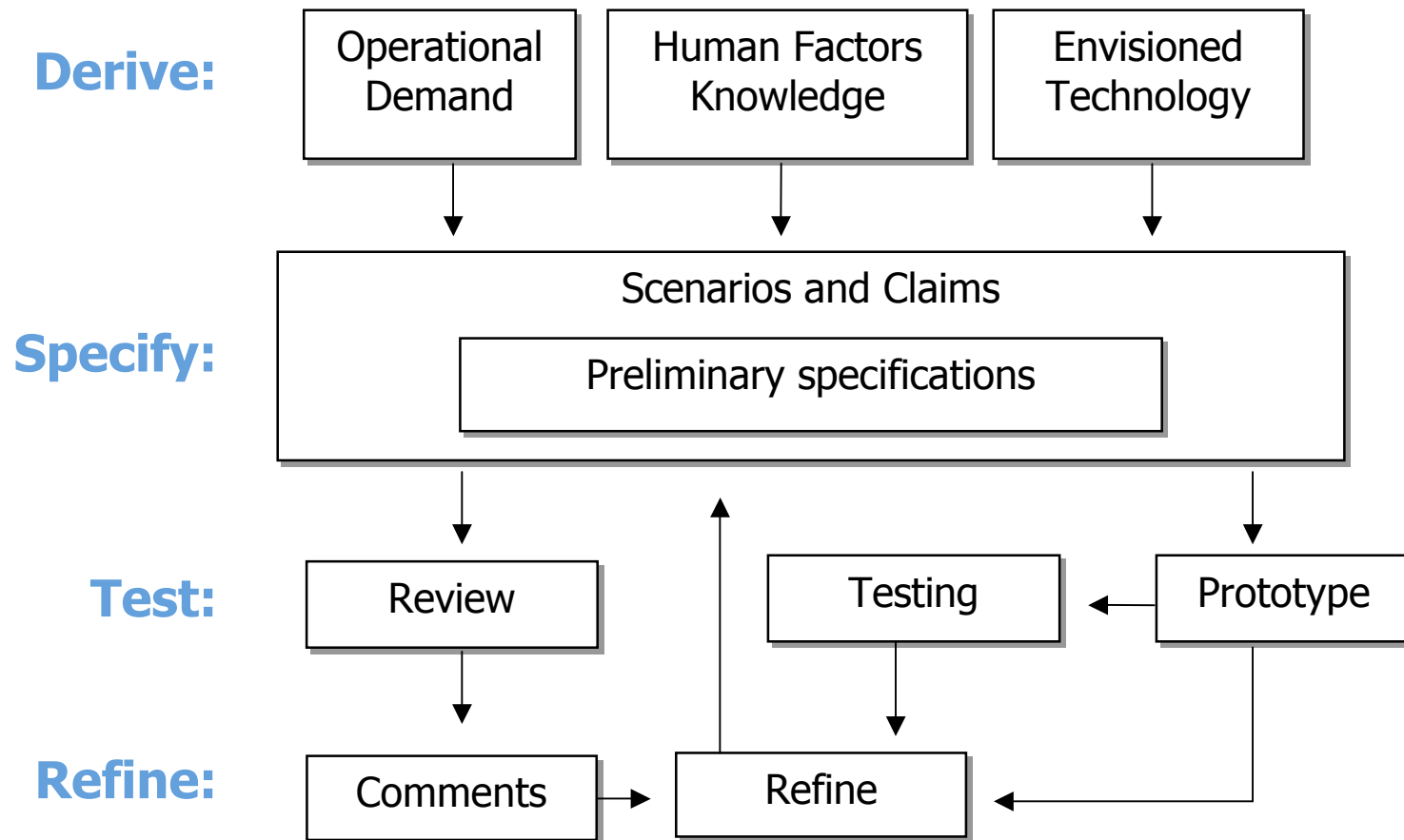
Efficient use of therapist resources?  
Can accessibility be improved?



# Envisioned situation



# Research approach



## *Situated Cognitive Engineering*



# 2.

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## *Scenario-based investigation*

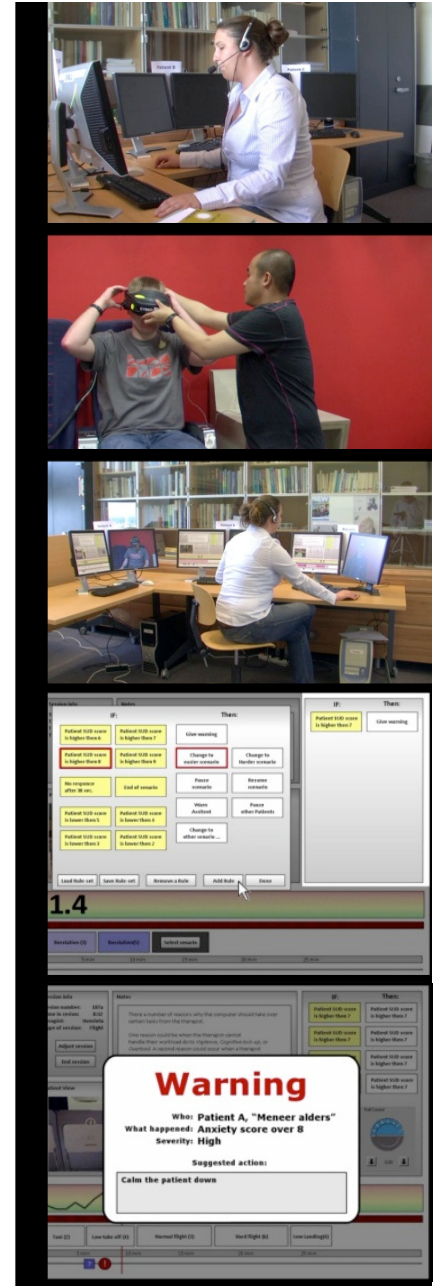
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# Creating Scenario

