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# Measures of Prefrontal System Dysfunction in Posttraumatic Stress Disorder

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Clinical observations have suggested that individuals who have suffered traumatic stressful events exhibit disruption in abilities mediated by frontal brain systems. Therefore, this study employed tasks sensitive to frontal lobe dysfunction, including delayed response (DR), delayed alternation (DA), object alternation (OA), delayed matching-to-sample (DMTS), and delayed nonmatching-to-sample (DNMTS), with participants having posttraumatic stress disorder (PTSD). Compared to controls, the PTSD participants were unimpaired on DA and DMTS, but they showed deficits on DR, OA, and DNMTS tasks. This pattern of results suggests disruption of functioning in selective prefrontal brain systems. Results are discussed in the context of the neuropsychological features of PTSD, as well as possible neuropathological and etiological underpinnings of this disorder. © 2001 Academic Press

*Key Words:* posttraumatic stress disorder; frontal brain systems; neuropsychology; comparative neuropsychology.

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## INTRODUCTION

Posttraumatic stress disorder (PTSD) is an anxiety disorder associated with exposure to a traumatic event outside the range of usual human experience, e.g., rape, combat, or natural disaster (APA, 1987). According to the *Diagnostic and Statistical Manual of Mental Disorders-Third Edition-Revised* (DSM-III-R; APA, 1987), the diagnosis of PTSD requires the presence of symptoms in each of three clusters including: reexperiencing the traumatic event through intrusive memories, flashbacks, and nightmares; avoidance and affective numbing; and hyperarousal. Many studies of individuals with PTSD have focused on the psychiatric aspects of the symptomatology, with little emphasis on neuropsychological underpinnings (Wolfe & Charney, 1991). However, patients with PTSD frequently report a variety of cognitive complaints that include difficulties with memory, learning, attention, and concentration (e.g., Sutker, Winstead, Galina, & Allain, 1991; Vasterling, Brailey, Constans, & Sutker, 1998; Wolfe, 1994). Some of the difficulties (e.g., concentration problems) are included in the diagnosis of PTSD and others are not (e.g., difficulty remembering daily tasks). One goal of the present study was to confirm and extend our knowledge of the cognitive sequelae of PTSD. A related purpose of the present study was to explore suggestions, based mainly upon clinical observations, that individuals who have suffered traumatic stressful events exhibit disruption in abilities mediated by frontal brain systems (Sutker et al., 1991; Vasterling et al., 1998; Wolfe, 1994). Research findings from other patient populations confirm that the frontal lobes play a critical role in the ability to sustain attention and concentration, hold information in memory, and execute judgments (Fuster, 1997; Knight, Grabowecky, & Scabini, 1995; Oscar-Berman & Bardenhagen, 1998; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994), but analysis of the possible role of prefrontal brain system involvement in PTSD has largely been neglected (Deutch & Young, 1995).

### *Neuropsychological Investigations of PTSD Patients*

The nature of the cognitive complaints by patients with PTSD have led to several investigations of possible neuropsychological deficits underlying PTSD symptomatology (Bremner et al., 1993; Everly & Horton, 1989; Sutker, Allain, Johnson, & Butters, 1992; Vasterling et al., 1998; Yehuda et al., 1995). Results of recent neuropsychological research have documented various performance deficits in PTSD, particularly in the areas of memory and learning. For example, Vasterling and her colleagues (Vasterling et al., 1998) reported that Persian Gulf War veterans demonstrated significant deficits on tasks involving sustained attention, mental manipulation, initial acquisition of information, and retroactive interference.

Impairments by individuals with PTSD also have been reported for other tests of memory and learning, including a four-word short-term memory test (Everly & Horton, 1989), the Auditory Verbal Learning Test, the Rey–Osterrieth Complex Figure Test, and the Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Uddo, Vasterling, Brailey, & Sutker, 1993). Bremner et al. (1993) specifically attempted to delineate and quantify memory disturbances. They found memory deficits in Vietnam combat veterans with PTSD, including significantly lower scores on the Russell Revision of the Wechsler Memory Scale (WMS) and on verbal and visual subtests of the Selective Reminding Test, when compared with performance of normal control participants. In addition, deficits in performance on the WMS by veterans with PTSD were associated with smaller right hippocampal volume as measured with magnetic resonance imaging (MRI) scans (Bremner et al., 1995). As a result of these studies, in the past decade, researchers have focused on the

role of frontal and limbic system pathology in PTSD (Krystal, Bennett, Bremner, Southwick, & Charney, 1995; Sapolsky, 1996).

*The Impetus for Assessing Frontal System Functioning in PTSD*

Increasingly detailed studies of other patient populations have confirmed that frontal brain systems play a critical role in the ability to sustain attention and concentration, execute judgments, and encode and retrieve information from memory (Keane & Wolfe, 1990; Knight et al., 1995; Oscar-Berman & Bardenhagen, 1998). The frontal lobes have also been widely implicated in the regulation of impulses, affect, mood stability, and disinhibition (including the control of abnormal perseverative responding) (Fuster, 1997). Because these functions often are problematic for patients with PTSD, Wolfe (1994) suggested the possibility of abnormalities in frontal brain systems. Results of recent studies (e.g., Vasterling et al., 1998) provide further support for dysfunction of frontal-subcortical systems in PTSD. Additionally, Deutch and Young (1995) and Krystal et al. (1995) have proposed useful frameworks for considering abnormalities of brain neurotransmitter systems, involving prefrontal cortical networks, in the acquisition of maladapted stress-elicited responses. In order to evaluate the possibility that frontal system functioning is disrupted in PTSD, we administered a variety of neurobehavioral tests sensitive to cognitive abnormalities of the frontal lobes.

