NEUROPSYCHOLOGICAL FUNCTIONING IN POSTTRAUMATIC STRESS DISORDER

Kristi Samuelson, PhD

Assistant Professor, University of Colorado at Colorado Springs

San Francisco VA

Lane Center Veteran Health and Trauma Clinic, UCCS

Outline

- Neuropsychological functioning in PTSD and alcohol abuse: Teasing out the effects of comorbid conditions
- Longitudinal changes in brain anatomy and neuropsychological functioning in PTSD: Is PTSD a risk factor for cognitive aging?
- Neuropsychological functioning and inflammation in current, remitted, and past PTSD
- Future research goals

Neuropsychological Functioning in PTSD and Alcohol Abuse

- Prior research: deficits in verbal memory, working memory, attention in patients with PTSD (Gilbertson et al., 2002; Vasterling et al., 1998; Vasterling et al., 2002)

- Unclear if deficits were in fact due to PTSD or common comorbid conditions -- alcohol abuse

Samuelson, K.W., Neylan, T., Metzler, T., Lenoci, M., Rothlind, J., Henn-Haase, C., Choucroun, G., Weiner, M., & Marmar, C. (2006). Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse, Neuropsychology, 20, 716-726.

Neuropsychological Functioning in PTSD and Alcohol Abuse

- Prior studies had statistically controlled for effects, or excluded patients with alcohol abuse from PTSD studies.
- Ideal model – removes effect of alcohol AND examines interactive effects of PTSD and alcohol

Neuropsychological Functioning in PTSD and Alcohol Abuse

2x2 Design

PTSD + **ETOH +** *(With PTSD and alcohol abuse or dependence in last 5 years)* **N=30**	**PTSD +** **ETOH -** *(With PTSD and without alcohol abuse or dependence)* **N=37**
PTSD - **ETOH +** *(Without PTSD and with alcohol abuse or dependence)* **N=30**	**PTSD -** **ETOH -** *(Without PTSD and without alcohol abuse or dependence)* **N=31**

128 veterans, ages 20-60 (*M* = 47), 90% male, 73% White, majority Vietnam era

PTSD assessed via Clinician-Administered PTSD Scale (CAPS)

Alcohol abuse and dependence assessed via Structured Clinical Interview for DSM Disorders (SCID) – past 5 year history

Sample

	PTSD+ ETOH+ (N=30) Mean (SD)	PTSD+ ETOH- (N=37) Mean (SD)	PTSD- ETOH+ (N=30) Mean (SD)	PTSD- ETOH- (N=31) Mean (SD)	*F* • Main effect for PTSD • Main effect for ETOH • Interactive Effect	*p*	Significant Differences
Age	48.57 (7.7)	47.89 (9.4)	43.6 (12.0)	46.42 (9.6)	*F* (3, 121) = 7.863 *F* (3,121) = .089 *F* (3,121) = .349	. 065 .537 .315	None
Education	13.50 (1.6)	14.89 (2.4)	14.17 (1.7)	15.39 (2.0)	F (3, 124) = 2.69 F (3, 124) = 13.58 F (3, 124) = .059	.104 .000 .809	ETOH+ <ETOH-
SCL-90 Depression	1.77 (.72)	1.85 (.96)	.70 (.47)	.46 (.72)	F (3, 124) = 85.14 F (3, 124) = .346 F (3, 124) = 1.40	.000 .557 .240	PTSD+ > PTSD-
WAIS-III Vocabulary	46.40 (10.63)	50.08 (9.58)	51.47 (7.54)	53.87 (8.17)	F (3, 124) = 7.55 F (3, 124) = 3.56 F (3, 124) = .157	.007 .061 .693	PTSD+ < PTSD-
LDH Total Drinks	88,614 (85039)	23,183 (38704)	48,453 (41218)	17,761 (45412)	F (3, 122) = 5.34 F (3, 122) = 23.78 F (3, 122) = 3.106	.022 .000 .081	PTSD+ > PTSD- ETOH+ > ETOH-

