DEFENSE CENTERS OF EXCELLENCE
For Psychological Health & Traumatic Brain Injury

The Limits of Adaptive Coping: Neurobiology of Extreme Stress

June 26, 2014, 1-2:30 p.m. (EDT)

Presenter

William P. Nash, M.D.
Assistant Clinical Professor of Psychiatry, University of California, San Diego
Chair, Military Committee of the Group for Advancement of Psychiatry

Moderator

Navy Capt. Anthony A. Arita, Ph.D.
Director, Deployment Health Clinical Center
Bethesda, Md.

DVBIC Defense and Veterans Brain Injury Center
DHCC Deployment Health Clinical Center
National Center for Telehealth & Technology

Webinar Details

- Live closed captioning is available through Federal Relay Conference Captioning (see the “Closed Captioning” box)
- Webinar audio is **not** provided through Adobe Connect or Defense Connect Online
  - Dial: CONUS **888-877-0398**; International **210-234-5878**
  - Use participant pass code: **3938468**
- Question-and-answer (Q&A) session
  - Submit questions via the Q&A box

Resources Available for Download

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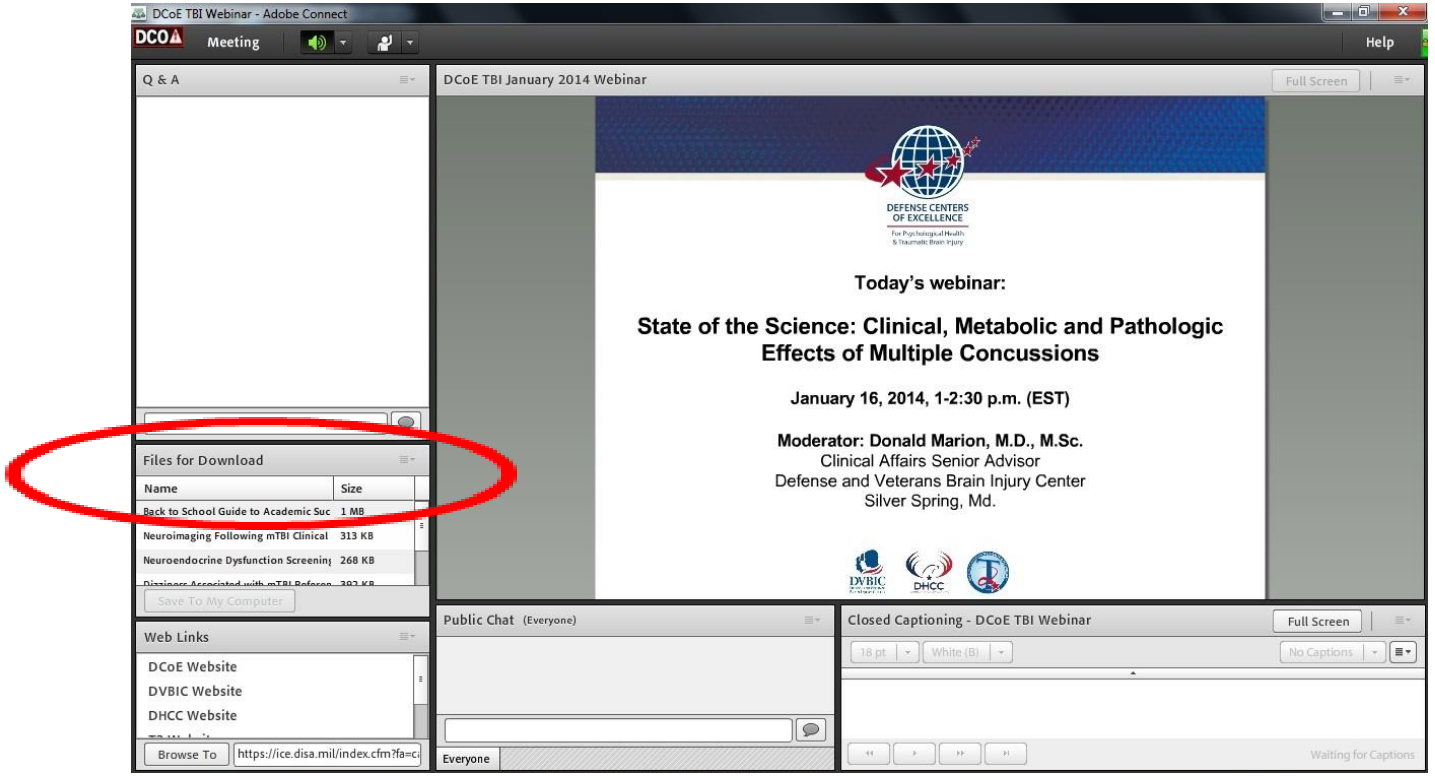

Continuing Education Details

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- All who registered **prior** to the deadline on **Thursday, June 26, 2014,** at 3 p.m. (EDT) and meet eligibility requirements stated above, are eligible to receive a certificate of attendance or CE credit.

Continuing Education Details (continued)

- If you pre-registered for this webinar and want to obtain CE certificate or a certificate of attendance, you must complete the online CE evaluation and post-test.

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- The Duke Medicine website online CE evaluation and post-test will be open through **Thursday, July 3, 2014** until 11:59 p.m. (EDT).

Continuing Education Details (continued)

- Credit Designation – The Duke University School of Medicine designates this live webinar for:
  - 1.5 AMA PRA Category 1 Credit(s)

- Additional Credit Designation includes:
  - 1.5 ANCC nursing contact hours
  - 0.15 IACET continuing education credit
  - 1.5 NBCC contact hours credit commensurate to the length of the program
  - 1.5 contact hours from the North Carolina Psychology Board
  - 1.5 NASW contact hours commensurate to the length of the program for those who attend 100% of the program

Continuing Education Details (continued)

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- NASW: **National Association of Social Workers (NASW),** North Carolina Chapter: Southern Regional AHEC will award contact hours commensurate to the length of the program to participants who attend 100% of the program.

Questions and Chat

Throughout the webinar, you are welcome to submit technical or content-related questions via the Q&A pod located on the screen. **Please do not submit technical or content-related questions via the chat pod**.

The Q&A pod is monitored during the webinar, and questions will be forwarded to our presenter for response during the question-and-answer session of the webinar.

Participants may also chat amongst each other during the webinar using the chat pod.

We will keep the chat function open 10 minutes after the conclusion of the webinar.

Webinar Overview

Despite unprecedented efforts over the course of the longest war in American history, existing programs in the Defense Department and Department of Veterans Affairs to prevent, identify and treat stress disorders among military service members, veterans, and their families remain hampered by factors that limit their effectiveness. Research studies indicate that stigma, as a barrier to care, remains high in military communities. One limitation of existing psychological health programs, including those designed to reduce stigma, may be their exclusion of emerging scientific perspectives on the role of the central nervous system (CNS) in extreme stress. This webinar will examine the evidence that stress disorders are fundamentally neurobiological as well as psychosocial, and will provide an overview of select CNS neurotransmitter systems and neuronal pathways implicated in normal and pathological stress states. Discussion will include biologically informed approaches for psychoeducation to reduce stigma and for prevention and treatment in both clinical and non-clinical settings.

During this webinar, participants will learn to:

- Identify CNS neurotransmitter systems and pathways implicated in persistent adverse stress outcomes such as posttraumatic stress disorder (PTSD)
- Correlate acute and chronic stress-induced changes in the functioning of CNS neurotransmitter systems with persistent changes in cognition, emotions and behavior
- Summarize clinical and non-clinical approaches to addressing stress-induced neurobiological dysfunction

William Nash M.D.

Psychiatric researcher, educator, and consultant for posttraumatic stress disorder prevention and treatment for the Defense Department and Department of Veterans Affairs

Holds academic appointments at the University of California, San Diego, and Virginia Commonwealth University

Chairs the Military Committee of the Group for Advancement of Psychiatry

Led the development of the Navy and Marine Corps Combat and Operational Stress Control doctrine

While on active duty provided far-forward psychological health services to the 1st Marine Division

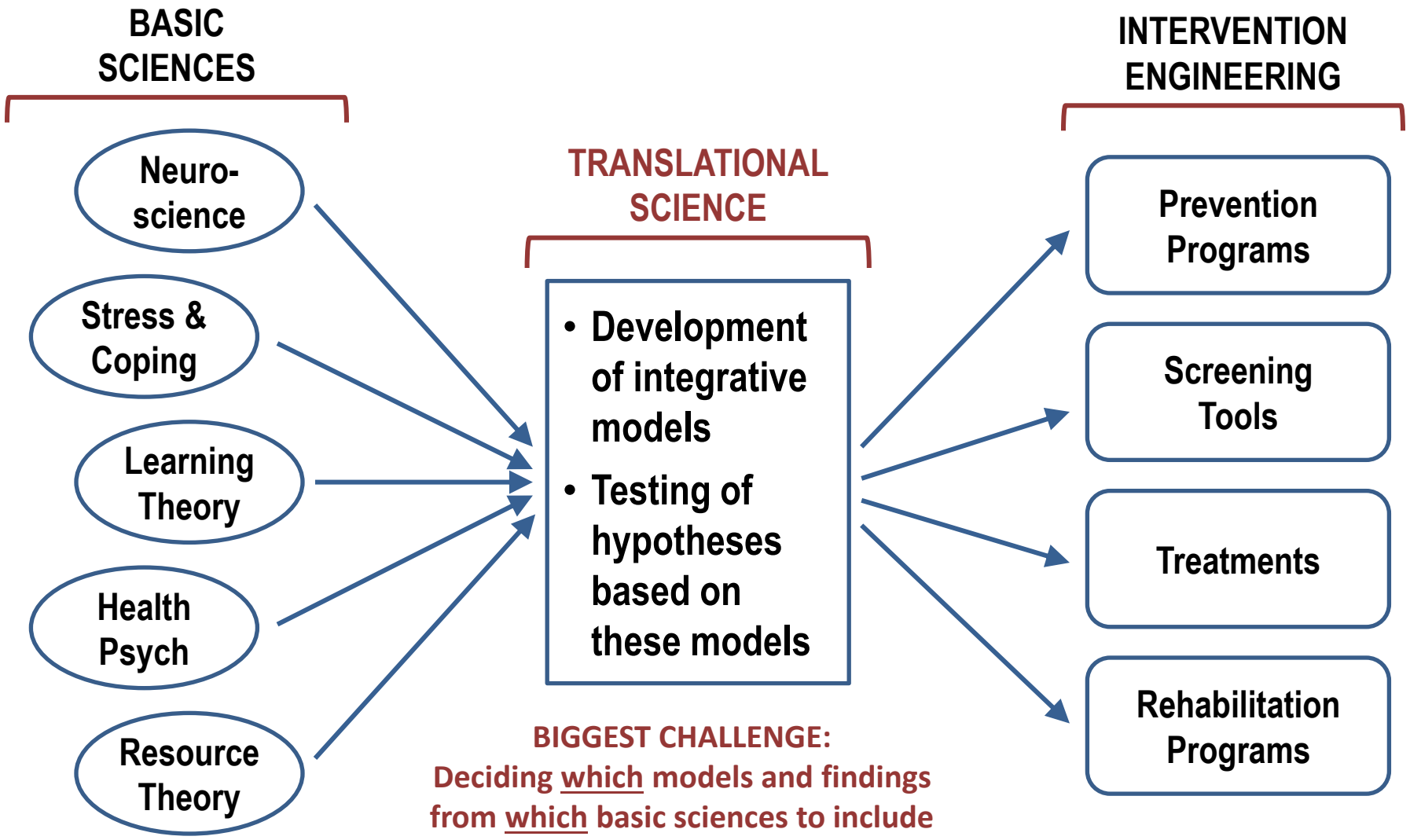
Authored numerous journal articles and book chapters, and co-edited the recent book, *Combat Stress Injury: Theory, Research, and Management*