3 scenarios to examine the following claims

- The possibility of treating a patient remotely
- Treating multiple patients simultaneously
- The possibility of using an automated assistant function

Initial scripts were first reviewed by prof Paul Emmelkamp (clinical psychology at the University of Amsterdam)





# Compilation video



# Method

- 6 Therapists
- Experience with treating patients in VR
- Showing video clip followed by in-depth interview

# Results

- Therapists were positive about
  - Remote-therapy
  - Physiological measurement
- Suggestion to reduce workload by using
  - Pre-programmed exposure scenarios
  - Auto-assist function
- Need possibility to ask for local assistant

# 3.

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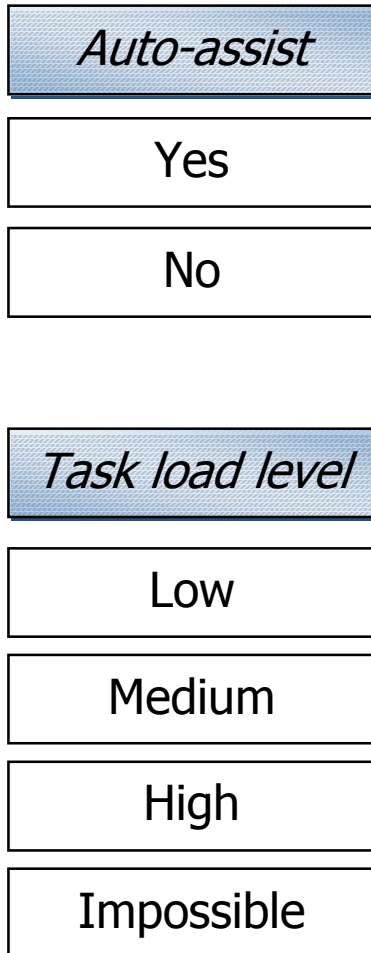
*Controlled lab experiment*

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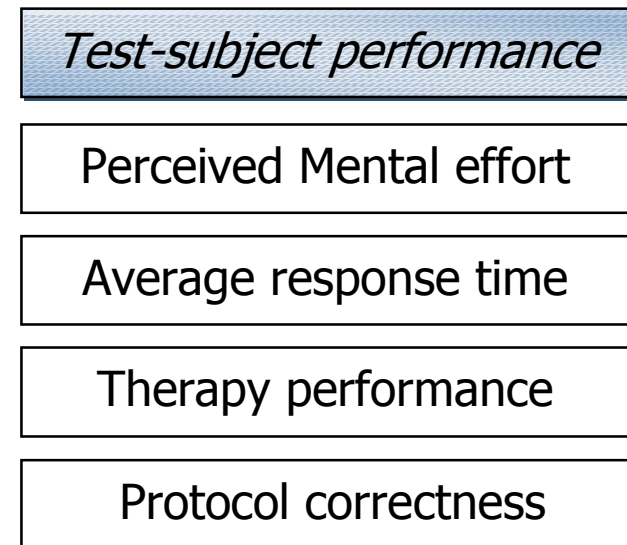