Neuropsychological Functioning in PTSD and Alcohol Abuse

Individual ANCOVAS (covarying for education, premorbid IQ estimate, depression, current alcohol use) on measures of:

- Verbal Learning
- Verbal Delayed Memory
- Visual Immediate Memory
- Visual Delayed Memory
- Working Memory
- Attention
- Processing Speed

Applied Bonferroni correction

Assessed main and interactive effects

Neuropsychological Functioning in PTSD and Alcohol Abuse

- Main effect of PTSD on:
  - Verbal learning
    - CVLT Total: F (3, 121) = 7.863, p = .006
  - Working memory
    - Digit Span: F (3, 121) = 12.90, p < .001
    - Letter Number Sequencing: F (3, 112) = 12.48, p = .001
  - Processing Speed
    - Digit Symbol: F (3,109) = 11.73, p = .001

Neuropsychological Functioning in PTSD and Alcohol Abuse

- Main effect of Alcohol Abuse on:
  - Visual Immediate Memory
    - WMS-III Visual Immediate Memory Index: F (3,121) = 6.41, p = .013
- No interaction effects or main effect of PTSD
- Significant differences, but functioning still in average range
- Neuropsychological differences are attributable to PTSD, and not confounding alcohol abuse diagnoses.

PTSD and the Aging Brain

Is PTSD a risk factor for dementia or accelerated aging?

- Examined longitudinal trajectory of neurocognitive performance and neuroanatomical changes in a sample of 47 primarily Vietnam-era veterans:

Samuelson, K.W., Neylan, T., Lenoci, M., Metzler, T., Cardenas, V., Weiner, M., & Marmar, C. (2009). Longitudinal effects of PTSD on memory functioning. Journal of the International Neuropsychological Society, 15, 853-861.

Cardenas-Nicolson, V., Samuelson, K.W, Lenoci, M., Studholme, C., Neylan, T., Marmar, C., Schuff, N., & Weiner, M. (2011). Changes in brain anatomy during the course of PTSD. Psychiatry Research, 193, 93-100.

Longitudinal Changes in Brain Anatomy and Neuropsychological Functioning in PTSD

Longitudinal images and neuropsychological data were analyzed to:

- Determine the extent to which PTSD accelerates brain atrophy and neurocognitive deficits
- Determine anatomy underlying any cognitive decline

Sample

	PTSD-	PTSD+	P-value
Baseline Age (yrs)	52 ± 6 (39-60)	51 ± 7 (33-60)	0.37
Follow-up Age (yrs)	55 ± 6 (41-63)	53 ± 7 (37-63)	0.44
Education (yrs)	16 ± 2 (12-20)	15 ± 2 (12-20)	0.01
Interval (yrs)	2.6 ± 0.4 (2.0-3.4)	3.0 ± 0.6 (2.0-4.0)	0.13
Baseline CAPS	2 ± 3 (0-11)	61 ± 15 (31-92)	<0.0001
Follow-up CAPS	2 ± 3 (0-11)	52 ± 18 (19-84)	<0.0001

- N = 47, assessed over 2-5 years
- Primarily Vietnam veterans
- ALL PTSD+ participants continued to meet PTSD diagnostic criteria at T2

Longitudinal Changes in Brain Anatomy and Neuropsychological Functioning in PTSD

- No evidence of a group x time x age interaction on neuropsychological performance
- Inconsistent with Yehuda et al. (2006) findings of worse decline in verbal memory performance in Holocaust survivors with PTSD
- Middle aged sample, high mean education (almost 16 years)

Longitudinal Changes in Brain Anatomy and Neuropsychological Functioning in PTSD

- No differences between PTSD+ and PTSD- groups: Longitudinal course of PTSD heterogeneous
- No evidence for accelerated aging in PTSD+ patients with *improving* symptomatology
- *Stable* or *declining* PTSD+ patients show accelerated aging in frontal and temporal lobes, subcortical white matter, brainstem, and cerebellum
- Longitudinal atrophy in the precuneus predicted longitudinal decline in verbal memory
  - Decreased precuneus activation during encoding in PTSD (Geuze et al., 2008); associated with dementia (Buckner, 2004)

