The DSM 5 revolution of anxiety disorder- conceptual background and practical implications

Prof. Joseph Zohar

Tel-Aviv University
Israel

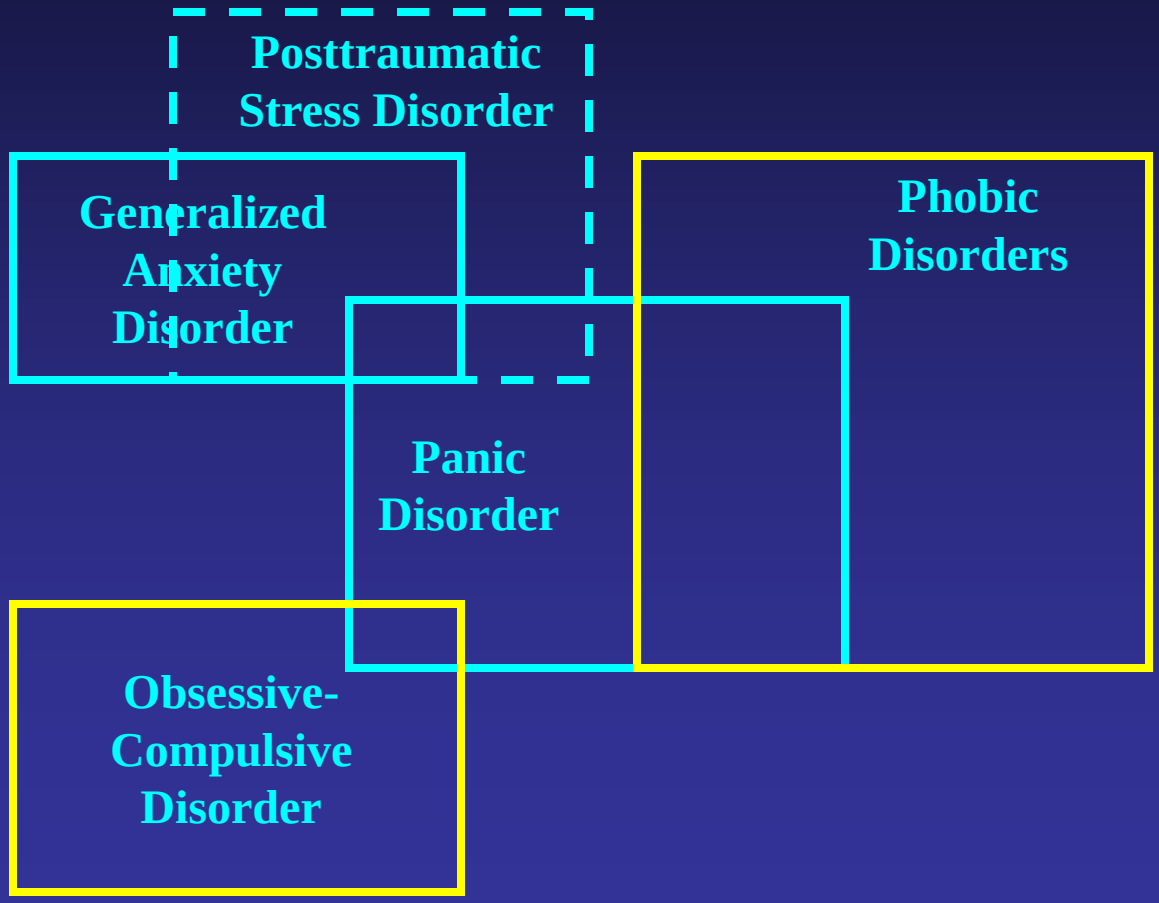
Classification

- Over the past 30 years the diagnosis has been focused on clinically based syndromes.

- Disorders were defined as syndromes, i.e symptoms that have been observed to co-vary together in individuals

DSM-IV – Descriptive approach

DSM IV Classification of Anxiety Disorders



The problem

- The phenotype might be misleading

- Syndromes appearing

  clinically similar

  may result from

  distinct etiology.

- e.g. diabetes mellitus.

diabetes mellitus♦

- ♦destruction of islet cells

versus

- ♦ insulin resistance

A different approach is to look beyond the symptoms

- To try to provide a better match between research in

  neuroscience

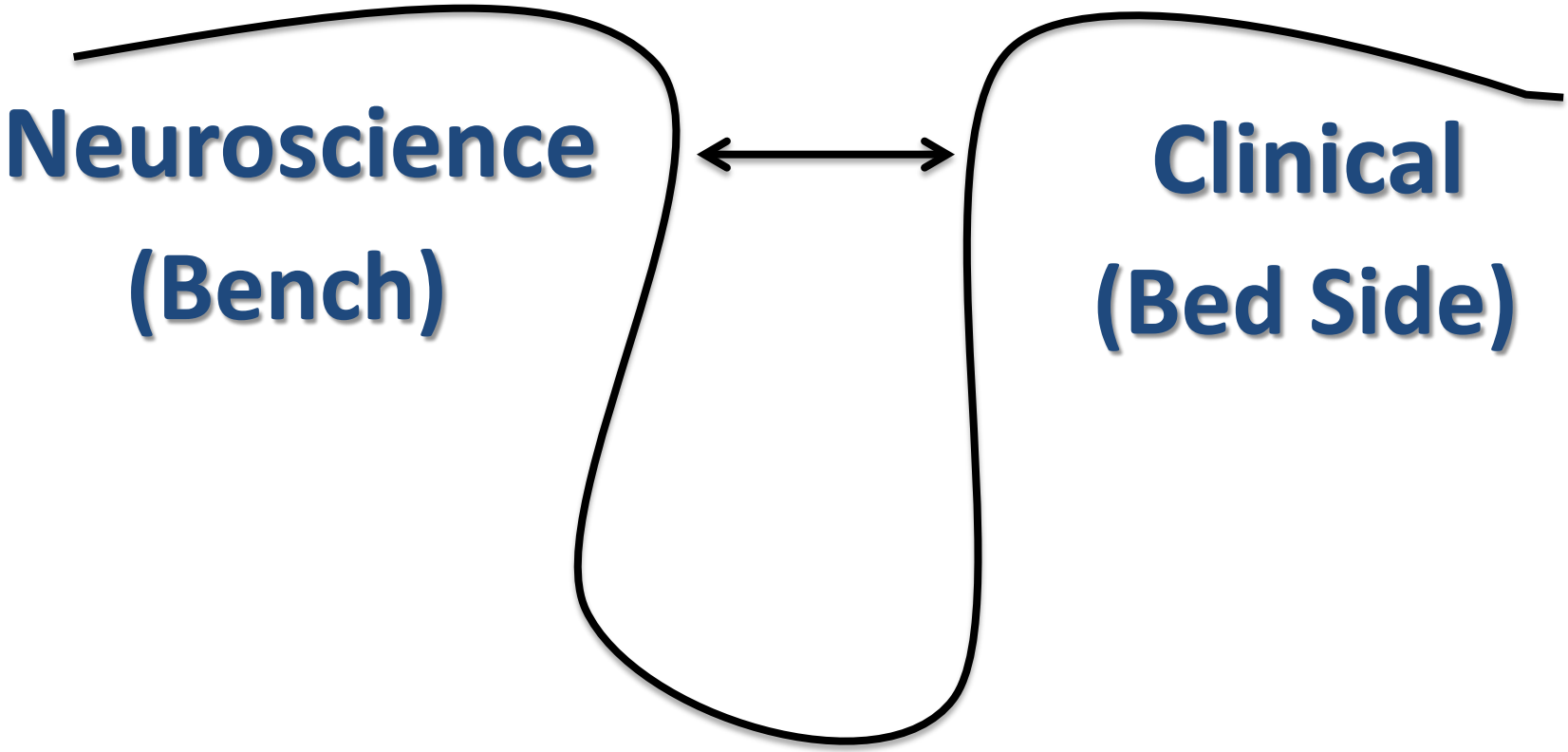
and

  classification

DSM IV → 5

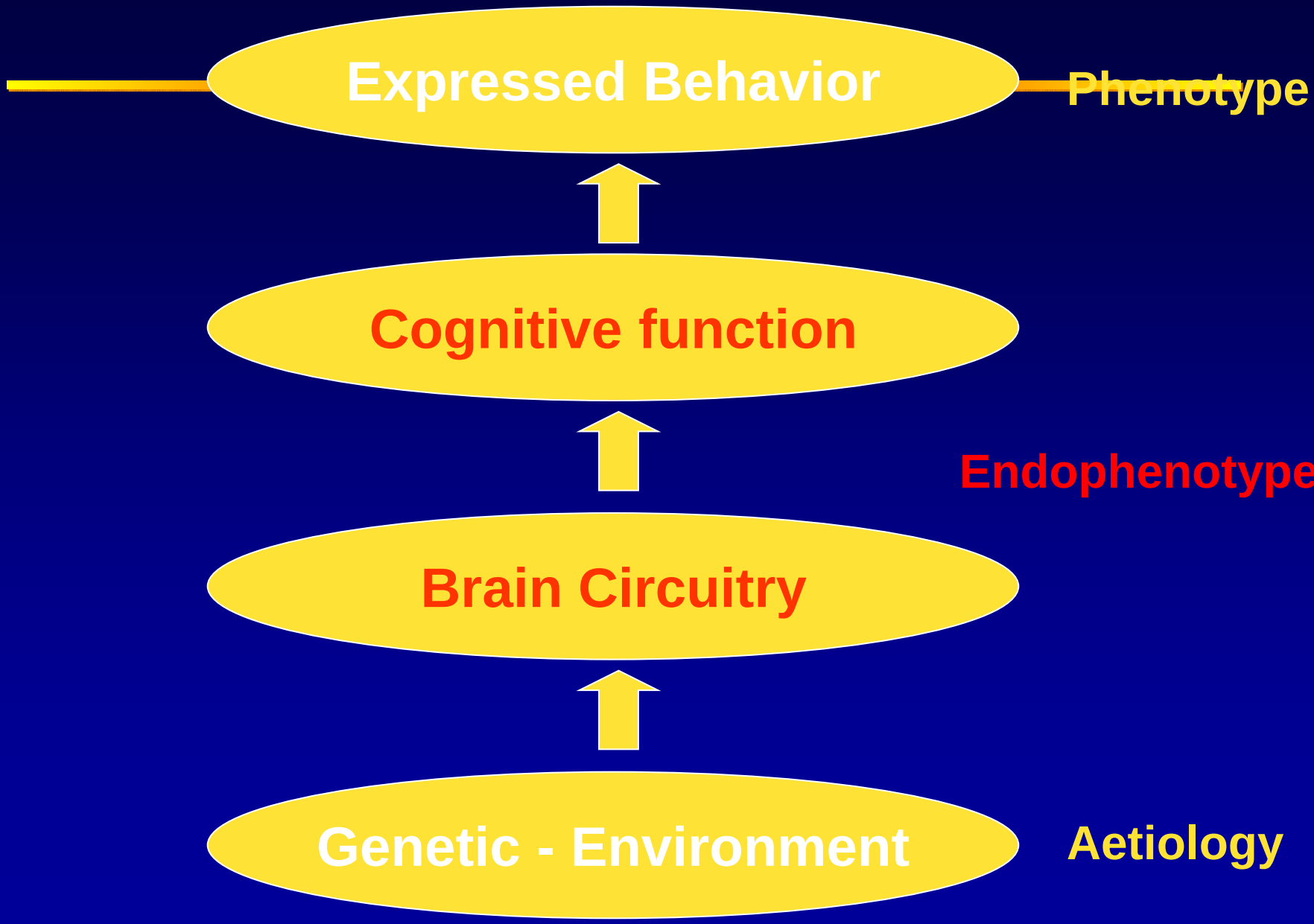
- Descriptive
- Syndromes
- Biomarkers
- Dimensional
- Developmental

Two ways Bridge



Endophenotypical

Approach


Expressed Behavior
Phenotype
Cognitive function
Endophenotype
Brain Circuitry
Genetic - Environment
Aetiology

Endophenotypical

Approach

Diagnosis in Psychiatry:

Can an

Endophenotypical

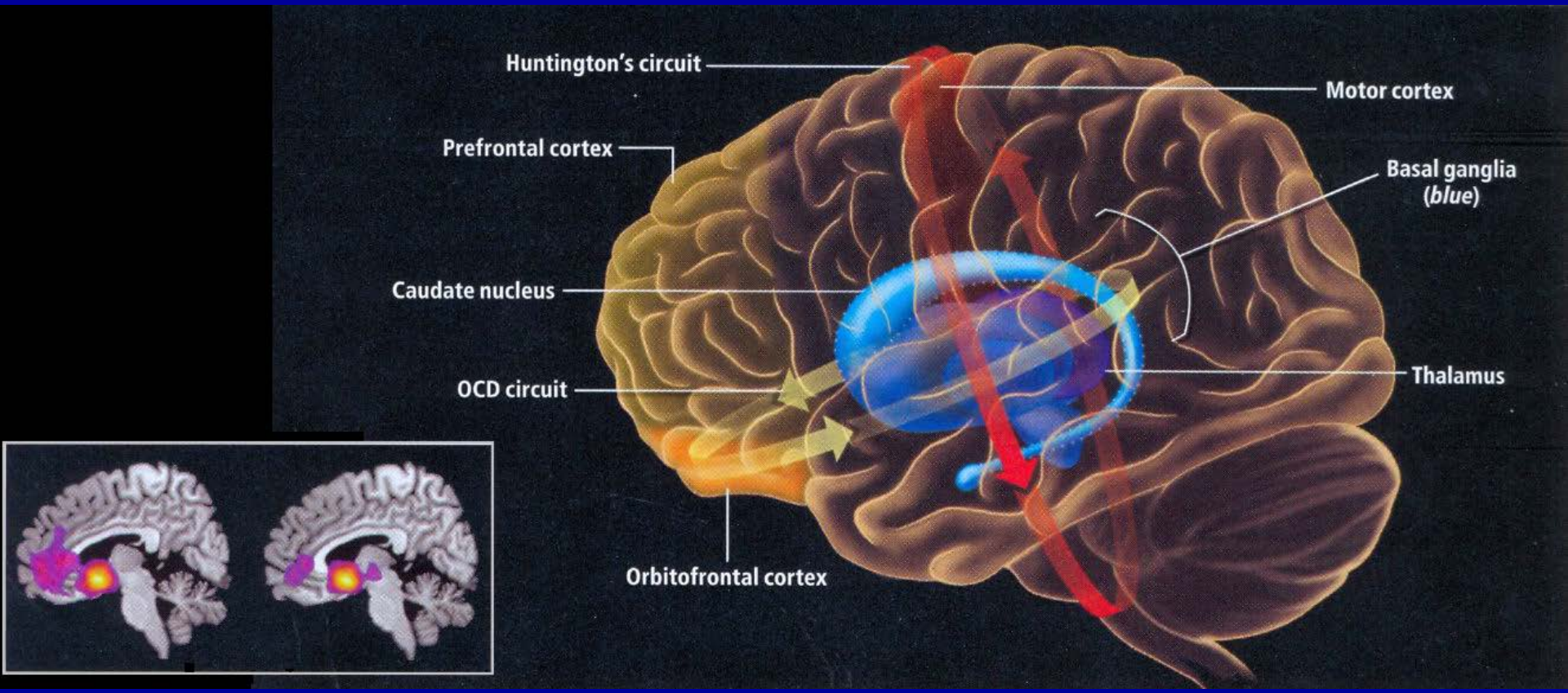
Approach Help?

Bio-signatures

Anxiety

- Integration of validators derived from neuro-science advances.