# Experimental Design

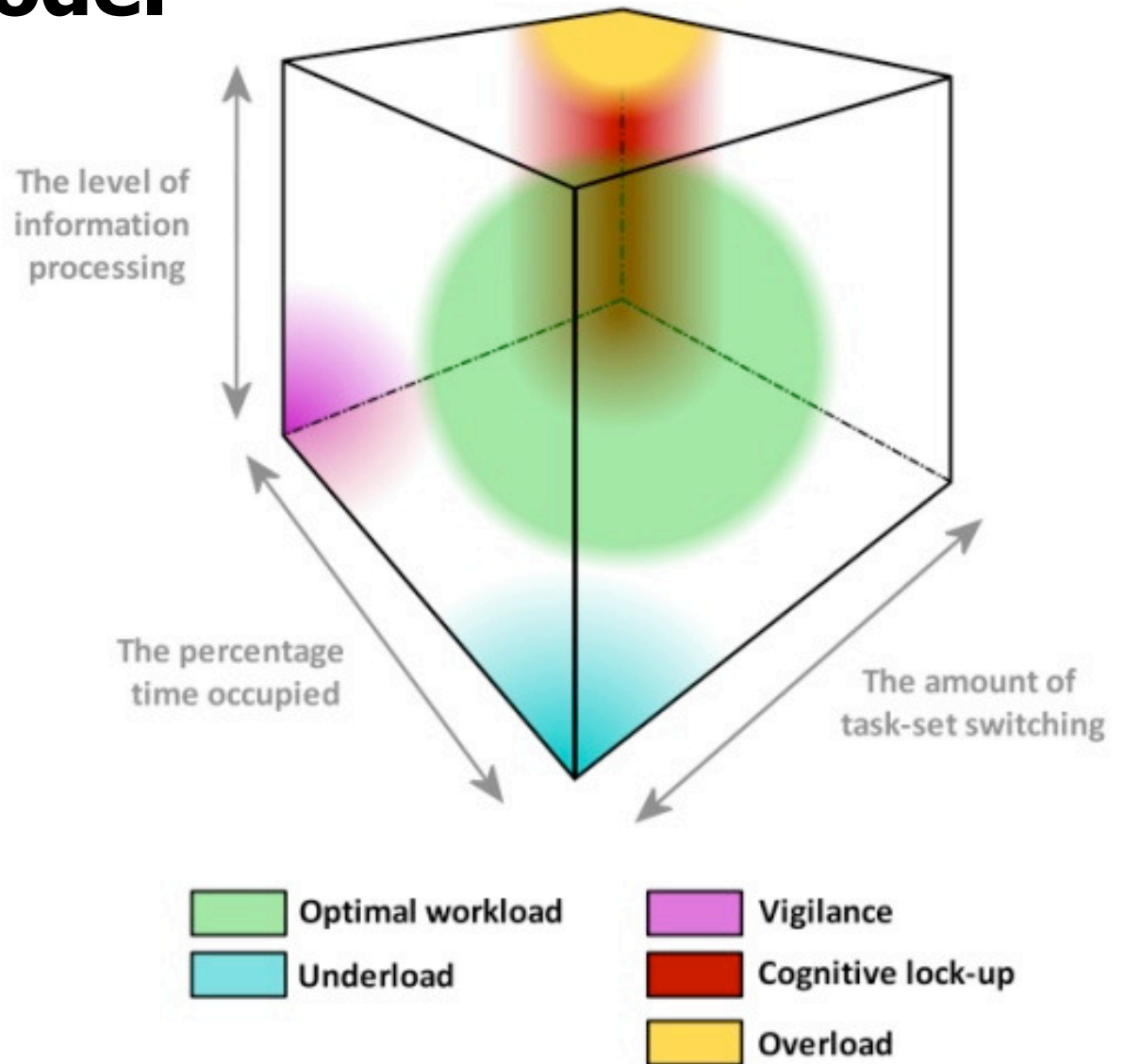
Independent variables:



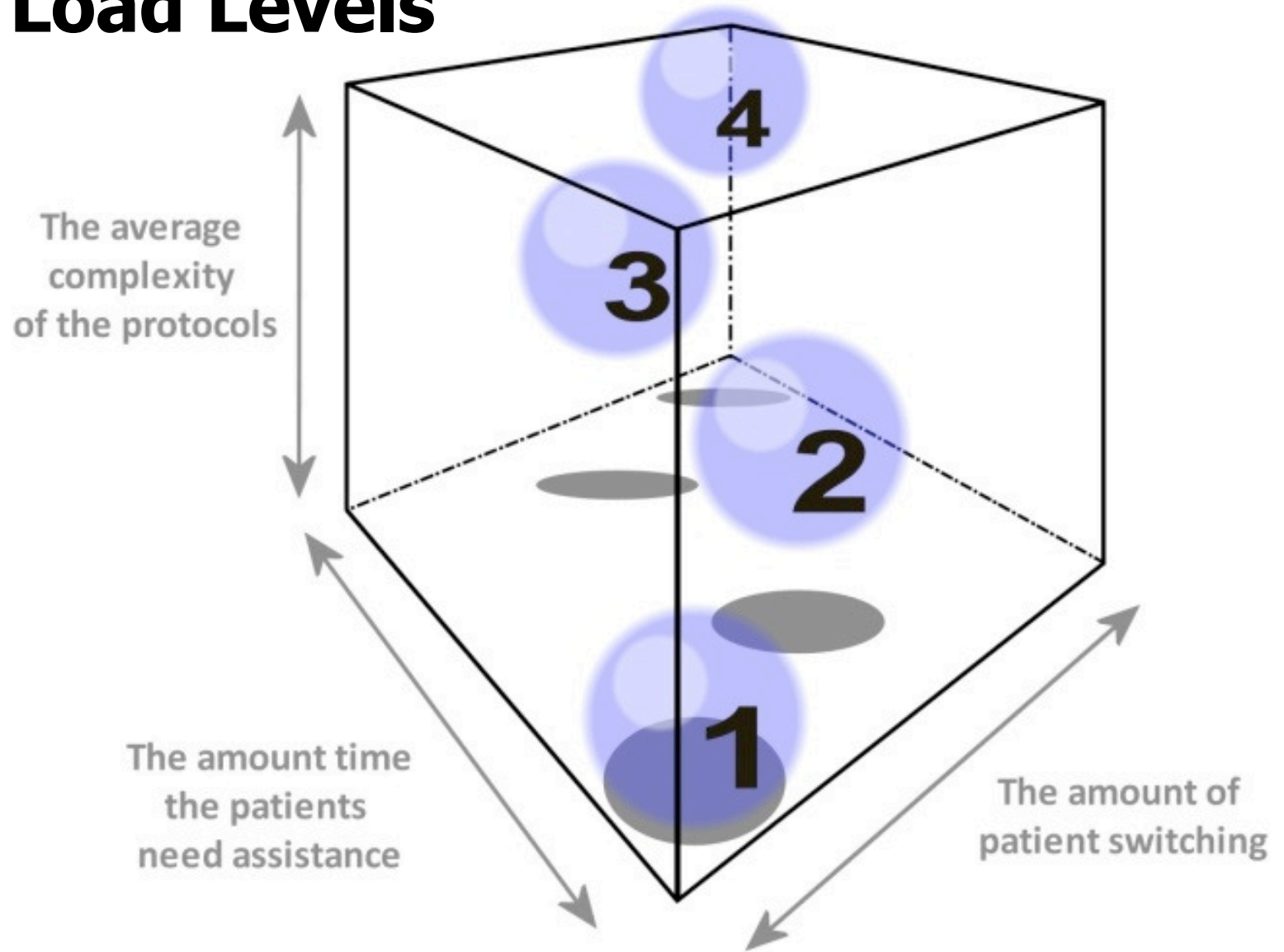
Dependant variables:



