*Neuroscience*

*Review*

# The extent of the neurocognitive impairment in elderly survivors of war suffering from PTSD: meta-analysis and literature review

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**Abstract:** *Objectives*: We performed a meta-analysis and systematic review on elderly survivors of war suffering from PTSD to estimate the variability in their cognitive impairment based on individual neuropsychological tests. *Methods*: We included case control studies that explored the association of cognitive deficits in elderly PTSD civilian survivor of wars (age >60 years), using MEDLINE, Embase and PsycINFO from the inception to January 2018. We compared the cognitive performances in three comparisons i) PTSD+ vs. PTSD− civilian survivors of war; ii) PTSD+ vs. Control and iii) PTSD− vs. Control. The risk of bias was assessed using the Newcastle-Ottawa Scale for case-control studies. *Results*: Out of 2939 titles and abstracts, 13 studies were eligible for data extraction. As compared to PTSD− civilian survivors of war, PTSD+ civilian survivors of war demonstrated significant deficits on TMT-A, TMT-B, Digit span backward, explicit memory low pair associate, CVLT recognition, WAIS- verbal and non-verbal tests. As compared to health controls, PTSD+ survivors demonstrated significantly lower performance on explicit memory low pair and high associate, RAVLT immediate and delayed recall, CVLT delayed and short cued recall. Performance on the neuropsychological test between PTSD− survivors of war and controls was not significant for all tests. *Conclusion*: The pattern suggests that PTSD+ survivors of war had poorer performance in tasks requiring processing speed, executive function, attention, working memory and learning. The magnitude of the cognitive deficits in our pooled analysis was small to moderate depending on the

neuropsychological test. Most of our pooled analysis suffered from a high risk of bias, which lowered the confidence in our results.

## 1. Introduction

Elderly patients with PTSD have been found to have greater impairments in their cognitive performance [1–3], which hinders their ability to cope and rehabilitate [4,5]. Prevalence of PTSD in survivors of war including war veterans and civilian population has been reported from 17% to 30% [6,7] and symptoms may appear two to four decades after the initial war-related trauma [8–10]. Elderly veterans and survivors of war have a higher prevalence of impairment in cognitive functioning [11–18] and comorbid ailments such as depression, head injuries and medical comorbidities [6,7]. They also experience a poor quality of life and impairments in their social lives [7,18–21]. The aging, cognitive impairments in elderly survivors of war and negative reaction such as intrusive memories, thought processing, physical and emotional changes further complicate the distress and reduce treatment responses [22–24].

Cook et al. [18] reported that cognitive impairment in elderly PTSD patients does not differ significantly from cognitive impairment in dementia patients without PTSD. By understanding the extent of cognitive impairments in elder PTSD patients, we can facilitate understanding to improve treatment modalities, functional outcomes, and health outcomes. The goal of our study was to systematically explore the extent of the neurocognitive domain in elderly survivors of war in five major domains such as i) learning and memory; ii) Attention; iii) executive functions; iv). language and v). visuospatial processing [25,26]. As in elderly patients, cognitive deficits can be confounded due to aging; therefore, we aim to explore the quality of evidence in outcomes across different comparisons i) PTSD+ vs. PTSD−; ii) PTSD+ vs. Healthy Controls and iii) PTSD− survivors of war vs. Healthy Controls.

Previous studies inconsistently reported major neurocognitive dysfunction in elderly survivors of wars suffering from PTSD, such as autobiographical memory [23,27], attention [8], verbal learning and memory [28,29], executive function and information processing speed [1,30–32]. Previous studies mostly focused on veterans and omitted civilians with wartime traumatic events [33–35]. As elderly survivors of war suffer from other ailments, previous reviews included studies duplicate studies on the same populations [11] or with heterogeneous populations [11,12] with mixed trauma and medical conditions which make it difficult to determine the independent association of PTSD with neurocognitive deficits. Previous reviews [11,12] also did not determine the quality of evidence in the outcomes. Studies exploring the overall extent of neurocognitive deficits in survivors of war have rarely been reported. Our goal was to explore the extent of performance on neuropsychological tests in elderly PTSD+ survivors of wars. Also, to our knowledge, no previous published meta-analyses on this topic have employed the GRADE criteria (Grading of Recommendations, Assessment, Development and Evaluation) to calculate the quality of evidence.

## 2. Methods

A systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines [36]. The search strategy was developed in OVID Medline, PsycINFO, and EMBASE from the inception to January 2018 (See the appendix for the search strategy). We also looked for the bibliographic references for the recently published systematic reviews (see PRISMA flowchart in the appendix). Literature screening for title and abstract, full text, the risk of bias and data extraction were done in duplicates and independently. Our protocol was registered on Prospero (CRD42018090134). For this review, we included studies that explored the neurocognitive deficits in outpatient elderly survivors of wars suffering from PTSD with validated neuropsychological tools. Studies compared PTSD+ survivors of war with healthy control or PTSD− the survivor of war and reported effect size were in mean and standard deviation. Studies were excluded if enrolled participants with traumatic brain injury, neurodegenerative/neuroinflammatory diseases, psychosis, or PTSD due to other conditions such as motor vehicle accidents, rape, or domestic violence. Studies were also excluded if they analyzed brain functional imaging in PTSD patients without reporting neuropsychological tests scores. We restricted the inclusion of eligible studies to the English language only.

### 2.1. Important definitions

Elderly age: As the elderly population is defined variably in different cultures, which may range from 60 to above 65 years. For this review, we included studies enrolling patients with average age of 60 or above [5,37,38].

