Journal of the International Neuropsychological Society (1997), **3**, 451–456.

Working memory deficits in HIV-seropositive drug users

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(RECEIVED July 25, 1996; REVISED March 10, 1997; ACCEPTED March 27, 1997)

Abstract

We studied the integrity of working memory operations in 38 HIV-seropositive and 20 seronegative drug users, using a modified version of the Tower of London task. This new task, the Tower of London–Working Memory version (TOL–WM), includes a delayed-response component in addition to the planning required for successful performance of the standard TOL. Symptomatic HIV-seropositive participants solved significantly fewer TOL–WM problems compared to matched seronegative controls. However, seropositive and seronegative subjects showed similar overall levels of planning efficiency, suggesting that the TOL–WM deficit may be associated primarily with failure to encode or maintain an adequate online memory representation. The results of this study confirm our previous report of a possible working memory deficit in HIV-1 infection and suggest that measures of working memory have particular utility in the evaluation of HIV-related cognitive deficits. (*JINS*, 1997, *3*, 451–456.)

Keywords: HIV, Dementia, Working memory, Drug abuse, Neuropsychological tests, AIDS

INTRODUCTION

Converging evidence has linked HIV-related cognitive deficits to dysfunction of frontal–subcortical systems, with particular involvement of the basal ganglia. Postmortem studies of AIDS patients with dementia but no history of opportunistic conditions (Brew et al., 1995; Navia et al., 1986) have documented that neuropathologic abnormalities and indices of productive infection are most severe in cerebral white matter and basal ganglia. Aylward et al. (1993) reported decreased basal ganglia volume on MRI for seropositive patients compared to controls, and basal ganglia atrophy was more strongly associated with dementia severity than cortical atrophy. PET studies have demonstrated selective abnormalities of glucose metabolism in the basal ganglia of AIDS patients (Rottenberg et al., 1987; Van Gorp et al., 1992; Hinkin et al., 1995).

Given these findings from the neuroimaging and neuropathology literature, investigators have proposed that the literature on cognition in patients with basal ganglia disease should provide a particularly useful framework for formulating and testing hypotheses on HIV-related cognitive deficits (A. Martin, 1994; E. Martin et al., 1995), and recent neuropsychological findings support this prediction. For example, HIV-seropositive patients show evidence of deficits in motor skill learning (A. Martin et al., 1993), consistent with deficits reported for patients with Huntington disease (Gabrieli, 1995) or Parkinson disease (Saint-Cyr et al., 1988). Further, cognitive slowing, a key clinical feature of all "subcortical–frontal" dementing disorders, can be detected subclinically in HIV-seropositive patients using reaction time tasks (e.g., E. Martin et al., 1992; Bornstein et al., 1993).

Some investigators have proposed that impaired working memory is a core cognitive deficit in patients with basal ganglia disease (e.g., Gabrieli, 1995). Models of working memory, defined broadly as the temporary storage and manipulation of memory representations in order to guide behavior in the absence of environmental cues (e.g., Baddeley, 1986; Goldman-Rakic, 1987), vary considerably in their specific component functions and relative emphasis on underlying neural circuitry. Baddeley's (Baddeley & Hitch, 1994) single-system working memory model, derived from human cognitive psychology, places particular emphasis on simultaneous storage and processing of information by two subsystems controlled by a central executive processor. By contrast, Goldman-Rakic's (1987) model, which developed

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from neuroanatomical and neurophysiological primate studies, incorporates multiple working-memory systems organized by informational domain and controlled by separate executive modules. Single-unit recordings in primates and functional MRI studies in humans have identified regions of prefrontal cortex, basal ganglia, and thalamus as critical elements of separate neural circuits underlying spatial and object working memory processing (e.g., Goldman-Rakic, 1987; Wilson et al., 1993; McCarthy et al., 1994).

Recent investigators have emphasized the differences among models of working memory and cautioned that human and primate models may describe different cognitive phenomena although employing similar terminology (e.g., Gold et al., 1996). However, most models share an emphasis on short-term processing of information that is "active and relevant . . . only transiently" (e.g., Goldman-Rakic and Friedman, 1991, p. 73) and must be maintained online to guide response selection in the absence of direct environmental cues. This aspect of working memory has been most influential in hypothesis formation and task selection in recent studies in our laboratory (e.g., Martin et al., 1995, 1996).

