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BRIEF REPORT

Posttraumatic stress disorder symptom severity is associated with reduced Montreal Cognitive Assessment scores in a sample of Vietnam War Veterans

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Abstract

The goal of the present study was to examine associations between posttraumatic stress disorder (PTSD) symptom severity, the number of stressors experienced, and cognitive outcomes in a sample of U.S. Vietnam War Veterans (N = 274). Adults between 60 and 85 years of age completed a Vietnam Veterans Alzheimer's Disease Neuroimaging Initiative Project visit. A modified version of the Life Stressor Checklist-Revised (LSC-R) was used to assess the number of stressful experiences participants experienced, current PTSD severity scores were measured via the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS-IV), and cognition was assessed using the Montreal Cognitive Assessment (MoCA). Linear regressions were conducted to examine the effect of CAPS-IV and LSC-R scores on cognitive performance. Higher CAPS-IV scores were associated with worse cognitive outcomes on the MoCA, $\Delta F(1, 264) = 12.686$, $p < .001$, $R^2 = .142$. In contrast, the number of reported stressful experiences was not associated with cognitive outcomes. After accounting for multiple comparisons, findings indicated that CAPS-IV severity scores were significantly associated with the MoCA memory index. In a sample of older Veterans, PTSD symptom severity, but not the number of reported stressors, was associated with poorer performance on a well-established cognitive function screening tool. Analyses of specific MoCA domains indicated that memory may be driving this association. These findings suggest that highly arousing stressors characteristic of PTSD, rather than stressful experiences more broadly, contribute to this association. Future work can use these findings to explore whether treating PTSD symptoms may help maintain cognitive function during the aging process.

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Exposure to chronic stress has long been associated with negative health outcomes in older adults. Mounting evidence suggests that stress causes hypothalamic–pituitary–adrenal (HPA) axis dysregulation (Miller et al., 2007), which may ultimately contribute to worse cognitive functioning in aging across various domains, including episodic memory, processing speed, and flexibility (Zuelsdorff et al., 2013). As the population ages, it is imperative to determine the role of stress in the development of mild cognitive impairment (MCI) and dementia. Stress is associated with negative performance on the Montreal Cognitive Assessment (MoCA; Clouston et al., 2016), which is a widely used MCI screening tool. The advantages of this screener include its ease of administration and utility for early detection of cognitive impairment (Nasreddine et al., 2005).

Previous work underscores the role of stress and cognitive dysfunction in aging. However, several questions regarding the association between stress and cognitive decline remain; an unresolved question is the extent to which the number of stress exposures an individual experiences, independent of posttraumatic stress disorder (PTSD) symptom severity, contributes to cognitive dysfunction in aging. In other words, does exposure to a multitude of life stressors influence cognitive function in older adults to the same extent as PTSD symptoms? Stressful events are associated with poorer episodic memory and more everyday memory problems (Rickenbach et al., 2014; VonDras et al., 2005). Longitudinal work by Dickinson et al. (2011) demonstrated an association between a reduction in stressors at 1-year follow-up with improvement in global cognition at 2-year follow-up in a sample of older adults. However, other work has challenged the notion that stressful experiences negatively influence cognition. In a longitudinal study of older adults in China, researchers found that nondepressed participants who reported stressful life events had a lower risk of incident dementia than those without stressful experiences (Tian et al., 2020). The authors suggested that the more favorable outcomes observed in the stressor group may reflect resilience and coping skills, which may contribute to preserved cognitive functioning. In another study, Payne et al. (2020) found that endorsing more stressful life events was associated with psychological outcomes including depression and PTSD, but not cognitive impairment. Taken together, although there are indications of potential associations between stressful experiences and cognitive outcomes, the current evidence is inconclusive.

Independent of the number of stressful events one experiences, PTSD symptom severity is associated with lower cognitive performance in older adults, including in the domains of memory and executive functioning. In a sample of older Veterans, PTSD was found to be associated with poorer performance on measures of both rate of learning and delayed free recall of a rote memory list (Yehuda et al., 2005). In another study, PTSD was associated with poorer performance on memory and executive functioning tasks following cardiac surgery (Hudetz et al., 2010). The findings from meta-analyses have demonstrated an association between highly arousing stressors that lead to subsequent PTSD symptoms and lower scores on measures of processing speed, attention, learning, and memory (Scott et al., 2015). These associations, though potentially meaningful, must be interpreted with caution when performance validity testing is not taken into account, and group differences may be smaller when validity is considered (Demakis et al., 2008; Wrocklage et al., 2016).

