Longitudinal Assessment of Cognitive Performance in Holocaust Survivors with and without PTSD

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Background: *There are currently no longitudinal studies of cognitive performance in older patients with Posttraumatic Stress Disorder (PTSD). It is therefore unclear whether relationships between memory and symptoms differ over time among older persons with and without PTSD.*

Methods: *Twenty-eight Holocaust survivors and nineteen comparison subjects were evaluated 5 years after they had received a memory assessment including paired-associates learning and the California Verbal Learning Test (CVLT).*

Results: *While Holocaust survivors with PTSD showed a diminution in symptom severity (*t = *2.99,* df = *12,* p = *.011), they still manifested a decline in paired associates learning, suggesting an acceleration in age-related memory impairment (related word pairs:* t = *2.87,* df = *13,* p = *.013; unrelated word pairs:* t = *2.06,* df = *13,* p = *.060). The survivors with PTSD showed improvements on several CVLT measures over time. These improvements correlated with symptom improvements, such that group differences at the follow-up were no longer detected.*

Conclusions: *The discrepancy in the pattern of performance on these two tests of memory following symptom improvement suggests possible differentiation between of aspects of memory functions associated with aging and trauma exposure and those associated with the severity of PTSD symptoms. Performance on the CVLT appeared related to clinical symptom severity while paired associate learning worsened over time in Holocaust survivors with PTSD, consistent with earlier cross-sectional findings.*

Key Words: Aging, California Verbal Learning Test, memory, paired associate learning, PTSD

Although many investigators have documented deficits in explicit memory performance in trauma survivors with Posttraumatic Stress Disorder (PTSD), there is variability across studies in these findings, and questions regarding the associations between memory impairments and characteristics of trauma exposure (Danckwets and Leathem 2003; Vasterling et al 2002). In our studies of elderly trauma survivors, we reported memory changes in PTSD not previously observed in younger trauma survivors. For example, Holocaust survivors with current PTSD demonstrated poorer explicit memory performance than unexposed persons and survivors without PTSD (Golier et al 2002). These deficits were not observed in younger subjects with PTSD (Gurvits et al 1995). Additionally, both Holocaust survivors (Yehuda et al 2004) and elderly combat veterans (Yehuda et al 2005a) showed reductions in performance on trial performance and total learning on the California Verbal Learning Test (CVLT), in contrast to younger participants with PTSD (Stein et al 1997; Yehuda et al 1995; Jenkins et al 1998). The similar deficits in combat veterans and Holocaust survivors (Yehuda et al 2005b), coupled with a greater negative correlation between age and paired associate learning deficits in Holocaust survivors with PTSD (Golier et al 2002), suggested an accelerated age-related decline in aging trauma survivors with PTSD. However, cross-sectional studies cannot definitively prove that the observed changes are related to the longitudinal course of memory changes in individual patients.

Though certain aspects of memory performance decline with normal aging (Lyketsos et al 1999; Hazlett et al 1998), PTSD symptoms appear to diminish with age. Longitudinal studies found a marked diminution in the proportion of subjects meeting criteria for PTSD 40 and 50 years following exposure (Kluznik et al 1986; Tennant et al 1997), and older PTSD subjects generally endorse only mild to moderate levels of symptom severity (Yehuda et al 1997). Accordingly, a longitudinal study of the convergence of memory and symptom changes provides an opportunity to examine the extent to which memory changes are related to the course of illness or to aging, or, rather, whether they are predicted by historical factors associated with trauma exposure or core vulnerabilities to PTSD.

In the current report, we present data from a five-year follow-up study of memory performance and PTSD symptoms in Holocaust survivors with and without PTSD and a nonexposed comparison sample. We anticipated a modest decline in explicit memory performance in all of these elderly subjects, but specifically hypothesized that subjects with PTSD would show a relatively greater decline in memory functioning. As we did not know whether our previous findings regarding memory impairments were associated with the severity of clinical symptoms, we also hypothesized that some aspects of memory functioning might be associated with the course of PTSD symptoms.

Methods and Materials

Participants

The sample consisted of 28 Holocaust survivors (11 men, 17 women) and 19 Jewish comparison subjects (8 men, 11 women), representing a subgroup of 82 participants who had five years earlier participated in a neuropsychological assessment (Golier et al 2002; Yehuda et al 2004). The study was approved by the IRB of the Mount Sinai School of Medicine, and all subjects provided written, informed consent. After IRB approval was received to re-contact the original cohort by mail, letters were sent out informing the subjects of the opportunity to partici-

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Table 1. Statistical Comparison between Subjects in Original Cohort Who Did Respond to Follow-up and Who Did Not

	Did Not Respond	Current Study	
	N = 43	*N* = 39	*t, df, p*
Demographics			
Age	67.4 ± 5.7	69.2 ± 2.7	1.64, 80, n.s.
Education	14.7 ± 4.3	14.1 ± 3.7	.69, 80, n.s.
WAIS Block	11.2 ± 2.8	10.0 ± 2.7	1.85, 70, n.s.
WAIS Vocabulary	56.1 ± 14.0	53.3 ± 11.9	.92, 70, n.s.
Total CAPS	40.4 ± 35.6	28.6 ± 27.6	.12, 71, n.s.
Memory			
High Associates	4.9 ± 1.2	4.6 ± 1.2	1.36, 80, n.s.
Low Associates	2.0 ± 2.1	1.3 ± 1.6	1.61, 80, n.s.
Attention	6.5 ± 2.3	5.8 ± 2.3	1.36, 72, n.s.
Total Learning	46.6 ± 14.8	45.3 ± 11.4	.40, 71, n.s.
List B	5.8 ± 2.9	5.9 ± 2.5	.18, 71, n.s.
Short Delay Free Recall	9.8 ± 3.1	8.7 ± 3.1	1.44, 71, n.s.
Long Delay Free Recall	10.3 ± 3.4	8.8 ± 3.5	1.76, 71, n.s.
Short Delay Cued Recall	10.9 ± 3.2	10.0 ± 2.6	1.34, 71, n.s.
Long Delay Cued Recall	11.2 ± 3.2	9.8 ± 3.1	1.87, 71, n.s.