As part of an extensive neuropsychological test battery we administered the delayed response (DR), delayed alternation (DA), and object alternation (OA) tasks (Fuster, 1997; Oscar-Berman & Bardenhagen, 1998). These tasks (called Comparative Neuropsychological tasks) have been studied extensively in nonhuman primates with lesions of frontal brain regions as well as in human neurological patients with frontal system pathology (Oscar-Berman & Bardenhagen, 1998). Importantly, impaired performance on these tasks has been found in the absence of any relationship to memory scores on the WMS in humans with bilateral damage to the prefrontal cortex (Freedman, 1990; Freedman & Oscar-Berman, 1986). It is believed that the tasks assess functioning of distinct, frontal-mediated memory systems known as working memory systems (Freedman, Black, Ebert, & Binns, 1998; Goldman-Rakic, Runagashi, & Bruce, 1990; Goldman-Rakic & Friedman, 1991). Working memory, the ability to hold information in a temporary short-term store, exists within several functional domains, including each of the sensory modalities; most research has explored the visual modality, in particular, object and spatial domains (Wilson, O'Scalaidhe, & Goldman-Rakic, 1993). Experimental evidence from human and nonhuman primates (Freedman et al., 1998; Wilson et al., 1993) as well as functional neuroimaging data in humans (Courtney, Ungerleider, Keil, & Haxby, 1996) suggest that working memory in the object and spatial domains are each mediated by different neuroanatomical systems. Thus, Freedman et al. (1998) and Wilson et al. (1993) demonstrated that working memory for objects is mediated by structures in the inferior frontal convexity, and Courtney et al. (1996) showed that working memory for objects and spatial location was functionally segregated, with the dorsal frontal region being important for spatial location memory and the more ventral region (middle, inferior, and orbital frontal areas) being important for object identification memory.

In addition to DR, DA, and OA tasks, we also administered matching- and delayed matching-to-sample-tasks (MTS and DMTS) and nonmatching- and delayed nonmatching-to-sample tasks (NMTS and DNMTS) to measure concept learning and memory (Oscar-Berman & Bardenhagen, 1998). To assess other cognitive functions, and to complement the measures obtained from the Comparative Neuropsychological tasks, we administered standard neuropsychological tests, some of which are known

to be sensitive to frontal system dysfunction. The standard neuropsychological tests consisted of the following: the Logical Memory and Visual Reproduction subtests of the WMS-R (Wechsler, 1987), the Vocabulary and Block Design subtests of the WAIS-R (Wechsler, 1981) used to estimate Full Scale IQ in the manner described by Brooker and Cyr (1986), the Trail Making Test (Trails A and B; Reitan, 1992), and the Controlled Oral-Word Association Test (also known as the FAS test; Lezak, 1995).

## METHODS

### Participants

Sixteen research participants with PTSD (2 men and 14 women) and 53 neurologically intact control participants (40 men and 13 women) took part in the study. The participants were recruited from advertisements distributed around the Boston Veterans Affairs Medical Center, in other medical clinics, at other locations throughout the community, and in newspapers. Three PTSD participants failed to return for a final testing session (all women); those three were similar to the remaining PTSD participants on demographic variables and comorbid diagnoses. Data obtained from 48 of the 53 control participants were available from prior testing of age- and demographically equivalent individuals (Covall, 1996; Oscar-Berman, Gansler, Renick, Evert, Kaplan, & Kirkley, 2000) and were used to supplement data in this report. The PTSD and Control groups were statistically equivalent with respect to age, years of education, and IQ (see Table 1). However, since the numbers of participants available for comparisons varied somewhat by test, the PTSD and Control groups were compared on demographic variables for each test conducted, and no significant differences were found for age, years of education, and estimated full-scale IQ. With respect to gender distribution, the PTSD and Control groups differed significantly. In order to examine whether gender difference might account for performance differences on dependent measures, *t* tests were conducted comparing the performance of gender-distinct subgroups of the Controls, and none approached statistical significance. Nonetheless, because gender differences between the PTSD and Control groups were significant on all comparisons of performance on the tasks in the present study, they also were evaluated in subsequent data analyses (see "Data Analyses").