# Task Load Model



# Task Load Levels



# Participants & Measures

## Participants

- 27 participants age 21-30 years ( $M = 24$ ,  $SD = 2.7$ )
- Students of Delft University of Technology
- Received written treatment protocol and (simulated) patient information

## Measures

- Rating Scale Mental Effort (RSME)
- NASA-TLX
- Response time to patient request for attention
- Accuracy of protocol execution (protocol correctness)
- Therapy performance (patient's anxiety level within set boundaries)
- Number of times remote assistant was requested

# Therapist Interface

### Session Information

Session Number: 1  
Session Patient: Mr.Aalders  
Therapy Type: Vlieg  
Session Time: 0:01:13  
Session Length: 0:05:00

Waiting for Server

### Log File

Logfile:  
Date: Sun 26 July 2009  
Patient name: None  
Session Number:  
Therapy type: None

### Notes and Flages

"Patient has a question"  
"Patient has no fear"  
"Patient is frightened"  
"Patient has a panic attack"  
"Patient is okay again"  
Add

### VR-Senario Control

Easier scenario  
Harder scenario  
Turbulence  
Thunder  
Redo Take off  
Redo landing

### Patient Control

Attend to patient  
Ask sud score  
Tell the patient we will continue  
Explain scenario  
Explain fear  
Ask if the patient is okay  
Calm patient down

### Alert Control


Stop Assisting Partient  
**Call for Remote Assistance**

### Connection: Connected

Host: 172.20.9.8  
Port: 2000  
Disconnect


### Patient Talk:

### VR View



### Assist Setup


0:01:13



4.5

0:01:00 0:02:00 0:03:00 0:04:00 0:05:00

Add VR-Senario



# Auto Assist Function

The screenshot shows a rule configuration window with two columns: 'IF:' and 'Then:'. The 'IF:' column contains several conditions, with 'Patient SUD score is higher then 8' highlighted in red. The 'Then:' column contains several actions, with 'Change to easier scenario' highlighted in red. At the bottom, there are buttons for 'Load Rule-set', 'Save Rule-set', 'Remove a Rule', 'Add Rule', and 'Done'.

IF:		Then:	
Patient SUD score is higher then 6	Patient SUD score is higher then 7	Give warning	
<b>Patient SUD score is higher then 8</b>	Patient SUD score is higher then 9	<b>Change to easier scenario</b>	Change to Harder scenario
No response after 30 sec.	End of senario	Pauze scenario	Resume scenario
Patient SUD score is lower then 5	Patient SUD score is lower then 4	Warn Assitent	Pauze other Patients
Patient SUD score is lower then 3	Patient SUD score is lower then 2	Change to other senario ...	

The warning dialog box is titled 'Warning' and contains the following text: 'Who: Patient A - Mr.Aalders', 'What happend: Anxiety score high threshold', and 'Auto Assit will take over in 12 seconds'. A 'Cancel Auto Assist' button is located at the bottom of the dialog. The background shows a simulation interface with a large '5.6' on a graph and various control buttons.

