

Does PTSD Cause Dementia?

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Dementia

Progressive memory impairment plus any of aphasia, agnosia, apraxia, or executive function problems.

Encompasses Alzheimer's disease, 'senile' dementia, vascular dementia, frontotemporal dementia, Lewy body dementia, and dementia NOS.

Prevalence starts to increase quickly after age 70.

PTSD post-traumatic stress disorder

Following exposure to a traumatic event(s) chronic recurrent re-experiencing of the trauma, avoidance behaviour, emotional numbing, and hyperarousal symptoms.

Prevalence of 10-20% among deployed veterans and ex-service members exposed to trauma.

Link between PTSD and dementia

Over last 10 years interest has increased in the possible causal association of PTSD with dementia (primarily Alzheimer's disease and vascular dementia, less commonly Lewy body disease and frontotemporal dementia).

A number of potential explanations have been proposed.

1. PTSD is a 'disorder of memory' – predisposes to dementia
- reduced cognitive reserve
2. Cognitive changes in PTSD may be early markers of dementia
3. Pre-existent Alzheimer's disease pathogenesis may increase vulnerability to developing PTSD following trauma exposure
4. PTSD is a stress-related condition - chronic stress is associated with altered cortisol levels and chronic inflammation, neurodegeneration, reduced hippocampal volumes, and reduced brain reserve
5. PTSD and dementia share common risk factors (vascular risks, traumatic brain injury, low IQ, limited education, tobacco and substance abuse)
6. PTSD may accelerate the aging process in brain
7. Cognitive decline may 'unmask' PTSD in older veterans
8. PTSD is frequently co-morbid with depressive disorder and dysthymic disorder in veterans - depressive disorder is linked to dementia

Is PTSD associated with premature senescence (accelerated aging)?

A recent review (Lohr et al 2016) of published studies shows PTSD linked with:

Reduced leukocyte telomere length (LTL)

Increased pro-inflammatory markers (CRP, Interleukin-1 beta and Interleukin-6, tumor necrosis factor)

Increased medical comorbidity (cardiovascular disease, type 2 diabetes, gastric ulcers)

Earlier mortality (average Hazard Ratio = 1.29)

Possible explanations – common vulnerability, increased initial mortality, or real increase in early or accelerated aging

Possible mechanism – Inflammation, increased allostatic load

Causation in medicine

Meet my friend:

Austin Bradford Hill (1897-1991)

1965 President's Address of newly formed
Section of Occupational Medicine of
The Royal Society of Medicine



Bradford Hill Criteria

1. Strength of association (effect size)
2. Consistency of association (most studies give similar results)
3. Temporal relationship (the factor comes before disorder)
4. Biological gradient (stronger the dose, more the effect)
5. Specificity (one factor, one condition)
6. Plausibility (not far fetched)
7. Experimental evidence (confounding factors controlled)
8. Analogy (similar relations seen in other conditions)
9. Coherence (no major conflict between strands of evidence)

PTSD and dementia

Strength, consistency, and temporal relationship

Two studies in 2010 -

Yaffe et al. PTSD and risk of dementia among US veterans. Arch Gen Psych 2010; 67: 608-613.

Qureshi et al. Greater prevalence and incidence of dementia in older veterans with PTSD. J Am Geriatr Soc 2010; 58: 1627-1633.

Study design

Both investigations are retrospective cohort studies over a seven to 10-year period (1998-2008) using US Department of Veterans Affairs administrative databases recording clinical contacts in VA clinics and facilities. Diagnoses of PTSD and dementia are based on ICD-9-CM criteria. Large numbers of subjects involved.

Yaffe study 2010

Used VA National Patient Care Database; clinical information on patients seen from 2000 to 2007. This is an incidence study of new cases of dementia over a seven-year period and the association of dementia with PTSD diagnosis at baseline. Dementia cases at baseline removed from sample. Potential confounder and shared risk factors between PTSD and dementia assessed and controlled in data analyses (adjusted Cox proportional hazard models giving Hazard Ratios [HR]).

181,000 subjects; 53,000 with PTSD, 128,000 without PTSD
Mean age 68 years, 96% men

Overall cumulative incidence of dementia 17.2%.
Cumulative incidence rate of dementia:

PTSD 10.6%, non-PTSD 6.6%* (*statistically significant)

HR (PTSD versus non-PTSD) 2.31*

HR after controlling for confounders 1.77*

No difference in HR for the different types of dementia

A comparison of PTSD with other non-PTSD psychiatric disorders
revealed a HR of PTSD for dementia of 1.47*

Qureshi study 2010

Used Veterans Integrated Service Network 16 Data Warehouse database (10 medical centers in south-central USA); clinical information on patients seen from 1998 to 2008. This is a prevalence and incidence study of cases of dementia over a 10-year period and the association of dementia with PTSD diagnosis at baseline. Potential confounder and shared risk factors between PTSD and dementia assessed and controlled in data analyses (multivariate logistic regression models giving Odds Ratios [OR]).

Two characteristics used to group subjects; PTSD or no PTSD, and Purple Heart recipient (PH) or no PH. Purple Heart a proxy for combat exposure.