The participants ranged in age from 20 to 64 years, and none reported a history of learning disability, attention deficit disorder, organic mental disorder, head injury, loss of consciousness exceeding 15 min, seizure or other neurological disorder unless clearly peripheral, intrathecal chemotherapy or radiation

TABLE 1
Demographic Characteristics and WMS-R Scores of the PTSD and Control Participants

| | PTSD ($N$ = 16) Mean ($SD$) | Controls ($N$ = 53) Mean ($SD$) | Significance |
|---|---|---|---|
| Age (years) | 42.69 (±11.66) | 45.04 (±12.34) | $t$ = *ns* ($p$ = .50) |
| Years of Education | 15.31 (±1.62) | 15.08 (±1.77) | $t$ = *ns* ($p$ = .50) |
| Estimated Full-Scale IQ[a] | 106.44 (±12.47) | 110.66 (±11.19) | $t$ = *ns* ($p$ = .50) |
| Gender: % Female | 87.5 ($n$ = 14/16) | 24.53 ($n$ = 13/53) | $X^2(1) = 20.461$ ($p < .00$) |
| | PTSD ($N$ = 16) Mean ($SD$) | Controls ($N$ = 28) Mean ($SD$) | |
| WMS-R | | | |
| Logical Memory (IR) | 61.06 (±25.94) | 66.96 (±29.27) | |
| Range | 18–94 | 15–97 | |
| Logical Memory (DR) | 59.69 (±23.60) | 63.43 (±27.08) | |
| Range | 19–94 | 8–98 | |
| Visual Reproduction (IR) | 62.13 (±31.43) | 75.36 (±21.19) | |
| Range | 15–96 | 29–99 | |
| Visual Reproduction (DR) | 51.18 (±33.21) | 62.89 (±22.08) | |
| Range | 3–97 | 20–99 | |

*Note.* IR = Immediate Recall; DR = Delayed Recall.
[a] IQ estimated according to the method of Brooker and Cyr (1986).

to the head, bipolar disorder, or schizophrenia or any other psychotic disorder. Potential participants with recent substance abuse (within the past month) or sensory impairment, such as uncorrected vision or color-blindness, which could adversely affect performance, were also excluded from participation. Participants in the Control group may have experienced the stressors, such as combat exposure and sexual assault, that contribute to the development of PTSD; however, no control participants met criteria for a PTSD diagnosis during their lifetime. All participants were right-handed, spoke English fluently, and had an estimated WAIS-R Full Scale IQ of at least 85. The participants gave informed consent upon entry into the study, and all were paid for their participation at the completion of testing.

Psychiatric diagnoses were determined using the Computerized Diagnostic Interview Scale-Revised (C-DIS, Robins et al., 1991) and the Clinician Administered PTSD Scale (CAPS; Blake et al., 1990). Determination of PTSD diagnosis was made using the CAPS. The CAPS is scored according to a standard algorithm that is used to determine caseness. PTSD symptom severity for each symptom group was determined by multiplying the frequency and intensity scores for each DSM criterion within a group and then adding their products. Absent symptoms were assigned a value of 0. Other major Axis I disorders were evaluated using the C-DIS according to DSM-III-R criteria (APA, 1987). Participants also were assessed for lifetime use of alcohol in order to determine whether they had a history of alcohol abuse or dependence. PTSD is characterized by high rates of comorbidity (Keane & Wolfe, 1990). In this sample, the PTSD participants had comorbidity with major depressive disorder, dysthymia, specific phobias, panic, and generalized anxiety disorder. The PTSD participants also reported more years of past alcohol abuse than the Controls [$t(70) = 3.812$, $p < .001$], and three of the 16 PTSD participants (but no Controls) were on antidepressants.

## Apparatus

### *DA, DR, and OA Tasks*

The DA, DR, and OA tasks were given in consecutive order in a modified version of the Wisconsin General Test Apparatus adapted for use with human participants and described previously (Oscar-Berman et al., 1991). The examiner sat facing participants across a table; they were separated by a wood frame approximately 61 cm wide and 53 cm high. A curtain was anchored to the top of the frame and could be raised to reveal a stimulus board (53 × 28 cm) containing two reinforcement wells (into which a nickel reward could be placed). The wells were 24 cm apart and were covered by identical black square stimulus plaques (7.6 × 7.6 × .5 cm) for the DA and DR tasks. For the OA task, each well was covered by a different three-dimensional stimulus object (a green cylinder and a red triple-octahedron) mounted on square black plaques (Freedman, 1990). When the curtain was lowered, participants could see neither the stimuli nor the investigator. When the curtain was raised for each trial, the participants could see the stimulus-covered wells and the hands of the investigator.

### *MTS, NMTS, DMTS, and DNMTS Tasks*

All of the matching- and nonmatching-to-sample tasks were administered with a Macintosh IIci computer, and icons were used as stimuli. The participants rested their hands on the keyboard of the computer. They pressed the "f" key if the stimulus on the left side of the display was selected as correct, or the "j" key if the stimulus on the right side of the display was selected as correct.

## Procedure

Diagnostic interviews were administered at the outset of the testing session, just after obtaining informed consent from the participants, and the interview results were reviewed for exclusion criteria. Participants who met the inclusion criteria were then given standardized tests of intelligence and memory. These tests were used to establish group equivalence in general cognitive functioning, specifically with regard to vocabulary, visual analytic abilities, and verbal and nonverbal memory.

### *Standard Neuropsychological Tests*

The Vocabulary and Block Design subtests of the WAIS-R and the Logical Memory and Visual Reproduction subtests of the WMS-R were administered according to the accompanying manuals (Wechsler, 1981, 1987). The FAS and Trail Making tests also were administered according to published instructions (Lezak, 1995; Reitan, 1992).