- Genetics
- Neuroimaging
- Cognitive Science
- Pathophysiology


Huntington's circuit
Motor cortex
Prefrontal cortex
Basal ganglia
(blue)
Caudate nucleus
Thalamus
OCD circuit
Orbitofrontal cortex

Brain Circuitry

OCD has:

a. Specific brain circuitry:

Prefrontal cortex - temporal cortex - thalamus - basal ganglia

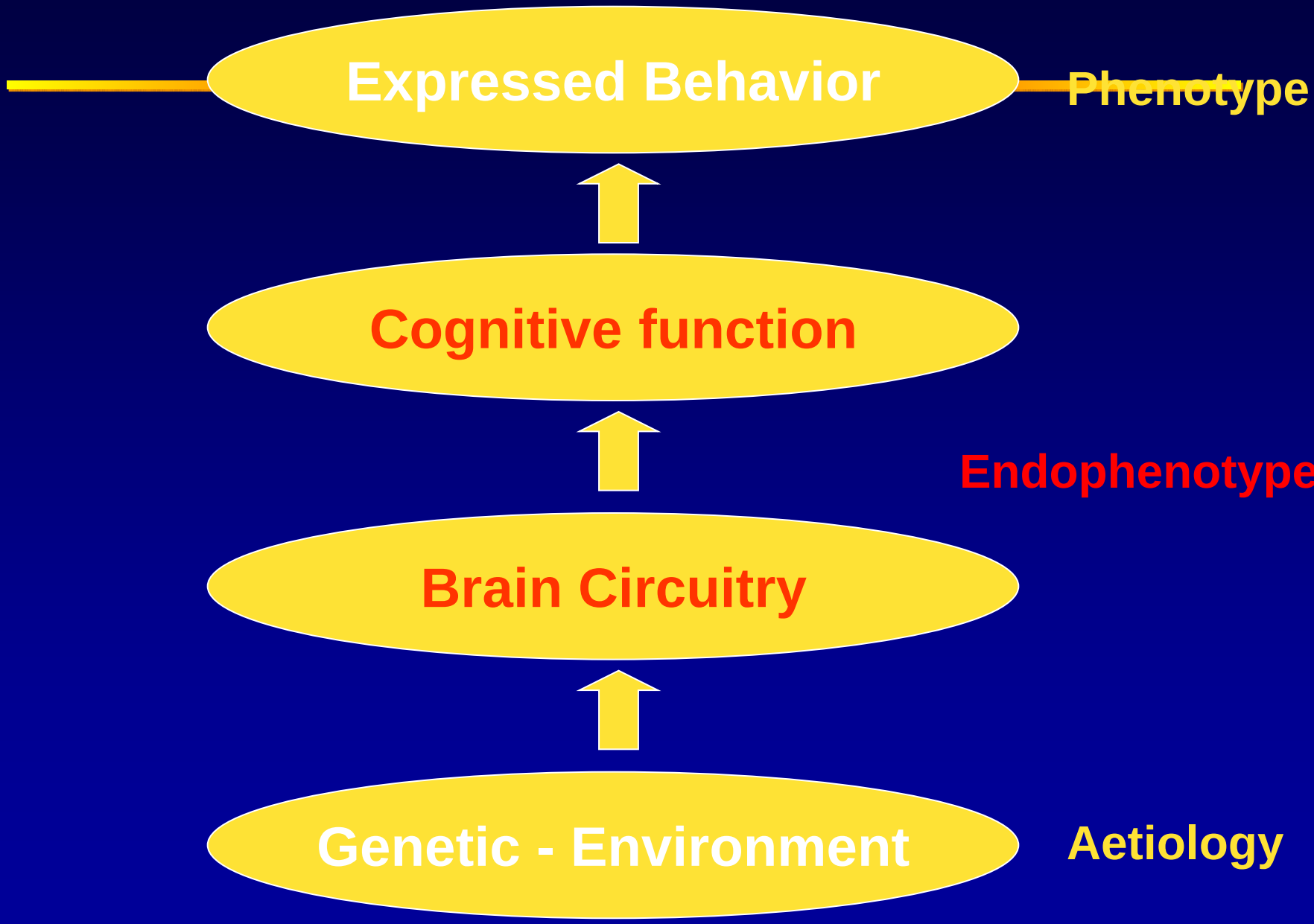
Is OCD part of Anxiety disorder ?

- Cortical- Basal circuit abnormalities in OCD

vs.

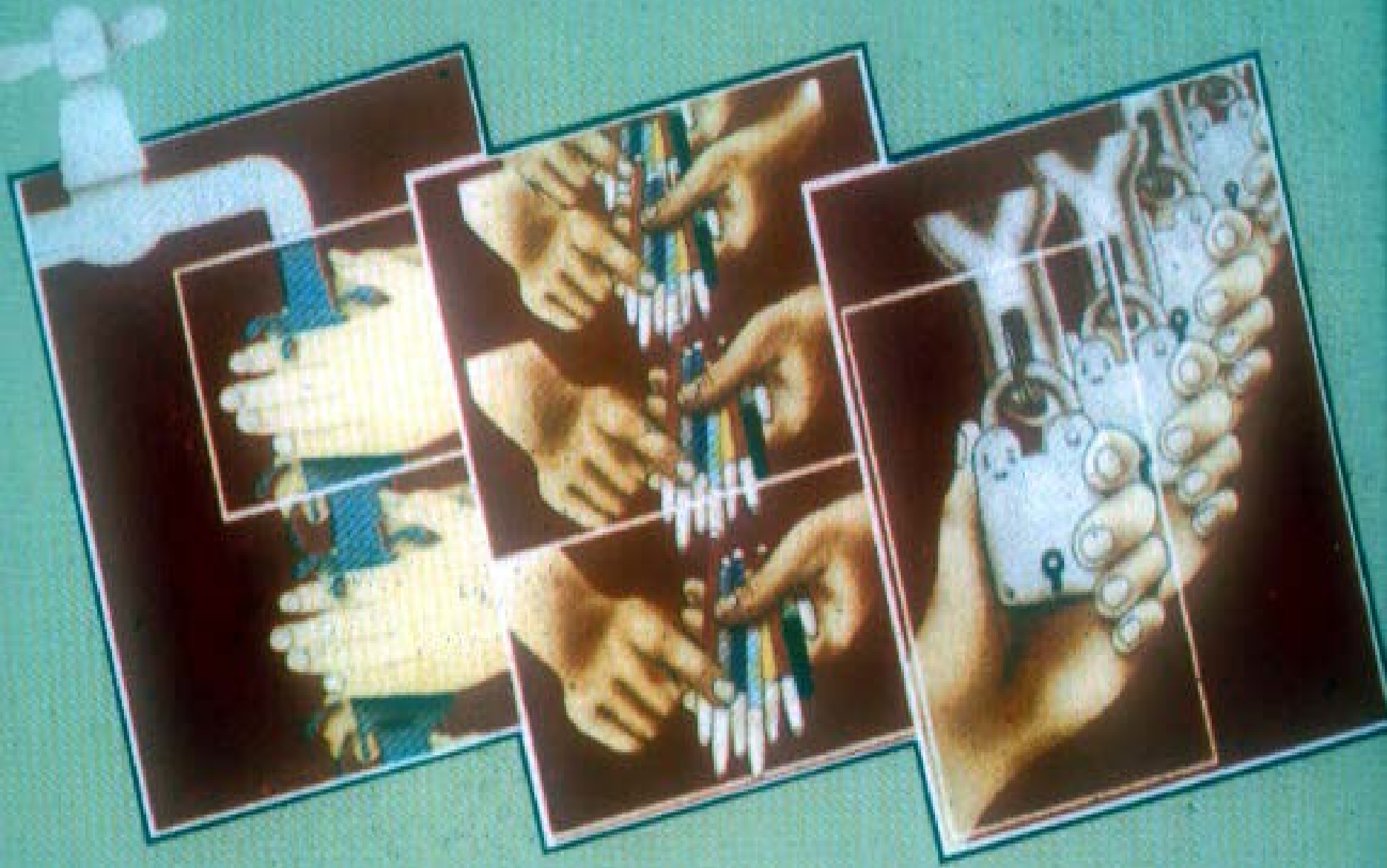
Limbic circuit abnormalities in

GAD ,SAnD and PD.


Expressed Behavior
Phenotype
Cognitive function
Endophenotype
Brain Circuitry
Genetic - Environment
Aetiology

Integration of validators derived from scientific advances in the last few decades:

- Genetics
- Neuroimaging
- Cognitive Science
- Pathophysiology



Cognitive Science

- NIMH is launching the Research Domain Criteria (RDoC) project.

- Fear extinction (instead of anxiety)
- Emotional bias (negative emotionality) (depression)
- Cognitive deficits (schizophrenia)
- Cognitive inflexibility (eg reversal learning) (OCD)
- Impulsivity
- Temperament

Possible tools to explore endophenotype

- Family aggregation
- Pharmacological dissection
- Pharmacological challenge
- Cognitive challenge
- Brain structure
- Brain Circuitry
- Epigenetic tools

In OCD patients and their clinically unaffected close relatives.

Orbitofrontal Dysfunction in Patients with Obsessive-Compulsive Disorder and Their Unaffected Relatives

Samuel R. Chamberlain,[1,2,3*] Lara Menzies,[1,2,3] Adam Hampshire,[4] John Suckling,[1,2] Naomi A. Fineberg,[1,3] Natalia del Campo,[1,2] Mike Aitken,[2,5] Kevin Craig,[1,2,3] Adrian M. Owen,[4] Edward T. Bullmore,[1,2,6] Trevor W. Robbins,[2,5] Barbara J. Sahakian[1,2]

SCIENCE VOL 321 18 JULY 2008

Researchers identified abnormally reduced activation of several cortical regions, including the orbitofrontal cortex, during reversal learning in OCD patients and their clinically unaffected close relatives, supporting the existence of an underlying endophenotype for this disorder.

Endophenotypical

Approach

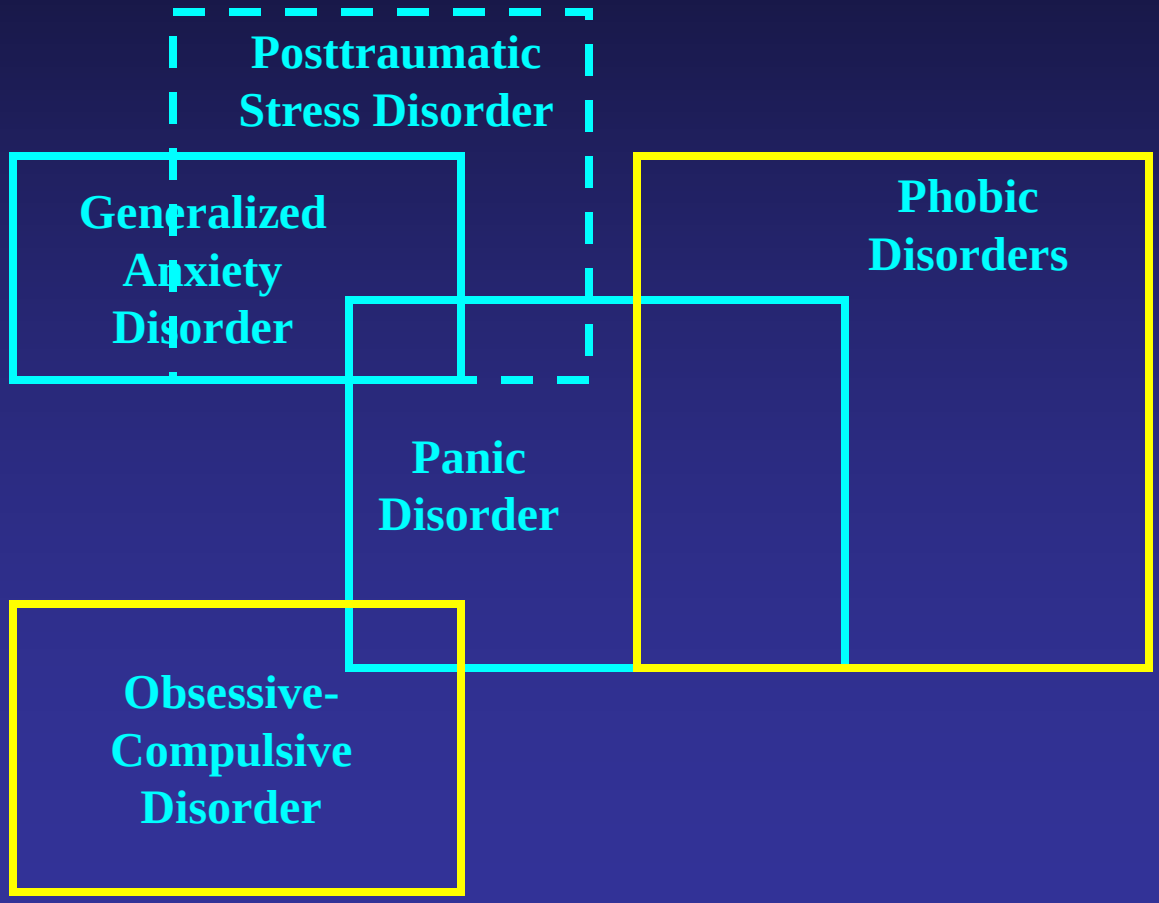
- Basis of classification

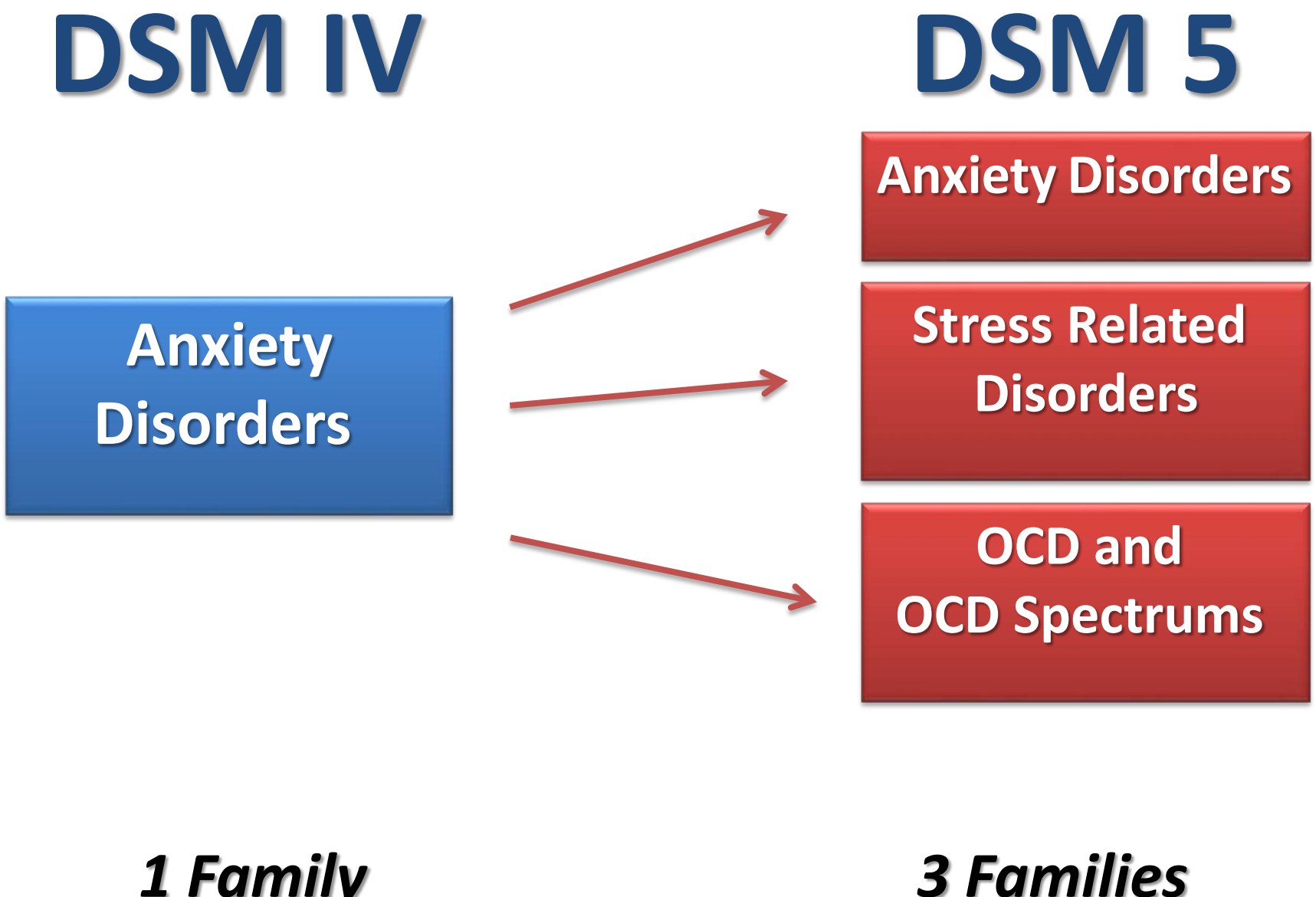
  changes in “anxiety”

  in DSM 5

Diagnoses of anxiety disorders

DSM IV Classification of Anxiety Disorders




DSM IV
DSM 5
Anxiety Disorders
Anxiety Disorders
Stress Related Disorders
OCD and OCD Spectrums
1 Family
3 Families

Section II: Diagnostic Criteria and Codes

* Neurodevelopmental Disorders
* Schizophrenia Spectrum and Other Psychotic Disorders
* Bipolar and Related Disorders
* Depressive Disorders
* Anxiety Disorders
* Obsessive-Compulsive and Related Disorders
* Trauma- and Stressor-Related Disorders
* Dissociative Disorders
* Somatic Symptom and Related Disorders
* Feeding and Eating Disorders
* Elimination Disorders
* Sleep-Wake Disorders
* Sexual Dysfunctions
* Gender Dysphoria
* Disruptive, Impulse-Control, and Conduct Disorders
* Substance-Related and Addictive Disorders