**Warning**

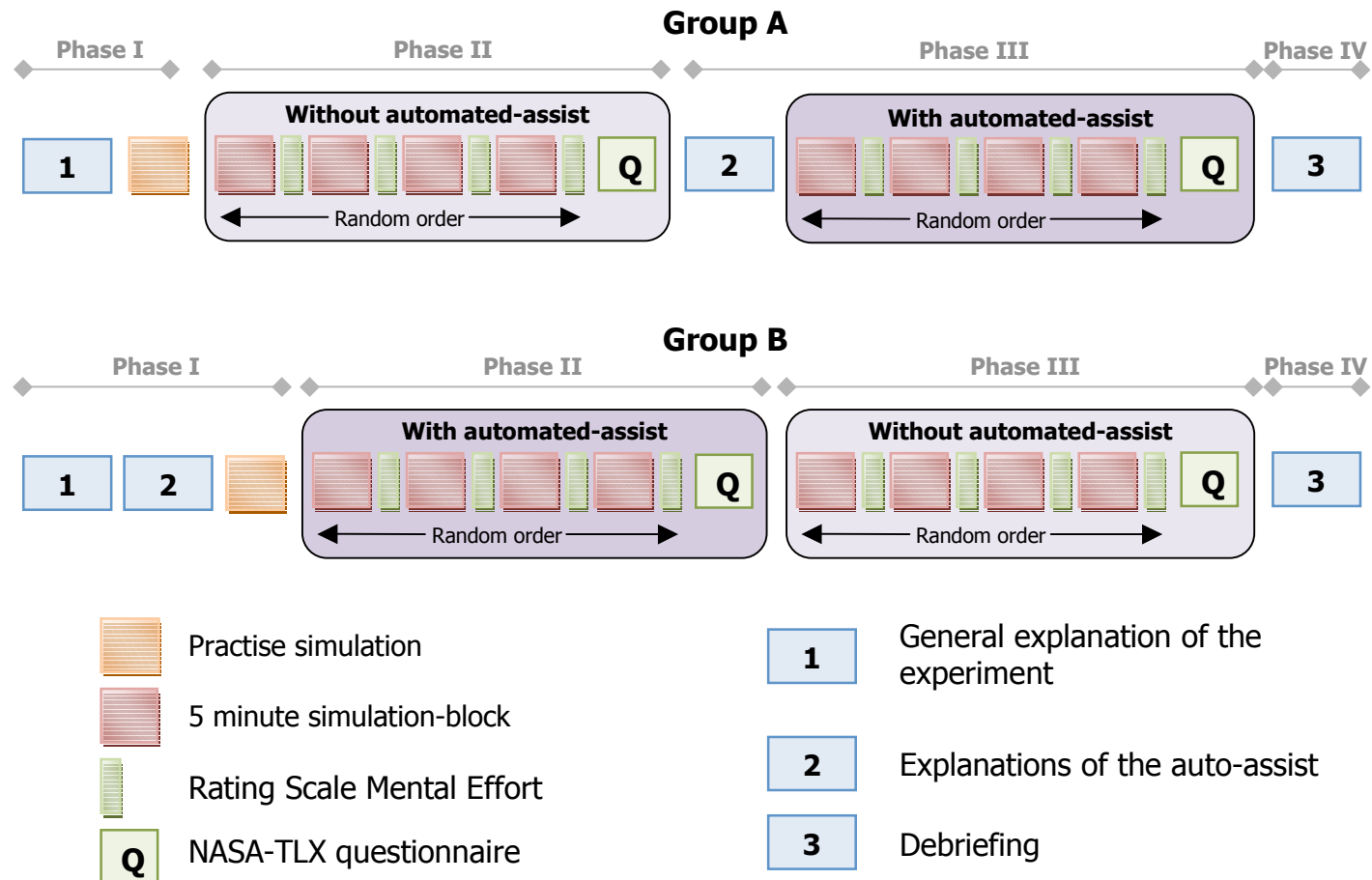
**Who: Patient A - Mr.Aalders**

**What happend: Anxiety score high threshold**

**Auto Assit will take over in 12 seconds**

Cancel Auto Assist