PTSD+ Survivors of war: PTSD status was determined if the study employed DSM criteria, CAPS criteria or explicitly determined by clinicians. For this review, combat veterans, prisoners of wars, and/or civilians, who were exposed to war trauma were considered survivors of war. For this review, combat veterans, prisoners of wars, and/or civilians, who were exposed to war trauma were considered survivors of war. The severity of PTSD was based on scores reported for Clinician-Administered PTSD Scale (CAPS) [39], Post-traumatic Stress Diagnostic Scale (PDS) [40], PTSD symptoms scale (PSS tests) [41,42] scales. The severity of CAPS is categorized as: 0–19 = asymptomatic/few symptoms; 20–39 = mild PTSD/subthreshold; 40–59 = moderate PTSD/threshold, 60–79 = severe PTSD symptomatology; >80 = extreme PTSD symptomatology. The severity on PDS is categorized as 0 no rating, 1–10 mild, 11–20 moderate, 21–35 moderate to severe, and >36 severe. Hart et al. [34] did not report the PTSD severity, whereas Golier et al. [43–45] and Yehuda [46,47] reported individual scores for the intrusion, avoidance and hyperarousal. As these studies used same population as Freeman et al. [48] and Yehuda et al. [49] respectively, we assumed the PTSD severity approximately the same as reported in the latter.

Comparison groups were either individual exposed to war-related trauma or healthy controls but were not diagnosed with PTSD. Our rationale to compare the cognitive impairment in PTSD+ with PTSD− survivor of wars was based, as war trauma can be potentially associated with other ailments such as depression, medical comorbidities, which confound the association if comparison with only healthy control made.

Neurocognitive domains and neuropsychological tests: We focused on five major neurocognitive domains such as learning and memory, attention, executive functions, language, and

visuospatial processing [25,26]. We further captured data on the subdomain [50] of each cognitive function such as inhibition and flexibility are subdomains of executive functions and pooled them separately according to the neuropsychological tests [51,52]. We included studies that used valid neuropsychological tests to measure cognitive functions. Common versions are listed in Table 1: Descriptive table of neuropsychological tests, and cognitive functions.

## 3. Risk of bias

The risk of bias was evaluated in the eligible studies using the Newcastle-Ottawa Quality Assessment scale for case-control studies [53]. Newcastle-Ottawa Scale (NOS) assesses the following three domains: the selection of study groups, comparability of study groups and ascertainment of exposure or outcome. For this analysis, case definition and control representations were rated if individuals were recruited through consecutive sampling, national databases and or veteran registries. If the source of participant recruitment was not clearly reported or if it were recruited with convenience sampling, the study was down rated. For the case comparison, we used two variables (age and premorbid IQ). If the study had a significant difference for age and/or premorbid IQ between case and control groups, the study was down rated. Outcome assessment (method of ascertainment) was determined downrated if the study did not employ validated neurocognitive test or if cognitive impairment was determined differently for case and control groups. Also, studies were down rated if the authors reported results selectively and did not report results for all outcomes in the method section.

## 4. Grade

The quality of evidence was determined with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [54]. We will use GRADE to rate the evidence separately for each cognitive sub domain. Assessment of GRADE is based on 5 variables i) Risk of bias; ii) Heterogeneity; iii) precision; iv) publication bias and v) indirectness. The risk of bias was determined component by component and heterogeneity was explored with the visual inspection of forest plot and $I^2$. The publication was assessed with the visual inspection of a funnel plot if we had 10 or more studies in a pooled analysis.

Subgroup analysis: we did not have enough studies to perform subgroup analysis described a priori in Prospero protocol.

**Table 1.** Descriptive table of neuropsychological tests, neurocognitive functions and authors.

| Cognitive Test | Description | Cognitive Domain(s) | Studies Employing this Test (authors) |
|---|---|---|---|
| Trail Making Test A | records the time required to connect numbered dots spread randomly over a page | Information Processing Speed, Visual Scanning, Attention | Green 2016, Hart 2008, Jelinek 2013 |
| Trail Making Test B | participants must alternate between ascending numeric and alphabetical characters in connecting the dots | Mental Flexibility, Executive functioning, Attention Shifting | Green 2016, Hart 2008, Jelinek 2013 |
| WAIS—Digit Span Forward | participants are asked to immediately repeat longer strings of digits in the same order (Forward subtest) | Attention efficiency and capacity | Hart 2008, Jelinek 2013 |
| Digit Span—Backward | Participants are asked to immediately repeat longer strings of digits in the reverse order (Backwards subtests) | Executive function dependent on working memory | Hart 2008, Jelinek 2013 |
| Color Word Interference | While being timed, participants were asked to say the ink color that various words were written in | Inhibition of cognitive interference | Green 2016, Wittekind 2010 |
| Pair Associate tests | Participants were given 6 pairs of related words (high) and 6 pairs of unrelated words (low) and were asked to recall immediately after tests and after 30 minutes of the test administration. Patients were shown one pair and were asked to recall the other word. For the implicit memory patients were asked to complete 48 three-letter word stems using "the first word that comes to mind" | Learning of complex information associated with Explicit Memory and implicit memory | Yehuda 2005, Yehuda 2006 |
| RAVLT—Immediate and delayed Recall | A word list is read out and participants attempt to immediately recall as many as possible in repeated trials. A new list is read out and immediately after the trial is completed. In delayed recall, patients are asked to recall the information 20-30 minutes | Short-term and long-term verbal memory, rate of learning, memory retention, effects of interference on verbal leaning | Freeman 2006, Green 2016, Wessel 2002, Yehuda 2004, Yehuda 2006 |