Disclosure

- These views expressed in this presentation are my own and do not reflect the official policy of the Defense Department, University of California or the Veterans Affairs Department.
- I have no relevant financial relationships to disclose.
- I do not intend to discuss the off-label, investigative, or other unapproved uses of commercial products or devices.

“Translational science comprises the process of turning observations in the laboratory and clinic into effective interventions that improve the health of individuals and the public — from diagnostics and therapeutics to medical procedures and behavioral changes.” (National Center for Advancing Translational Sciences, 2014)

Translational Science: Link Between Basic Sciences and Health Promotion

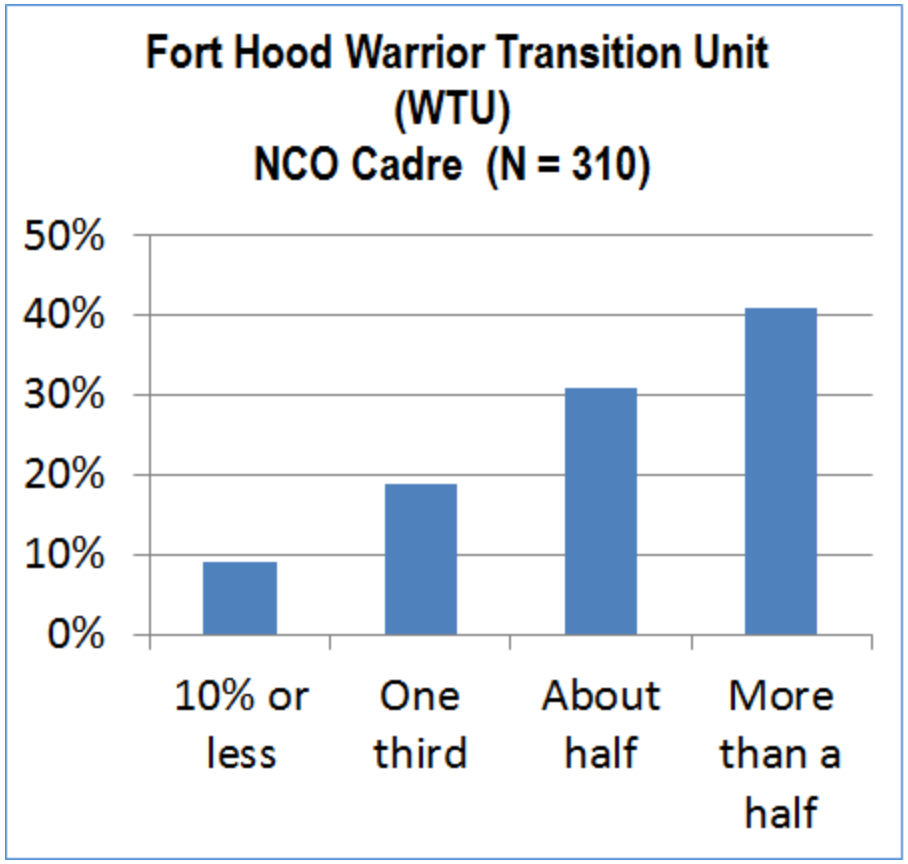


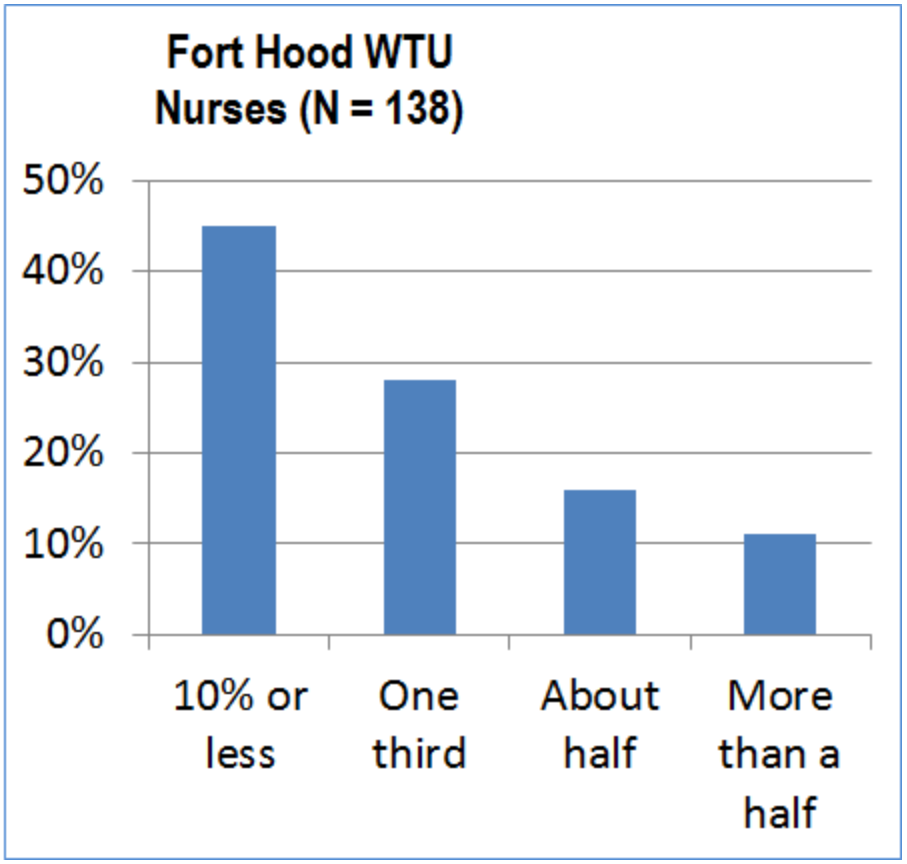
Why Neuroscience Is the One Indispensable Behavioral Stress Science

- There can be no cognition or behavior without a central nervous system (CNS)
- Brain systems that mediate normal and pathological stress states are becoming increasingly understood
- Neuroscience is our best chance to explain heterogeneities and comorbidities
- Any explanation of behavioral responses to stress that excludes neuroscience must necessarily be allegorical
- More precise explanations based on neuroscience may make more sense to non-mental health professionals
- They also reduce stigma ("it's not me, it's my brain!") while offering sound strategies for recovery (Nash, Silva, & Litz, 2009)

How Might Healthcare Professionals Contribute to Mental Health Stigma?

QUESTION: What percentage of soldiers claiming to have symptoms of PTSD do <u>you</u> think are faking or exaggerating?