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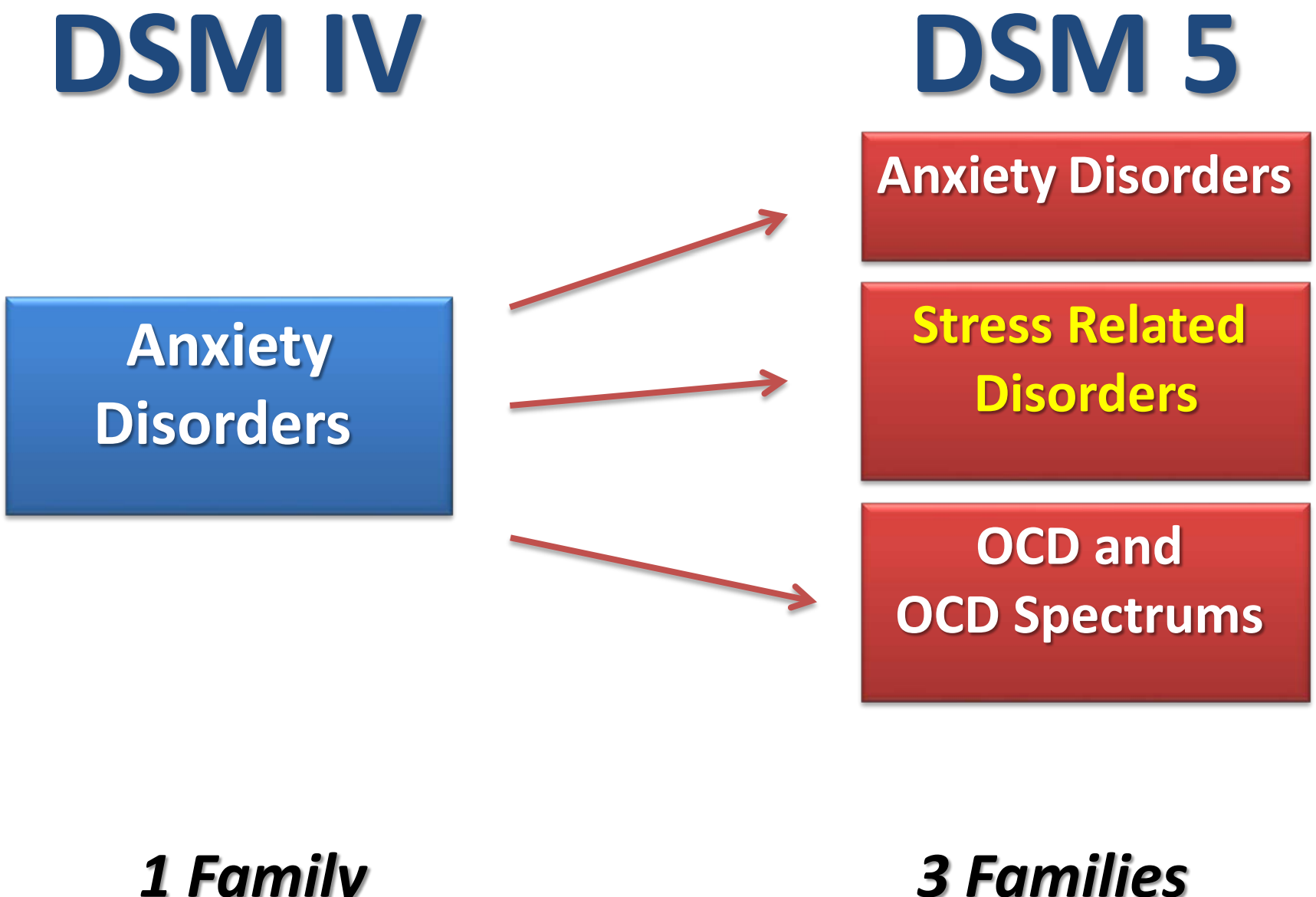
DSM IV
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3 Families

DSM 5

OCD and OCD Spectrums

Obsessive-Compulsive Disorder

Body Dysmorphic Disorder

Hoarding Disorder

Trichotillomania (Hair-Pulling Disorder)

Excoriation (Skin-Picking) Disorder

Substance/Medication-Induced Obsessive-Compulsive and Related Disorder

Obsessive-Compulsive and Related Disorder Due to Another Medical Condition

Other Specified Obsessive-Compulsive and Related Disorder

Unspecified Obsessive-Compulsive and Related Disorder

DSM 5

Stress Related Disorders

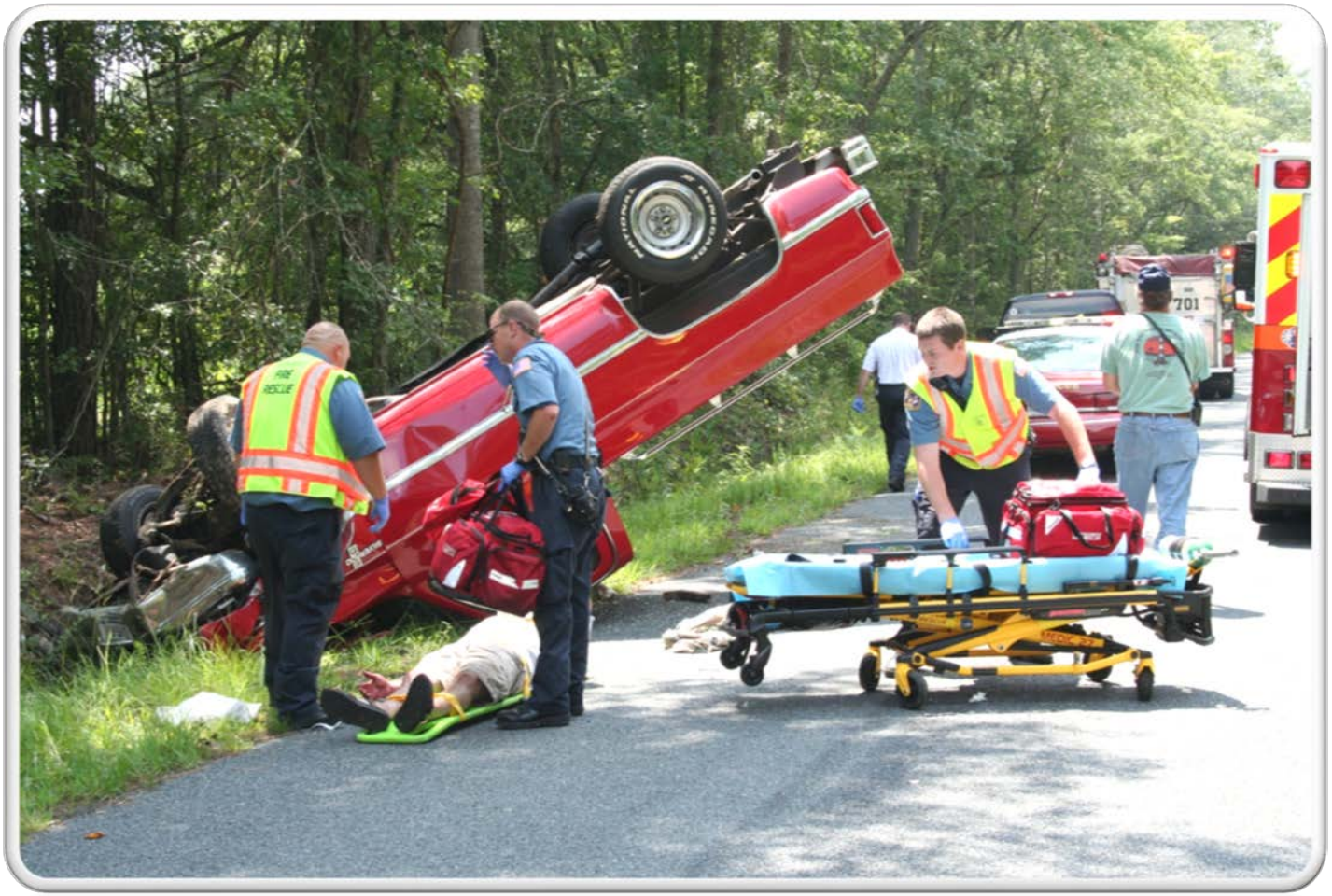
Reactive Attachment Disorder
Disinhibited Social Engagement Disorder
Post Traumatic Stress Disorder
Acute Stress Disorder
Adjustment Disorders
Other Specified Trauma- and Stressor-Related Disorder
Unspecified Trauma- and Stressor-Related Disorder

What is unique about stress related disorders ?

What is unique about PTSD ?

Clear point of onset.

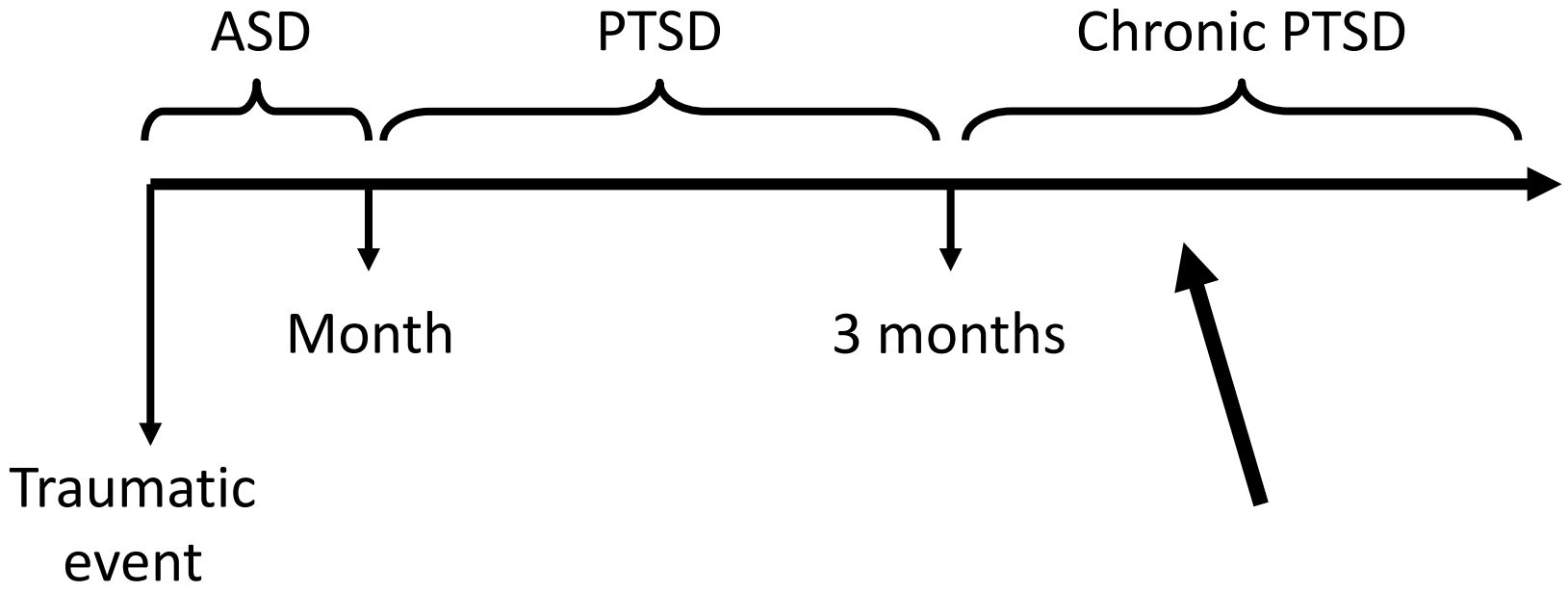
Illustrations by Matt Hansen



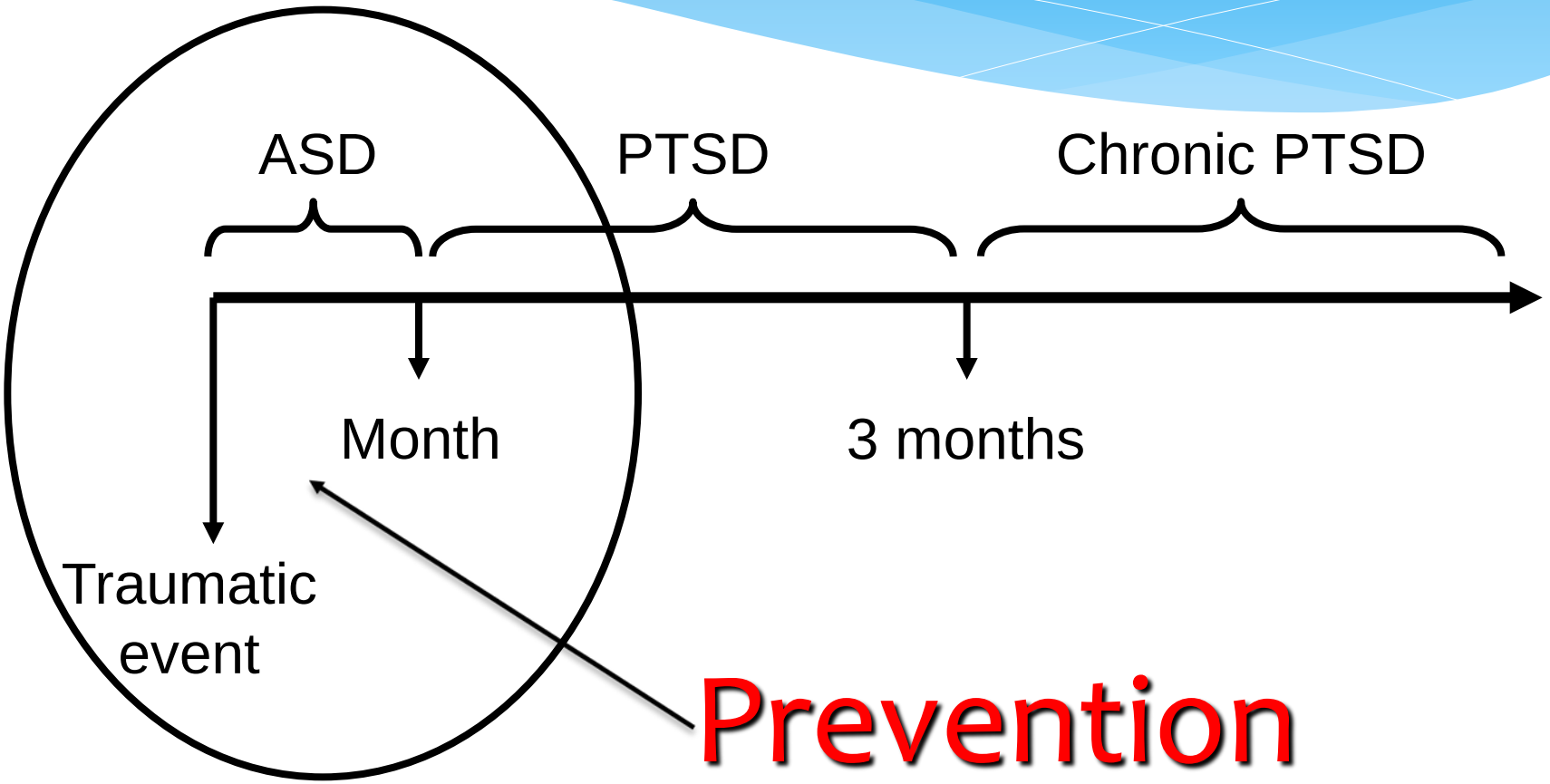
Window of opportunity

“Golden hours”

Treatment of Chronic PTSD



“Window of Opportunities”



What do we do with patients who come to the ER after experiencing a trauma?

What do we do with patients who come to the ER after experiencing a trauma?