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| Cognitive Test | Description | Cognitive Domain(s) | Studies Employing this Test (authors) |
|---|---|---|---|
| CVLT—Short Cued and Delayed Cued Recall | List of nouns repeated aloud in the same order, from categories (fruit, clothing, etc.) followed by interference list. Participants must recall words in any order, when given categories (cued) | Short-term and long-term memory retrieval or recall in response to cues | Yehuda 2004, Yehuda 2005, Yehuda 2006 |
| CVLT—Recognition Memory | Participants must recognize words in a list of 44 words with target and distracter words | Verbal memory and learning associated with the recognition memory associated with objects, naming | Freeman 2006, Hart 2008, Yehuda 2004 |
| Digit Symbol—Processing Speed | Each number is assigned a symbol and the participant must write the corresponding symbol when given a list of numbers | Information Processing Speed, short-term memory | Hart 2008 |
| WAIS—Vocabulary | 12-word pairs: 6 pairs of mildly related words (high associate) and 6 pairs of unrelated words (low associate), which the participants viewed and were then asked to read and memorize for recall. They were then shown a single word from each pair and attempted to recall the other | Verbal Intelligence, working memory | Golier 2003, Yehuda 2004, Yehuda 2005, Yehuda 2007 |
| WAIS nonverbal intelligence | Participants rearranged blocks by hand that had various color patterns on various sides to match an arbitrary pattern | short-term memory, mental manipulation, holding time, motor skill, Spatial Visualization | Yehuda 2004, Yehuda 2005, Yehuda 2007 |
| Boston Naming Test | subjects are asked to name objects that were presented visually in two dimensional lines. Measured with correct number of names produced | Naming objects | Hart 2008 |
| COWA test | Spontaneous production of words beginning with the same letter | Verbal fluency | Hart 2008 |
| Corsi Block Tapping Test | Tapping on a sequence of up to nine blocks mimicking a researcher | Visuospatial memory | Jelnik 2013 |

| Cognitive Test | Description | Cognitive Domain(s) | Studies Employing this Test (authors) |
|---|---|---|---|
| Groningen Intelligence Test (GIT) | Patients were asked to produce words related to a category | Semantic fluency | Wessel 2002 |
| Animal fluency | Patients were asked to produce words related to a category | Semantic fluency | Hart 2008 |
| Symbol Digit Modalities Test | Patients were asked to write or say the correct number for each symbol that was shown earlier | Information processing speed, attention | Hart 2008 |
| Autobiographical memory test | Patients were asked to recall in response to specific cues provided to them in a specific time; The cues could be emotionally positive or negative valence | Learning and memory | Wessel 2002 |
| WMS—Logical memory | Participants were asked to recall the details and themes of the two passages read immediately and after 20–30 minutes | Learning and memory | Freeman 2006 |

## 5.    Analysis and data pooling

We reported study characteristics narratively. As a neuropsychological test can be used to measure more than one cognitive function, we pooled our analysis according to the neuropsychological tests rather than neurocognitive functions. We further captured data on the subdomain of each cognitive function such as working memory, inhibition and mental flexibility are subdomains of executive functions and pooled them separately according to the neuropsychological tests. If a test had subcomponents such as Trails Making Test (TMT) has two components TMT-A and TMT-B we pooled each component separately [51,52]. Also, if different tests seemed homogenous in measuring cognitive function, were also pooled for the analysis purposes. A similar approach to standardize the comparison was also adopted in Schuitevoerder et al. [12]. We performed a meta-analysis if a neuropsychological test was reported in two or more studies. We also extracted data on commonly used neuropsychological tests if reported in a single study; Wechsler Memory Scale (WMS) Logical memory, recall score, WMS- logical memory thematic score, WMS-digit symbol, symbol digit modalities, corsiblock tapping test, Controlled Oral Word Association Test (COWA), and semantic fluency.

Also, to explore, an association of cognitive deficits with PTSD, we performed 3 different comparisons: PTSD+ vs. PTSD−, PTSD+ vs. Healthy Controls, and PTSD− vs. Healthy Controls. We observed variability in measuring and final reporting of results in the three comparisons. After extracting data, we determined studies if pooling was feasible. In the case of duplicate studies or multiple studies using the same population, we extracted data with a larger sample size and study matched for important variables for the risk of bias components. Results for pooled analysis were reported in mean difference (MD) with 95% CI. We performed pooling with a fixed effect model (FEM) if we had two studies in a meta-analysis and with random effect model (REM) if we had three or more studies. Meta-analysis was performed using Review Manager Software 5.3.

## 6.   Results

Out of 4598 title and abstracts, 13 studies were eligible for data extraction (Figure 1). The summary of the included studies and neuropsychological tests are given in tables 1 and 2 respectively. Three studies [34,49,55] were duplicate for Golier et al. [56], Freeman et al. [49] and Jelenik et al. [57] respectively; therefore, we reported data only for tests if it were not reported in previous studies. The median sample size for PTSD+ survivors of war, PTSD− survivors of war and control groups were 20, 16 and 19, respectively. The median age for PTSD+, PTSD− and healthy control groups were 69.7, 68.4, and 70.9, respectively. Except for four studies [33–35,58]; all other studies included both men and women. Most studies enrolled patients who survived World War II, whereas two studies [34,48] recruited survivors of Korean Wars and one study [58] enrolled survivors of Dutch or Dutch-Indonesian civilians including those who survived Japanese concentration camps. Golier et al. [43,44], reported data on the same population but tests were different. All studies excluded patients with substance abuse except for one study [58]. The PTSD severity was within the moderate range, except for the two studies [55,57] with participants in moderate to severe range. Except for Freeman et al. [48], no other study reported combat related stress in the participants.