pate in a five-year follow-up study. Fifty-three participants from the original cohort responded (out of a possible 82) and were scheduled for evaluations. As shown in Table 1, the sub-sample of subjects ($n = 53$) who participated in the follow-up study did not differ from the original cohort.

Clinical diagnoses of PTSD at baseline and follow-up periods were generated through a consensus process with at least two experienced diagnosticians (RY, JG, RG) using DSM-IV criteria. The diagnoses were based on all available information including data collected using the Structured Clinical Interview for DSM-IV (First et al 1995) and the Clinician Administered PTSD Scale (CAPS) (Blake et al 1995). The diagnosticians arrived at the diagnosis after reviewing all information and discussing the case with the interviewer who colleted the rating scale information. Diagnosis of PTSD was based on the diagnostic evaluation at the initial evaluation. CAPS sores at the follow-up evaluation were obtained for the purpose of comparing symptom severity in subjects' overtime.

The same inclusion/exclusion criteria were used as in the earlier study, and participants were re-evaluated to determine that they still fulfilled these criteria. On this basis, we excluded three non-exposed subjects who developed depression between evaluations, two Holocaust survivors who developed dementia, and one with current alcohol abuse. Subjects with an unstable medical illness would have also been excluded, but this criterion did not result in new exclusions. Six Holocaust survivors (2 PTSD+, 4 PTSD−) were taking stable doses of antidepressants, as before (Golier et al 2002).

The Wechsler Adult Intelligence Scale-III (WAIS-III) (Wechsler 1997) vocabulary and block design subtests was administered to detect severe cognitive disability. Diagnoses were made according to DSM-IV criteria with data collected using the Structured Clinical Interview for DSM-IV (First et al 1995) and the Clinician Administered PTSD Scale (CAPS) (Blake et al 1995).

Neuropsychological Testing

The same neuropsychological testing measures were given at the initial and follow-up assessment. The paired-associate learning and word stem completion tests (Lupien et al 1994) were administered as previously described (Golier et al 2002). The learning phase consists of twelve pairs of words, six pairs of moderately related words (high associates) and six pairs of unrelated words (low associates) that the participants are shown, asked to read aloud and learn for later recall. The testing phase involved showing participants one word of each pair and asking them to recall the other (explicit recall). The dependent measures were the mean number of high and low associate word-pairs (out of six in each condition) correctly recalled over four learning trials. This test represents a form of explicit and cued recall.

To test implicit memory, subjects were given a word stem completion test immediately after they completed the explicit memory test, in which they were asked to complete 48 three-letter word stems (e.g., R_ _ _ E) as fast as possible using "the first word that comes to mind." Half of the stems correspond to words presented in the paired-associate learning task. Implicit memory was inferred if the completed stems formed previously presented stimulus words in the absence of explicit instructions to do so.

The CVLT (Delis et al 1987) was administered to assess verbal learning and memory, as previously described (Yehuda et al 2004). In the CVLT, a list of 16 words (list A) is presented five times in succession, and subjects are instructed to recall as many words as possible after each presentation of the word list. After five test trials of list A, a new list of words (list B) is read to the subjects, who are instructed to recall as many words as possible from list B. Subjects are then asked to recall list A again (short delay) and, after a 20-minute interval, are asked to recall list A (long delay). Cued recall is also measured after the short and long delay free recall conditions and recognition memory is examined after the long-delay cued recall. The dependent variables were number of words recalled: following Trial 1 (initial attention), from Trials 1 through 5 (total learning), after short and long delay cued and free recall.

Statistical Methods

The main question, concerning group differences in changes in performance on cognitive measures over time, was addressed using repeated-measures analysis of variance. Because of the small sample sizes and resulting reductions in statistical power, these ANOVA models used two-group comparisons (e.g., PTSD+ vs. PTSD−). In the case of significant group × time interactions, Student's *t*-test were used to compare data from the initial evaluation (time 1) and 5-year follow-up (time 2) within each group separately. Similar to our previous report, education and measures of intelligence were not used as covariates because they were not randomly distributed in the groups (Miller et al 2001). Furthermore, lower education and IQ may be risk factors for PTSD (Macklin et al 1998).

To allow a direct comparison of the findings from this smaller cohort to the larger one from which it was drawn, we first determined whether there were differences between the subgroups who did and did not complete the five year follow-up at initial assessment, and also insured that the same pattern of findings reported at the baseline assessment (Golier et al 2002; Yehuda et al 2004) were replicated. These comparisons are reported in Table 1. No systematic differences were present for demographic, clinical or cognitive variables among the two subgroups.

Correlational analyses were performed using the Pearson correlation coefficient. Relationships between cognitive performance and age, and changes in cognitive performance and symptoms, were conducted separately for the three groups.