Four groups are compared:

PTSD+/PH-, PTSD-/PH-, PTSD+/PH+, PTSD-/PH+

10,481 subjects

Incidence of dementia

	N	Incidence %
PTSD+/PH-	3660	9.5
PTSD-/PH-	5165	4.0
PTSD+/PH+	153	6.8
PTSD-/PH+	1503	5.6

Odds ratio after controlling for confounders

	Incidence OR
PTSD+/PH- v PTSD-/PH-	2.2*
PTSD+/PH+ v PTSD-/PH+	1.1

This study also used anti-dementia medication use (cholinesterase inhibitors and memantine) as a proxy for dementia diagnosis – no change in pattern of results observed.

PTSD and dementia

Strength, consistency, and temporal relationship

Further studies -

Meziab et al. Prisoner of war status, posttraumatic stress disorder, and dementia in older veterans. *Alzheimers Dementia* 2014; 10: 236-241.

Meziab study 2014

Retrospective cohort study. 182,897 US veterans over 55 (Cox proportional hazard models giving adjusted Hazard Ratios [HR]). Incident risk of dementia over 10 years from 2000:

POWs only HR = 1.65*

PTSD only HR = 1.52*

PTSD plus POWs HR = 2.24*

PTSD and dementia

Strength, consistency, temporal relationship, and biological gradient

Further studies -

Mawanda et al. PTSD, psychotropic medication use, and the risk of dementia among US veterans: a retrospective cohort study. *Journal of American Geriatric Society* 2017; 65:1043-1050

Roughead and Morris et al. Posttraumatic stress disorder, antipsychotic use and risk of dementia in veterans. *Journal of American Geriatric Society* 2017; 65:1521-1526.

Mawanda study 2017

Retrospective cohort study. 417,172 US veterans over 65. Sample stratified by baseline use of psychotropic medications (benzos, SNRIs, novel antidepressants, atypical antipsychotics). Incident risk of dementia over 8 years from 2003:

PTSD minus psychotropics HR = 1.55*

PTSD plus psychotropics HR = 1.99-4.21*

Benzos or SNRIs independent of PTSD increased risk of dementia

Roughead study 2017

Retrospective cohort study. 15,612 Australian veterans aged 55-65. Sample stratified by baseline use of antipsychotic medications. Incident risk of dementia over 12 years from 2001:

PTSD minus antipsychotics HR = 1.7*

PTSD plus antipsychotics HR = 2.22*

Antipsychotics but no PTSD HR = 4.3*

PTSD and dementia

Specificity and plausibility

Further studies -

Weiner et al. Effects of traumatic brain injury and posttraumatic stress disorder on development of Alzheimer's disease in Vietnam Veterans using the Alzheimer's Disease Neuroimaging Initiative: Preliminary report. *Alzheimers Dementia* 2017; 3(2): 177-188.

Mohamed et al. Amyloid pathology fingerprint differentiates post-traumatic stress disorder and traumatic brain injury. *Neuroimage: Clinical* 2018; 19: 716-726.

Weiner study 2017

Cross-sectional study of 180 US Vietnam veterans. Divided into PTSD only (63), Traumatic Brain Injury only (22), PTSD plus TBI (32), and healthy controls (63). Examined with MRI brain volumetrics, and B-amyloid florbetapir PET, and CSF amyloid and tau markers (not presented). PET analysis of whole cerebral cortex as single ROI.

Findings:

Slightly lower superior parietal volume in PTSD plus TBI group

Lower odds (likelihood) of amyloid PET positivity in PTSD group relative to controls

No evidence of increased brain amyloid in TBI group

No evidence of medial temporal lobe atrophy in PTSD or TBI or both relative to controls

Mohamed (Qld Brain Institute) study 2018

Cross-sectional study of 160 US Vietnam veterans from the database of the Alzheimer's Disease Neuroimaging Initiative. Divided into PTSD only (57), Traumatic Brain Injury only (21), PTSD plus TBI (29), and healthy controls (57). Examined with MRI brain volumetrics, and B-amyloid florbetapir PET, and CSF amyloid and tau markers. PET analysis by voxel-wise statistical comparison, and non-Caucasians excluded.

Findings:

Increased amyloid tracer uptake in PTSD, PTSD plus TBI, and TBI groups compared with controls with PTSD > PTSD plus TBI > TBI

Condition specific pattern: PTSD - widespread cortical, PTSD plus TBI - white matter, TBI - cerebellum and precuneus

Tracer uptake correlated negatively with CSF amyloid levels and positively with CSF tau concentrations in TBI only

PTSD amyloid accumulation resembles Alzheimer's disease pattern

Discussion

These studies represent a first step in establishing a causal link between PTSD and dementia. They provide information about:

1. Strength of association (effect size is moderate in most studies)
2. Consistency of association (most studies give similar results)
3. Temporal relationship (PTSD comes before dementia)
4. Biological gradient (more severe PTSD associated with dementia)
4. Specificity and plausibility (not yet convincing, but some evidence of differentiated pattern of biomarkers, and distinctive role of PTSD)

Further studies are called for, especially prospective cohort studies looking at specific types of dementia.

Thank You