In the present study, we directly compared the number of stressful experiences participants had experienced and PTSD severity to determine their relative influence on cognitive performance. The number of stressful experiences a participant had experienced was measured using a modified version of the Life Stressor Checklist–Revised (LSC-R; Wolfe et al., 1997), and PTSD symptoms, based on criteria in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*; American Psychiatric Association, 1994), were assessed using the Clinician-Administered PTSD Scale for *DSM-IV* (CAPS-IV; Blake et al., 1998). Cognition was assessed using the MoCA. In addition, we examined the influence of traumatic brain injury (TBI) and neurodegenerative disease biomarkers, including β-amyloid (Aβ) and phosphorylated tau (pTau) on cognitive performance. TBI and PTSD co-occur at high rates in veteran samples (Hayes, 2019), and, therefore, we examined if PTSD symptoms would be related to cognition after taking TBI into account. Furthermore, we examined the influence of Aβ and pTau, which are important biological markers of Alzheimer's disease (AD) and can be detected before the onset of clinical symptoms (Villemagne et al., 2013). Aβ accumulation has been associated with reduced cognitive functioning in individuals with PTSD, suggesting a possible link between PTSD and AD (Mohamed et al., 2018). Though Aβ and pTau are more traditional biomarkers of AD, the pTau–Aβ ratio may be a more stable biomarker of AD (Harari et al., 2014). As such, a secondary goal of this study was to examine whether the association between stress and cognition was significant even after accounting for Aβ, pTau, and their ratio. Analyses for this study were conducted on a large sample of Vietnam War Veterans from a publicly available dataset, the Department of Defense Alzheimer's Disease Neuroimaging Initiative (DoD-ADNI).

METHOD

Participants

DoD-ADNI recruited Veterans of the Vietnam War who either had a history of moderate-to-severe nonpenetrating TBI and/or PTSD. In addition, veteran control participants matched on age, sex, and educational attainment were included in DoD-ADNI. Individuals were excluded from DoD-ADNI if they had a history of clinical evidence of a stroke, psychotic illness, neurologic illness, mild cognitive impairment, or dementia. The full list of inclusion and exclusion criteria can be accessed at DoD-ADNI. All participants who completed a baseline visit as a part of DoD-ADNI and had available demographic information and CAPS-IV, LSC-R, and MoCA scores were included in the current analyses. The current sample included 274 participants from DoD-ADNI.

Procedure

Data used in the preparation of this article were obtained from the DoD-ADNI. DoD-ADNI is a nonrandomized, observational study that recruited Vietnam War Veterans without dementia from the U.S. Department of Veterans Affairs compensation and pension records to undergo testing. DoD-ADNI was launched in 2012 to understand risk factors commonly present in Veterans, such as PTSD and TBI, that can influence dementia. For additional information, see DoD-ADNI (http://www.adni-info.org). Data used in this manuscript were downloaded from the DoD-ADNI database on May 7, 2020, from the following datasheets: CAPSCURR.csv, LSCR.csv, MoCA.csv, PTDEMOG.csv, TBISERIES.csv, UPENNBIOMK_DOD_2017.csv, and MEDHXSELF.csv.

Measures

Stressful life events

The number of stressful events was assessed using a modified version of the LSC-R administered in DoD-ADNI (Wolfe et al., 1997). This checklist includes both events that qualify as *DSM* Criterion A traumatic events (e.g., "Have you ever been in a serious disaster [for example, a massive earthquake, hurricane, tornado, fire, explosion]?", "Have

you ever seen a serious accident [for example, a bad car wreck or an on-the-job accident]?"), as well as events that are stressful but do not meet *DSM* Criterion A (e.g., "Was a close family member ever arrested or sent to jail?", "Have you ever had serious money problems [for example, not enough money for food or place to live]?"). The modified LSC-R included 23 of the 30 original items. The included items are broad and do not solely pertain to military-related stressful experiences that occurred while deployed to Vietnam. Excluded items were related to parental separation and divorce, having been in foster care or put up for adoption, personal separation and divorce, caring for someone who had a severe physical or mental handicap who was not the participant's child, and the death of a loved one that was not sudden or unexpected. Items related to nonlisted stressors (i.e., "Are there any events we did not include that you would like to mention?") and events that happened to a loved one but were distressing to the participant were also excluded.