- Talk with them about the trauma
- Encourage them not to suppress, not to repress
- BNZ

PTSD Diagnosis

Trauma

Re-experiencing

Avoidance

Numbing

Increased arousal

Time requirement – at least **over a month** after the exposure

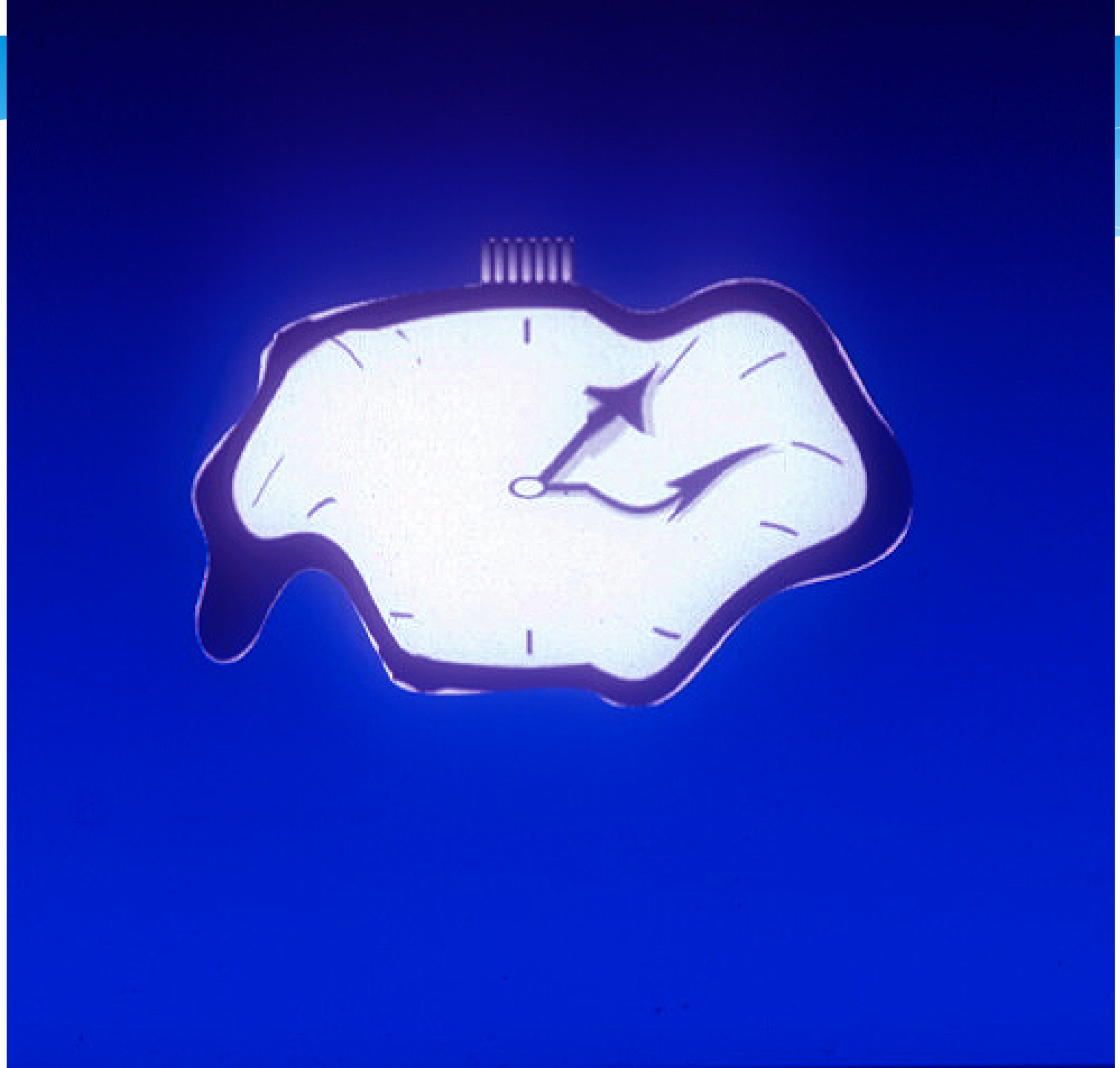
Clinically **significant distress or impairment** of functioning

PTSD: *Re-experiencing Symptoms*

- ☑Recurrent, intrusive, distressing recollections
- ☑Recurrent, distressing dreams
- ☑Flashbacks/Re-living
- ☑Triggers lead to intense psychological distress
- ☑Triggers lead to intense physiological reactivity

Re-experiencing Haunted by the memory of the event

The past is always present



Re-experiencing the traumatic memory of the event

What would happen if we **erase** the traumatic memory?

Consolidation

Labile short-term memory (STM)

Fixed long-term memory (LTM)

Reconsolidation

Consolidation

The transition from unstable memory to stable memory.

PTSD

Event

Short term memory

Memory consolidation **(protein synthesis)**

Retrieval

Reconsolidation

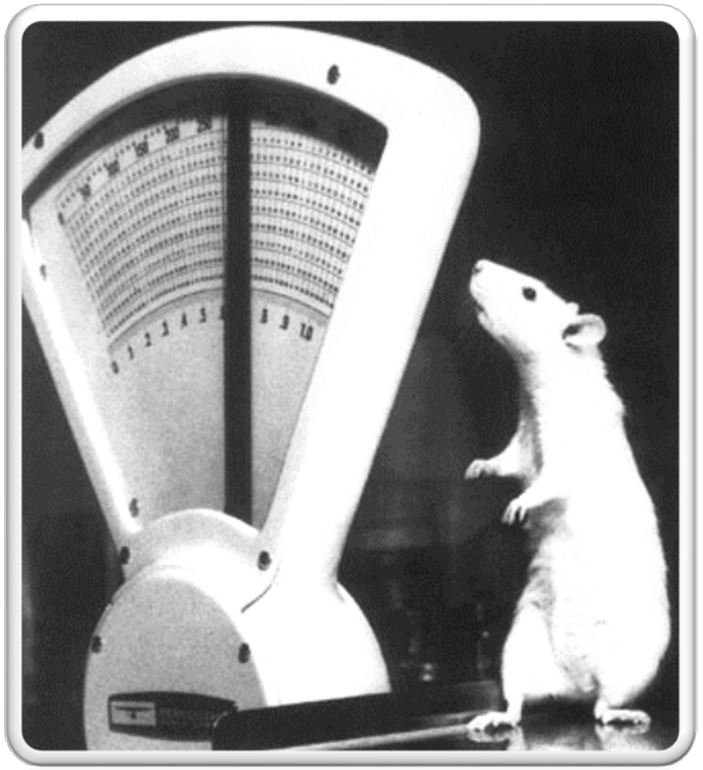
Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval

Karim Nader, Glenn E. Schafe & Joseph E. Le Doux

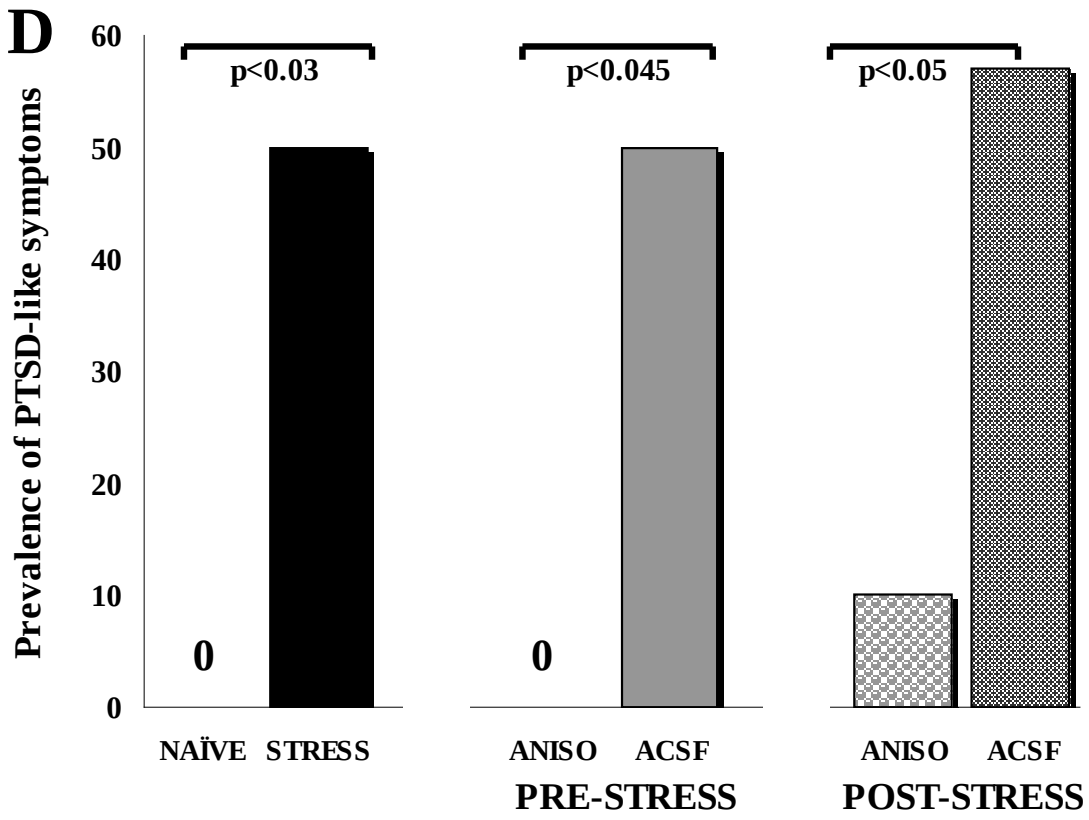
NATURE | VOL 406 | 17 AUGUST 2000 | www.nature.com

What will be the effect of administration of ***anisomycin*** (protein-synthesis inhibitor) on PTSD ?

Translational Research



Treatment : Anisomycin – a Protein Synthesis Inhibitor



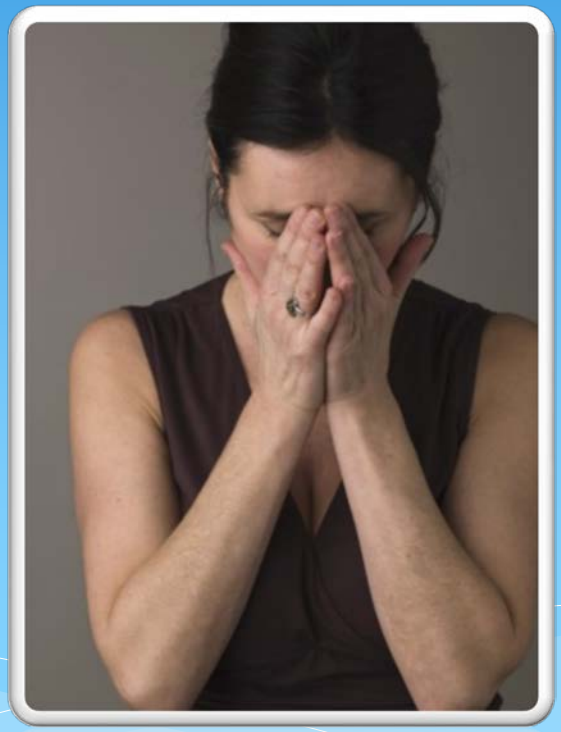
Cohen H, Kaplan Z, Matar M, Loewenthal U, Kozlovsky N, Zohar J. 2006
Anisomycin, a Protein Synthesis Inhibitor, Disrupts Traumatic Memory Consolidation and Attenuates Post Traumatic Stress Response in Rats.

Back to the clinic …

If a reduction in fear memories associated with trauma is beneficial, then:

Would amnesia of traumatic events reduce the rate of PTSD ?

Does amnesia of traumatic events decrease the risk for PTSD?



Does Memory of a Traumatic Event Increase the Risk for Posttraumatic Stress Disorder in Patients With Traumatic Brain Injury? A Prospective Study

Sharon Gil, Ph.D.

Yael Caspi, Ph.D.

Irit Zilberman Ben-Ari, Ph.D.

Danny Koren, Ph.D.

Ehud Klein, M.D.

(Am J Psychiatry 2005; 162:963-969)

(Am J Psychiatry 2005; 162:963-969)

6% of individuals with no memory of the traumatic event 24 hours after the event, presented PTSD symptoms at 6 months, as opposed to 23% in individuals with memory of the traumatic event

The Relation Between Memory of the Traumatic Event and PTSD: Evidence From Studies of Traumatic Brain Injury

Ehud Klein, MD[1], Yael Caspi, SeD, MA[2], Sharon Gil, PhD[3]

Can J Psychiatry, Vol 48, No 1, February 2003

Impaired memory for the traumatic events seems to reduce the risk for developing PTSD.

Pharmacologic disruption of traumatic memories might be therapeutically beneficial in people with PTSD

If a reduction in fear memories associated with trauma is beneficial, then:

Amnesia of traumatic events reduces the rate of PTSD

How can we

mimic

amnesia ?

What type of "defense mechanism" mimics amnesia?

If a reduction in fear memories associated with trauma is beneficial, then:

a) Amnesia

b) A repressive coping style

Repressive Coping Style

Repressive coping style – cognitive and emotional effort to ignore or divert attention from a threat

Roth & Cohen (1986), Am Psychol, 41: 813-9

If a reduction in fear memories associated with trauma is beneficial, then:

Would repressive coping style be beneficial ?

Repressive Coping Style, Acute Stress Disorder, and PTSD After Myocardial Infarction

Ginzburg et al, Psychosomatic Medicine

(2002) 64(5) 748-757

Repressive Coping Style

	Repressive N=28	Low Anxious N=20	High Anxious N=36	Defensive N=29
Sub-clinical ASD	14.3%	10%	27.8%	20.7%
Clinical ASD	3.6%	0%	36.1%	20.7%
Sub-clinical PTSD	10.7%	10%	44.4%	37.9%
Clinical PTSD	7.1%	20%	19.4%	17.2%

Ginzburg et al (2002), Psychosomatic Medicine 64: 748-757

Repressive Coping Style

Avoidance, suppression and denial (avoidance coping strategies) are effective in reducing traumatic stress-induced distress

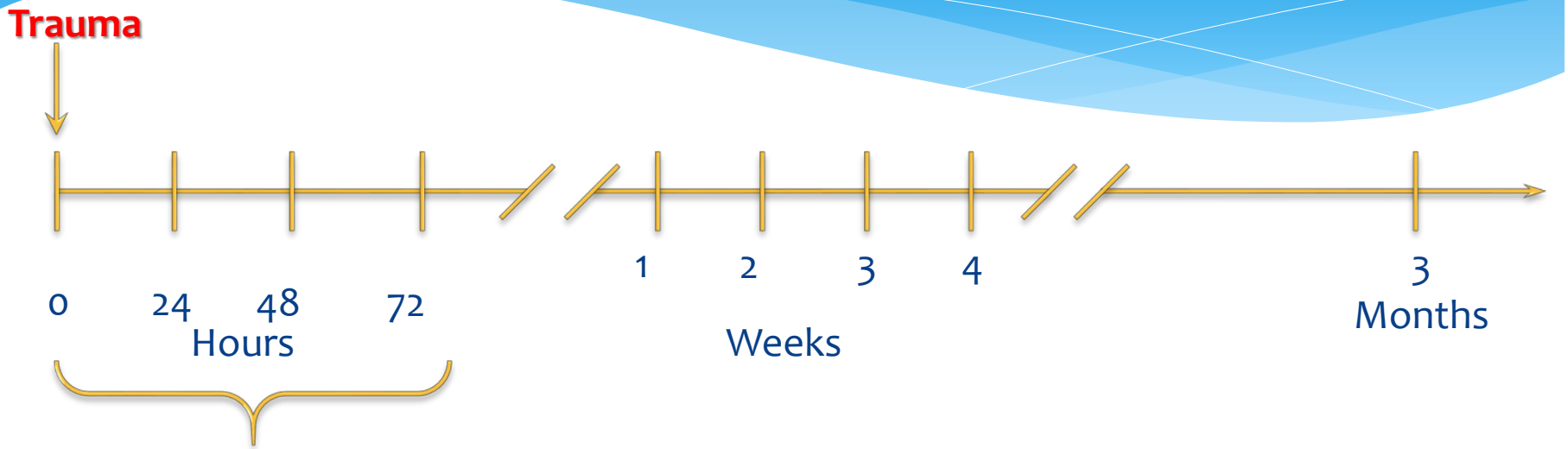
Lazarus, RS (1983) The Costs and Benefits of Denial. In S Breztitz (ed), The denial of stress

If a reduction in fear memories associated with trauma is beneficial, then:

Psychological interventions which enhance memories of the trauma (e.g. debriefing) – How does it fit in?

Would they be associated with a better / worse out-come ?