**Table 2.** Study characteristics of included articles.

| Authors | Population | Sample size | | | Female-Sex (%) Age in Mean (SD) | | | Exclusion Criteria | | | PTSD severity score | Psychological interventions |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PTSD+ | PTSD− | Healthy Control | PTSD+ | PTSD− | Healthy Control | Substance Abuse Disorder | Psychological Deficits | Brain Injury/ Neurological Deficits | | |
| Freeman 2006 | POW— WWII, Korean War | 10 | 10 | 6 | All male patients Age: 79.6 (3.2) | Age: 79.8 (2.8) | Age: 80.8 (3.5) | Yes | Yes, except depression | Yes | CAPS = 53.3 (13.9) | No |
| Golier 2002 | Holocaust Survivors | 31 | 16 | 35 | 67.7% Age: 67.7 (5.6) | 68.8% Age: 67.4 (5.8) | 57.1% Age: 69.9 (6.6) | Yes | Yes, except depression | Yes | CAPS = 64.9 (15.4) | Yes |
| Golier 2003 | Holocaust Survivors | 31 | 16 | 34 | 67.7% Age: 67.7 (5.6) | 68.8% Age: 67.4 (5.8) | 57.1% Age: 69.9 (6.6) | Yes | Yes, except depression | Yes | CAPS = 68.8 | Yes |

| Authors | Population | Sample size | | | Female-Sex (%) Age in Mean (SD) | | | Exclusion Criteria | | | PTSD severity score | Psychological interventions |
|---------|-----------|-------|-------|---------|-------|-------|---------|-----------|-------------|---------------|-------|-------|
| | | PTSD+ | PTSD− | Healthy Control | PTSD+ | PTSD− | Healthy Control | Substance Abuse Disorder | Psychological Deficits | Brain Injury/ Neurological Deficits | | |
| Golier 2005 | Holocaust Survivors | 14 | 13 | 20 | 63.4% Age: 70.5 (5.6) | 53.84% Age: 68.5 (7.3) | 35% Age: 71.4 (6.4) | Yes | Yes, except depression | Yes | CAPS = 64.9 (15.4) | Yes |
| Green 2016 | Vietnam Veteran | 55 | 33 | NA | All male patients Age: 61 (4.3) | Age: 66.1(7.5) | | Yes | Yes | Yes | CAPS = 46.5 (23.04) | NR |
| Hart 2008 | POW, WW II, Korean War | 7 | 11 | NA | All male patients Age: 80.9 (2.51) | Age: 80 (2.2) | NA | Yes | Yes, except depression | Yes | CAPS = 53.3 (13.9) | No |
| Jelinek 2013 | WW II | 20 | 24 | 11 | 70% Age: 70.95 (2.51) | 62.5% Age: 70.88 (1.78) | 63.3% Age: 72.27 (2.87) | Yes | Yes, except depression | Yes | PDS = 21.05 (7.20) | NR |

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| Authors | Population | Sample size | | | Female-Sex (%) Age in Mean (SD) | | | Exclusion Criteria | | | PTSD severity score | Psychological interventions |
|---------|-----------|------|------|------|------|------|------|------|------|------|------|------|
| | | PTSD+ | PTSD− | Healthy Control | PTSD+ | PTSD− | Healthy Control | Substance Abuse Disorder | Psychological Deficits | Brain Injury/ Neurological Deficits | | |
| Wessel 2002 | WW II, Indonesian War | 25 | NA | 15 | 60% Age: 60.3 (3.8) | 0% NA | 40% Age: 62.3 (4.3) | No | No | Not Clear | PSS = 24.5 (10.9) | NR |
| Wittekind 2010 | WW II | 22 | 24 | 11 | 68.2% Age: 71 (2.39) | 62.5% Age: 70.88 (1.78) | 63.60% Age: 72.27 (2.87) | Yes | Yes, except depression | Yes | PDS = 20.05 (7.61) | NR |
| Yehuda 2004 | Holocaust Survivors | 36 | 26 | 40 | 67.74% Age: 69.2 (5.6) | 65.4% Age: 68.4 (6.4) | 55% Age: 70.4 (6.8) | Yes | Yes, except depression | Yes | CAPS = 64.9 (15.4) | PTSD+ = 19% PTSD− = 23.1% |
| Yehuda 2005 | Holocaust Survivors | 19 | 16 | 28 | 63.12% Age: 69.7 (5) | 56.25% Age: 70.2 (6.9) | 53% Age: 73 (6.3) | Yes | Yes, except depression | Yes | CAPS = 64.9 (15.4) | Yes |

| Authors | Population | Sample size | | | Female-Sex (%) Age in Mean (SD) | | | Exclusion Criteria | | | PTSD severity score | Psychological interventions |
|---------|-----------|-------------|---|---|---------|---|---|--------------------|---|---|---------------------|-----------------------------|
| | | PTSD+ | PTSD− | Healthy Control | PTSD+ | PTSD− | Healthy Control | Substance Abuse Disorder | Psychological Deficits | Brain Injury/ Neurological Deficits | | |
| Yehuda 2006 | Holocaust Survivors | 14 | 13 | 19 | All male patients Age: 72.9 (6) | Age: 72.7 (6.3) | 57.9% Age: 76.4 (6.8) | Yes | Yes, except depression | Yes | CAPS = 64.9 (15.4) | No |
| Yehuda 2007 | Holocaust Survivors | 17 | 16 | NA | All male patients Age: 60.6 (7) | Age: 65.1 (9.9) | | Yes | Yes, except depression | Yes | CAPS = 45.5 (25.6) | No |

PDS = Post-traumatic Stress Diagnostic Scale, CAPS = Clinician-Administered PTSD Scale, PSS = PTSD symptoms scale, WW II = World war II, POW = Prisoner of War

## 6.1. Risk of bias and quality of evidence

The risk of bias of the eligible study is given in table 3. Except for Wessel [58], all studies recruited patients with consecutive sampling. For a case comparison, significant difference between premorbid IQ was reported in Freeman 2006 [48], Golier 2002 [43], Golier 2003 [44], Golier 2005 [45], Green 2016 [33], Hart 2008 [34], Wessel 2002 [58], and Yehuda 2005 [46], Golier 2002 [43], Golier 2003 [44] and Golier 2005 [45], were downrated for poor response rate.