Following item endorsement, participants in DoD-ADNI were asked, "At that time or shortly after, did you experience feelings of intense helplessness, fear, or horror?" Moreover, they were asked to specify if the event was a single instance or recurrent event and indicate their age at the time the event occurred, and, for recurrent events, their age the first and last time the event occurred. As such, follow-up analyses defined life stressors in the following ways: (a) the number of recurrent stressful experiences endorsed and (b) the number of different types of stressors that led to subsequent feelings of intense helplessness, fear, or horror. For example, to examine the contribution of recurrent stressful events, a total sum score of recurrent events was entered into the regression analysis; if a participant reported 20 stressors that occurred one time and three recurrent stressors, then a score of 3 would be assigned to that participant to examine the contribution of recurrent stressful events. This sum was entered into the regression analysis to examine the contribution of recurrent stressful events.

PTSD symptoms

The DoD-ADNI protocol used the 30-item CAPS-IV (Blake et al., 1995), which includes items related to symptom frequency and intensity in reference to symptoms stemming from Criterion A traumatic events. Prior work has demonstrated that the CAPS-IV has well-established reliability and validity; in a review of Vietnam Veterans, Cronbach's alpha values were found to range from .82 to .88 (Weathers et al., 2001). Answers from this interview were rated and scored to create a combined severity score. This severity score was used as a continuous measure of PTSD symptoms. The severity score was used rather than PTSD diagnostic status because it captures individual variability in resilience and vulnerability to experiencing stressful events.

Cognitive function

Cognitive performance was assessed using the MoCA (Nasreddine et al., 2005; Cronbach's $\alpha = 0.83$). MoCA total scores were calculated for each participant (range: 0–30). Additionally, MoCA scores were divided into six domains based on methods used in previous research (Goldstein et al., 2018; Julayanont et al., 2014). The Memory Index score (MoCA-MIS) was calculated by adding the number of words remembered in the free delayed recall, category-cued recall, and multiple-choice–cued recall, multiplied by 3, 2, and 1, respectively. Scores for the MoCA-MIS ranged from 0 to 15 points. The Executive Index score (MoCA-EIS) was calculated by adding raw scores for the trail-making, clock, digit span, letter a tapping, serial 7 subtraction, letter fluency, and abstraction assessments, with scores ranging from 0 to 13. The Visuospatial Index score (MoCA-VIS) consisted of raw score sums from the cube copy, clock drawing, and naming assessments, with scores ranging from 0 to 7. The Language Index score (MoCA-LIS) included sums of raw scores for naming, sentence repetition, and letter fluency tasks, with scores ranging from 0 to 6. The Attention Index score (MoCA-AIS) was calculated by adding the raw scores of digit span, letter a tapping, serial 7 subtraction, sentence repetition, and words recalled in both immediate recall trials, with scores ranging from 0 to 18 points. The MoCA Orientation Index score (MoCA-OIS) included the sum of points for all items related to orientation, with scores ranging from 0 to 6.

Data analysis

All data were analyzed using IBM SPSS Statistics for Macintosh (Version 26). Correlations were conducted between selected measures of stress (i.e., LSC-R and CAPS-IV) and select demographic and health information (i.e., age, educational attainment, gender, race, ethnicity, cardiovascular symptoms or disease, and TBI).