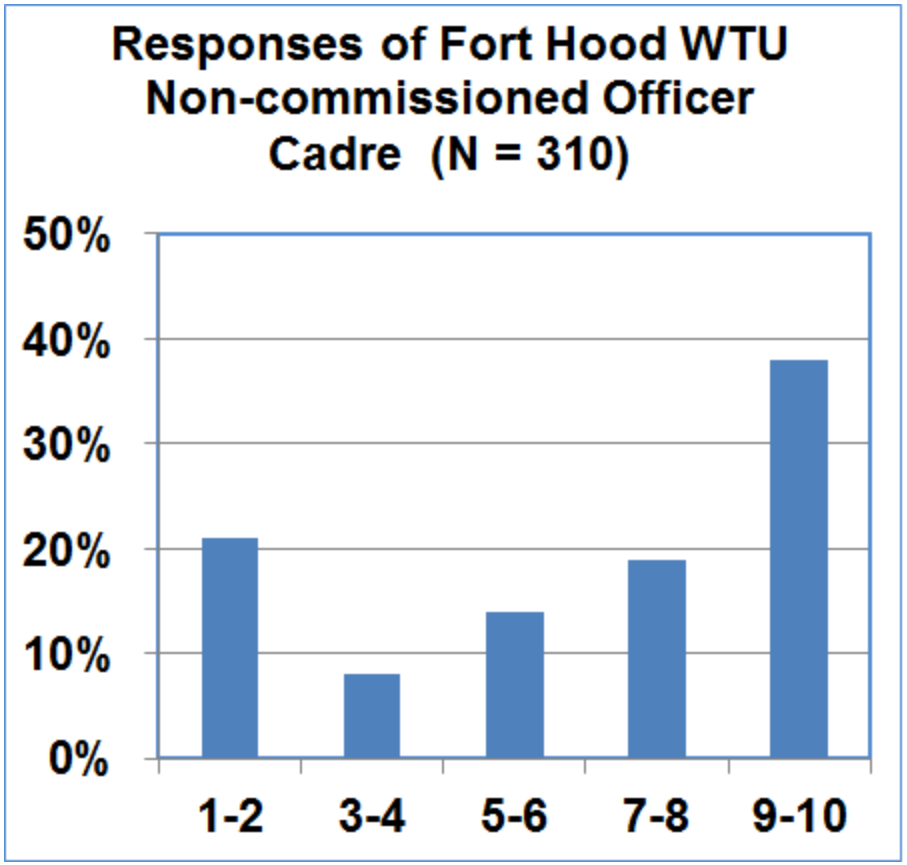


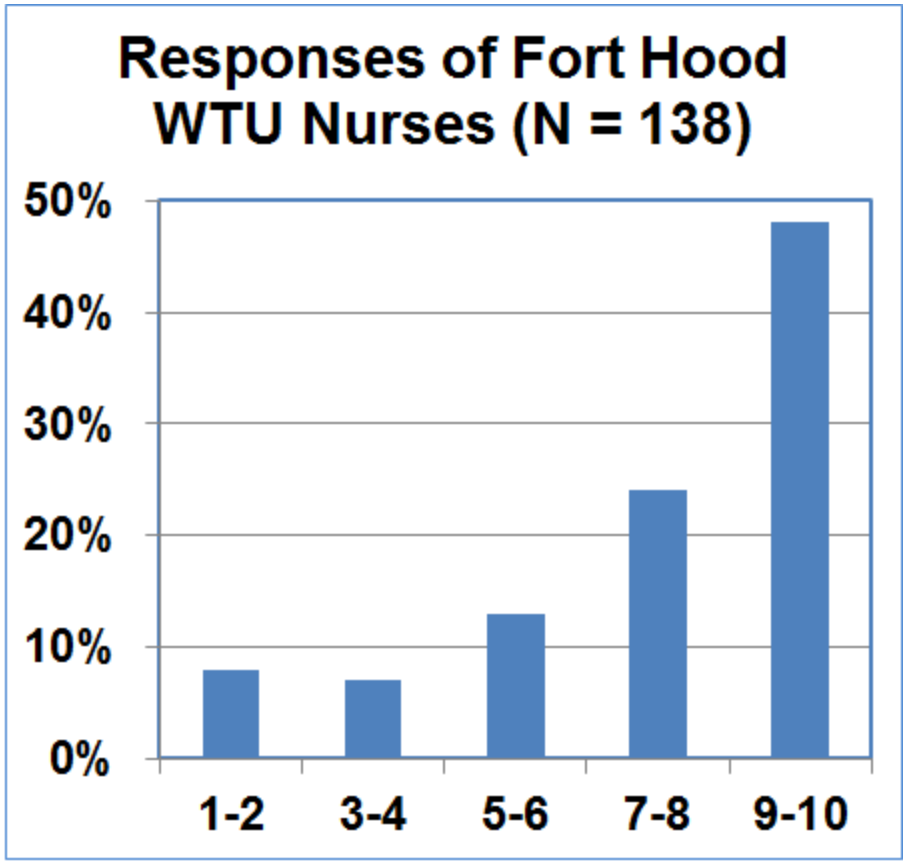
(Stahl, 2009)

How Might Healthcare Professionals Contribute to Mental Health Stigma?

QUESTION: How confident are you that PTSD is a real illness caused by military service? Likert Scale

1 = Little or no confidence **10 = Extremely confident**



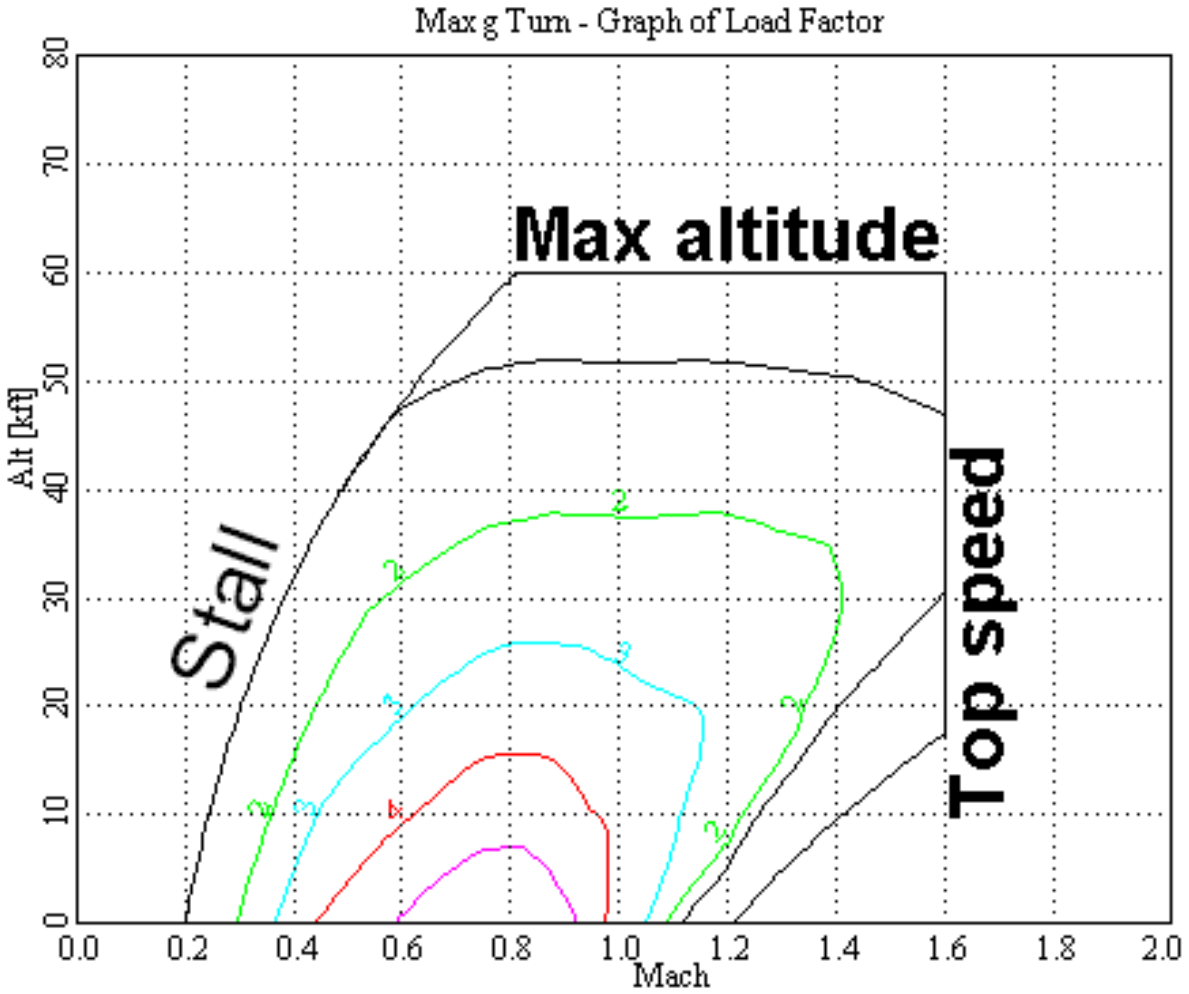


(Stahl, 2009)

The Brain Is the Organ of Coping

- **Coping:** "the person's constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the person's resources." (Lazarus & Folkman, 1984)
- Coping (whether adaptive or maladaptive) depends on intact higher cortical functioning
  - Cognitive appraisal (thinking)
  - Enacting a coping strategy (doing)
- The performance limits of the brain, therefore, define the limits of adaptive coping

Performance Envelope for a Tactical Jet



A pilot who didn't understand the performance limits of his/her aircraft might think that a stall (free-fall due to loss of lift) was merely "maladaptive flying."

A stall is not maladaptive flying.

A stall is the absence of flying.