**Table 3.** Risk of bias of the included studies (Newcastle-Ottawa scale)

| Authors | case definition | Representativeness of the cases | Selection of Controls | Definition of Controls | Comparing Case/Control | | Ascertainment of exposure | method of ascertainent | Response rate |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Age | Premorbid IQ | | | |
| Freeman 2006 | green | green | green | green | green | RED | green | green | green |
| Golier 2002 | green | green | green | green | green | RED | green | green | RED |
| Golier 2003 | green | green | green | green | green | RED | green | green | RED |
| Golier 2005 | green | green | green | green | green | RED | green | green | RED |
| Green 2016 | green | green | green | green | RED | RED | green | green | green |
| Hart 2008 | green | green | green | green | green | RED | green | green | green |
| Jelinek 2013 | green | green | green | green | green | green | green | green | green |
| Wessel 2002 | RED | RED | green | green | green | RED | green | green | green |
| Wittekind 2010 | green | green | green | green | green | green | green | green | green |
| Yehuda 2004 | green | green | green | green | green | green | green | green | green |

| Authors | case definition | Representat-iveness of the cases | Selection of Controls | Definition of Controls | Comparing Case/Control | | Ascertainment of exposure | method of ascertain-ent | Response rate |
|---------|-----------------|----------------------------------|------------------------|------------------------|------------------------|------------------|---------------------------|--------------------------|---------------|
| | | | | | Age | Premor bid IQ | | | |
| Yehuda 2005 | | | | | | | | | |
| Yehuda 2006 | | | | | | | | | |
| Yehuda 2007 | | | | | | | | | |

Low risk of Bias          High risk of Bias

## 6.2 Pooled analysis

Table 4 shows the meta-analysis for three comparisons PTSD+ vs. PTSD−, PTSD+ vs. Health control and PTSD− vs. Healthy control. Results are reported in according to the neuropsychological tests and the neurocognitive functions (Figures 2–9). The quality of evidence is reported in table 5.

## 6.3. PTSD+ vs. PTSD− survivors of war

Among the significant tests, moderate quality evidence was reported for Trail Making Test-A (TMT-A) (−6.05 [−11.04, −1.06]; $p = 0.02$; $I^2 = 28\%$); TMT-B (−25.80 [−43.70, −7.89]; $p = 0.005$; $I^2 = 46\%$]; Digit Span Backward (−0.82 [−1.63, −0.01]; $p = 0.05$; $I^2 = 0\%$); Stroop Color Word Interference (−8.35 [−16.50, −0.20]; $p = 0.04$; $I^2 = 0\%$); California Verbal Learning Test (CVLT)—Recognition Memory (−2.43 [−4.56, −0.30]; $p = 0.03$; $I^2 = 0\%$); CVLT—Delayed Cued Recall (−1.12 [−2.17, −0.07]; $p = 0.04$; $I^2 = 0\%$), Wechsler Adult Intelligence Scale (WAIS)—verbal intelligence (−2.64 [−3.38, −1.90]; $p < 0.00001$; $I^2 = 0\%$) and WAIS—nonverbal intelligence (−1.55 [−2.55, −0.54]; $p = 0.002$; $I^2 = 0\%$). Low quality evidence reported significant association on Explicit Memory—Low Pair Associate (−1.64 [−2.65, −0.63]; $p = 0.001$; $I^2 = 70\%$).

Among non-significant neuropsychological tests were Explicit Memory—High Pair Associate; Implicit Memory—High Pair Associate ; Implicit Memory—Low Pair Associate; Rye Adult learning test (RAVLT)—Immediate Recall RAVLT-Delayed Recall; CVLT—Short Cued Recall; Free Recall—Delayed and Digit Span Forward .

## 6.4. PTSD+ vs. healthy control

Among the significant tests, moderate quality evidence was reported for Explicit Memory—High Pair Associate (−1.48 [−2.02, −0.94]; $p < 0.00001$; $I^2 = 0\%$); Explicit Memory—Low Pair Associate (−1.61 [−2.51, −0.71]; $p = 0.0005$; $I^2 = 87\%$); RAVLT—Immediate Recall (−1.08

[−1.90, −0.26]; $p$ = 0.01; $I^2$ = 70%); Free Recall—Delayed (−2.23 [−3.38, −1.09]; $p$ = 0.0001; $I^2$ = 0%); and CVLT—Recognition Memory [−4.10 [−6.67, −1.42]; $p$ = 0.003; $I^2$ = 0%]. Among the significant tests, high quality evidence was reported for CVLT Delayed Recall (−1.82 [−2.95, −0.69]; $p$ = 0.002; $I^2$ = 0%); CVLT—Short Cued Recall (−1.98 [−3.14, −0.81]; $p$ = 0.0009; $I^2$ = 50%); and CVLT—Delayed Cued Recall (−1.24 [−2.25, −0.23]; $p$ = 0.02; $I^2$ = 0%). Finally, low quality evidence was reported for the following significant test: WAIS—verbal intelligence (−3.46 [−4.29, −2.63]; $p$ = 0.00001; $I^2$ = 0%) and WAIS—non-verbal intelligence (−1.73 [−2.84, −0.62]; $p$ = 0.002; $I^2$ = 0%).