PTSD and the Aging Brain

- Archival Dementia Study at SFVA – N = 181,903. Vets with PTSD had almost twice risk of dementia (10.6% to 6.6%) (*Yaffe et al., 2010, Archives of General Psychiatry)*

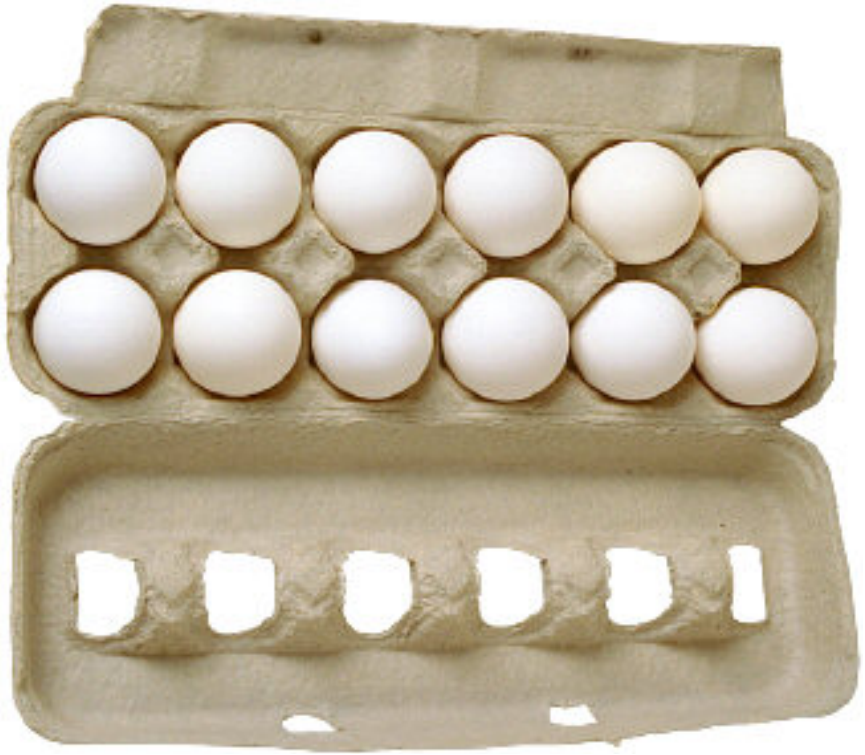
- Current SFVA Study: Effects of TBI and PTSD on Alzheimer's disease in Veterans (Weiner, PI)
  - Longitudinal study of Vietnam veterans (age 60-80) with TBI or PTSD
    - Will TBI and PTSD groups show accelerated rates of atrophy and cognitive decline (amyloid PET scans, MRI, neuropsych testing)?

Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

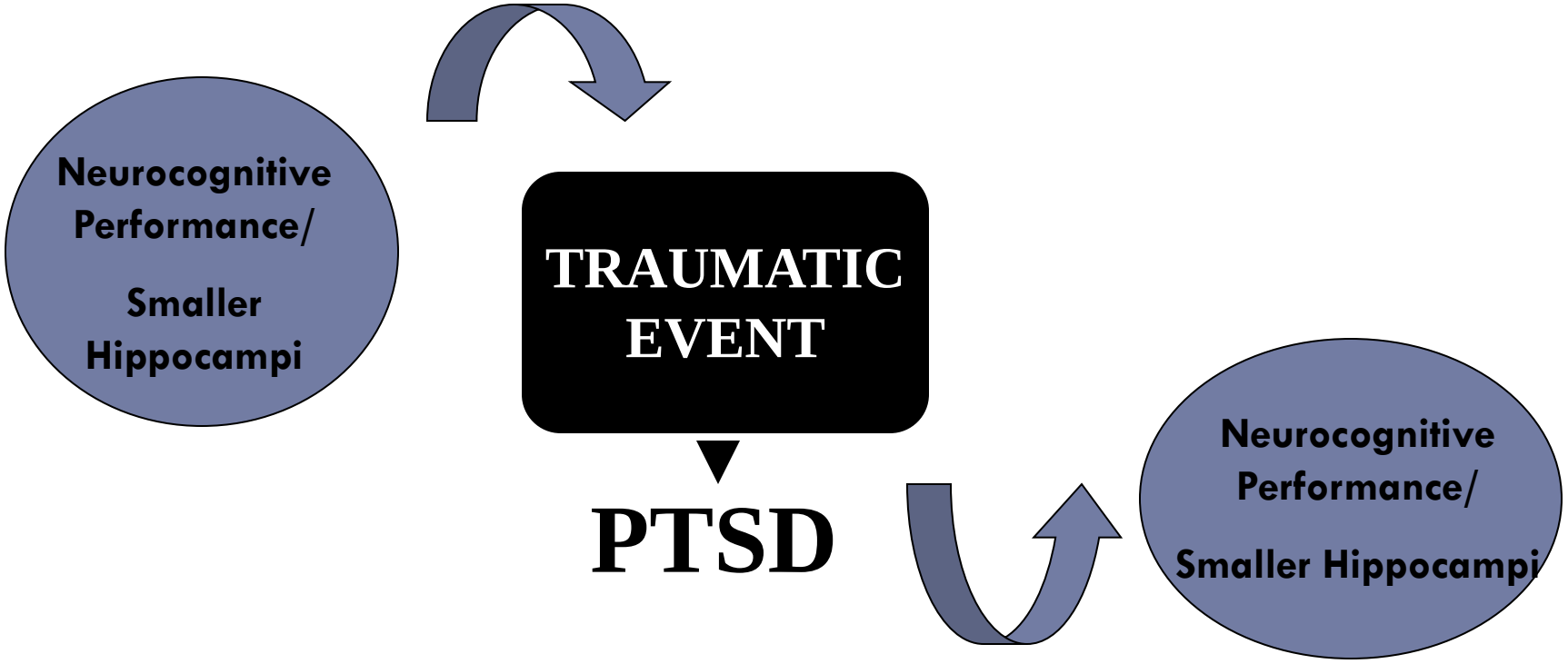
- Do neuropsychological deficits persist following remission of PTSD symptoms?
- Are the neuropsychological deficits associated with PTSD a risk factor or a consequence of the disorder?
- What are the potential mechanisms underlying the process of remission in PTSD?

Paulson, J., Samuelson, K., Neylan, T., Chao, L., Weiner, M., & O'Donovan (in preparation). Neuropsychological functioning and inflammation in past and current PTSD.

Neuropsychological and Neurological Abnormalities in PTSD: Cause or Effect?



VULNERABILITY ?



TOXICITY ?

Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

Apfel et al. 2011, *Biological Psychiatry*:

- Examined hippocampal volume in current, remitted, and no PTSD
- Current PTSD had significantly smaller hippocampal volume compared to other 2 groups
- Suggest hippocampal volume loss is reversible and a consequence of PTSD
  - Or, smaller hippocampi is associated with resistance to recovery

Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

- Chronically elevated levels of systemic inflammatory markers (Interleukin-6 (IL-6) and Tumor necrosis factor-alpha (TNF-α) are found in PTSD (meta-analysis: Passos et al., 2015)

- Associated with memory deficits (Reichenberg et al., 2001; Yirmiya & Goshen, 2011)

Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

Neural Plasticity

- High levels of IL-6 and TNF-α inhibit neurogenesis and suppress neuronal proliferation which impairs neural plasticity (Ben-Hurr et al., 2003; Monje et al, 2003; Vallieres et al., 2002)

- Fluctuations in inflammation may also be the mechanisms which drives the chronicity, and remission of PTSD

Neuropsychological Functioning and Inflammation in Current versus Remitted PTSD

Purpose of the Study:

- Determine if improved verbal memory functioning is seen in PTSD remission
- Examine if inflammation mediates the relationship between PTSD status and neuropsychological functioning

Methods

Gulf War Study:
Effects of Gulf War service on the brain

- N = 241
  - Current PTSD (n = 45)
  - Past PTSD (n = 40)
  - No PTSD (n = 156)

- Interlukin-6 (IL-6) –
- Tumor Necrosis Factor – alpha (TNF-α) - Soluble receptor II of TNF-α (sTNF-RII)
- CVLT
- Logical Memory of WMS

Demographic Differences: PTSD Status

	No PTSD	Past PTSD	Current PTSD	F or Chi-Square	Sig.
Age	45.32	43.21	41.49	3.01	.051
Gender	138 M/18 F	31 M/8 F	35 M/8 F	2.58	.257
Years of Education	14.82	14.39	14.19	2.14	.120
Body Mass Index	27.52	29.51	28.13	3.68	.027
GWI status	69(84%)	10(12%)	3(4%)	24.97	< .001
Vocabulary Score	46.36	46.28	44.80	.454	.635
Lifetime CAPS Score	8.10	63.03	81.69	424.99	< .001
Current CAPS Score	3.25	18.95	62.89	562.53	< .001

Note. GWI = Gulf War Illness; CAPS = Clinician Administered PTSD Scale

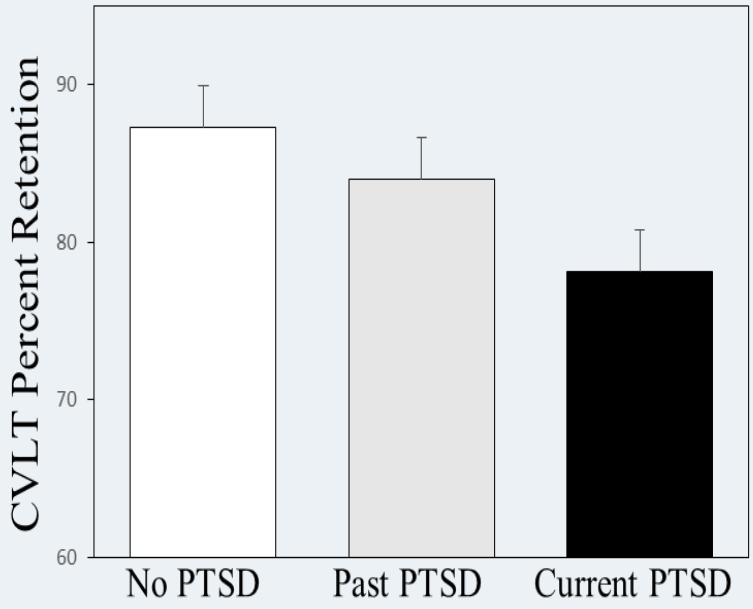
PTSD Group Differences in Verbal Memory

	No PTSD	Past PTSD	Current PTSD	F	Sig.
CVLT Immediate Recall	.043 (51.38)	-.183(48.84)	-.210(48.74)	1.58	.208
CVLT Percent Retention[a]	.443(87.3%)	.456(84.0%)	.504(78.1%)	3.36	**.036**
LM Immediate Recall	-.032(41.28)	.162(43.03)	-.112(40.33)	1.19	.306
LM Percent Retention	.005(59.4%)	.246(61.8%)	-.333(55.8%)	3.76	**.025**

Note. CVLT = California Verbal Learning Test; LM = Logical Memory; Raw values are presented in parentheses; [a]CVLT Percent Retention was transformed with a reflection and log 10 transformation; Covariates appearing in the model are Vocabulary score and Gulf War Illness