Hierarchical linear regressions were conducted to examine the effects of stressful experiences and PTSD symptoms on MoCA performance. Covariates were entered into the first model. In the second model, the stress variable of interest (i.e., LSC-R or CAPS-IV) was entered. Scores from the LSC-R were included as a covariate for the analysis assessing the impact of PTSD symptom severity, whereas

CAPS-IV scores were entered as a covariate in the analysis examining the impact of life stressors on cognitive outcomes. A Bonferroni correction was implemented to correct for multiple comparisons of these two linear regressions; corrected significance was defined as $p < .025$ for this primary set of analyses. Follow-up analyses were conducted to determine the associations between stress and MoCA subdomains. As described, all relevant covariates (i.e., age, education, race, ethnicity, gender, history of TBI, and cardiovascular disease and symptoms) were entered into Model 1, and stress variables were entered separately into Model 2. To account for multiple comparisons, we implemented a Bonferroni correction for the six MoCA subdomains. Thus, a p value of .008 or lower was required to meet the significance threshold in these follow-up analyses.

Because we aimed to disentangle the impact of objective stressful events and PTSD symptoms associated with stressors, follow-up analyses were conducted to include only stressors for which participants endorsed the item, "At that time or shortly after did you experience feelings of intense helplessness, fear, or horror?" Moreover, follow-up analyses were conducted to include stressors that occurred more than once (i.e., recurrent stressors). We also examined whether the association between stress and cognitive outcomes remained significant after accounting for the effects of cerebrospinal fluid (CSF) biomarkers (i.e., Aβ, pTau, and pTau–Aβ ratio). A subset of DoD-ADNI participants took part in a biomarker assessment; thus, Aβ data were available for 121 participants. CSF was collected via a lumbar puncture, and CSF analyses were performed using Roche Elecsys immunoassay following Roche Study protocol (Bittner et al., 2016). We replicated the main hierarchical linear regressions using all covariates described previously for participants with available biomarkers.

The following covariates were included in all hierarchical regressions: age, educational attainment, race, ethnicity, gender, history of military-related TBI, and cardiovascular symptoms or disease. Cardiovascular symptoms or disease was dichotomized based on a question from a self-report medical history questionnaire that asked, "Yes or no, problems with your heart or cardiovascular disease?" Similarly, a dichotomous value (i.e., "yes" or "no") for TBI was incorporated into the analysis. See the Supplementary Materials for additional details about TBI assessment. Accounting for the contribution of TBI was particularly important in our analyses given the elevated comorbidity rates of PTSD and TBI in veteran populations, the role of TBI in conferring risk for the development of PTSD, and the documented outcomes each disorder may have on cognition (Hayes, 2019).

RESULTS

Sample characteristics and correlations

Participant demographic and health characteristics are shown in Supplementary Table S1. The sample was composed primarily of White (84.3%) men (99.3%). The results of chi-square and independent-samples t tests indicated that there were significant differences between the sample with and without available biomarker data such that individuals without available biomarkers were significantly older and more likely to have a history of military-related TBI. Participants with biomarkers were more likely to identify as Hispanic. LSC-R scores were significantly correlated with age, CAPS-IV severity scores, and endorsement of cardiovascular symptoms or disease. For stressful experiences that occurred once, the average age reported was 38.15 years ($SD = 12.67$). For recurrent events, the average age of first occurrence was 23.71 years ($SD = 6.72$). CAPS-IV severity scores were significantly correlated with age, educational attainment, LSC-R score, and TBI history. For more information on the associations between stress and sample characteristics. see Supplementary Table S2.

Associations among cognition, stressful experiences, and PTSD symptoms

Higher CAPS-IV scores, indicating higher levels of PTSD symptom severity, were associated with worse MoCA scores after adjusting for age, race, ethnicity, gender, educational attainment, LSC-R score, TBI history, and cardiovascular symptoms or disease, $\Delta F(1, 264) = 12.686$, $p < .001$, $\Delta R^2 = .041$, $\beta = -.222$ (see Table 1). This result remained significant after applying a Bonferroni correction for multiple comparisons. In contrast, the results of linear regressions indicated that the LSC-R scores were not significantly associated with MoCA scores after adjusting for PTSD symptoms and demographic and health-related variables, $p = .329$. Similarly, additional follow-up analyses revealed no significant effects on cognition of either stressors that participants endorsed as being recurrent, $p = .196$, or those that led to subsequent feelings of intense helplessness, fear, or horror, $p = .208$.