Here is My Point

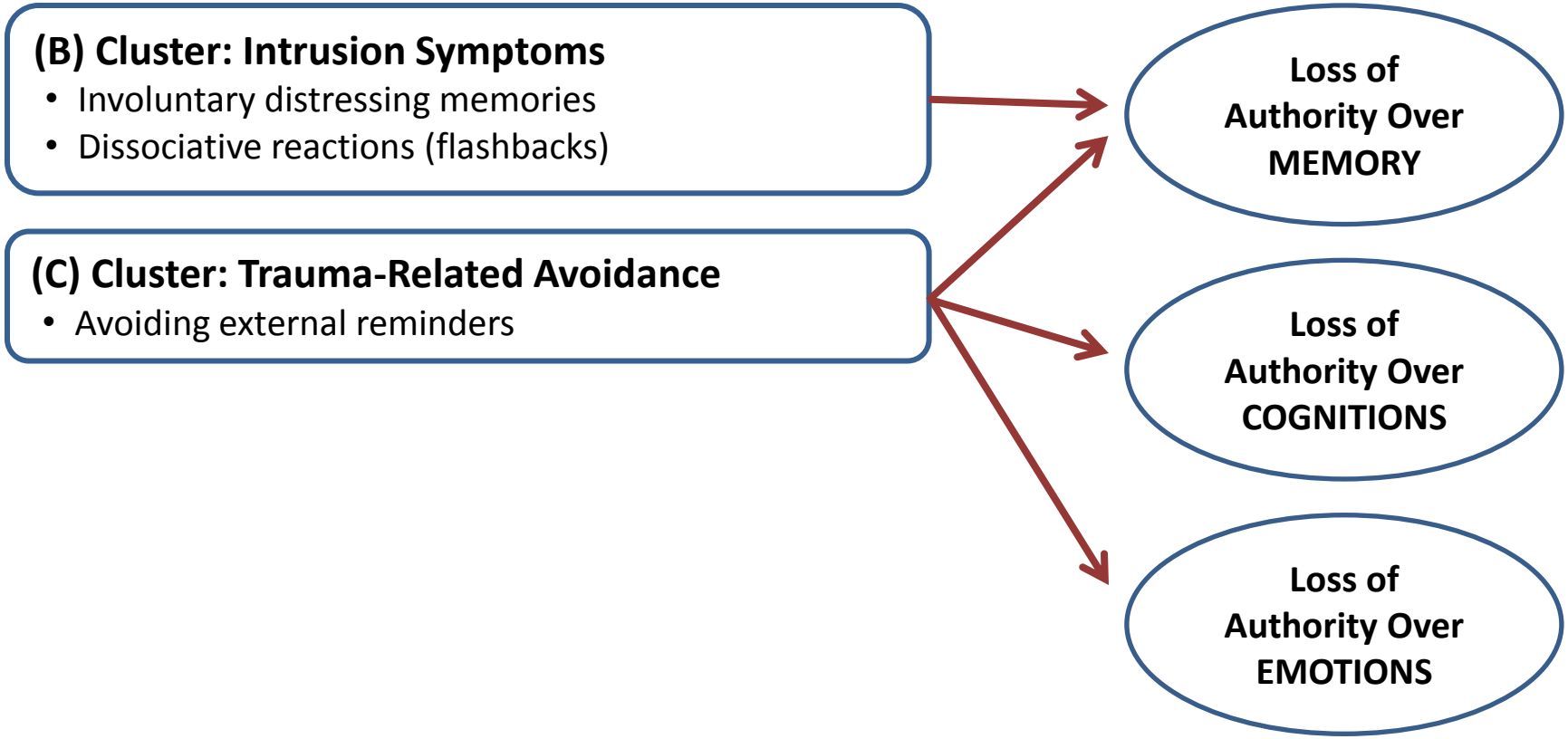
- The structure and functioning of the CNS set limits on capacities for coping and all other behavior
- Mental disorders are the result of losses of integrity in the CNS rather than maladaptive coping choices
  - PTSD
  - Major depressive disorder
  - Generalized anxiety disorder
  - Psychotic disorders
- To think and teach otherwise is to blame our patients for their own suffering

Case in Point: Many DSM-5 PTSD Symptoms Reflect Losses of Higher Cortical Functioning

(B) Cluster: Intrusion Symptoms

- Involuntary distressing memories
- Dissociative reactions (flashbacks)

Case in Point: Many DSM-5 PTSD Symptoms Reflect Losses of Higher Cortical Functioning



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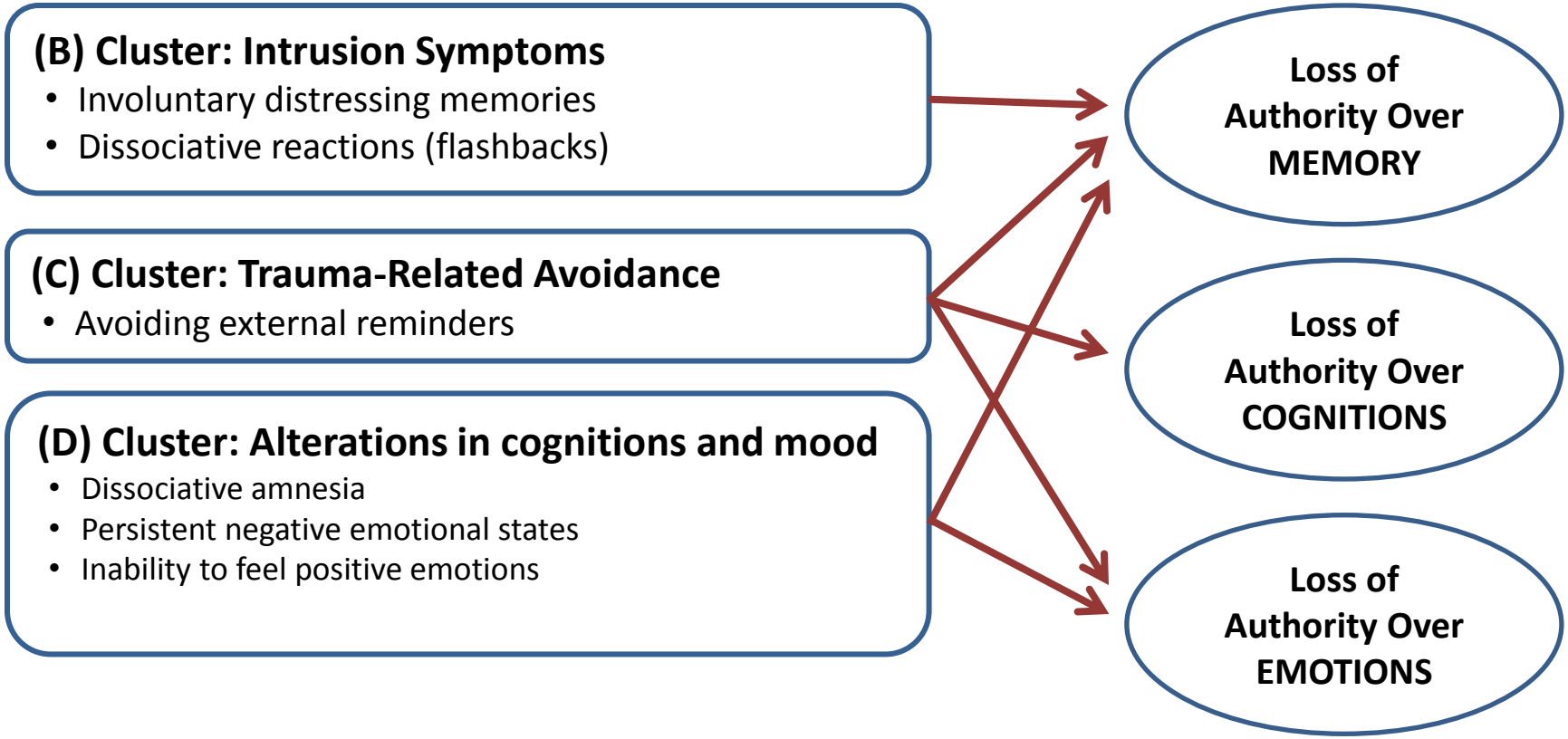

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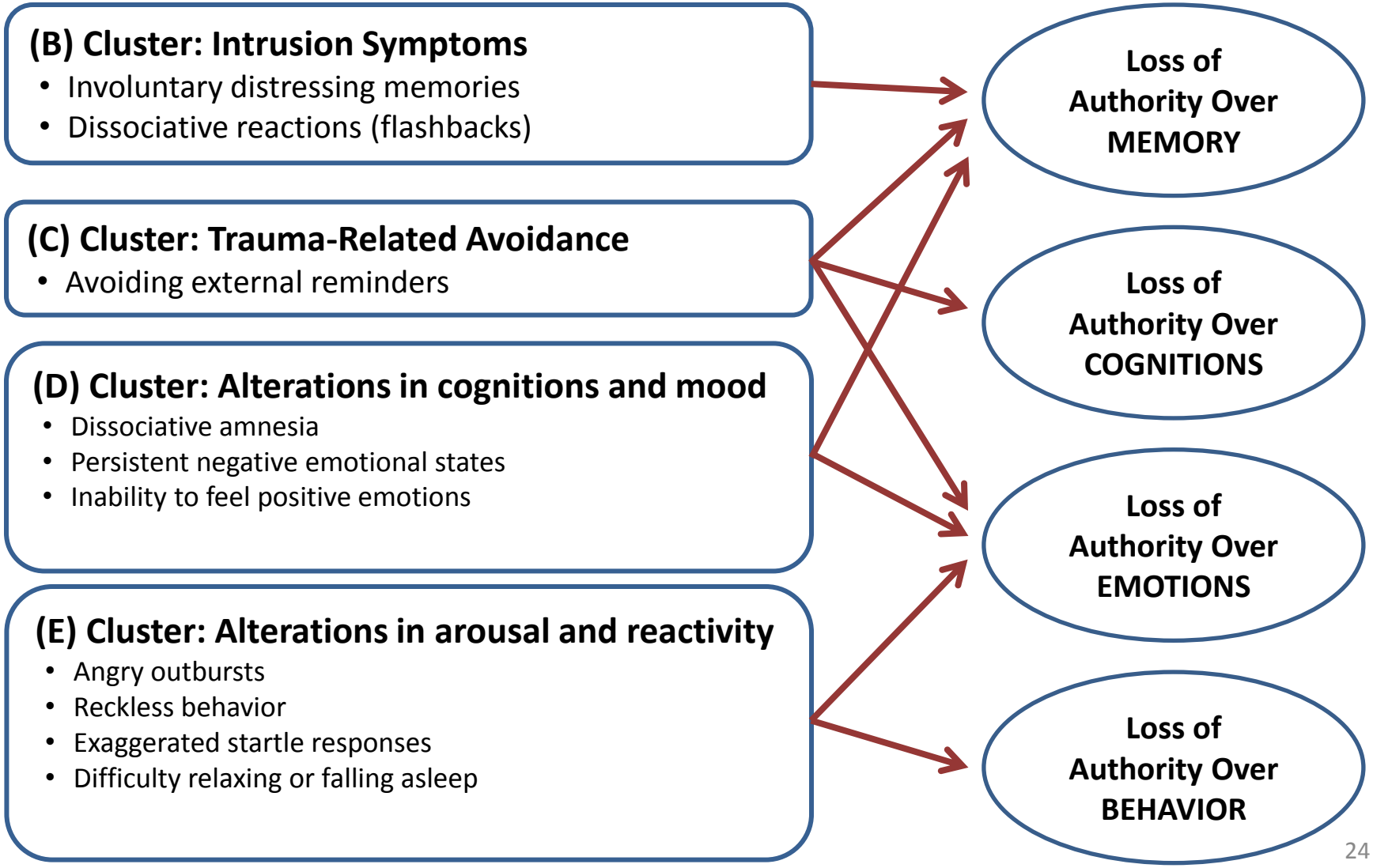
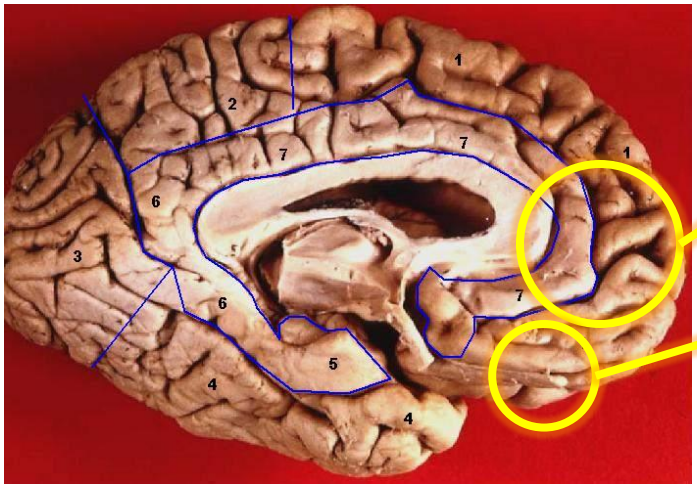
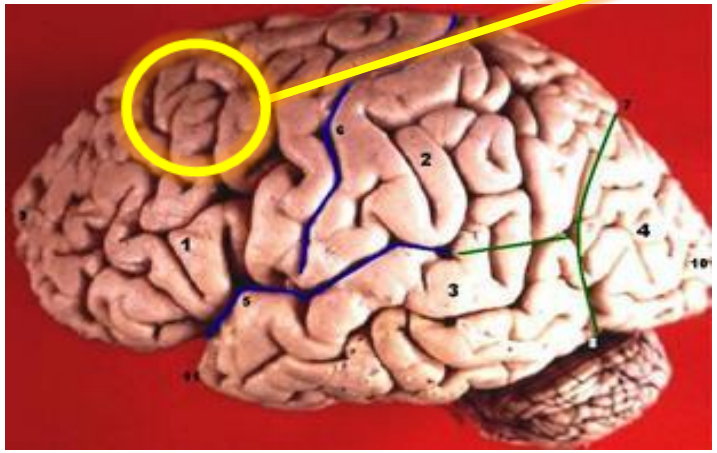