## *Comparative Neuropsychological Tasks*

*DA, DR, and OA Tasks.* The DA, DR, and OA tasks were carried out as previously described (Freedman, 1990; Oscar-Berman, Zola-Morgan, Oberg, & Bonner, 1982). The participant and the investigator were seated at opposite sides of a table, separated by the testing apparatus, and with the curtain lowered between them. For each of the tasks, the investigator explained the procedure to the participants in general terms. On DA, DR, and OA tasks, for example, the participants were told that they were to try to determine under which lid a nickel was hidden every time the curtain was raised and that at the end of the session they could keep all the money they earned. (For the matching and nonmatching tasks, the participants were told that they were to going to see three pictures on the computer screen, and they should select either the one on the right or the one on the left.) They were told that they would receive five cents each time they chose the correct one and that at the end of the session they could keep all the money they earned.

On the first trial of the DA problem, both lids were baited with nickels. For the second trial, the nickel was put under the side not chosen on the preceding trial. A correction procedure was used on this task so that the nickel remained on one side until participants made a correct response. On the trial after a correct response, the opposite side was baited. There was a 5-s intertrial interval, and the learning criterion was 12 consecutive correct responses. Failure criterion was 50 trials. Scores were the total number of trials to attain the learning criterion and the total of all perseverative errors on the task. Perseveration for the DA and OA tasks was defined in terms of repeated errors on a single trial; the second and subsequent consecutive errors were scored as perseverative errors.

There were four DR problems with 0-, 10-, 30-, and 60-s delays, respectively. The reinforcement wells were baited in full view of the participants according to a modified random schedule (Gellermann, 1933). For the 0-s delay condition, the curtain was lowered for a brief instant and then quickly raised again. For the 10-, 30-, and 60-s delays, the examiner explained that there would be a short wait before the curtain was raised. When the curtain was raised at the end of the delay period, the participants retrieved the nickel from the well if their choice had been correct. No correction procedure was employed for DR problems. Learning criterion for each DR delay condition was nine correct responses in a block of 10 trials. The failure criterion was 40 trials per delay interval (e.g., four blocks of 10 trials containing two or more errors in each block). If a participant failed four consecutive trials in the 0- or 10-s delay conditions, the test was discontinued, and the errors were prorated; this procedure had to be used only for one PTSD participant. Scores used were the number of errors at each time delay and the sum of errors from all four delay conditions.

For the OA task, the participants had to learn that the nickel was located under the stimulus object that was not rewarded on the previous correct trial. The objects were placed in the left and right positions according to a modified random schedule (Gellermann, 1933). On the first trial of the OA task, the reinforcement wells under both objects were baited with nickels. For the second trial, the nickel was placed under the object not chosen on the preceding trial. A correction procedure was used such that the nickel remained under the same object until the participant made the correct response (although this was not necessarily on the same side). On trials following correct responses, the reinforcement well beneath the other object was baited. The intertrial interval was approximately 5 s. The learning criterion was 12 consecutive correct responses, and the failure criterion was 50 trials. Scores used were the number of total and perseverative errors, and the total number of trials to reach criterion.

*MTS, NMTS, DMTS, and DNMTS Tasks.* The MTS, DMTS, NMTS, and DNMTS tasks were administered with a Macintosh IIci computer. On the MTS and NMTS tasks, participants were shown three stimuli. The stimulus in the center of the computer screen was the sample, and the two outside stimuli were choice stimuli. In MTS, the participants were rewarded for choosing the side stimulus that matched the sample. In NMTS, the participants were rewarded for choosing the odd (nonmatching) stimulus. In the DMTS and DNMTS tasks, the participants were shown each of the sample stimuli for a brief period of time, and then after a predetermined delay period, the participants were able to choose a the matching stimulus (or the odd stimulus) from a test pair. For both DMTS and DNMTS, the duration of stimulus exposure was varied from trial to trial, making the task more difficult than classic versions of the test (Oscar-Berman & Bardenhagen, 1998).

The same stimuli were used for both the DMTS and the DNMTS tasks, which were administered consecutively. The stimuli for each of the tasks consisted of black and white icons; on each task, three stimuli were arranged horizontally across the computer screen. The middle icon was surrounded by a border. Icons consisted of different designs: some were identifiable objects such as a duck or a letter and others were abstract geometrical patterns. The participants were given minimal instructions about how to solve the tasks. They were told to select either the right or the left response keys (the "j" or the "f" keys on a standard keyboard) and to listen for two different tones that signaled whether their response was correct or incorrect. The tone corresponding to an incorrect response was described as being "less pleasant" than the tone corresponding to correct responses. Both tones were interpreted by

the examiner as they sounded during the learning trials. During the learning trials (i.e., MTS and NMTS tasks), all three icons appeared simultaneously. The MTS task required participants to choose the icon appearing on the right or left that matched the center icon by pressing either the right or left response keys. The NMTS task required participants to choose the icon appearing on the right or left that differed from the center icon. MTS and NMTS trials were presented until the participant reached a learning criterion of at least 90% correct responses.