# Procedure

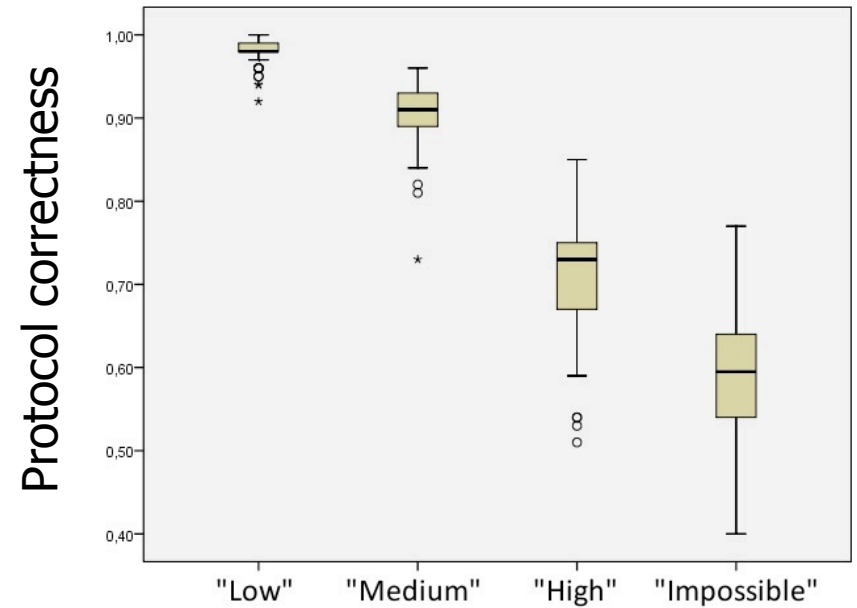
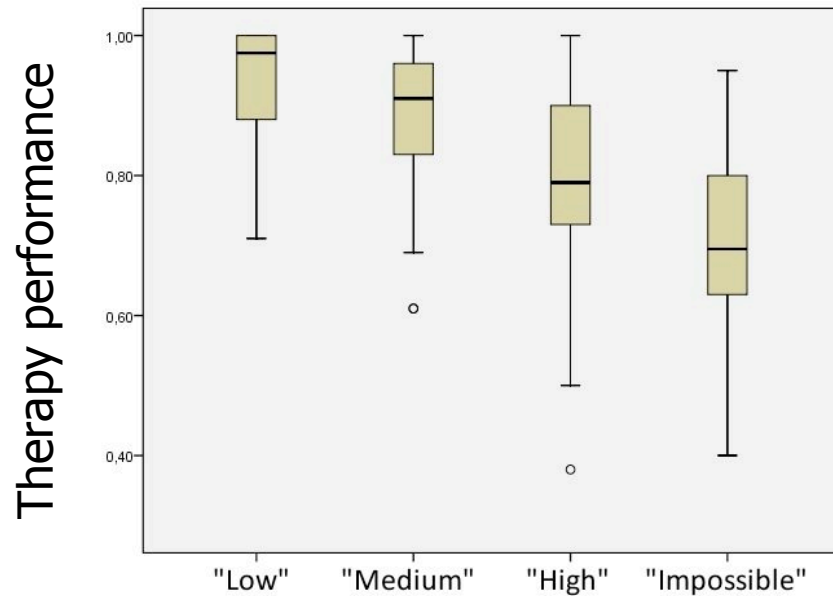
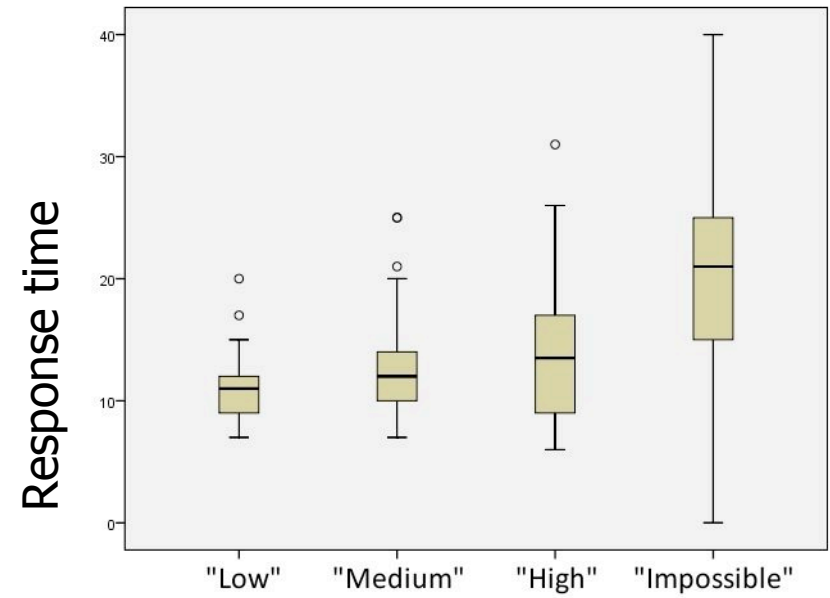
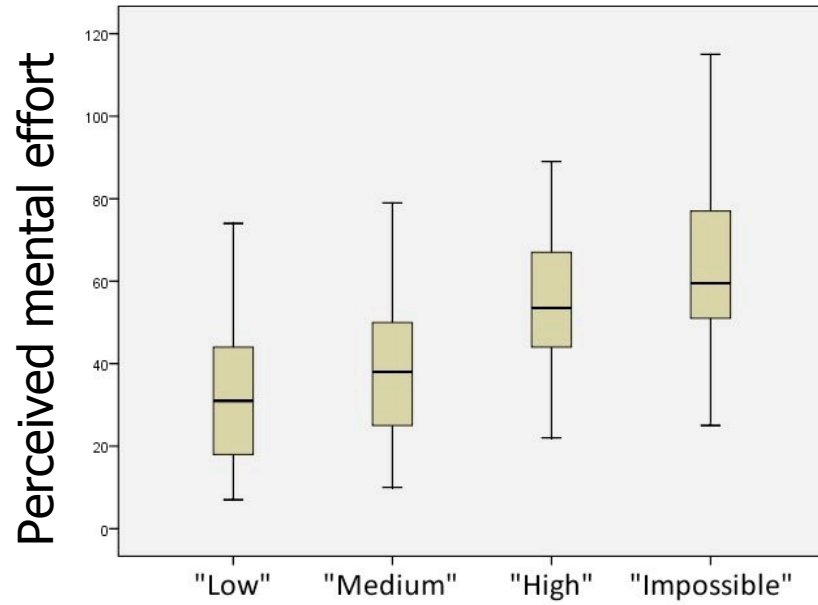