Regions of Cortex Involved in Self Regulation



"Human brain inferior-medial view" by John A. Beal, Ph.D., is licensed under CC BY



"Human brain lateral view" by John A. Beal, Ph.D. is licensed under CC BY

Medial PFC
- Volitional control of emotion

Orbitofrontal PFC
- Decision making

Dorsolateral PFC
- Volitional control of attention

Insula (not visible)
- Volitional control of arousal

Together, these regions of prefrontal and insular cortex make possible inhibition and control of emotions, thoughts, behaviors, and physiological arousal

(Bari & Robbins, 2013; Gamo & Arnsten, 2011)

Polling Question #1

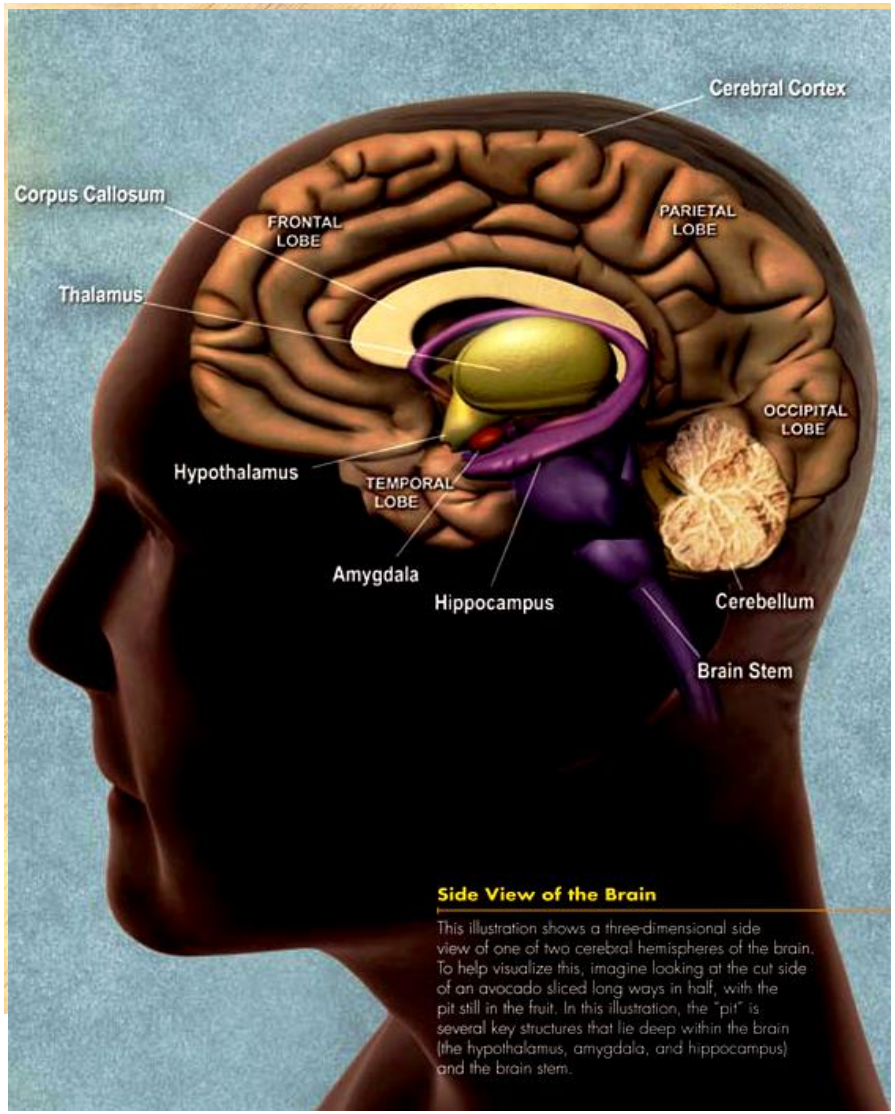
What structure was damaged on both sides of the brain of Drew Barrymore's character in "50 First Dates" making it impossible for her to record new long-term memories?

A. Hippocampus
B. Amygdala
C. Nucleus accumbens
D. Orbitofrontal pre-frontal cortex (PFC)

Hippocampus: Gray-Matter Partner to PFC

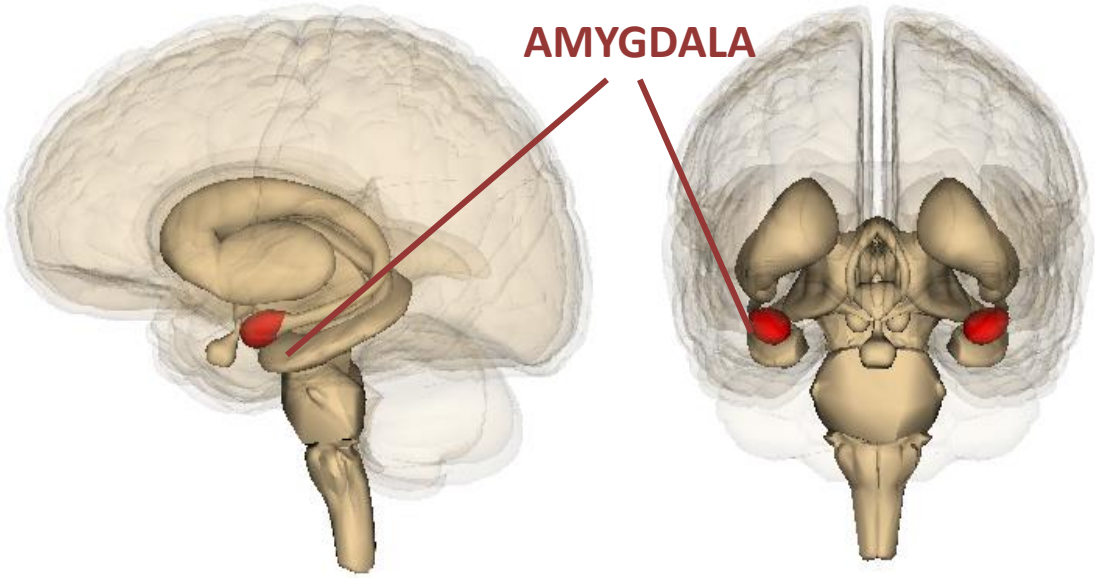
FUNCTIONS

- Declarative memory: laying down and consolidation of recallable memory
- Inhibition (along with PFC)
- Fear extinction
- Spatial mapping (GPS)
- May also be crucial for constructing a coherent mental image, whether from current perception or memory (Bird, Bisby, & Burgess, 2012)



"Side view of the brain" graphic courtesy of the National Institute on Aging

Amygdala: Important Target for Control by PFC and Hippocampus



FUNCTIONS

- Puts "emotional stamp" on memories
- Fear, anger, (etc.?)
- Threat detector
- Social recognition
- Fear conditioning
- Appetitive conditioning?

(Fernando, Murray, & Milton, 2013)

Polling Question #2

Which neurotransmitter in the brain is most directly involved with experiences of pleasure, including the “rush” of engaging in risky behavior?