Several investigators have recently reported working memory deficits in HIV-seropositive subjects. We (E. Martin et al., 1995) found that nondemented HIV-seropositive drug users performed significantly more poorly compared to matched controls on the spatial Delayed Recognition Span Test (DRST), a delayed nonmatch to sample task failed by patients with Parkinson's disease (Taylor et al., 1986). The DRST requires patients to monitor the spatial locations of an increasing series of identical dots over a time delay, and identify each new addition to the stimulus set. The DRST can be considered a measure of spatial working memory, since patients must maintain and update memory representations of spatial positions online in order to respond correctly. Similarly, Sahakian et al. (1995) reported that seropositive gay men showed deficits compared to controls on a computerized task requiring participants to monitor and update information about spatial location. Finally, Stout et al. (1995) found that seropositive gay men showed impairment on a reading span task compared to controls, suggesting that multiple working memory domains are affected in HIV-seropositive individuals. These three studies, although driven by differing theoretical models, provide converging evidence that some aspects of working memory processing are selectively impaired in HIV-seropositive subjects.

The aim of the present study is to investigate further the working memory deficit in HIV-seropositive drug users, using a new procedure based on the Tower of London Test (Krikorian et al., 1994). The measure used in the present study, the Tower of London–Working Memory version (TOL–WM), adds an explicit delayed memory component to the planning required for successful performance of the standard TOL (Shallice, 1982). We reasoned that administering a task that stressed both short-term information storage and processing should engage working memory processes, and might permit us to explore putative mechanisms of the working memory deficit in HIV-seropositive subjects.

METHODS

Research Participants

We studied 32 male and 6 female HIV-seropositive patients and 18 male and 2 female ELISA-verified seronegative patients, all with a history of drug abuse. We recruited study participants from the Infectious Disease Clinic and the Drug Dependence Treatment Center at the Veterans Affairs Medical Center–West Side in Chicago. All seropositive participants were nondemented on interview and by clinical history and all were tested as outpatients. Eighteen seropositive patients were clinically asymptomatic or had lymphadenopathy only (CDC Stage A; Centers for Disease Control, 1993). Twenty seropositive patients were clinically symptomatic, including 15 with constitutional disease or minor opportunistic infections (CDC Stage B) and 5 with nonneurologic opportunistic conditions (Stage C). The mean CD4 count ($N = 36$) was 422 (median = 350), and 11 patients had AIDS-defining (i.e., below 200) CD4 counts. Sixteen patients were on antiretroviral therapy at the time of testing.

Table 1 shows demographic data for the three groups. The seropositive (asymptomatic and symptomatic) and seronegative groups did not differ significantly in mean age ($F < 1$), education ($F < 1$), ethnicity ($\chi^2 < 1$), past psychiatric history ($\chi^2 < 1$), history of injection drug use [IDU; $\chi^2(2) = 4.23$, $p < .12$], or history of closed head injury

Table 1. Demographic data for all participants

	Participant group		
Variable	Controls	HIV+/asymptomatic	HIV+/symptomatic
N	18	18	20
Age in years, *M* (*SD*)	42.4 (6.8)	39.4 (9.3)	40.4 (6.0)
Education in years, *M* (*SD*)	12.4 (1.5)	12.4 (1.1)	12.7 (2.0)
AmNART IQ, *M* (*SD*)	102.4 (9.2)	105.1 (7.6)	99.2 (8.3)
CD4 count, *M* (*SD*)	—	611 (405.0)	252 (275.2)

https://doi.org/10.1017/S1355617797004517 Published online by Cambridge University Press

($\chi^2 < 1$). Mean estimated verbal IQ by the American National Adult Reading Test (AmNART; Grober & Sliwinski, 1991) was slightly but nonsignificantly lower for the symptomatic seropositive participants [$F(2,55) = 2.54$, $p < .09$]. Nine seropositive participants were treated with antidepressants or anxiolytics at the time of testing. There were no significant differences between the three groups in incidence of reported use of alcohol [$\chi^2(2) = 1.82$, $p < .41$], cocaine [$\chi^2(2) = 1.98$, $p < .38$], or opiates [$\chi^2(2) = 2.50$, $p < .29$]. The total sample was 88% African American, 5% Hispanic and 7% White. Urine toxicology screens confirmed that participants had abstained from street drug use at the time of testing.