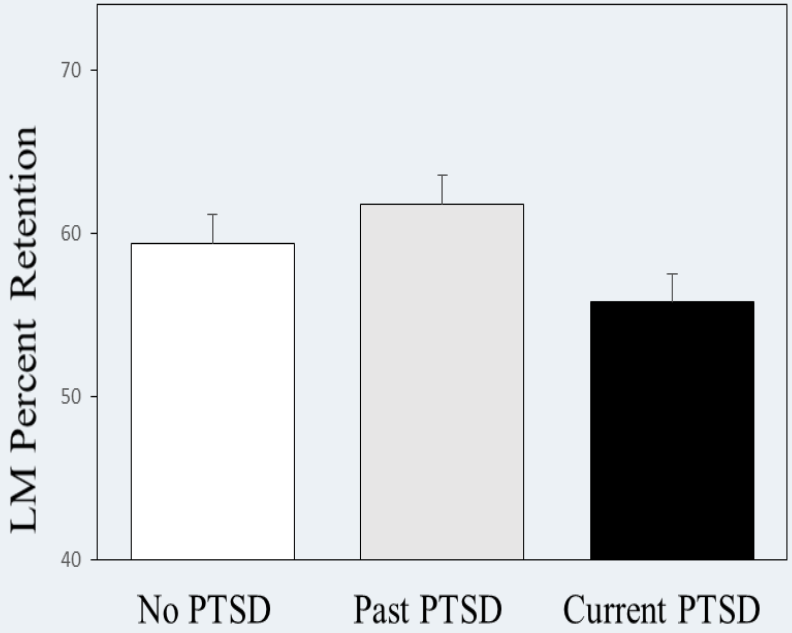
PTSD Group Differences on Delayed Verbal Memory Tasks

Figure 1



Note. Raw scores presented.

Figure 2



Note. Raw scores presented.

Cytokines Results

- No significant differences were seen between PTSD groups on cytokines
- Cytokines were not related to memory measures in overall sample
  - In veterans with current and past PTSD only, higher sTNF-RII was related to poorer CVLT immediate ($p = .004$) and Logical Memory delayed ($p = .020$) performance
- Inflammatory markers did not mediate relationship between PTSD status and neuropsychological performance

Discussion

- Differences between current PTSD and past PTSD groups suggest that verbal memory deficits remit when symptoms improve
- Verbal memory deficits may be a feature of current PTSD rather than a risk factor
- Provide preliminary support for the exploration of anti-inflammatory interventions in the treatment of PTSD
  - SSRI use – improvements in neuropsychological performance?

Discussion

- No group differences in PTSD status on cytokines
  - Heterogeneity in PTSD/subset of individuals with elevated inflammatory levels – further exploration needed
  - Issue with Gulf War Illness control group?

- Current and Past PTSD
  - sTNF-RII uniquely accounted for:
    - 10.8% of variance in verbal learning (CVLT)
    - 3.17% in immediate memory (LM)
    - 8.20% in delayed memory (LM)

Current Research

- Neuropsychological functioning in mTBI and PTSD in OEF/OIF/OND veterans

- Interventions for neuropsychological impairments related to PTSD and mTBI

Future Research Plans

Extinction Learning, Neuropsychological Functioning, and Cognitive Training

- Impaired extinction learning in PTSD (Milad et al., 2008; 2009)
- Decreased hippocampal and vmPFC (rostral ACC) activation during extinction retention in PTSD
- Extinction retrieval is associated with vmPFC activity and thickness (Milad et al., 2005, 2007)
- Strengthening vmPFC activation is a target for clinical interventions that could improve extinction learning

Extinction Learning, Neuropsychological Functioning, and Cognitive Training

- Rostral ACC – inhibitory control and emotion regulation

- Tasks of inhibitory control associated with decreased rostral ACC activation in PTSD (Carrion et al., 2008; Falconer et al., 2008)

Extinction Learning, Neuropsychological Functioning, and Cognitive Training

- PFC is a neuroplastic brain region (changes following SSRI, therapy)

- Neuroplasticity-based computer trainings – improve response inhibition and emotion reactivity → bolster extinction learning
  - Prior fMRI support with MDD and GAD (Gvurak et al. 2013)

Questions and Comments

Thank you!