Among the non-significant tests were Implicit Memory—High Pair Associate; Implicit Memory—Low Pair Associate; and RAVLT—Delayed Recall.

*6.5. PTSD− vs. healthy outcomes*

In this comparison, none of the cognitive domains shows a significant association with the PTSD− survivor of war and healthy controls.

Summary of the neuropsychological tests that were reported by single studies that were not poolable is reported in table 6. PTSD+ survivor of war performed significantly poor on information process speed and autobiographical memory than the PTSD− survivors of war and healthy controls.

## 7. Discussion

Our aim was to systematically explore the association of neurocognitive impairments in elderly survivors of war suffering from PTSD. Our review identified elderly survivors of war with PTSD exhibited neurocognitive deficits on the neuropsychological tests requiring complex functions such as attention, information processing speed, executive functioning, learning and memory and intelligence tests. Attention and information processing showed elderly survivors of war with PTSD exhibited significant impairment as compared to elderly survivors of war who did not have PTSD. Attention measured on the digit span forward was not significant. Performance on tests measuring executive function was consistently reported significantly poor in elderly survivors of war than the non-PTSD survivors of war. The effect size was reported on the performance on TMT-B (MD = −25.80) and Stroop color word inhibition (MD = −8.35). We noted non-consistent association of neurocognitive deficits with test measuring learning and memory. As compared to PTSD− survivors of war, the elderly PTSD+ survivors of war exhibited poor performances on tests that measured delayed recall, information retrieval or on complex tasks such as low pair associates for explicit memory.

**Table 4.** Pooled analysis.

| Neurocognitive function | Cognitive test/ subcomponent of cognitive test | PTSD+ vs. PTSD− survivor of wars | | PTSD+ vs. Health Control | | PTSD− vs. Health Control | |
|---|---|---|---|---|---|---|---|
| | | Sample size | MD (95% CI) | Sample size | MD (95% CI) | Sample size | MD (95% CI) |
| Attention and Information processing speed | TMT-A | 150 | −6.05 [−11.04, −1.06] | NA | NA | NA | NA |
| | WAIS—Digit span Forward | 62 | −0.07 [−1.24, 1.09] | NA | NA | NA | NA |
| Executive function | TMT-B | 150 | −25.80 [−43.70, −7.89] | NA | NA | NA | NA |
| | WAIS—Digit span Backward | 62 | −0.82 [−1.63, −0.01]. | NA | NA | NA | NA |
| | Stroop color word interference | 134 | −8.35 [−16.50, −0.20]. | NA | NA | NA | NA |
| Learning and memory | Explicit Memory— High Pair Associate | 74 | −0.61 [−1.25, 0.03] | 99 | −1.48 [−2.02, −0.94]. | 83 | −0.39 [−1.24, 0.45] |
| | Explicit Memory— Low Pair Associate | 74 | −1.64 [−2.65, −0.63] | 99 | −1.61 [−2.51, −0.71] | 83 | −0.29 [−1.23, 0.65,] |
| | Implicit Memory— High Pair Associate | 62 | −0.40 [−1.78, 0.99] | 80 | −0.05 [−1.35, 1.24] | 76 | −0.43 [−2.01, 1.14] |
| | Implicit Memory— Low Pair Associate | 62 | −0.90 [−2.58, 0.78] | 80 | −0.86 [−2.41, 0.70] | 76 | −0.03 [−1.72, 1.66] |
| | RAVLT—Immediate Recall | 82 | −0.77 [−2.04, 0.50] | 132 | −1.08 [−1.90, −0.26] | 82 | −0.96 [−2.24, 0.32] |

| Neurocognitive function | Cognitive test/ subcomponent of cognitive test | PTSD+ vs. PTSD− survivor of wars | | PTSD+ vs. Health Control | | PTSD− vs. Health Control | |
|---|---|---|---|---|---|---|---|
| | | Sample size | MD (95% CI) | Sample size | MD (95% CI) | Sample size | MD (95% CI) |
| Learning and memory | RAVLT⸺Delayed Recall | 197 | −0.98 [−1.80, −0.16] | 165 | −1.74 [−2.74, −0.73] | 114 | −0.46 [−1.81, 0.90] |
| | CVLT⸺Short Cued Recall | 89 | −1.04 [−2.36, 0.28]. | 109 | −1.98 [−3.14, −0.81] | 98 | −0.71 [−1.89, 0.48] |
| | CVLT⸺Delayed Cued Recall | 89 | −1.12 [−2.17, −0.07] | 109 | −1.24 [−2.25, −0.23] | 98 | −0.12 [−0.94, 0.70] |
| | CVLT⸺Recognition Memory | 100 | −2.43 [−4.56, −0.30]. | 92 | −4.10 [−6.77, −1.43] | 83 | −0.09 [−0.93, 0.75] |
| Verbal comprehension and Intelligence | WAIS⸺Verbal IQ | 157 | −2.64 [−3.38, −1.90] | 188 | −3.46 [−4.29, −2.63] | 160 | −0.73 [−1.55, 0.10] |
| Performance intelligence | WAIS⸺Non-Verbal IQ | 95 | −1.26 [−2.44, −0.08] | 156 | −1.46 [−2.46, −0.47] | 110 | −0.13 [−1.03, 0.78] |