A. Adrenaline
B. Epinephrine
C. Serotonin
D. Dopamine

Nucleus Accumbens: Another Important Target for Control By PFC and Hippocampus

FUNCTIONS

- Reward, pleasure
- Well-being
- Motivation
- Focus, attention
- Goal-directed behavior
- Addiction, craving

(Burton, Nakamura, & Roesch, 2014)

NUCLEUS ACCUMBENS
and Mesocortical Dopamine Pathway

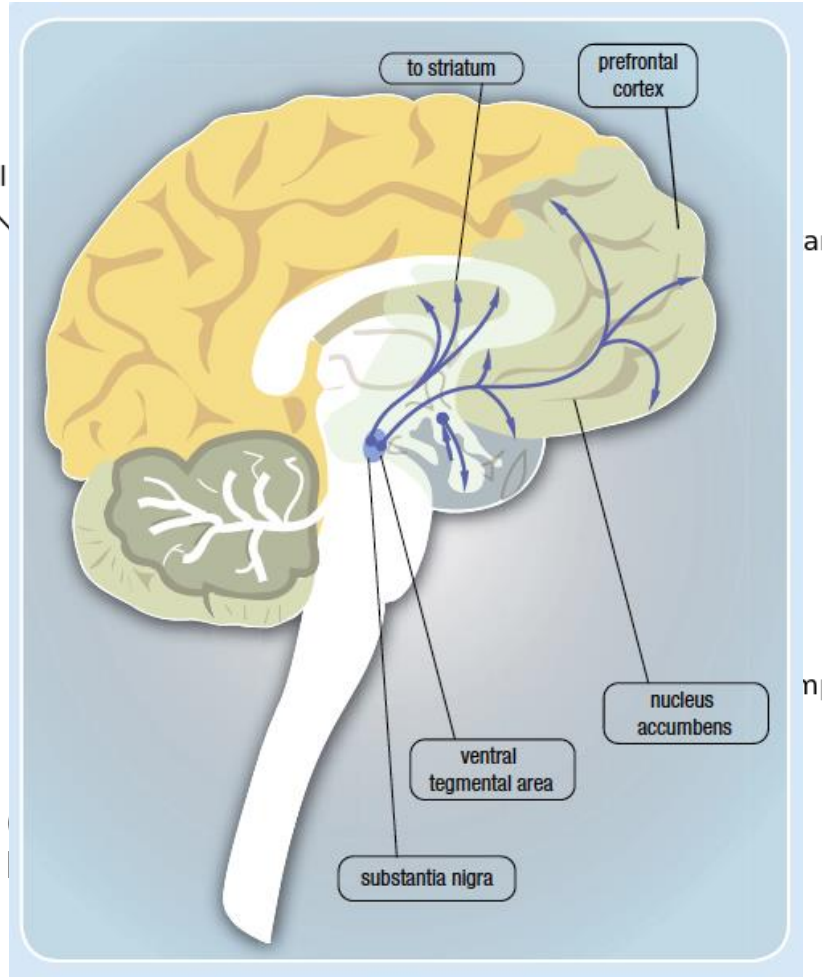
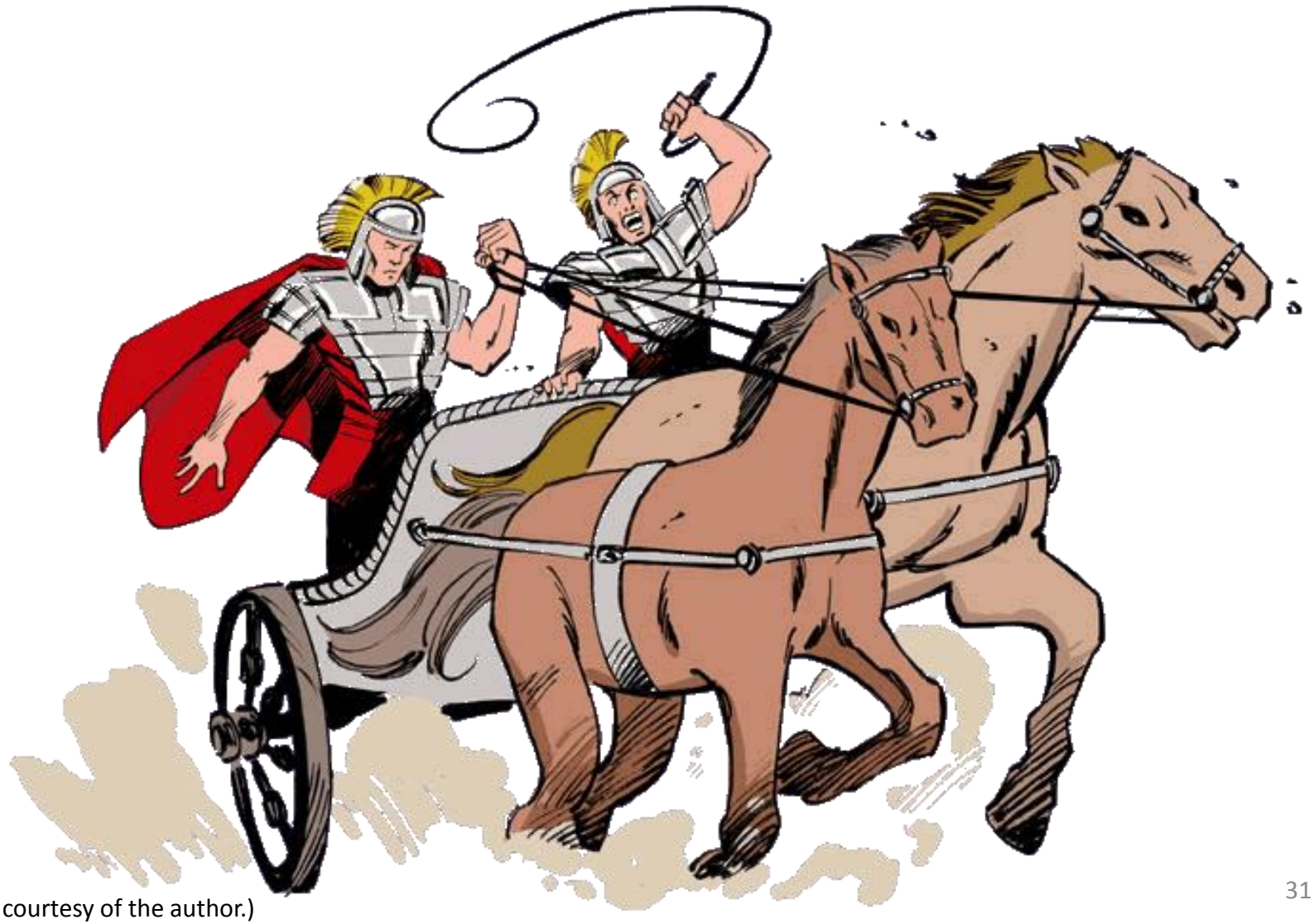


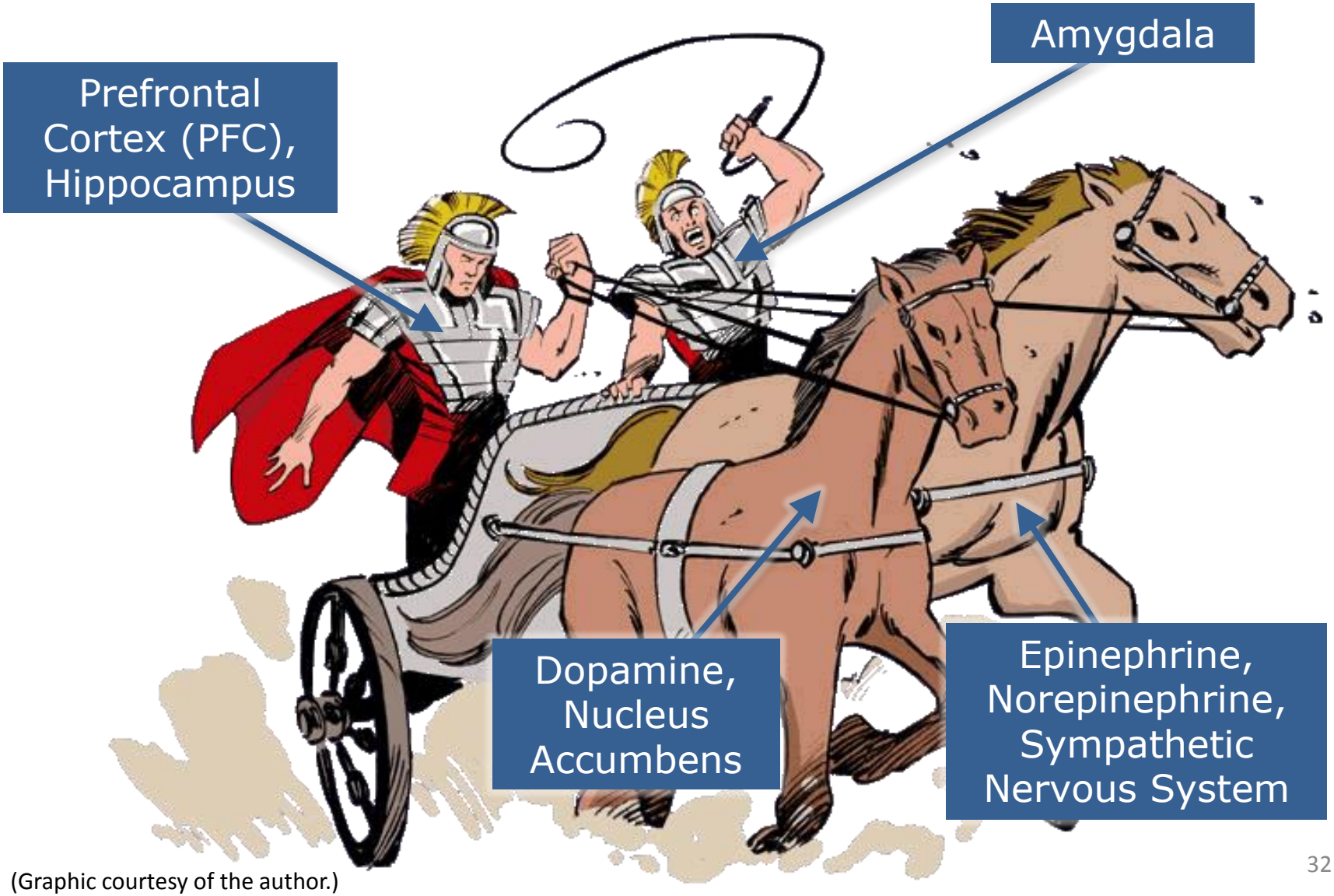
Image courtesy of the National Institute of Drug Abuse

Crude Analogy for Neurobiology of Stress



(Graphic courtesy of the author.)

Neurobiology of **Normal** Stress



(Graphic courtesy of the author.)