Associations between MoCA domains and PTSD symptoms

Follow-up analyses were conducted to examine the association between PTSD symptoms and MoCA domains. We observed significant associations between PTSD severity

TABLE 1 Summary of regression analysis for association of between Clinician-Administered Posttraumatic Stress Disorder Scale for *DSM-IV* (CAPS-IV) scores with Montreal Cognitive Assessment (MoCA) scores

	Model 1[a]				Model 2[b]			
Variable	***B***	***SE***	***β***	***p***	***B***	***SE***	***β***	***p***
Age	−0.029	0.042	−.043	.494	−0.054	0.042	−.079	.199
Education	0.318	0.074	.258	.000*	0.266	0.074	.216	.000*
LSC-R	0.010	0.064	.009	.881	0.063	0.064	.060	.329
TBI	−0.686	0.379	−.108	.072	−0.570	0.372	−.090	.127
Gender	1.830	2.056	.052	.374	1.521	2.014	.043	.451
Ethnicity	0.674	0.611	.065	.271	0.539	0.599	.052	.369
Race	0.361	0.252	.084	.153	0.346	0.247	.081	.161
Cardiovascular symptoms or disease	−.634	0.388	−.098	.104	−0.578	0.380	−.090	.129
CAPS-IV					−0.025	0.007	−.222	.000*
R^2	.101				.142			
ΔF	3.729*				12.686*			

Note: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th ed.); LSC-R = Life Stressor Checklist–Revised; TBI = traumatic brain injury.
[a]Included relevant covariates (i.e., age, race, ethnicity, gender, education, LSC-R scores, history of TBI, and cardiovascular symptoms or disease. [b] Included all covariates in model one and the CAPS-IV, with MoCA score as the dependent variable.
*$p < .01$.

and MoCA-MIS, $\Delta F(1, 264) = 19.223$, $p < .001$, $\Delta R^2 = .066$, $\beta = -.280$, and MoCA-EIS scores, $\Delta F(1, 264) = 7.207$, $p = .008$, $\Delta R^2 = .023$, $\beta = -.166$. The MIS, but not EIS, remained significant after correcting for multiple comparisons. The following domains of the MoCA were not significant: MoCA-AIS, $p = .070$; MoCA-VIS, $p = .429$; MoCA-LIS, $p = .525$; and MoCA-OIS, $p = .520$.

Associations between cognitive screeners and PTSD symptoms after adjusting for Aβ

We also examined the associations between CAPS-IV severity scores and MoCA outcomes after adjusting for AD biomarkers (i.e., Aβ, pTau, and the pTau–Aβ ratio). We reran our analyses on the 121 participants with available Aβ, pTau, and pTau–Aβ ratio data. The results indicated that higher levels of PTSD symptom severity were associated with worse MoCA total scores even after adjusting for the effects of Aβ, $\Delta F(1, 115) = 0.385$, $p = .025$, $\Delta R^2 = .037$, $\beta = -.213$; pTau, $\Delta F(1, 110) = 8.988$, $p = .003$, $\Delta R^2 = .065$, $\beta = -.281$; and pTau/Aβ, $\Delta F(1, 110) = 8.680$, $p = .004$, $\Delta R^2 = .063$, $\beta = -.277$. As such, there is evidence from these analyses that PTSD symptom severity can predict cognition over and above markers of AD pathology.

DISCUSSION

This study examined the associations between cognitive function and two measures of stress: PTSD symptom severity and the number of reported stressful experiences. Two main findings emerged. First, in our sample of Vietnam War Veterans, PTSD symptom severity, but not the number of stressful experiences, was associated with worse cognitive performance on the MoCA. Second, when examining particular domains of the MoCA, we observed an association between PTSD symptom severity and the MoCA memory domain. Although we found a significant association between PTSD and the executive domain, it did not survive multiple comparison corrections. No other significant relationships emerged.

Disentangling the contributions of the number of stressors an individual experiences and PTSD symptoms on cognitive outcomes is beneficial, particularly as stress has been linked to a risk for subsequent dementia (Burnes & Burnette, 2013). The present results suggest that reduced cognitive functioning is primarily driven by PTSD symptoms over and beyond the impact of living through stressful experiences. In contrast, the number of stressful experiences, number of recurrent stressful events, and number of stressors that led to subsequent feelings of intense helplessness, fear, or horror did not account for MoCA performance above and beyond what is explained by PTSD symptoms. These results provide evidence that the chronic symptoms related to a stressful event rather than the event itself are associated with cognitive outcomes. This aligns with consistent findings from previous cross-sectional and longitudinal studies demonstrating associations between PTSD symptoms and cognitive functioning (Clouston et al., 2016; Wrocklage et al., 2016). Moreover, the current work aligns with a prior review that

demonstrated an association between PTSD and various cognitive domains, including verbal memory and executive functioning (Polak et al., 2012).