For the DMTS and DNMTS tasks, the participants were told they would be rewarded with five cents for every correct response, and they were informed that the center stimulus would precede the right and left stimuli and would appear for only a very brief duration. The center stimuli were presented randomly at five differing durations (1, 2, 3, 10, and 20 ms). There were four sets of 25 DMTS trials and four sets of DNMTS trials. Each set had an increasingly long delay between presentation of the central, sample stimuli and the appearance of the right and left comparison stimuli. The delay periods were 0, 1, 5, and 10 s. Scores used were the number of total errors and the percentage of correct responses for each delay and duration condition.

## Data Analyses

In order to protect against inflation of Type 1 error, data analyses incorporated multivariate omnibus tests of significance (as recommended by Cliff, 1987). The omnibus tests were performed separately on data from the standard neuropsychological tests and the Comparative Neuropsychological tasks. To evaluate the influence of gender differences between the PTSD and Control groups on dependent measures, MANCOVAs were conducted with Gender as the covariate using a single factor of Group. The covariate of Gender was not significant for any MANCOVA except for one stimulus-duration condition of DNMTS (see Results); therefore, with that exception, Gender was eliminated as a covariate in subsequent analyses. Significant multivariate $F$ ratios were followed by corresponding univariate analyses.

Dependent variables were examined by domain of functioning as follows: Dependent variables for multivariate analysis of variance (MANOVA) on measures of memory included the WMS-R percentile equivalents of raw scores by age for both the Immediate and Delayed Recall sections of the Logical Memory and Visual Reproduction tasks. For the FAS test, a repeated-measures ANOVA was conducted with Group as the between-subjects factor and Letter (F, A, or S) as the within-subjects factor. For the Trail Making test, repeated-measures ANOVAs were conducted with Group as the between-subjects factor and errors as within-subjects factors. In addition, MANOVAs were performed on the number of corrected errors on Trails A, the number of corrected errors on Trails B, the number of uncorrected errors on Trails A, and the number of uncorrected errors on Trails B. MANOVAs also were conducted on the total number of errors on DA, the total number of perseverations on DA, and the total number of nonperseverative errors on DA. The results of the DR task were analyzed using repeated-measures ANOVAs with Group as the between-subjects factor and Delay as the within-subjects factor. For the OA task, MANOVAs were conducted on the total number of errors and the total number of perseverations. The MTS and NMTS tasks were analyzed using separate MANOVAs with total errors and number of trials to achieve criterion as the dependent variables. The DMTS and DNMTS tasks were analyzed using repeated-measures ANOVAs with Group as the between-subjects factor and Duration and Delay as within-subjects factors. If group differences on dependent variables were established with the above analyses, then subsequent analyses were conducted to examine those differences and interpret the effects.

# RESULTS

### *Standard Neuropsychological Tests*

Table 2 summarizes the results of the PTSD and Control groups on the standard neuropsychological tests, i.e., WMS-R, FAS, and Tail Making tests. The PTSD and Control groups were statistically equivalent on the Immediate and Delayed Recall sections of the WMS-R Logical Memory and Visual Reproduction tasks, as revealed by multivariate comparisons. A repeated-measures analysis of variance (ANOVA) across conditions on the FAS test revealed a trend for the PTSD group to perform more poorly than the Control group [$F(2, 37) = 2.876$, $p = .069$]. However, no significant group differences were found using a $t$ test with total correct on the FAS as the dependent variable [$t(38) = .439$, $p = .663$]; likewise, multivariate $F$ ratios

TABLE 2
Comparison of Scores by PTSD and Control Groups on the FAS and Trails A and B

| Tasks and group sizes | PTSD group | | Control group | |
|---|---|---|---|---|
| | Mean (*SD*) | Range | Mean (*SD*) | Range |
| FAS total score | 42.88 (6.51) | 34.00–60.00 | 44.37 (12.55) | 26.00–76.00 |
| PTSD ($N$ = 16) | | | | |
| Control ($N$ = 24) | | | | |
| Trails A and B | | | | |
| PTSD ($N$ = 15) | | | | |
| Control ($N$ = 27) | | | | |
| Trails A time (seconds) | 32.16 (±12.42) | 20.13–60.00 | 36.54 (±21.04) | 19.00–124.00 |
| Trails B time (seconds) | 78.63 (±54.52) | 42.00–250.59 | 64.44 (±22.89) | 33.00–120.00 |
| Trails A no. corrected errors | .38 (±.89) | 0.00–3.00 | .25 (±.52) | 0.00–2.00 |
| Trails B no. corrected errors | .63 (±1.15) | 0.00–4.00 | .21 (±.57) | 0.00–2.00 |
| Trails A no. uncorrected errors | .20 (±.56) | 0.00–2.00 | 1.39 (±4.86) | 0.00–25.88 |
| Trails B no. uncorrected errors | .53 (±.83) | 0.00–2.00 | .43 (±.69) | 0.00–2.00 |

revealed no significant differences between the PTSD and Control groups on the Trail Making tests.