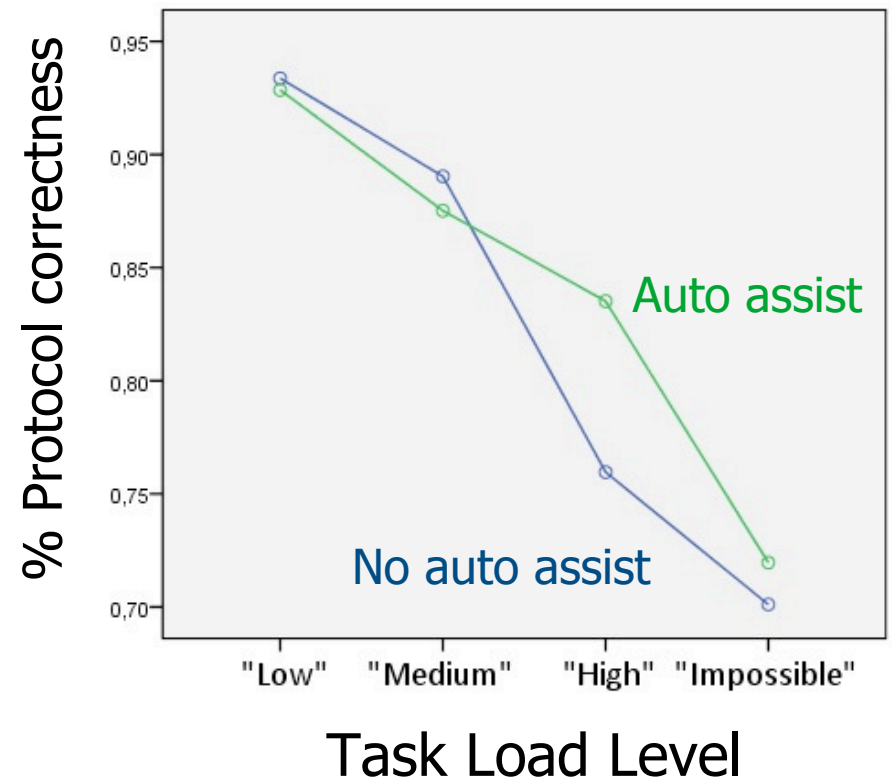
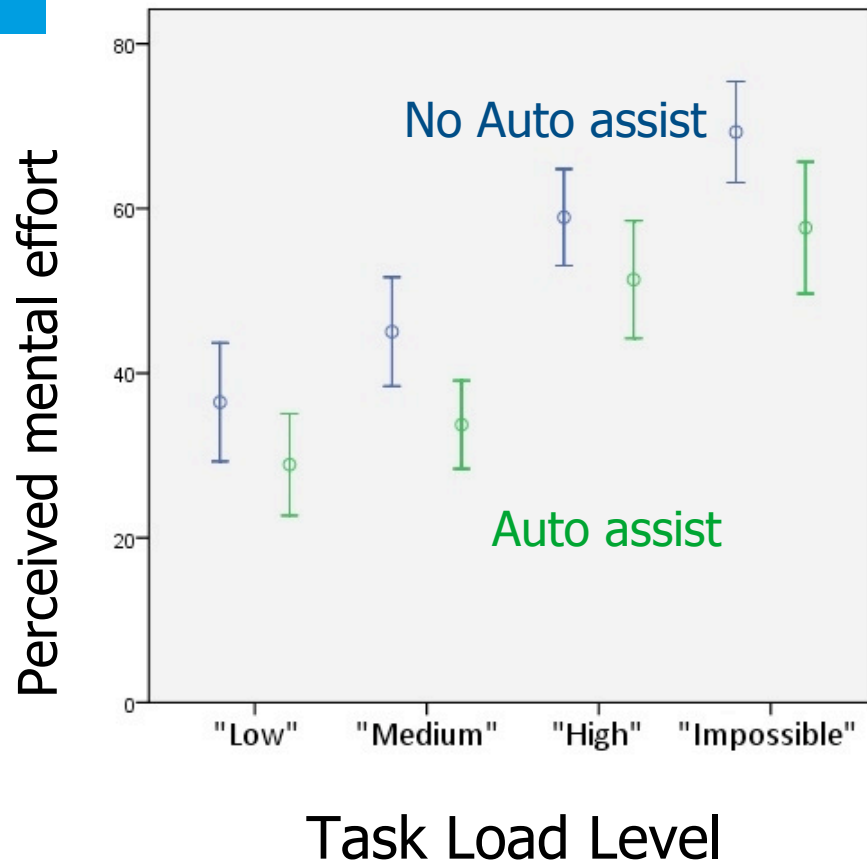
# Set up