The association between PTSD symptoms and cognition may be driven by biological processes that occur in response to stress. Cortisol is a glucocorticoid released by the adrenal cortex in response to chronic or traumatic stress, such as that experienced in PTSD. The hippocampus, a brain region important for memory, is particularly prone to damage from glucocorticoids, as it has a high density of relevant receptors (Miller et al., 2007). The findings from a recent meta-analysis involving 1,868 participants demonstrated that individuals with PTSD had significantly smaller hippocampal volumes than those who were trauma-exposed without PTSD (Logue et al., 2018). However, a smaller hippocampal volume may also represent a preexisting vulnerability factor for PTSD (Gilbertson et al., 2002), and the association between PTSD and cognition may be bidirectional; whereas PTSD may confer risk of cognitive decline, cognitive functioning at baseline plays a role in determining who is most susceptible to developing PTSD (Vasterling et al., 2018). Moreover, prior work suggests that PTSD symptoms may worsen as individuals' cognition deteriorates; that is, cognitive impairment may unmask symptoms of PTSD (Johnston, 2000). Further longitudinal work is necessary to disentangle which factors represent more of a preexisting vulnerability for PTSD versus an acquired PTSD symptom.

This study had several limitations that should be considered. Because of the cross-sectional design, causal associations between stress and cognitive functioning cannot be determined. Longitudinal investigations of the intersection between stressful experiences, PTSD symptoms, and cognitive functioning can further clarify these associations. An additional limitation was the lack of available symptom and performance validity data. Prior work suggests that outcomes may vary between studies that incorporate validity testing compared with those that do not (Wisdom et al., 2014). This is particularly important because our data were drawn from a compensation and pension sample, and prior work has outlined positive associations between validity test failure and PTSD severity (Miskey et al., 2020). Although a strength of the study was the utilization of AD pathology biomarkers as covariates, it is important to acknowledge that the association between CSF Aβ and plaque burden is likely nonmonotonic. Instead, this association is more likely biphasic; animal models have demonstrated that CSF Aβ increases at the time of initial plaque deposition, which is followed by a subsequent decline as plaques continue to form (Maia et al., 2015).

Our use of the MoCA to examine cognition represents another study limitation. The benefits of this brief screening instrument include the timing of administration and frequency of use; however, a comprehensive neuropsychological evaluation is necessary to detect specific patterns of impairment. Similarly, the CAPS-IV was used in the study, as CAPS-5 (i.e., updated to reflect *DSM-5* criteria) data were not collected in DoD-ADNI. As such, the present results should be used to guide future research using more up-to-date methodologies. In addition, because the sample was composed of Veterans who were primarily White men and participants who may have a more severe history of PTSD symptoms and/or TBI compared to Veterans who did not volunteer to participate in this study, the results may not be generalizable to other veteran populations or the general public. Importantly, women and Black, Indigenous, and people of color may experience chronic, stressful events that may influence their cognitive functioning. Future research is essential to better understand the associations between stress exposure, PTSD symptoms, and cognition in a more diverse sample.

The present results clarify the association between stress and cognitive functioning in a sample of Vietnam War Veterans. Specifically, the findings suggest that PTSD symptoms, rather than stress exposure, can better explain reductions in cognitive functioning with age. Moreover, when examining various domains of cognition, memory was found to be particularly impacted by PTSD symptoms. The results from this study could be used to inform treatment plans for ensuring individuals preserve cognitive function as they age. Specifically, treating symptoms of PTSD as soon as possible following trauma may be essential in preserving cognitive status into older age.

OPEN PRACTICES STATEMENT

The analyses reported in this article were not formally preregistered. Deidentified data along with a codebook and the data analysis scripts are posted at www.long.ucla.edu/ADNI; access to the data is limited to qualified researchers. The materials used in these studies are widely publicly available.

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