Importance of Early Intervention



Treatment with emphasis on:

-Expectation
-Proximity
-Ventilation
-Rest

Acute Stress Disorder

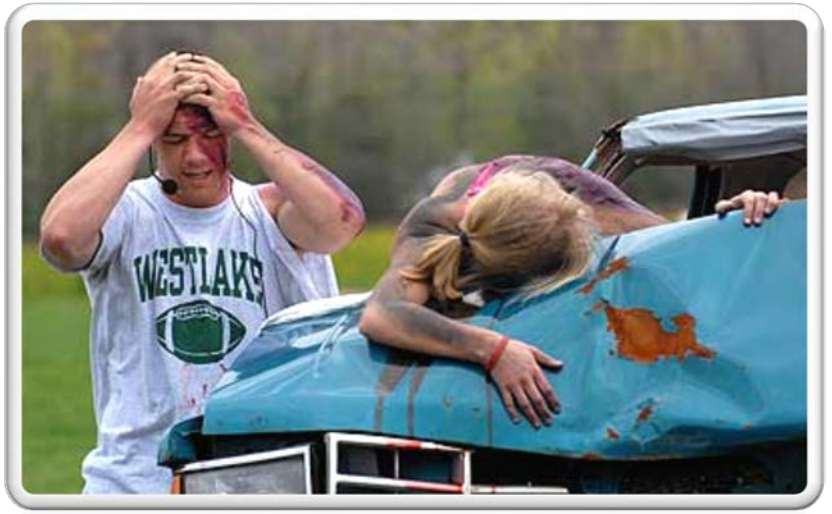
Acute PTSD

Debriefing is a "must" in early intervention

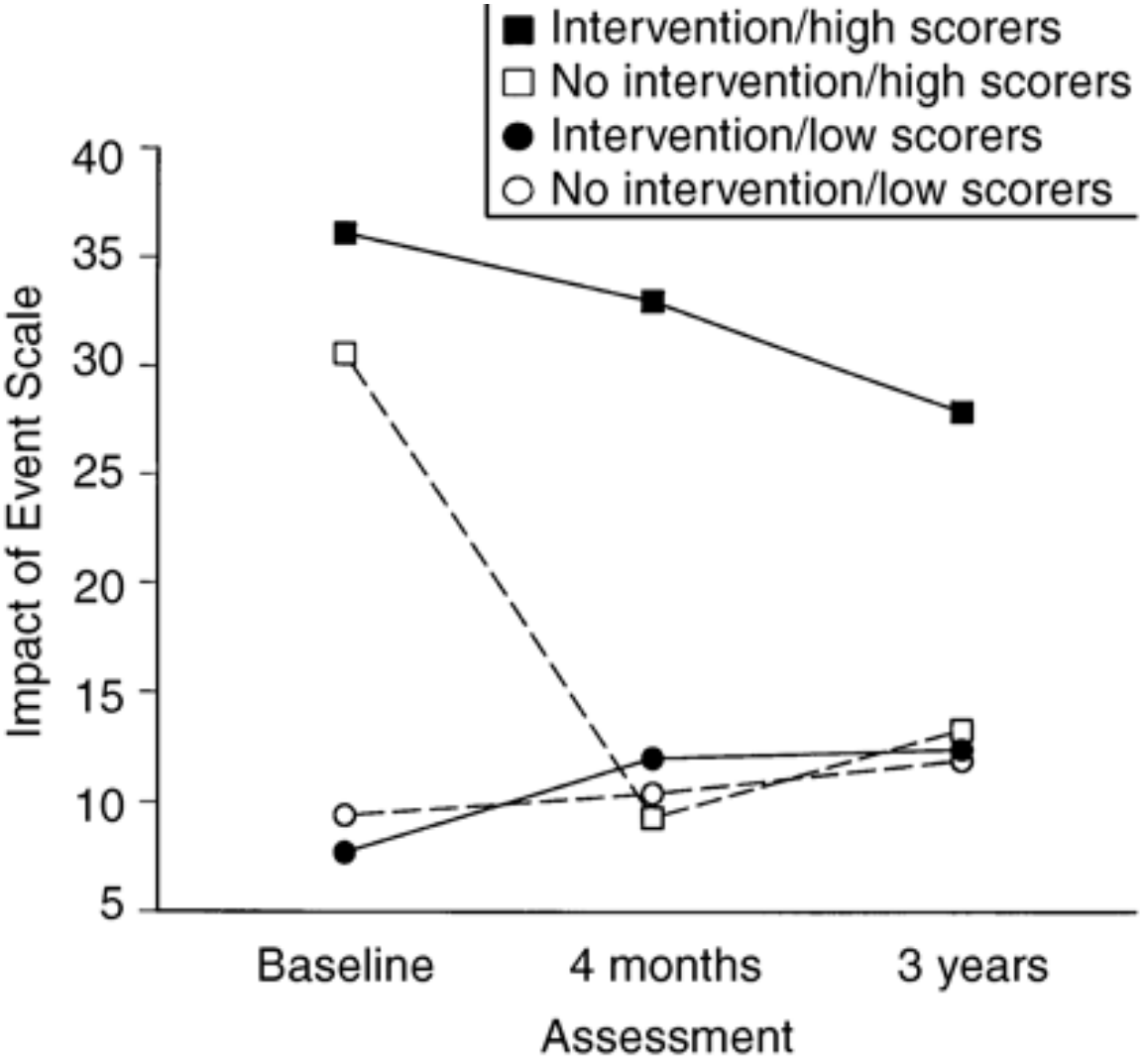
Psychological debriefing for road traffic accident victims

Mayou et al

British Journal of Psychiatry, 2000, 176:589-593



Mayou et al 2000



Emotional or educational debriefing after psychological trauma*

Randomised controlled trial

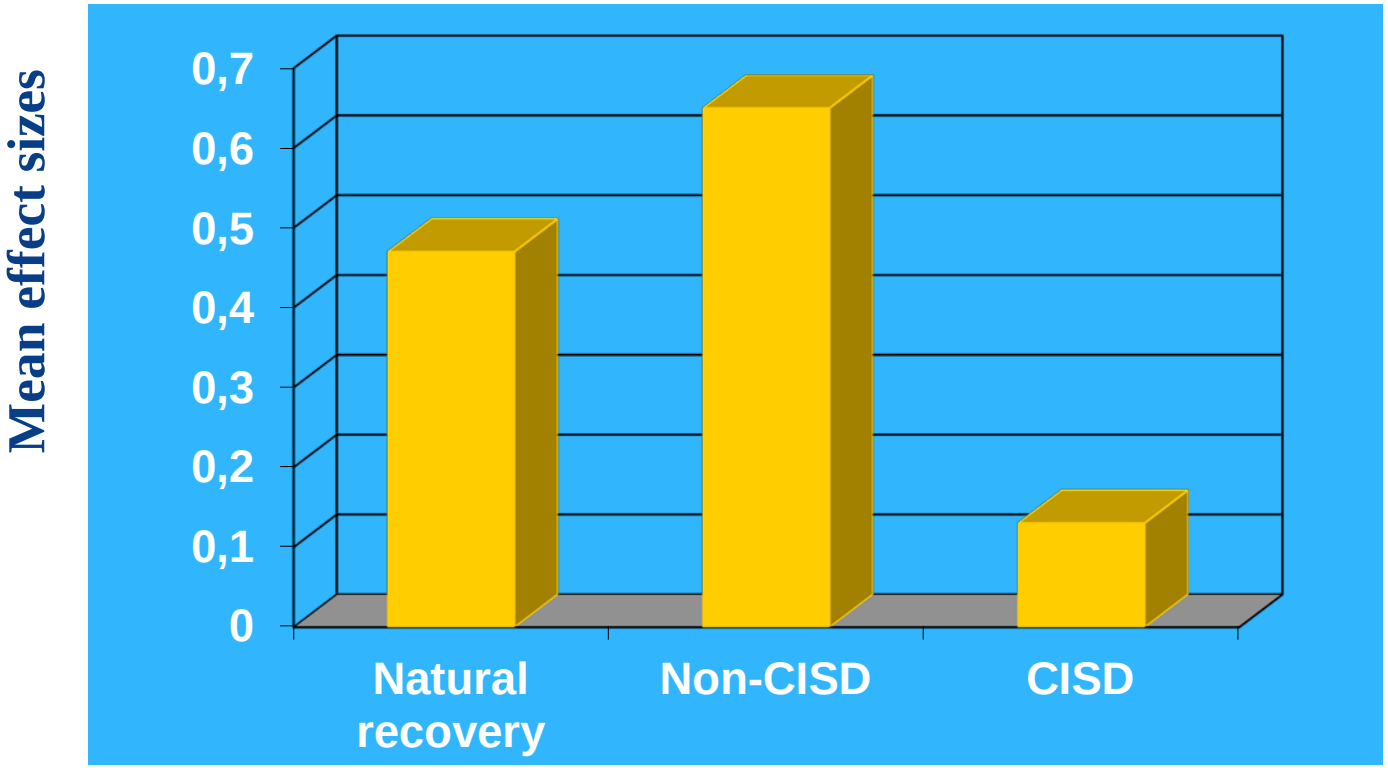
MARIT SIJBRANDIJ, MIRANDA OLFF, JOHANNES B. REITSMA, INGRID V. E. CARLIER and BERTHOLD P. R. GERSONS

BRITISH JOURNAL OF PSYCHIATRY (2006), 189, 150–155. doi: 10.1192/bjp.bp.105.021121

Method We randomised 236 adult survivors of a recent traumatic event to either emotional ventilation debriefing, educational debriefing or no debriefing (control) and followed up at 2 weeks, 6 weeks and 6 months.

Results Psychiatric symptoms decreased in all three groups over time, without significant differences between the groups in symptoms of PTSD ($P=0.33$). Participants in the emotional debriefing group with high baseline hyperarousal score had significantly more PTSD symptoms at 6 weeks than control participants ($P=0.005$).

Debriefing: Meta-analyses Show No or Negative Effect



Debriefing

"Recent studies suggest that at times debriefing might be associated with a **worse outcome**"

McFarlane, (2006) "Can debriefing work? Critical appraisal of theories of interventions and outcomes with directions for future research."

If a reduction in fear memories associated with trauma is beneficial, then:

a) Amnesia
b) A repressive coping style
c) Avoiding psychological interventions which **enhance** memories of the trauma
d) Medications which interfere with memory ?

PTSD and Cortisol

Stress

Activation of HPA axis

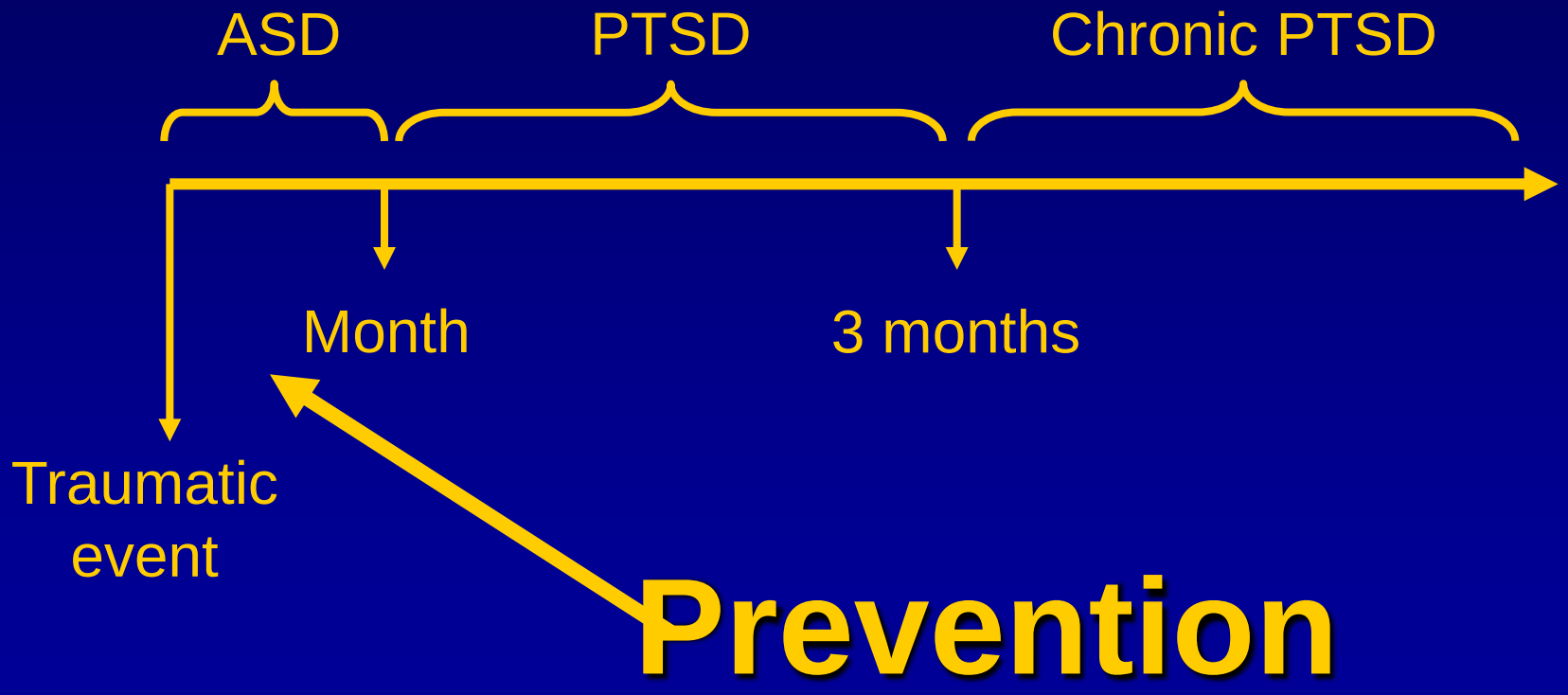
PTSD

Hypoplasticity of HPA axis

Pre-clinical study support the concept of “golden hours” and window of opportunity

Back to the clinic ....

“Window of Opportunities”



What do we do with patients who come to the ER after experiencing a trauma?

- Talk with them about the trauma
- Encourage them not to suppress, not to repress
- BNZ

סיוע מישראל

יחידת החילוץ של

ניצולים בארמניה. "פתאום הכל התמוטט עלינו".

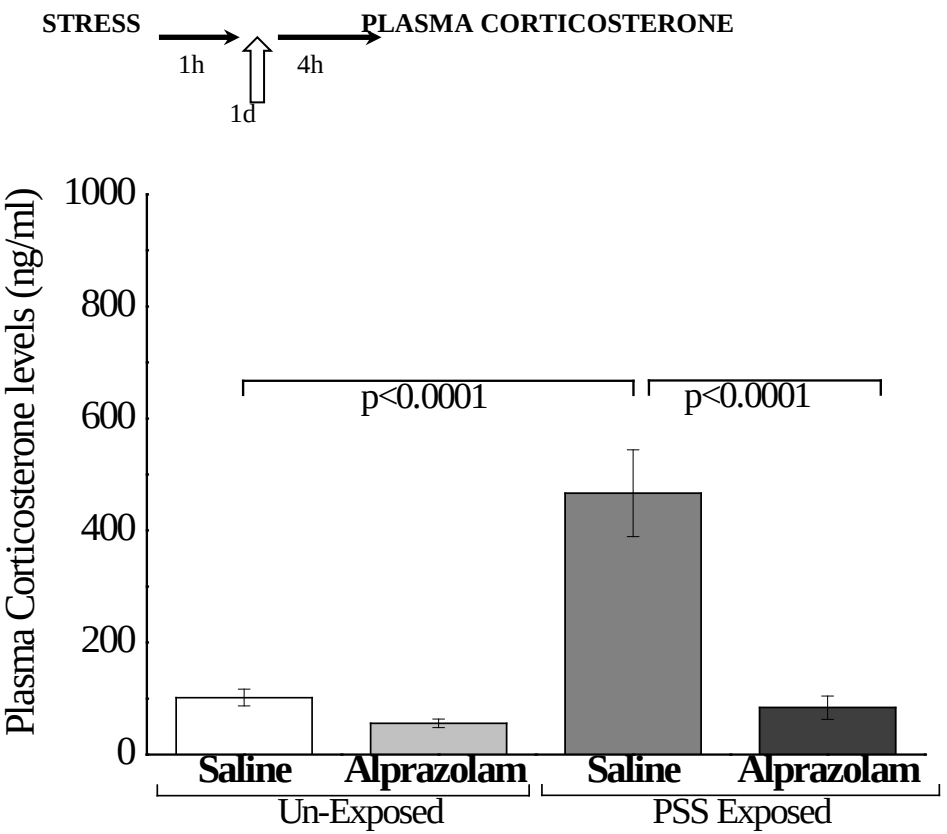
תצלום: אי־פי

Benzodiazepines

Benzodiazepines and PTSD

What is the effect of BNZ on HPA axis?

Figure 12


STRESS
1h
1d
4h
PLASMA CORTICOSTERONE
Plasma Corticosterone levels (ng/ml)
1000
800
600
400
200
0
p<0.0001
p<0.0001
Saline
Alprazolam
Saline
Alprazolam
Un-Exposed
PSS Exposed

Blocking the normal response of the HPA.

PTSD

Hypoplasticity of HPA axis

If decrease level of cortisol is associated with PTSD what would be the affect of giving BNZ ?