*Comparative Neuropsychological Tasks*

*DA, DR, and OA tasks.* Performance on the DA, DR, and OA tasks is summarized in Fig. 1. Compared to the Controls, the PTSD participants were significantly impaired on the OA [$F(2, 44) = 3.549, p = .037$] task. Univariate comparisons indicated that the PTSD group had more perseverations [$F(1, 45) = 6.472; p = .014$] but not total errors [$F(1, 45) = 1.126, p = .294$] on OA. On DR, while there was a trend toward significant effect of Groups [$F(3, 43) = 2.586, p = .065$], the PTSD participants were not impaired on DA [$F(3, 43) = .674, p = .573$]. For the DR task, given the nearly significant ANOVA Group effect, univariate comparisons were conducted using Student's $t$ test (one-tailed) on total errors, as well as for each of the separate DR delay intervals, as the dependent variables. Overall, the PTSD group made sig-

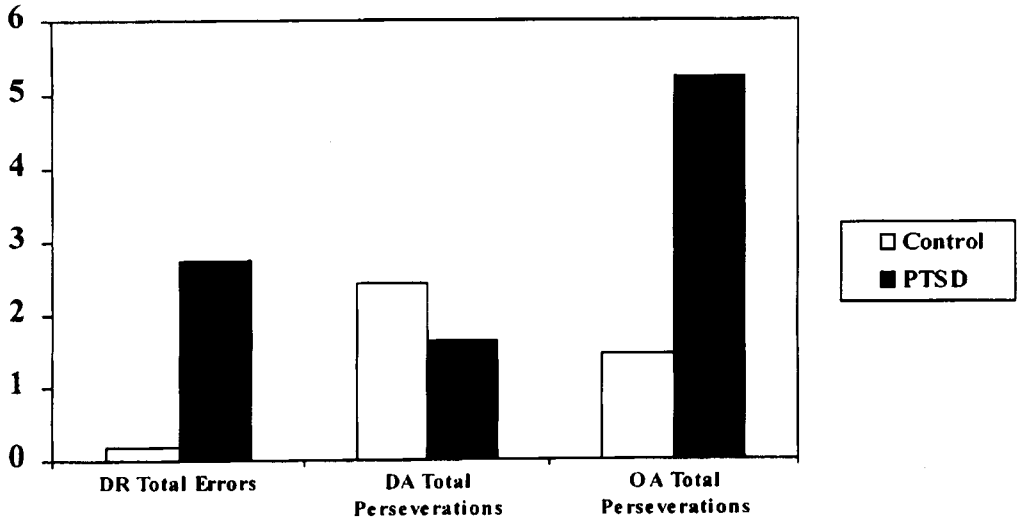


**FIG. 1.** Mean number of errors made by PTSD and Control participants on the DA, DR, and OA tasks.

nificantly more total errors than the Control group [$t(45) = 1.895$, $p = .032$]; the scores of the PTSD group also were significantly worse for the 60-s delay period [$t(45) = 1.949$, $p = .029$]. Since the data were skewed, nonparametric univariate tests also were run and produced the same pattern of results.

In order to examine whether alcohol history may have contributed to group differences in performance on the DR and OA tasks, Pearson correlation coefficients were computed between number of years of past alcohol use and the total number of errors on DR and on the number of perseverative errors on OA. Significance levels of correlation coefficients were measured by two-tailed $t$ tests. Scores on DR and OA were not significantly correlated with years of past alcohol abuse. Correlational analyses also were conducted to examine the relationship between severity of the three PTSD symptom clusters (reexperiencing, avoidance/numbing, and arousal) and performance on the DR and OA tasks. While perseverative errors on OA were not significantly correlated with any PTSD symptom cluster severity score, total errors on the DR task correlated positively with all three PTSD symptom clusters as follows: .44 ($p < .01$) with reexperiencing symptoms, .44 ($p < .01$) with avoidance/numbing symptoms, and .34 ($p < .01$) with arousal symptoms. In order to examine which symptom clusters contributed most to deficits on DR task performance, a stepwise multiple-regression analysis was conducted with the three PTSD cluster severity scores as the independent variables and total errors on the DR as the dependent variable. The resulting model showed that only the avoidance/numbing symptom cluster entered as an independent variable was significant, with a multiple correlation ($R$) of .477, and it accounted for 22.8% of the variance in total errors on DR ($t = 3.260$, $p < .01$).

*MTS, NMTS, DMTS, and DNMTS tasks.* On most of the Matching and Nonmatching tasks (MTS, NMTS, and DMTS), multivariate $F$ tests revealed no significant differences between the PTSD ($n = 14$) and Control groups ($n = 5$). However, despite the small number of Control participants, on the DNMTS task the PTSD group performed significantly worse than the Controls on trials with a 2-ms duration of stimulus presentation. It should be noted that on the DNMTS task with 2-ms stimulus exposures, a multivariate analyses of covariance (MANCOVA) with Gender as the covariate had revealed Gender to be a significant covariate; therefore, in subsequent analyses, Gender had been entered as a covariate, with four levels of Delay as within-subjects factors and Group as a between-subjects factor. As can be seen in Fig. 2, the differences between the groups appeared across delay intervals [$F(3, 13) = 4.176$, $p = .028$], with the PTSD group showing consistent deficits.