Procedures

All participants were administered a new version of the Tower of London (TOL) procedure (Shallice, 1982), modified to include a delayed memory component. The standard version of the TOL requires participants to rearrange three colored balls on three pegs of varying length to match a pictured goal position, which is displayed continuously. In the 12-trial Tower of London–Working Memory version (TOL–WM), the examiner displayed a picture of the goal position for 10 s at the start of each new problem, and then removed the picture from sight. After a 10-s delay, the examiner presented the participant with the TOL–WM apparatus, which had previously been hidden from the participant's view. Participants were instructed to rearrange the balls on the pegs to match the memorized goal position in the fewest moves possible. The pictured goal position and the initial position of the balls on the TOL–WM apparatus both varied across the problems; thus participants could not engage in planning during the delay interval. We administered a total of 12 problems, which varied in difficulty from one to six minimum moves; two problems were administered for each difficulty level.

Dependent variables for the TOL-WM procedure included (1) the total number of problems solved correctly, and (2) the total number of moves made to solve the 12 problems. We used these data to derive a third variable, the corrected move score. We hypothesized that the total number of problems solved correctly indexed the delayed memory component of the TOL–WM, because the participant could only construct a correct solution if the goal position had been maintained adequately over the delay interval. The corrected number of moves reflected both planning ability and delayed memory (i.e., a participant would make more moves before reaching a correct solution if planning was less efficient, or the memory representation of the goal position was compromised, or both). We computed the corrected move score by summing the number of moves the participant made for each problem solved correctly, dividing the summed moves by the minimum number of moves required to solve these problems, and then multiplying the resulting ratio by 42, which is the sum of the minimum number of moves needed to solve all 12 problems. This adjustment allowed a direct comparison across participants, while controlling for the number of correctly solved problems.

In addition, we administered the Modified Porteus Maze Test (M–PMT: Levin et al., 1991; Ross, 1995) to all participants in order to obtain an independent measure of planning ability. The M–PMT consisted of the six most difficult mazes from the original Vineland Edition of the Porteus Maze Test (Porteus, 1965). Unlike the original version, each maze was presented only once, and the participant was allowed to make errors without correction from the examiner (Levin et al., 1991; Ross, 1995). The dependent variable used from the M–PMT was the number of errors.

We also administered a slightly modified version of the Corsi Block (CB) procedure in order to obtain a measure of spatial memory capacity (Milner, 1971). We administered five trials at each level of difficulty (e.g., five three-item sequences, five four-item sequences etc.), up to a maximum sequence length of nine items. The test was terminated when the participant failed all five trials at a given level. The dependent variable was the total number of items correct across levels.

Finally, we administered the Beck Depression Inventory (BDI; Beck et al., 1961) to all participants to determine if depressive distress accounted for any differences in cognitive performance between the groups.

RESULTS

Figure 1 and Table 2 show the means for the three groups (HIV seropositive–symptomatic, HIV seropositive–asymptomatic, and HIV–seronegative control) on the neuropsychological variables. The seropositive symptomatic subjects solved significantly fewer TOL–WM problems correctly compared with seropositive asymptomatic and seronega-

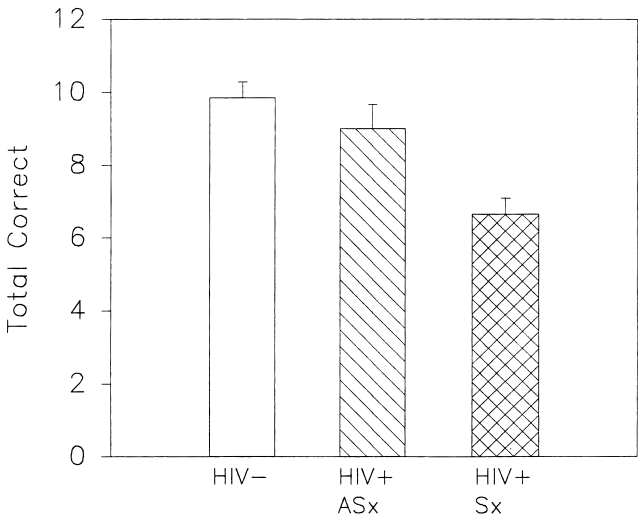

Fig. 1. TOL–WM performance for all participants: total number of problems solved correctly.