TMT (Trail making Test); WAIS (Wechsler Adult Intelligence Scale); RAVLT (Rey Auditory Verbal Learning Test); CVLT (California Verbal Learning Test); IQ (Intelligence quotient)

**Table 5.** GRADE quality of evidence.

| Neurocognitive Domain | Neuropsychological Tests | Risk of bias | Heterogeneity | Precision | Indirectness | Publication bias | Final decision |
|---|---|---|---|---|---|---|---|
| Attention and Information processing speed | TMT-A | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| | WAIS—Digit span Forward | Low Risk | Low Risk | High Risk | Not detected | Not assessed | 0 + + + (moderate) |
| Executive function | TMT-B | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| | Digit Span Backward | Low Risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| | Color Word Interference—Inhibition | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| Learning and memory | RAVLT—Immediate Recall | High risk | Low Risk | High Risk | Not detected | Not assessed | 0 0 + + (Low) |
| | RAVLT—Delayed Recall | High risk | Low Risk | High Risk | Not detected | Not assessed | 0 0 + + (Low) |
| | Explicit Memory—High Pair Associate | High risk | Low Risk | High Risk | Not detected | Not assessed | 0 0 + + (Low) |
| | Explicit Memory—Low Pair Associate | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| | Implicit Memory—High Pair Associate | High risk | Low Risk | High Risk | Not detected | Not assessed | 0 0 + + (Low) |
| | Implicit Memory—Low Pair Associate | High risk | Low Risk | High Risk | Not detected | Not assessed | 0 0 + + (Low) |
| | CVLT—Short Cued Recall | High risk | Low Risk | High Risk | Not detected | Not assessed | 0 0 + + (Low) |
| | CVLT—Delayed Cued Recall | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| | CVLT—Recognition Memory | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| Verbal Intelligence | WAIS—Vocabulary | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |
| Performance intelligence | WAIS Nonverbal IQ | High risk | Low Risk | Low Risk | Not detected | Not assessed | 0 + + + (moderate) |

**Table 6.** Tests that are reported by single study and were not poolable.

| Neurocognitive function | Cognitive test/ subcomponent of cognitive test | PTSD+ vs. PTSD− survivor of wars | | PTSD+ vs. Health Control | | PTSD− vs. Health Control | |
|---|---|---|---|---|---|---|---|
| | | Sample size | MD (95% CI) | Sample size | MD (95% CI) | Sample size | MD (95% CI) |
| Information processing speed | symbol Digit modalities (Hart 2008) | 18 | −1.77 [−2.92, −0.62] | | | | |
| | WAIS—Digit Symbol (Green 2016) | 18 | −0.44 [−0.88, −0.01] | | | | |
| visuo-spatial working memory | Corsi Block Tapping Test—Forward (Jelnik 2013) | 44 | −0.13 [−0.72, 0.47] | 31 | 0.36 [−0.38, 1.10] | 35 | 0.45 [−0.27, 1.17] |
| | Corsi Block Tapping Test—Backward (Jelnik 2013) | 44 | −0.48 [−1.08, 0.12] | 31 | −0.35 [−1.10, 0.39] | 35 | 0.13 [−0.58, 0.85] |
| Language | COWAT (Phonemic fluency) (Hart 2008) | 18 | −0.98 [−2.00, 0.03] | | | | |
| | Boston Naming Test (Hart 2008) | 18 | −0.84 [−1.84, 0.16] | | | | |
| | Groningen Intelligence Test (GIT) fluency (Wessel 2002) | | | 40 | −0.63 [−1.29, 0.02] | | |
| | Animal Fluency— Semantic fluency (Hart 2008) | 18 | −0.39 [−1.35, 0.57] | | | | |

| Neurocognitive function | Cognitive test/ subcomponent of cognitive test | PTSD+ vs. PTSD− survivor of wars | | PTSD+ vs. Health Control | | PTSD− vs. Health Control | |
|---|---|---|---|---|---|---|---|
| | | Sample size | MD (95% CI) P value; $I^2$ | Sample size | MD (95% CI) P value; $I^2$ | Sample size | MD (95% CI) P value; $I^2$ |
| Learning and memory | Autobiographical positive cues (Wessel 2002) | | | 40 | −1.52 [−2.25, −0.79] | | |
| | Autobiographical negative cues (Wessel 2002) | | | 40 | −1.43 [−2.15, −0.71] | | |
| | WMS—Logical memory—Thematic scores (Freeman 2006) | 20 | −0.08 [−0.96, 0.80] | 16 | −0.05 [−1.06, 0.96] | 16 | 0.02 [−0.99, 1.04] |
| | WMS—Logical Memory—Recall score (Freeman 2006) | 20 | −0.56 [−1.46, 0.33] | 16 | −0.4 [−1.45, 0.61] | 16 | 0.14 [−0.88, 1.15] |

WAIS (Wechsler Adult Intelligence Scale); COWA (Controlled Oral Word Association Test); WMS (Wechsler Memory Scale)

Due to inconsistently reporting across the studies PTSD+ vs. healthy control was only noted in learning and memory functions. Most of the results remained consistent in comparing PTSD+ survivors of war with healthy controls. Performance on many neuropsychological tests that were initially nonsignificant between PTSD+ and PTSD− elderly survivors of war became significant when comparing PTSD+ elderly survivors of war with the control population not suffering from PTSD. Some variables such as explicit memory, short cued recall, delayed cued recall and delayed free recall were significant in PTSD+ survivors of war as compared to the healthy control that was non-significant in the PTSD+ survivor of wars vs. PTSD− survivors of war. This trend possibly indicates an association of sub-threshold neurocognitive deficits in PTSD− survivors of war; therefore, the performance on tests that are nonsignificant for PTSD+ vs. PTSD− survivors of war became apparent in the second comparison. This can be further supported by comparing the effect sizes for performance for explicit memory, RAVLT, and CVLT. PTSD+ survivors exhibited larger effect measures when compared to healthy controls than compared with PTSD− survivors of war. Many commonly used tests in practice such as COWA, fluency tests were not pooled due to not meeting our criteria as reported in 2 or more studies; however, as these tests are commonly used we reported them as a single study effect. Performance on tests measuring visuospatial function and language were not significant.