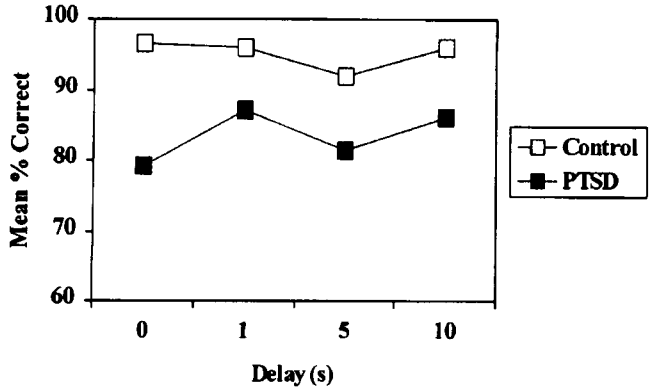


**FIG. 2.** Mean percentage of correct responses on DNMTS tasks with a 2-ms sample-stimulus duration across the 0-, 1-, 5-, and 10-s delay conditions. (Data for 1 of the 14 PTSD participants are missing from the 10-s delay condition.)

## DISCUSSION

The primary goal of this study was to evaluate cognitive deficits in PTSD, with a special focus on the contribution of abnormalities of prefrontal brain systems. We evaluated cognitive abilities by using standard neuropsychological tests in combination with Comparative Neuropsychological tasks sensitive to frontal lobe damage: DA, DR, OA, DMTS, and DNMTS. Expectations were that the PTSD participants would exhibit greater deficits on frontally mediated tasks than would nontraumatized controls. To a large extent, our expectations were confirmed. That is, while the PTSD participants were unimpaired on standard neuropsychological tests, they did display performance deficits on tests of frontal functioning, including DR, OA, and DNMTS.

With respect to deficits on the Comparative Neuropsychological tests, DR, DA, and OA tasks are sensitive to different aspects of prefrontal damage. DR is more sensitive than DA and OA to visual-spatial attention deficits, whereas DA and OA are more sensitive than DR to abnormal perseveration (Freedman et al., 1998; Oscar-Berman, McNamara, & Freedman, 1991). Accurate performances on the tasks rely upon two different but interconnected prefrontal cortical subsystems, the dorsolateral and ventral systems. These subsystems have different cytoarchitectures, connections to other areas of the brain, and neurotransmitter sensitivities (Fuster, 1997; Goldman-Rakic et al., 1990; Oscar-Berman et al., 1991). Investigations of monkeys with frontal lesions have demonstrated that performance on the DR task depends heavily upon integrity of the dorsolateral system, which includes the dorsolateral prefrontal cortex, the head of the caudate nucleus, the dorsomedial thalamus, and the subthalamus. The dorsolateral system, for example, is closely linked with the catecholaminergic neurotransmitter system, and it has more projections to and from other neocortical sites than limbic sites (reviewed by Oscar-Berman et al., 1991). In contrast, the ventral system has more projection neurons to limbic sites than does the dorsolateral system (Oscar-Berman et al., 1991). Performance on DA and OA tasks relies strongly on the ventral (orbitofrontal) system, which has intimate connections with the hippocampus, the amygdala, and the hypothalamus. The DMTS and DNMTS tasks are different from DR, DA, and OA tasks in a number of ways. They require memory for specific and multiple stimulus characteristics over the delays, and the tasks are sensitive to lesions in the limbic system as well as to frontal dysfunction. The type of memory they involve has been called declarative—or explicit—memory (Squire, 1992). Declarative memory differs from working memory in that the former is archival in nature; declarative memory can be demonstrated by tasks that require free recall, stimulus recognition, or familiarity judgments (Olton, Markowska, & Voytko, 1992; Squire, 1992).

Goldman-Rakic and her colleagues (Goldman-Rakic et al., 1990) have noted that the prefrontal cortex and hippocampal formation are part of a common network that shares domains, but that subserves different cognitive functions. Results of recent investigations employing MRI have indicated reduced hippocampal volume in PTSD (reviewed by van der Kolk, 1996). In one study of Vietnam War veterans, hippocampal volume reduction was bilateral in those having PTSD compared to veterans without PTSD (Pitman, 1996). In another study, right hippocampal volume was significantly reduced in Vietnam combat veterans with PTSD compared to Controls (Bremner et al., 1995). It would follow that the ventral prefrontal system, and therefore DA and OA performance disruption, would occur if the extensive limbic projections to the ventral system are affected by decreased hippocampal size in PTSD. Likewise, performance on DMTS and DNMTS tasks would be expected to be compromised by limbic system abnormalities. Although in the present study, PTSD participants did not exhibit performance deficits on DA nor on DMTS, they were im-

paired on performance of DR, OA, and DNMTS tasks, suggesting a specific pattern of prefrontal and limbic abnormalities. First, deficits on DR implicate abnormalities of the dorsolateral prefrontal cortex (e.g., deficiency in spatial working memory). Second, the OA task is more sensitive than DA to abnormal perseveration, and for discerning dysfunction of orbitofrontal cortex, which is part of the ventral prefrontal system and is intimately connected with limbic-system sites (Freedman et al., 1998; Goldman-Rakic et al., 1990). Third, DNMTS is more difficult than DMTS and, therefore, may be more sensitive to limbic lesions [see review by (Oscar-Berman & Bardenhagen, 1998)]. This pattern of results supports the view that PTSD involves disruption of dorsolateral prefrontal functioning combined with limbic abnormalities (Bremner et al., 1995; Pitman, 1996; Vasterling et al., 1998; Wolfe, 1994).