Benzodiazepines and ASR
Prospective study

N=26

Treatment – 6.7 days after trauma (range 2-18 days)

BNZ – Clonazepam 2.7 mg/day or
Alprazolam 2.5 mg/day

Design – Prospective F/U 1 and 6 months after trauma
13 patients with BNZ and 13 pair matched

Scales – Horowitz Impact of Event Scale
Mississippi rating scale
CAPS (Clinically administered PTSD scale)

Gelpin et al, J Clin Psychiatry, 1996

Results: BNZ and ASR prospective study

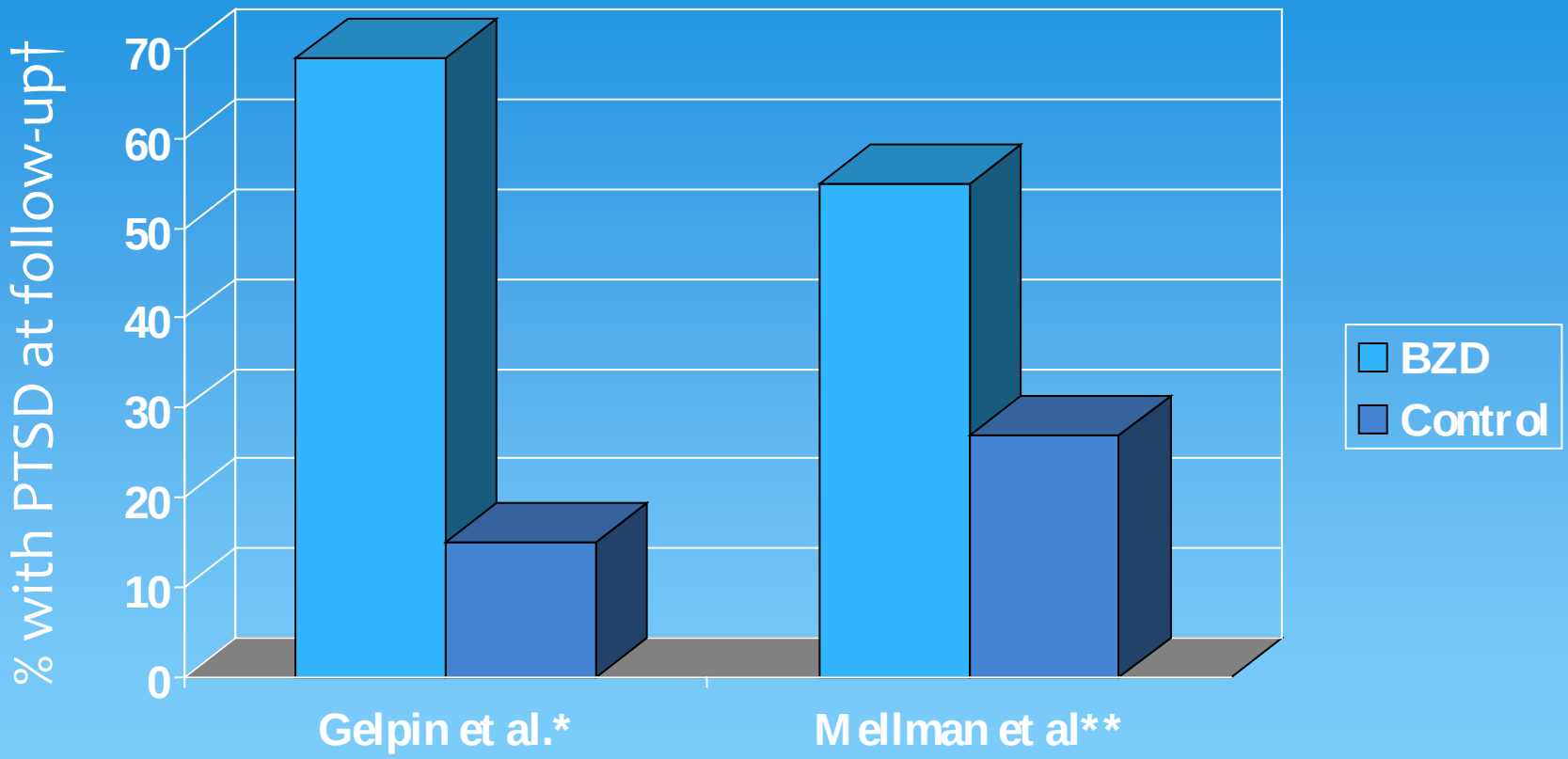
PTSD score &
Anxiety score
} no difference between BNZ and control at 1 and 6 months

PTSD diagnosis: **9**/13 BNZ vs. **3**/13 Control

Conclusion: Early administration of BNZ is not associated with a beneficial effect on the course of the illness

Gelpin et al, J Clin Psychiatry, 1996

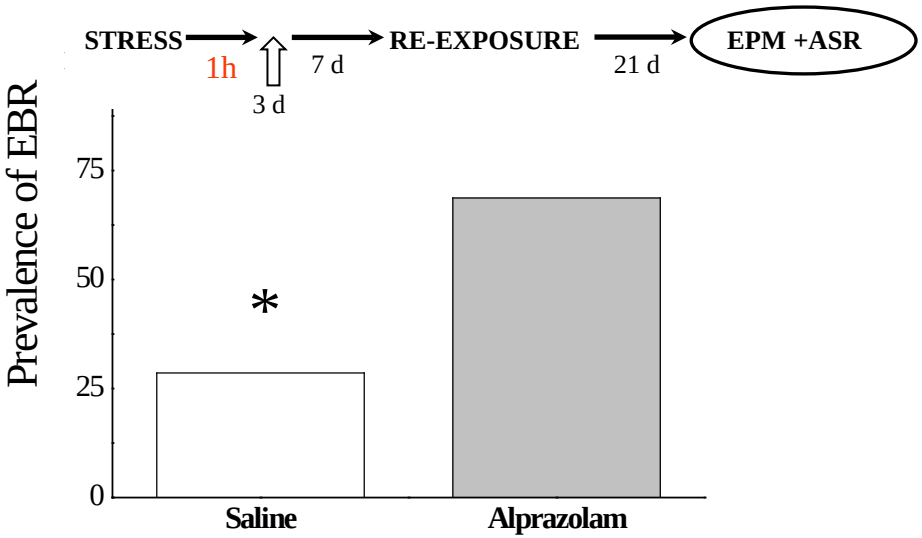
Benzodiazepines: Studies Show Increased Risk of PTSD With Prolonged Use



†6 months and 6 weeks, respectively. All of depression occurred in the BZD group.
*Alprazolam (n=3) or clonazepam (n=10) vs cases. no treatment (n=10)
**Temazepan (n=11) vs placebo (n=10)

Gelpin E et al. *J Clin Psychiatry*. 1996;57:390-394
Mellman TA et al. *J Clin Psychiatry*. 2002;62:1183-1184

Figure 7



Long-term effects of alprazolam in the double-exposure (PSS) model on behavior at day 31 on anxiety-like behaviors:

A) Time spent in the open arms of the EPM.

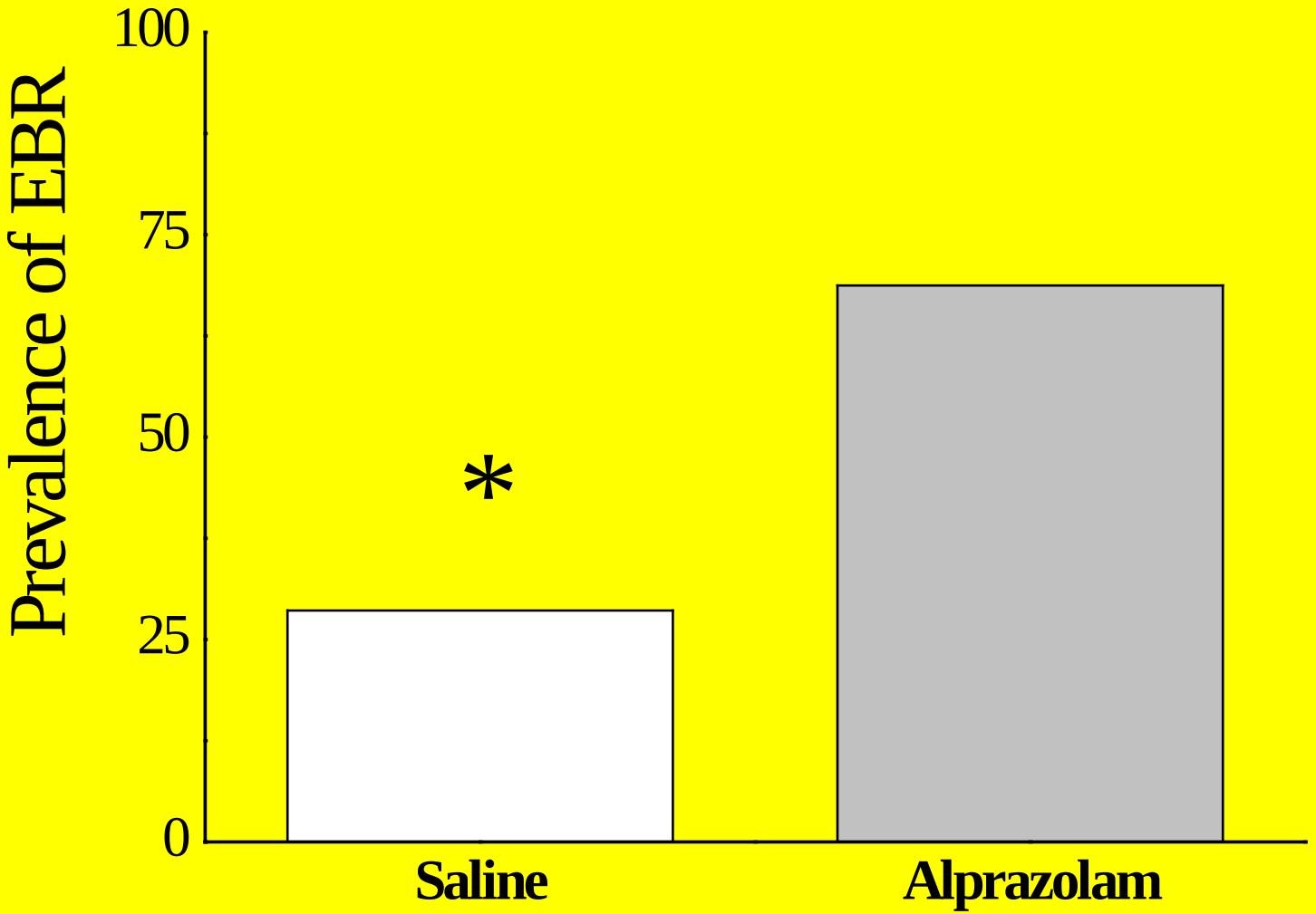
B) Number of entries to the open arms

C) Total exploration.

D) Anxiety Index.

Double PSS-with the Alprazolam treatment regimen resulted in significantly decreased time spent in the open arms and total exploration on the maze, with a significantly increased Anxiety-Index, as compared to PSS-exposure with the saline by treatment regimen.

All data represent group mean ± S.E.M


Prevalence of EBR
100
75
50
25
0
*
Saline
Alprazolam

VA/DoD Clinical Practice Guideline

Management of Post-Traumatic Stress

2010

VA/DoD Evidence Based Practice

Benzodiazepines and Stress related Disorders

DSM 5

Stress Related Disorders

Reactive Attachment Disorder
Disinhibited Social Engagement Disorder
Post Traumatic Stress Disorder
Acute Stress Disorder
Adjustment Disorders
Other Specified Trauma- and Stressor-Related Disorder
Unspecified Trauma- and Stressor-Related Disorder

Bereavement and Benzodiazepines

The British National Formulary (British Medical Association & Royal Pharmaceutical Society of Great Britain 2000), and the Committee on Safety of Medicines (Committee on Safety of Medicines 1998) advise against using benzodiazepines after bereavement and suggest that these agents may inhibit the grieving process.

British Medical Association & Royal Pharmaceutical Society of Great Britain (2000) *British National Formulary* (September). London & Wallingford: BMJ Books & Pharmaceutical Press.

Committee on Safety of Medicines (1988) *Current Problems*, No. 21.

PTSD and "golden hours"

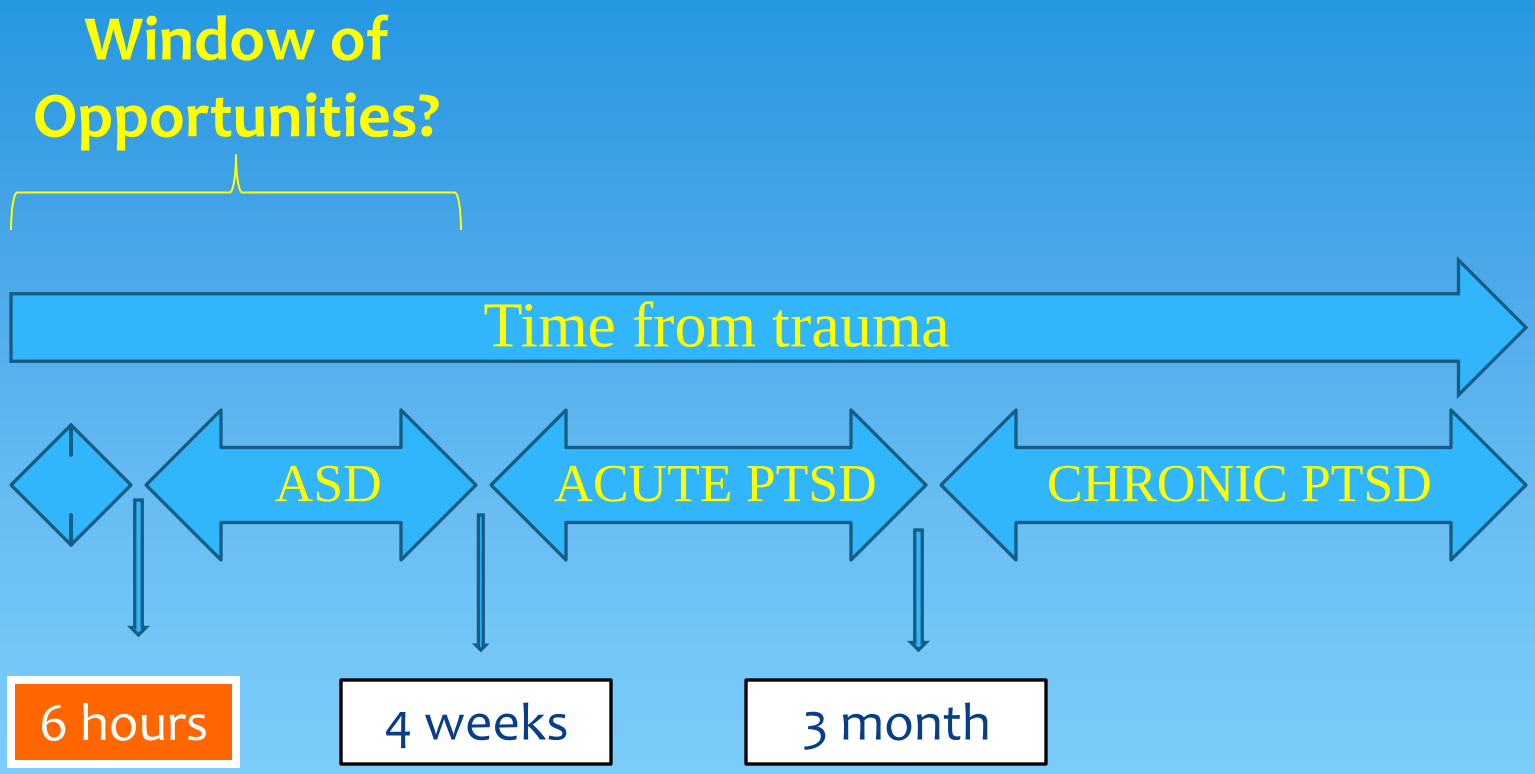
Does psychiatry have a window of opportunity for treatment, as there is in other medical fields (such as in stroke or MI)?

Does psychiatry have a window of opportunity for treatment, as there is in other medical fields (such as in stroke or MI)?

Can we reach people within a short time of the trauma?

Could a single high dose of iv hydrocortisone prevent the development of PTSD?

Is there a window of opportunity for secondary prevention of PTSD?