Our review also had a few limitations. One of the limitations of our review was that some studies Golier 2002 [43], Yehuda 2005 [46], Freeman [48], Jelinek [57], and Hart [34] were duplicates and analyzed data on the same population. To avoid overestimation in our pooled analysis, we restricted our analysis to tests that were not reported in the original studies. Secondly, most studies in our pooled analysis had a small sample size and did not account for premorbid IQ; therefore, results of analysis need to be interpreted cautiously as we were unable to explore for publication bias, moderator effect of premorbid IQ and subgroup analysis respectively. Estimation of premorbid intelligence is important to determine whether the change in the neurocognitive function is greater than one can expect or is due to the measurement errors [59].

As compared to previous reviews our review also had much strength. Firstly, Schuitevoerder et al. reported their results based on the main neurocognitive function. Different neuropsychological tests measuring the same neurocognitive function require mental process in detecting the specific neurocognitive function [60]. There is always a potential that one aspect of the cognition might be working adequately than the other, therefore, pooling based on the neuropsychological tests provided better interpretation. This pattern was also noticeable in our analysis. For example, TMT-A and WAIS digit span forward both measured attentions. But performance on TMT-A is more complex and further requires information processing speed, as compared to the digit span forward test. Similarly, when compared digit span forward vs. digit span backward, the digit span forward measures attention efficiency whereas digit span backward is the measure of executive function and dependent on the working memory and mental flexibility.

Both Qureshi et al. [11] and Schuitevoerder et al. [12] categorized their results according to the trauma type. We did not have restrictions based on the war trauma type, which potentially increases the generalizability of our results. Schuitevoerder et al. [12] also identified duplicate publications during their review and used the average effect estimate, which in our opinion, is potential for overestimation. We excluded the duplicate study with a small sample size from our analysis. We included studies that recruited outpatient PTSD survivors of wars as compared to previous reviews [11,12], which included studies with inpatients patients with major systematic

comorbidities such as coronary artery bypass graft. Our rationale to exclude studies with inpatient PTSD patients and other major systematic ailments was that these patients potentially had a complicated course of illness, which can be a potential confounder to describe the association of cognitive impairments in PTSD survivors of war. We explored the quality of evidence with GRADE across the pooled analysis to determine confidence in our outcomes. We performed three different analyses to explore the possible effect of age on the association of cognitive deficits in elderly PTSD+ survivors of war and the normal ageing process. As compared to Qureshi et al, we excluded patient suffering from PTSD due to other reasons such as MVA, surgical process, and injuries due to which we had a more homogenous population in our pooled analysis.

## 7.1. Implications and future directions

As compared to the general population, PTSD is more prevalent in the survivors of war [6,9,61]. The combat traumas in the elderly may persist long after the initial exposure and can invariably affect the neurocognitive functions requiring complex tasks, retrieval of information and memory. Understanding the neurocognitive impairment in elderly patients is vital because the age-related changes in cognitive function can further compound the neurocognitive impairment and activities of daily livings [62,63]. Based on our findings, these deficits were more pronounced in function requiring information processing speed and executive function, inhibition, mental flexibility, and delayed retrieval of information. A potential explanation for deficits in information processing speed, executive function and memory is preoccupation with the traumatic thoughts, intrusion, flash back, nightmares and sleep disruption and avoidance in PTSD. As the emotional symptoms persist beyond many years and act viciously to allocate the information processing towards the fear and traumatic events [64]. This preponderance of information processing speed towards fear and traumatic thoughts potentially makes disengaging from the traumatic memory harder, slows the formation of new memory, planning and executive functions [64].

One of the key implications of our review is that merely providing the symptomatic treatment to elderly survivors of war suffering from PTSD may not suffice and requires detailed neurocognitive assessment. The neurocognitive impairment in elderly survivors of war can hasten the recovery process [64–66]. Understanding the extent of neurocognitive deficits can potentially facilitate to stratify the support and management plan for the elderly survivors of war. For example, various components of cognitive behavioral therapy involve recalling past events or describing traumatic scenes, which may trigger traumatic flash backs, sleep impairment and avoidance behavior. It is possible that intrusive thoughts or negative processing associated with the trauma may hasten the recovery process [67]. On the other hand, other treatment strategies such as support therapy, recreational therapy, or educational intervention require more intact mental processing, and cognitive ability to learn new information. Not addressing the issues with complex mental processing, mental flexibility, attention processes can hinder the effectiveness of psychotherapies. As patients with PTSD experiences emotional symptoms such as avoidance, intrusion, and flash back of traumatic memories.

In conclusion, elderly survivors of war with PTSD exhibited poor performance on a neuropsychological test that required complex functioning or delayed information retrieval. The relatively poor performance was noted on PTSD+ survivors of war in comparison to the healthy control group and PTSD− survivors of war. There is a need for good quality, studies with large

sample sizes and controlling for important variables such as ages, and premorbid IQ. Future studies may consider performing multiple comparisons such as PTSD patients with comorbidities, other psychological conditions for a better understanding of neurocognitive deficits in PTSD patients particularly in elderly survivors of war.

**Conflict of interest**

No conflict of interest.

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