*Video clip*

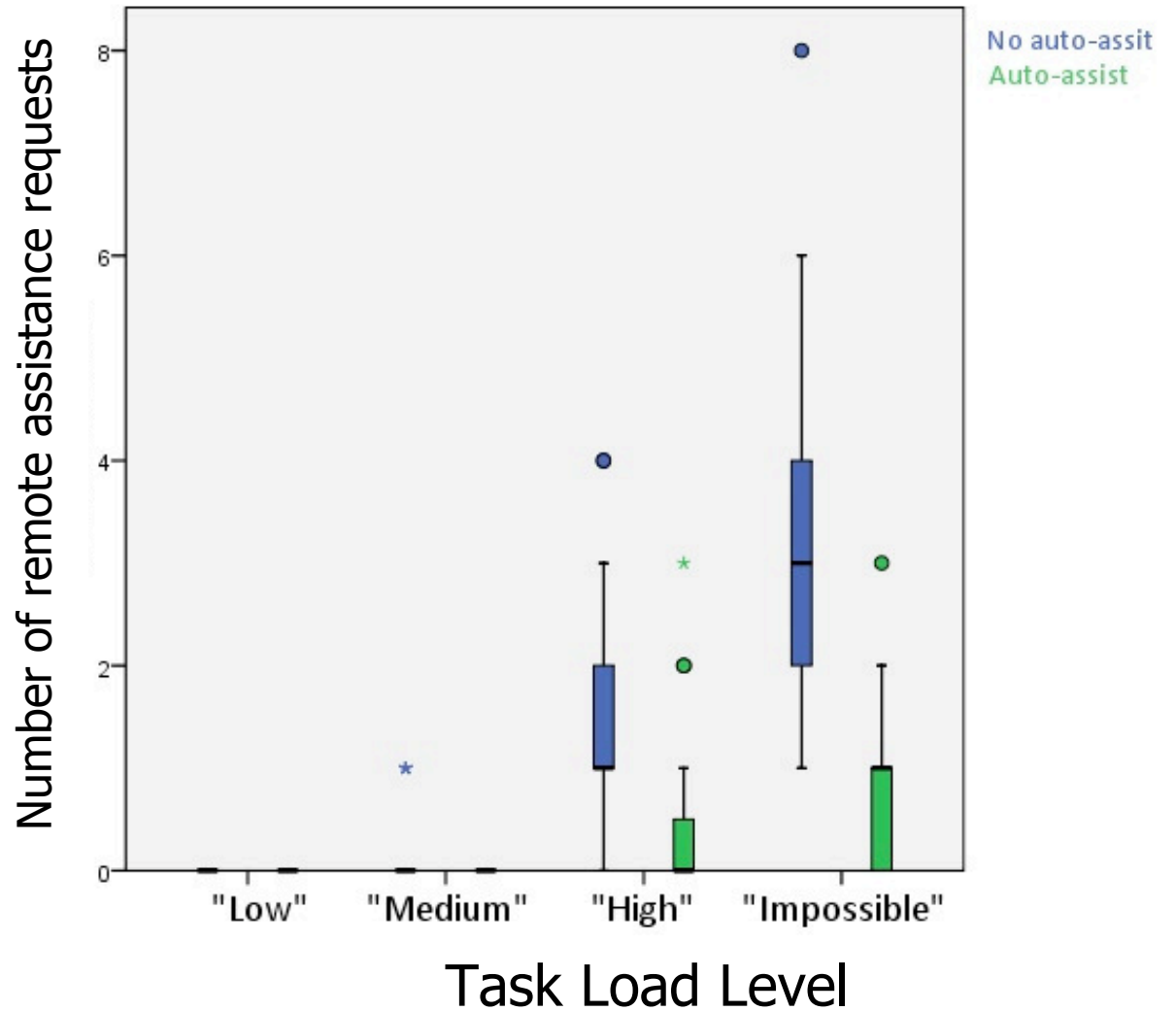




# Auto Assist Function



# Remote Assistance



# 4.

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## *Conclusion and Discussion*

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# Main Conclusion

1. Experienced VR therapists were open to the idea of a remote multi-patient VRET system
2. Therapist workload can significantly affect
  1. Perceived mental effort
  2. Response time
  3. Therapy performance
  4. Protocol correctness
3. Auto assist function can
  1. Reduce mental work effort
  2. Increase protocol correctness in high task load conditions
4. No indication of Cognitive lock-up situations



# Discussion and future work

1. Need to repeat experiment with real therapists
2. What is the effect of varying the number of remote patients?
3. What is the patient's view on this set up?
4. How effective is this treatment?



**Thank you for your attention!**

**Any questions?**

**<http://mmi.tudelft.nl/vret>**