Consolidation

Labile short-term memory (STM)

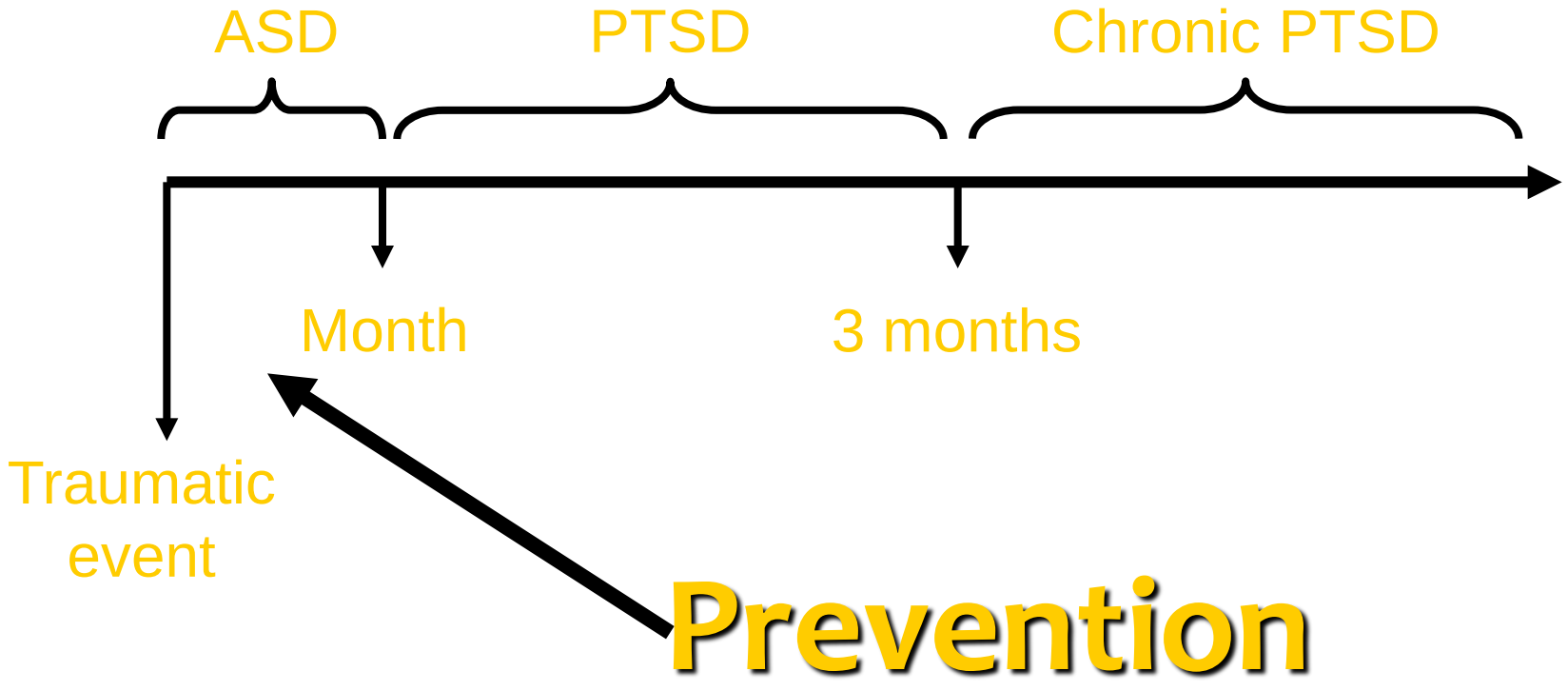
Fixed long-term memory (LTM)

Reconsolidation

Consolidation

* The transition from unstable memory to stable memory.

“Window of Opportunities”



Acute Treatment after Trauma

a. Examining the conventional approach.

b. Harnessing neuroscience to change the trajectory.

What do we do with patients who come to ER after experiencing a trauma?

What do we do with patients who come to ER after experiencing a trauma?

* Talk with them about the trauma
* Encourage them not to suppress, not to repress
* BNZ

* If we are not supposed to give BNZ
  and not to do debriefing
  what should we do?

What should we do with patients who come to the ER after a trauma?

Acute stress management

Carried out not by mental health profession (MEP) and therefore should be simple.

It includes :

Goals -- 3R (Ra, Rb, Rc)

1.) Return to full activity/functioning.

Acute stress management

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Acute stress management

Carried out not by mental health profession (MEP) and therefore should be simple.

It includes :

Goals -- 3R (Ra, Rb, Rc)

1) Return to full activity/functioning.

2) Regain behavioral / emotional control

3) Restore interpersonal communication

Acute stress management

Carried out not by MEP and therefore should be simple.

It includes

Goals -- 3R (Ra, Rb, Rc)

How to do it – ABN via RAISE.

What not to do-- 3P.

Management

ABN

Addressing

Basic

Needs.

via ERASE

ABN- Addressing Basic Needs. via ERASE

* Reduce Exposure to stress (i.e. finding secure place etc.)
* Restore physiological needs (food, drink, hygiene etc.)
* Provide InformAtion/ orientAtion.
* Locate source of Support. (family, friends etc.)
* Emphasizing the Expectation of returning back to normal.

Acute stress management

Carried out not by MEP and therefore should be simple. It includes

* Goals -- 3R (Ra, Rb, Rc)
* How to do it – ABN via RAISE.
* What not to do-- 3P.

What not to do-- 3P.

What not to do-- 3P.

* Don't

Pathologize.

“Normal response to Abnormal situation.”

What not to do-- 3P.

* Don't Pathologize.
* Don't Psychologize.

What not to do-- 3P.

* Don't Pathologize.
* Don't Psychologize: i.e. don't facilitate emotional reaction via group therapy, debriefing etc.

What not to do-- 3P.

* Don't Pathologize.
* Don't Psychologize: ie don't facilitate emotional reaction via group therapy, debriefing etc.
* Don't P

What not to do-- 3P.

* Don't Pathologize.
* Don't Psychologize: ie don't facilitate emotional reaction via group therapy, debriefing etc.
* Don't Pharmacologize.

“Window of Opportunities”

* BNZ - not a good idea
* Debriefing- “ “ “ “
* Propanolol pilot data ~
* Morphine retrospective data +
* Cortisol animal data + pilot data +
* SSRI animal data + human data +
* Oxcytocin animal data +

SSRIs and sigma$_1$

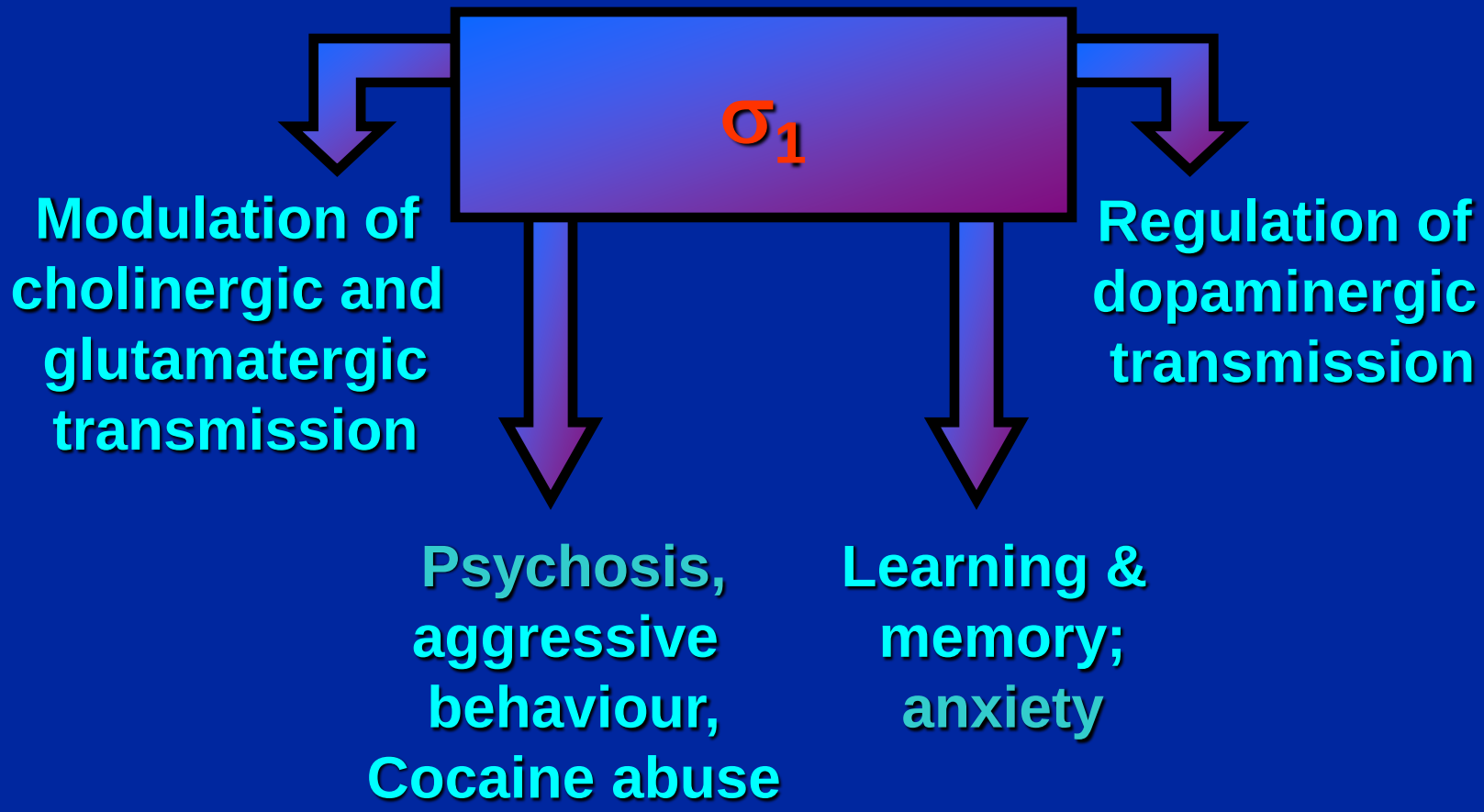
- ***Relative affinity[1]***

  Fluvoxamine ***≥ Sertraline > Fluoxetine > Citalopram >> Paroxetine***

[1]Narita et al (1996); [2]Zanardi et al (1996); [3]Gatti et al (1996)

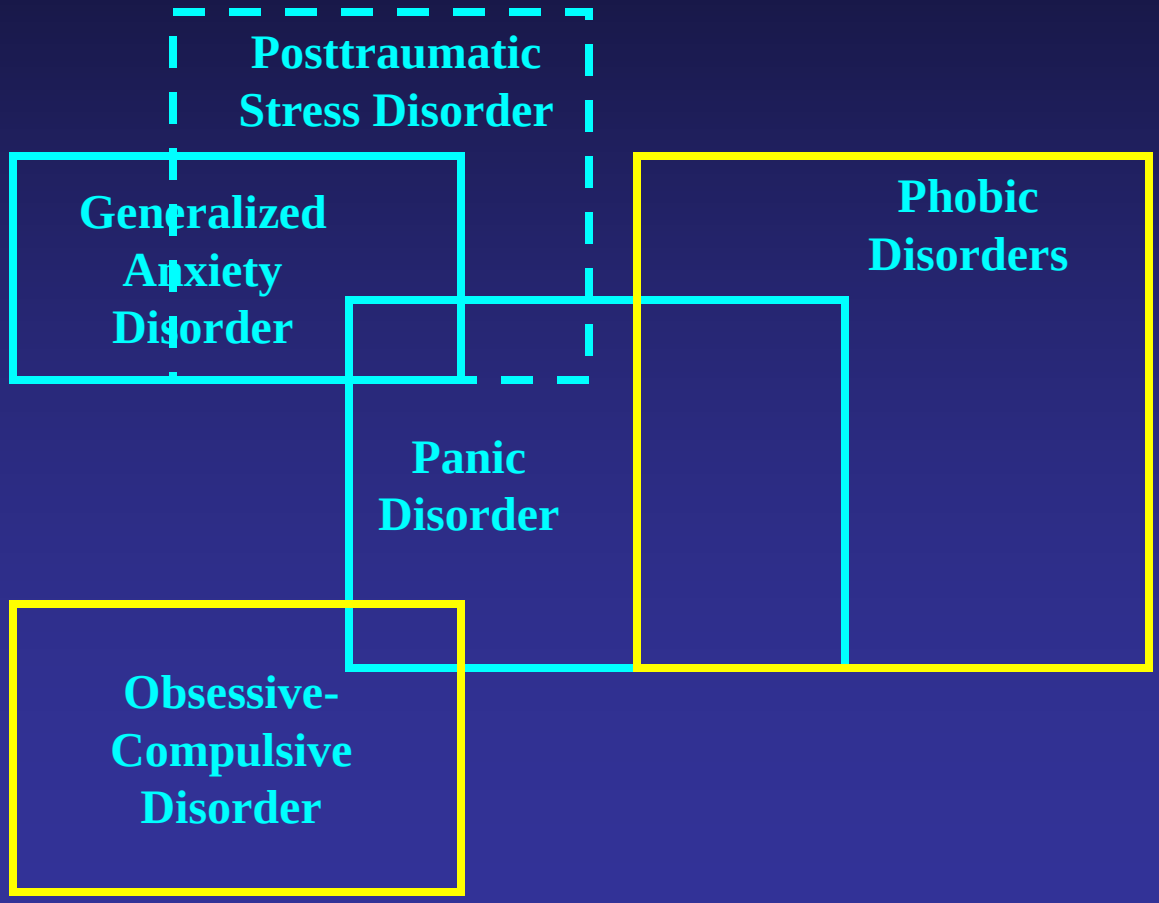
The clinical consequences of sigma$_1$ activity

Where does σ_1 fit in?



Conclusion

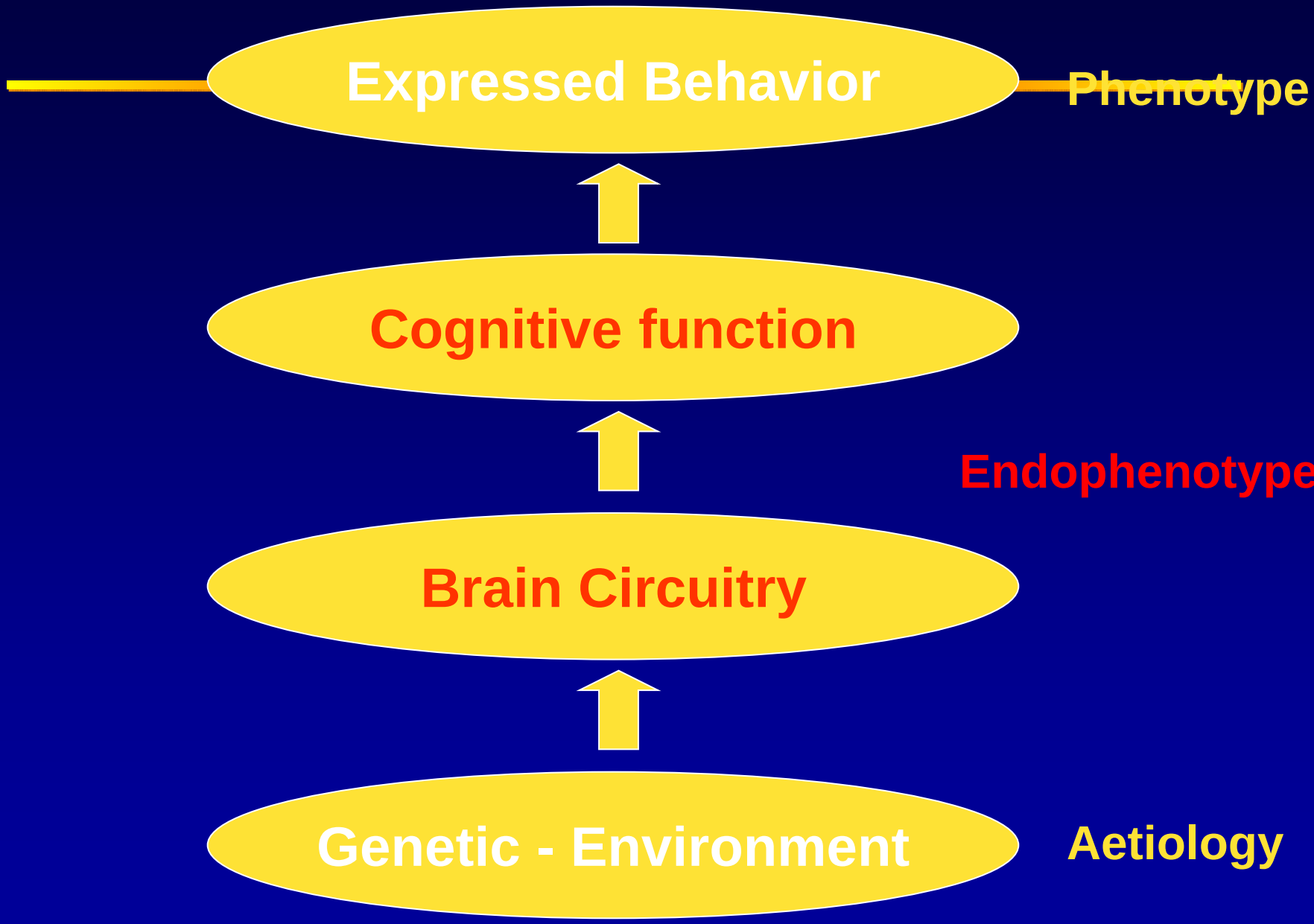
DSM IV Classification of Anxiety Disorders