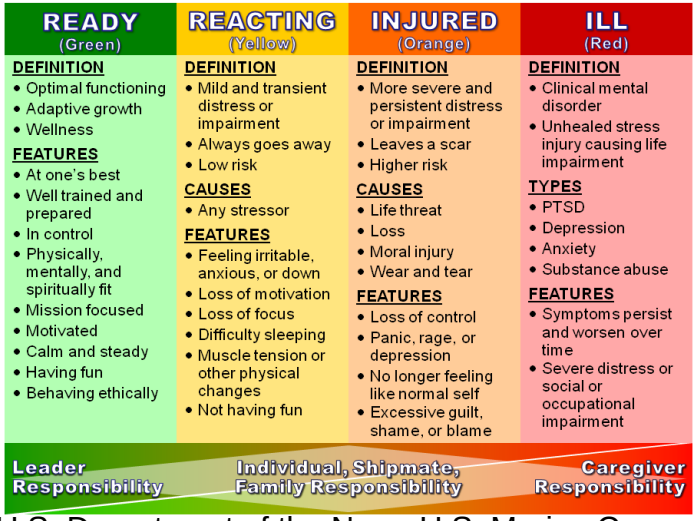
The U.S. Navy and U.S. Marine Corps Stress Continuum Model

Normal Stress (Yellow Zone)

- Of moderate intensity & short duration (stress reaction)
- Controllable
- All effects are reversible
- Constructive

Extreme Stress (Orange Zone)

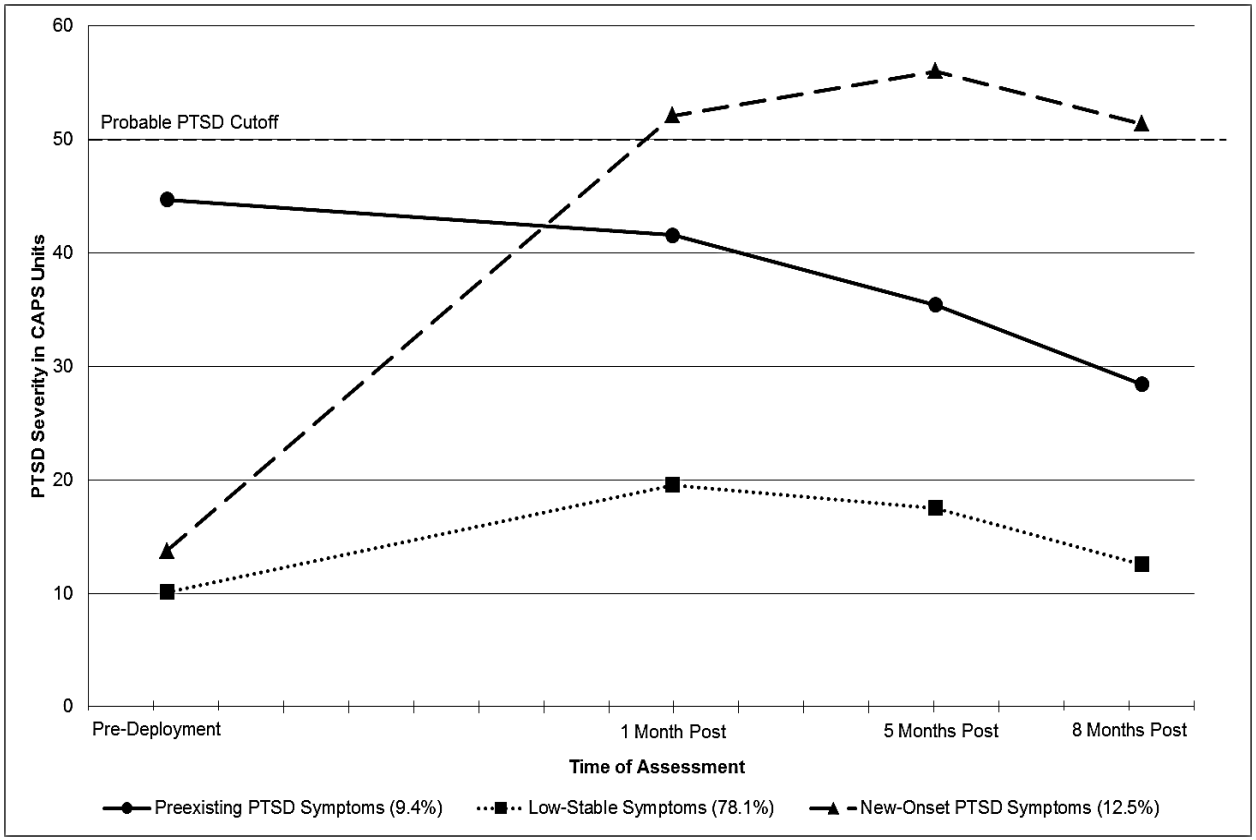
- Of high intensity or long duration (stress injury)
- Uncontrollable
- Some effects are irreversible
- Destructive



U.S. Department of the Navy, U.S. Marine Corps, 2010

Disruption in Functioning at the Time of Trauma is a Strong Predictor of PTSD

PTSD trajectories in N = 867 highly combat-exposed Marines



Predictors of new-onset PTSD Symptoms (relative to low-stable symptoms):

- Prior lifespan trauma: *p*=.036
- Combat experiences: *p*=.071
- Peritraumatic dissociation: *p*<.001

(Nash, Boasso, Steenkamp, Larson, Lubin, & Litz, manuscript submitted for publication)

A Few Molecular Modulators of Stress

- Corticotropin-releasing factor (CRF)
- Cortisol
- Brain-derived neurotrophic factor (BDNF) and other neurotropins
- Glutamate (Glu) acting at N-methyl-d-aspartate (NMDA) receptors

Polling Question #3

What type of chemical messenger is corticotropin-releasing factor (CRF)?

A. A hormone released into a bloodstream as part of the endocrine system
B. A neurotransmitter released into synapses by specialized neurons in the brain
C. Both A and B

CRF, Cortisol, and BDNF

- CRF is the master stress modulator ("on" switch for stress)
- CRF is both:
  - A hormone released in the hypothalamus triggering release of corticosteroids like cortisol from adrenal cortex
  - A neurotransmitter used by a diffuse network of neurons in the brain
- Both CRF and cortisol have biphasic activity in the brain:
  - At low to moderate levels, they improve performance, learning, and well-being
  - At high or sustained levels, they degrade performance, learning, and well-being
- Cortisol interacts with BDNF to stimulate growth of new dendrites, synapses, and entire neurons, but in different brain systems depending on stress level

(Sapolsky, 2003; Bennet & Lagopoulos, 2014)

Differential CRF, Cortisol, and BDNF Effects at Low–Moderate versus Extreme Stress

Brain systems	Low–Moderate Stress	Extreme Stress
PFC & Hippocampus	• ↑ in density of dendrites and synapses • ↑ in numbers of neurons	• ↓ in density of dendrites and synapses • ↓ in numbers of neurons
Amygdala	• ↓ in density of dendrites and synapses • ↓ in numbers of neurons	• ↑ in density of dendrites and synapses • ↑ in numbers of neurons
Nucleus accumbens	• ↑ in dopamine release • ↑ in well-being • ↑ in motivation, problem-solving (active coping)	• ↓ in dopamine release • ↓ in well-being • ↓ in motivation, problem-solving (avoidant coping)

(Bennet & Lagopoulos, 2014; Davidson & McEwen, 2012; de Quervain, Aerni, Schelling & Roozendaal, 2009; Lemos et al., 2012; McEwen, 2013; Sapolsky, 2003)

Polling Question #4

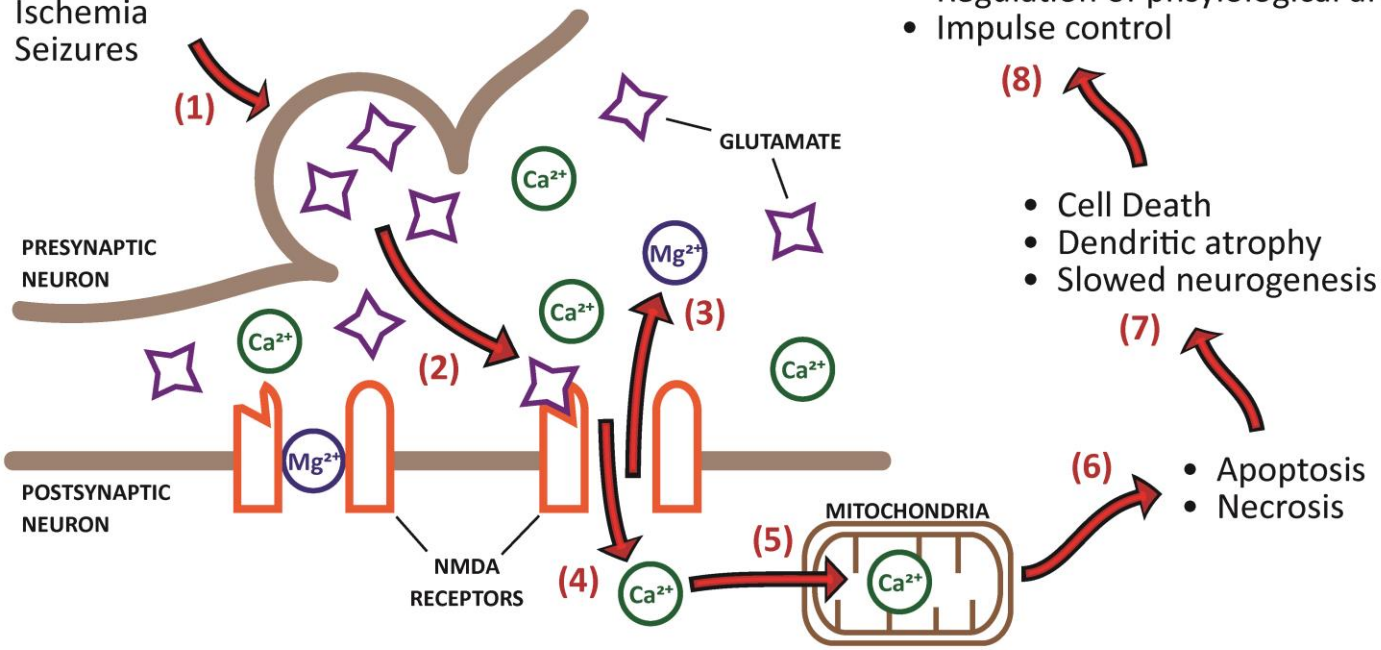
In which of the following tissues can excessive glutamate signaling mediated by NMDA receptors result in the death of neurons?