Comparative Neuropsychological tasks (e.g., DR, DA, OA, DMTS, and DNMTS) have been administered to nonhuman primates and to a variety of human neurological patients (for an excellent summary, see Oscar-Berman & Bardenhagen, 1998). Among other conditions, prefrontal system dysfunction has been associated with schizophrenia, alcoholic Korsakoff's syndrome, Huntington's disease, Alzheimer's disease, and Parkinson's disease (with dementia). These disorders involve overlapping pathology of the dorsolateral and ventral prefrontal systems. In most instances, the groups displayed greater deficits on DA and OA than on DR. (We know of only two studies—in alcoholic and aging groups—that compared DMTS and DNMTS performance; DMTS was easier than DNMTS, but deficits were equivalent on both tasks; Oscar-Berman & Bonner, 1985, 1989).

In the present study, the lack of performance deficits on the standard neuropsychological tests of frontal functioning (FAS and Trails) by PTSD participants despite performance deficits on DR, OA, and DNMTS, may perhaps be understood in terms of the very different requirements of the tasks. The DR task is more sensitive than FAS and Trails to attentional deficits (Fuster, 1997; Oscar-Berman & Bardenhagen, 1998), and OA and DNMTS are more sensitive than the FAS and Trails to abnormalities of perseverative responding. Further, although deficits on FAS, Trails, and the Comparative Neuropsychological tests have been associated with prefrontal brain damage, the validity of the FAS and Trails as measures of specific domains of frontal system integrity has not been as firmly established as for the Comparative Neuropsychological tasks (Fuster, 1997; Lezak, 1995; Oscar-Berman & Bardenhagen, 1998).

Hyperarousal, avoidance/numbing, and reexperiencing phenomena with intrusive memories of the trauma are defining features of PTSD. Emotional and mnemonic functions are disrupted by medial temporal lobe (limbic system) pathology (Zola-Morgan & Squire, 1993). We speculate that many of the symptoms of PTSD result from hyperactivity of limbic structures, which may, via their abundant projections to the ventral prefrontal cortex, contribute to dysfunction of this system; consequently, our observed performance deficits would be expected. This postulated hyperactivity could be the physiological correlate of a *cognitive fear structure* (hypothesized by Foa, Feske, Murdock, Kozak, & McCarthy, 1991) which purportedly is readily activated and can trigger emotional abnormalities such as bursts of arousal and feelings of terror.

Prefrontal dysfunction could also result from catecholaminergic excess leading to receptor downregulation, or from complex interactions between limbic structures, the basal ganglia, and the prefrontal cortex, that could conceivably result in excitatory neurotoxicity (Gray, Feldon, Rawlins, Hemsley, & Smith, 1991). Catecholaminergic dysregulation appears to underlie states of hyperarousal that PTSD patients experience (Deutch & Young, 1995; Southwick, Bremner, Krystal, & Charney, 1994). Based on these observations, we expected subsequent dysfunction of the richly inner-

vated dorsolateral prefrontal cortical areas; this prediction was realized by PTSD participants' DR performance deficits. Conversely, pathologic changes in the prefrontal cortex, particularly early in development, may result in secondary lesions in limbic regions (Benes, 1997; Weinberger, Berman, & Zec, 1986) and may account for the frequent observations of neurological soft signs in childhood in PTSD, which are associated with vulnerability to developing the disorder (Gurvits et al., 1993). Our data on cognitive performance profiles, in conjunction with particular PTSD symptoms, may provide further support for models of cortical dysregulation. We found a specific association between "C" criterion (numbing/avoidance) PTSD symptoms and performance on the DR task, in particular, increasing error rates with longer delays. Neurobiologic research in PTSD increasingly confirms that particular symptoms are subserved in part by distinct dopamine neurotransmitter pathways (Deutch & Young, 1995; Southwick et al., 1994; Southwick, Yehuda, & Morgan III, 1995). It should be noted that patients with dementia in advanced stages of Parkinson's disease exhibited a pattern of impaired performance on DR and OA tasks that we observed with PTSD participants; demented Parkinson patients have deficient dopamine levels and cortical atrophy resulting from degeneration of fibers connecting the basal ganglia and prefrontal regions (Cummings & Benson, 1992; Taylor, Saint-Cyr, & Lang, 1986).

Whatever the underlying neuropathological mechanisms, be they prefrontal cortical pathology, limbic system dysfunction, or—most likely—some combination of the two, our observations of DR, OA, and DNMTS impairments in PTSD clearly implicate frontal system involvement suggestive of overlapping dysfunction of both the dorsolateral and ventral prefrontal brain systems. Although most neurodegenerative disorders are characterized by diffuse structural lesions or functional brain abnormalities, precise localization of anatomical dysfunction underlying psychiatric disorders has only recently become an area of intense research interest. To that end, it would be interesting to apply structural and functional MRI techniques in association with performance on Comparative Neuropsychological tasks in order to further delineate neuropathological deficits associated with PTSD. Further, we suggest that future treatment plans for PTSD patients incorporate strategies designed to address behavioral changes, such as difficulties with decision making and impulsivity, that are typically associated with frontal system dysfunction.

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