A different approach is to look beyond the symptoms

Endophenotypical

Approach


Expressed Behavior
Phenotype
Cognitive function
Endophenotype
Brain Circuitry
Genetic - Environment
Aetiology

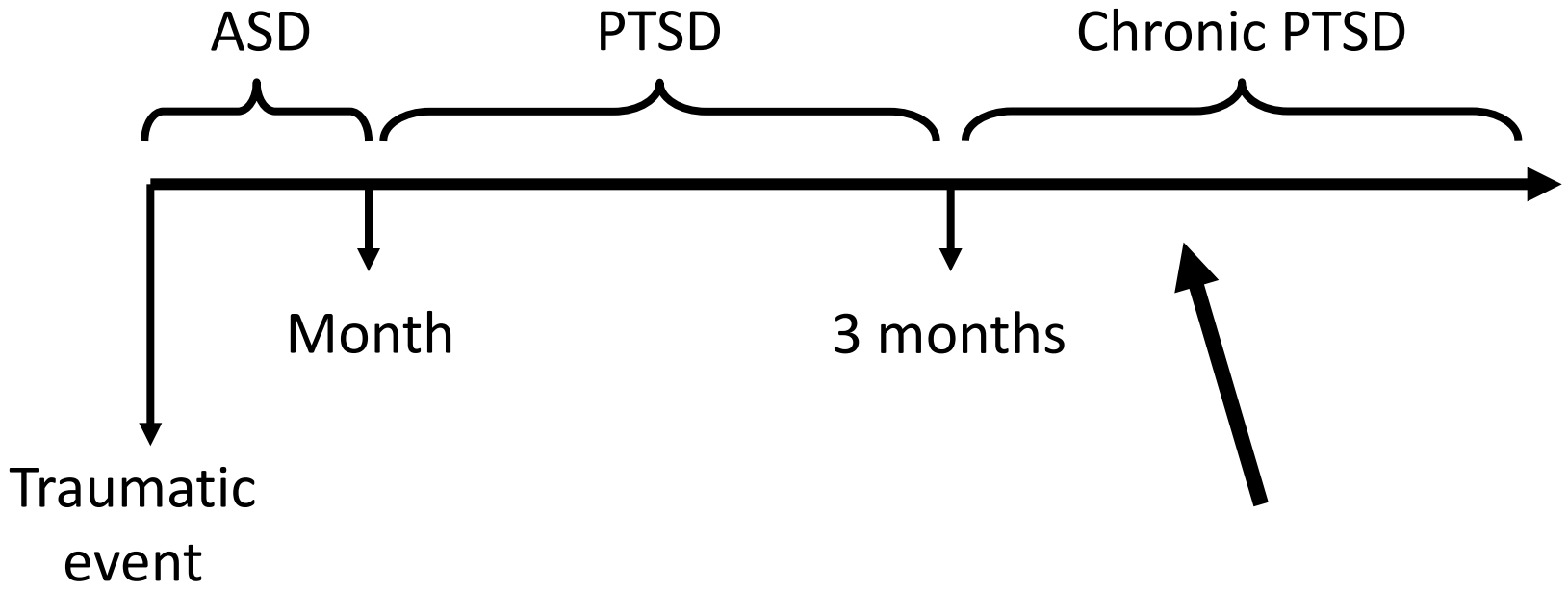
Section II: Diagnostic Criteria and Codes

* Neurodevelopmental Disorders
* Schizophrenia Spectrum and Other Psychotic Disorders
* Bipolar and Related Disorders
* Depressive Disorders
* Anxiety Disorders
* Obsessive-Compulsive and Related Disorders
* Trauma- and Stressor-Related Disorders
* Dissociative Disorders
* Somatic Symptom and Related Disorders
* Feeding and Eating Disorders
* Elimination Disorders
* Sleep-Wake Disorders
* Sexual Dysfunctions
* Gender Dysphoria
* Disruptive, Impulse-Control, and Conduct Disorders
* Substance-Related and Addictive Disorders

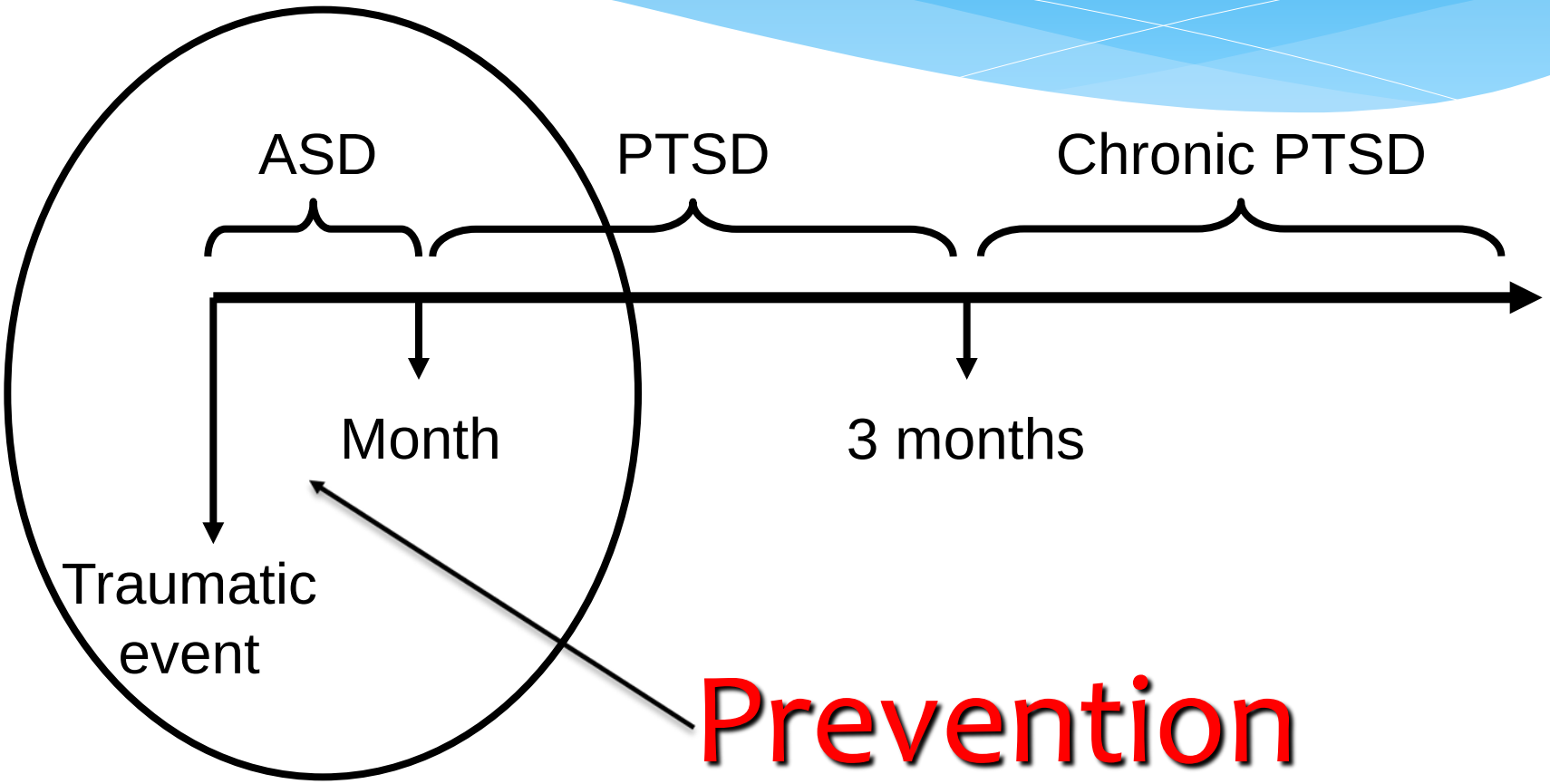
When –

1. Time of intervention

Treatment of Chronic PTSD

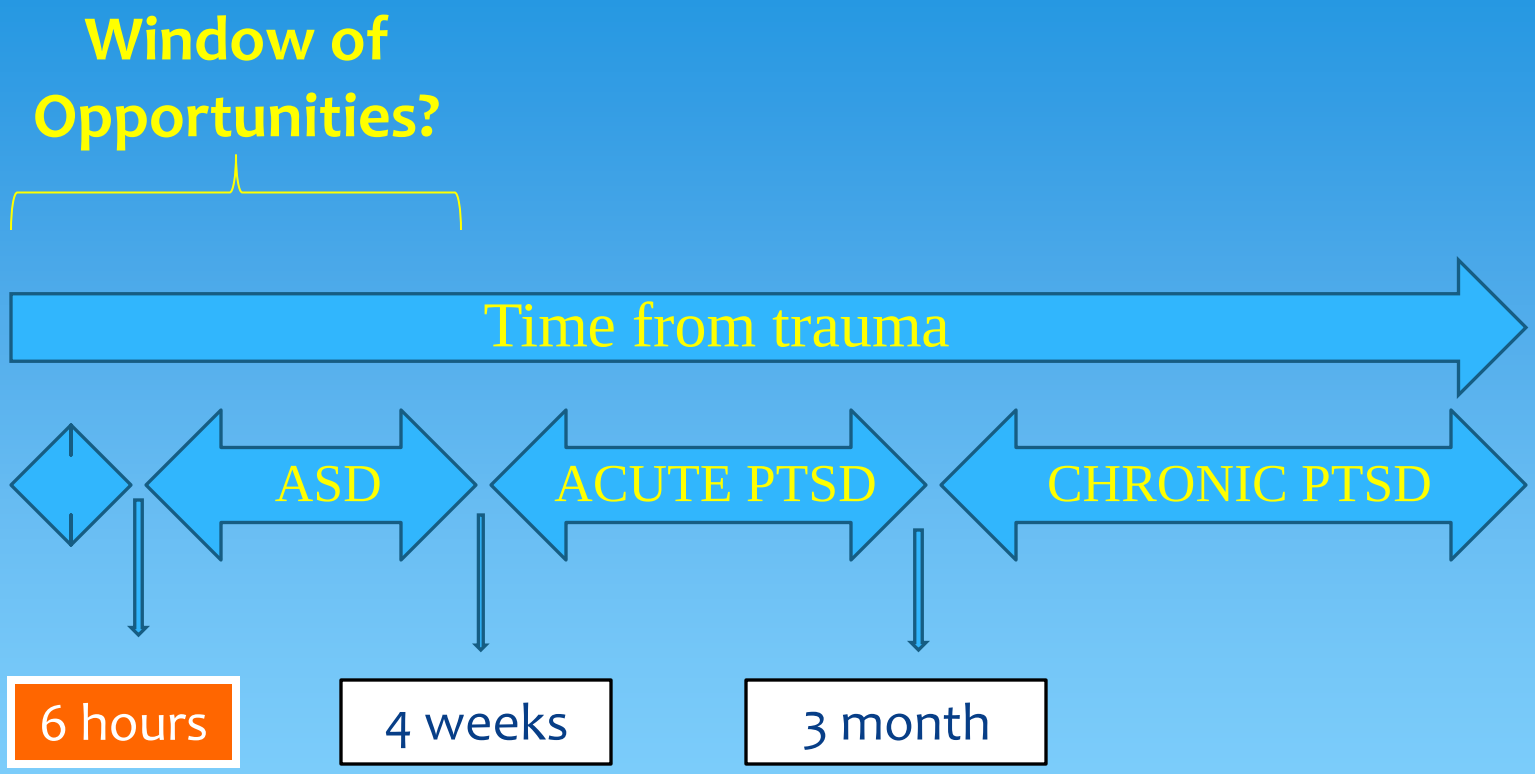


“Window of Opportunities”



Does psychiatry have a window of opportunity for treatment, as there is in other medical fields (such as in stroke or MI)?

Is there a window of opportunity for secondary prevention of PTSD?



Consolidation

Labile short-term memory (STM)

Fixed long-term memory (LTM)

Reconsolidation

Consolidation

* The transition from unstable memory to stable memory.

PTSD and Cortisol

“Window of Opportunities”

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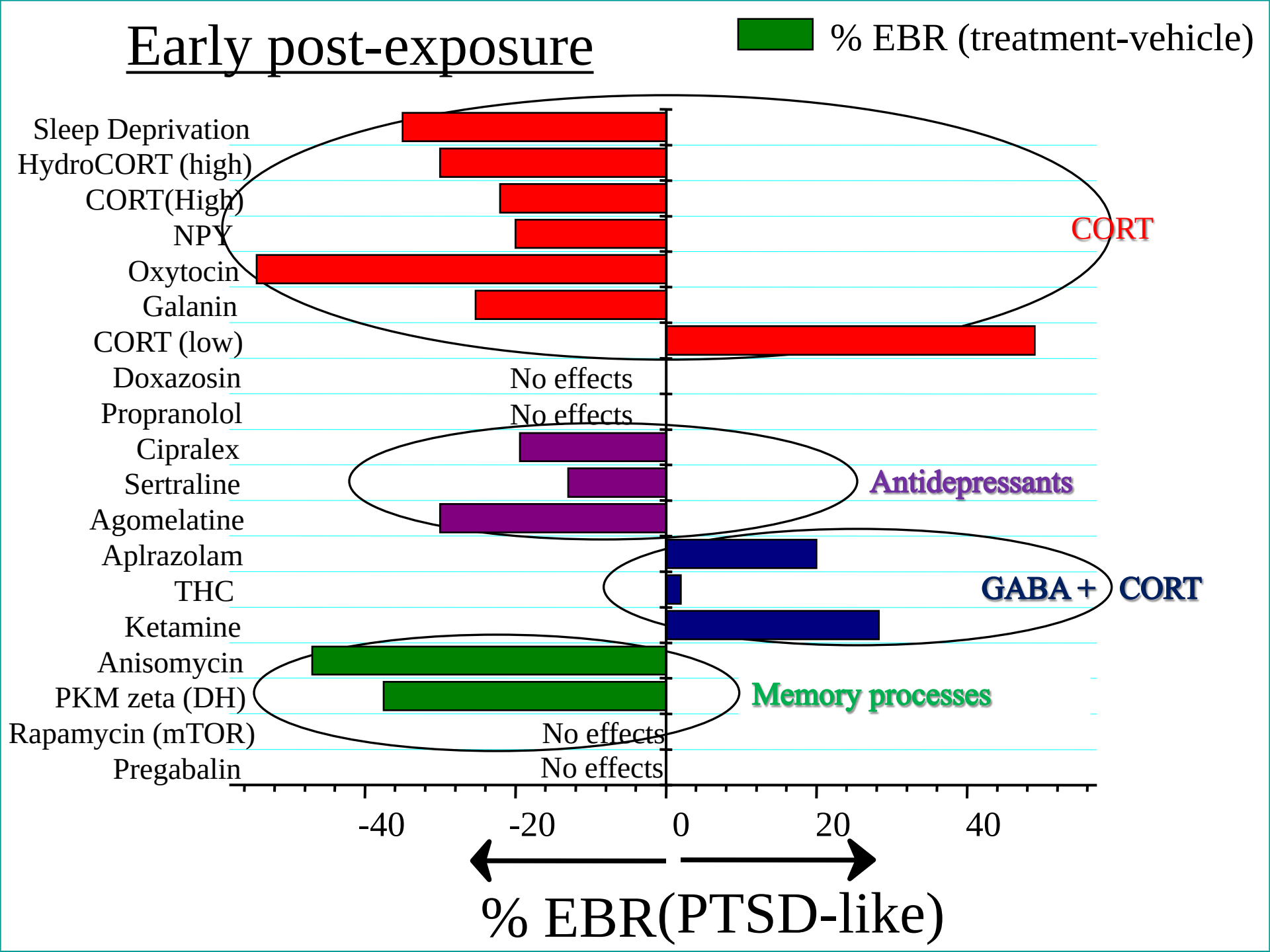
Early post-exposure



An Integrative Approach to Secondary Prevention of PTSD

1. Expectation that individuals return to full activity
2. Ensuring support
3. 3P

What not to do-- 3P.

* Don't Pathologize.
* Don't Psychologize: ie don't facilitate emotional reaction via group therapy, debriefing etc.
* Don't Pharmacologize.

To be further explored – An Integrative Approach to Secondary Prevention of PTSD

1. Early and short (3 to 4 months) SSRI's administration ?
2. Cortisol administration ?
3. Sleep deprivation ?
4. Oxytocin administration ?
5. Specific cognitive task ?

Thanks