A. Retina of the eye
B. Hair cells of the inner ear
C. Hippocampus
D. Prefrontal cortex
E. All of the above

Excitotoxicity

Excessive Glutamate Neuron Excitation Due To:

- Acute stress (e.g., trauma)
- Chronic stress
- Traumatic brain injury (TBI)
- Ischemia
- Seizures



Functional Impairment of:

- Integration of memory
- Extinction of fear-based learning
- Emotional regulation
- Regulation of phsyiological arousal
- Impulse control

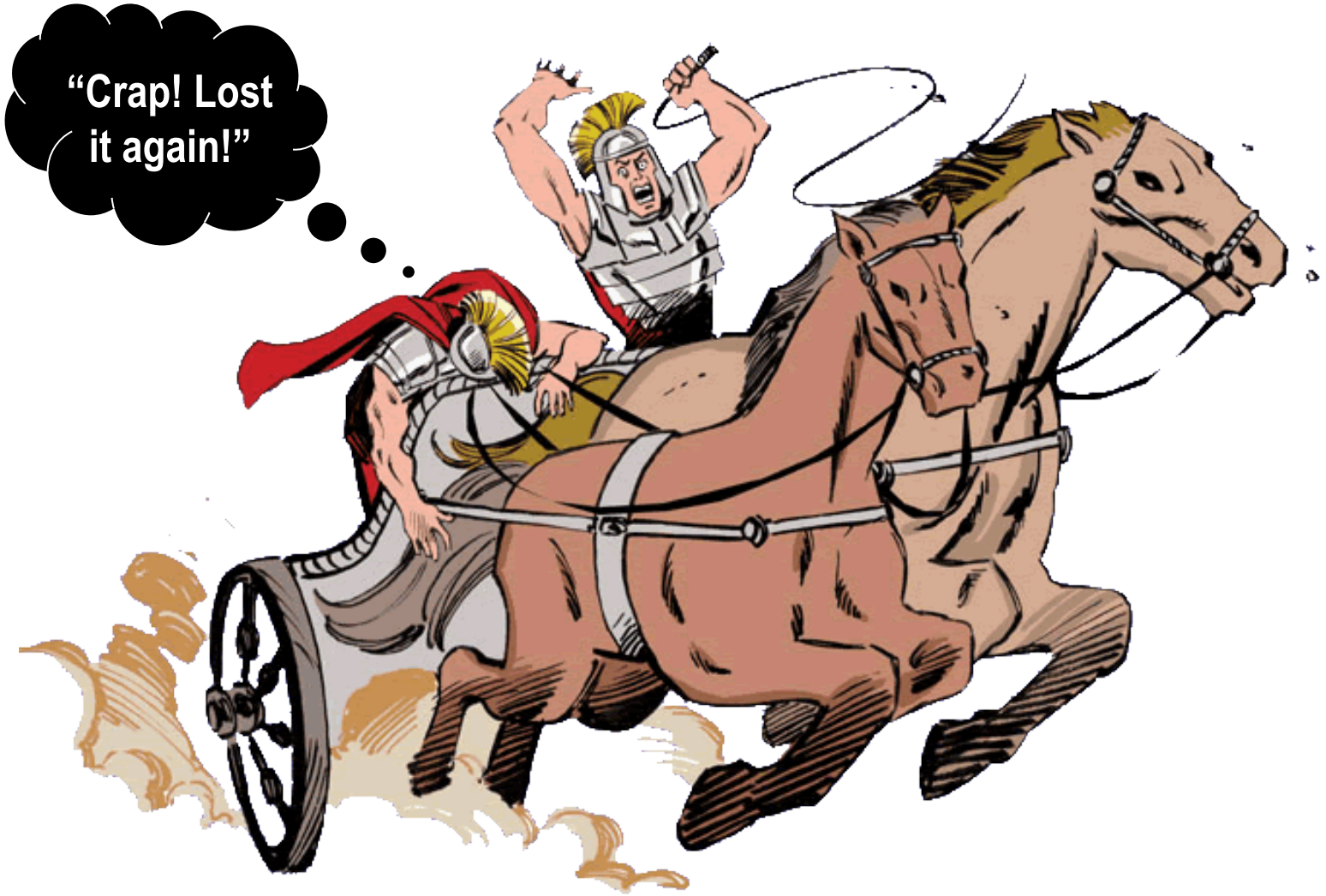
- Cell Death
- Dendritic atrophy
- Slowed neurogenesis

- Apoptosis
- Necrosis

Figure 1. Excitotoxic cascade leading to damage of glutamate neurons, mediated by N-methyl-D-aspartate (NMDA) receptors. Sequence: (1) Glutamate neuron excitation,; (2) Synaptic release of glutamate and binding to NMDA receptors; (3) Removal of Mg^{2+} from pore; (4) Influx of Ca^{2+}; (5) Uptake of Ca^{2+} by mitochondria; (6) Premature programmed cell death (apoptosis) or necrosis triggered by Ca^{2+}; (7) Cell death, atrophy, or slowed regrowth; (8) Functional impairment.

Graphic courtesy of Robert P. Nash

Neurobiology of **Extreme** Stress



(Graphic courtesy of the author.)

Conclusions

- Whereas normal stress promotes learning, functioning, and well-being, extreme stress damages the CNS
- Health promotion programs that ignore neurobiology have limited relevance to situations of extreme stress
- Indicated prevention programs should target signs and symptoms of crossing the threshold from normal to extreme stress (e.g., peritraumatic dissociation)
- Treatment programs should incorporate neurobiology to enhance validity and reduce stigma

References

Bari, A., & Robbins, T. W. (2013). Inhibition and impulsivity: Behavioral and neural basis of response control. *Progress in Neurobiology, 108*, 44-79. doi:10.1016/j.pneurobio.2013.06.005

Bennet, M. R., & Lagopoulos, J. (2014). Stress and trauma: BDNF control of dendritic-spine formation and regression. *Progress in Neurobiology, 112*, 80-99. doi:10.1016/j.pneurobio.2013.10.005

Bird, C. M., Bisby, J.A., & Burgess, N. (2012). The hippocampus and spatial constraints on mental imagery. *Frontiers in Human Neuroscience, 6*, 1-12. doi:10.3389/fnhum.2012.00142

Burton, A. C., Nakamura, K., & Roesch, M. R. (2014). From ventral-medial to dorsal-lateral striatum: Neural correlates of reward-guided decision-making. *Neurobiology of Learning and Memory*. Advance online publication. doi:10.1016/j.nlm.2014.05.003

Davidson, R. J., & McEwen, B. S. (2012). Social influences on neuroplasticity: Stress and interventions to promote well-being. *Nature Neuroscience, 15*(5), 689-695. doi:10.1038/nn.3093

de Quervain, D.J., Aerni, A., Schelling, G., & Roozendaal, B. (2009). Glucocorticoids and the regulation of memory in health and disease. *Frontiers in Neuroendocrinology, 30*(3), 358-370. doi:10.1016/j.yfrne.2009.03.002

Fernando, A. B .P., Murray, J. E., & Milton, A. L. (2013). The amygdala: Securing pleasure and avoiding pain. *Frontiers in Behavoiral Neuroscience, 7*, 1-15. doi:10.3389/fnbeh.2013.00190

Gamo, N. J., & Arnsten, A. F. T. (2011). Molecular modulation of prefrontal cortex: Rational development of treatments for psychiatric disorders. *Behavioral Neuroscience, 125*(3), 282-296. doi:10.1037/a0023165

Lazarus, R. S., & Folkman, S. (1984). Stress, appraisal, and coping. New York: Springer.

References

Lemos, J. C., Wanat, M. J., Smith, J. S., Reyes, B. A. S., Hollon, N. G., Van Bockstaele, E. J.,…Phillips, P. E. M. (2012). Severe stress switches CRF action in the nucleus accumbens from appetitive to aversive. *Nature, 490*(7420), 402-407. doi:10.1038/nature11436

McEwen, B. S. (2013). Brain on stress: How the social environment gets under the skin. *Proceedings of the National Academy of Sciences, 109*(S2), 17180-17185. doi:10.1073/pnas.1121254109

Nash, W. P., Boasso, A. M., Steenkamp, M. M., Larson, J. L., Lubin, R. E., & Litz, B. T. Posttraumatic stress in deployed Marines: Prospective trajectories of early adaptation. Manuscript submitted for publication.

Nash, W. P., Silva, C., & Litz, B. T. (2009). The historical origins of military and veteran mental health stigma and the stress injury model as a means to reduce it. *Psychiatric Annals, 39*(8), 789-794. doi:10.3928/00485713-20090728-05

National Center for Advancing Translational Sciences. (2014). About NCATS. Retrieved 19 June 2014, from http://www.ncats.nih.gov/about/about.html

National Institute on Drug Abuse. (Revised 2013). Methamphetamine. Retrieved 18 June 2014 from http://www.drugabuse.gov/publications/research-reports/methamphetamine

Sapolsky, R.M. (2003). Stress and plasticity in the limbic system. *Neurochemical Research, 28*(11), 1735-1742.

Stahl, S. M. (2009). Crisis in Army psychopharmacology and mental health care at Fort Hood. *CNS Spectrums, 14*(12), 677-684.

U.S. Department of the Navy, U.S. Marine Corps. (2010) *Combat and operational stress control* (NTTP 1-15M/MCRP 6-11C). Retrieved from http://www.med.navy.mil/sites/nmcsd/nccosc/coscConference/Documents/COSC%20MRCP%20NTTP%20Doctrine.pdf

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