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Table 2. Neuropsychological test scores

Test score	Participant group: Controls *M* (*SD*)	HIV+/asymptomatic *M* (*SD*)	HIV+/symptomatic *M* (*SD*)
TOL-WM correct	9.8 (1.9)	9.0 (2.5)	6.6* (2.0)
TOL-WM moves	56.4 (8.8)	56.9 (19.7)	61.0 (25.3)
Corsi total	25.0 (3.1)	23.8 (3.5)	23.2 (3.9)
PMT errors	6.7 (6.4)	6.6 (4.8)	5.9 (3.6)
Beck Depression Inventory total	12.2 (8.2)	12.9 (10.9)	16.6 (11.2)

*$p < .05$ *versus* HIV–seropositive-asymptomatic, $p < .01$ *versus* seronegative control

tive subjects [$F(2,55) = 8.90$, $p < .0005$; $p < .01$ for controls *vs*. symptomatics; and $p < .05$ for asymptomatics *vs*. symptomatics by the Duncan test; see Figure 1]. The asymptomatic seropositive participants solved slightly but nonsignificantly fewer TOL–WM problems correctly compared to controls ($p < .16$).

The three groups' mean total number of TOL–WM moves and mean corrected number of moves did not differ significantly ($F < 1$ for each comparison). The number of TOL–WM problems solved correctly correlated significantly and inversely with the corrected number of moves ($r = -.34$, $p < .009$), but not with the total number of moves ($r = -.07$, $p < .60$). We reanalyzed the mean number of TOL–WM problems solved correctly with the corrected number of moves covaried and results were unchanged [$F(2,54) = 8.86$, $p < .001$].

The mean total scores for the Corsi block procedure and mean M–PMT errors did not differ significantly for the three groups [Corsi: $F(2,55) = 1.30$, $p < .28$; M–PMT: $F < 1$; see Figure 2]. PMT errors were nonsignificantly correlated with TOL–WM total correct ($r = -.13$, $p < .35$). Performance on the Corsi, however, was significantly correlated with the number of TOL–WM problems solved correctly ($r = .33$, $p < .02$). Accordingly, we reanalyzed the mean TOL–WM number correct with Corsi total scores covaried, and results were unchanged [$F(2,54) = 7.45$, $p < .001$].

Participants with a history of injection drug use (IDU) solved significantly fewer TOL–WM problems correctly than participants with no history of IDU [$F(1,56) = 5.92$, $p < .02$]. We reanalyzed TOL–WM data with data for the 9 seropositive participants on antidepressants or anxiolytics excluded, and results were unchanged [$F(2,46) = 4.98$, $p < .02$]. There were no significant differences in TOL–WM performance for seropositive participants on antiretroviral therapy compared with untreated seropositive participants ($F < 1$), and TOL–WM performance did not correlate significantly with CD4 lymphocyte count ($r = -.12$).

Finally, there were no significant differences between groups for mean Beck Depression Inventory somatic or subjective item clusters [somatic: $F(2,55 = 1.39$, $p < .26$; subjective: $F < 1$].

Subgroup Analyses

In order to address the possibility that a subgroup of seropositive participants was impaired on the planning component of the TOL–WM, we converted each participant's corrected number of moves to *z* scores, using the mean and standard deviation for the seronegative control group. We defined operationally an abnormal TOL-WM corrected move score as a *z* score greater than or equal to 2. Using this criterion, 8 seropositive (4 asymptomatic and 4 symptomatic) but no seronegative participants scored in the abnormal range [$\chi^2(1) = 4.88$, $p < .05$]. We performed a similar analysis for the TOL–WM number correct, again using the mean and standard deviation for the controls but a *z*-score cutoff of -2. By this criterion, 2 seronegative and 13 seropositive (10 symptomatic and 3 asymptomatic) participants scored in the abnormal range [$\chi^2(1) = 4.00$, $p < .05$].

DISCUSSION

In this study, we demonstrated clear impairment of HIV-seropositive patients compared to seronegative controls on a version of the Tower of London task modified to stress working memory processes. These differences in TOL–WM performance could not be attributed to differences in education, age, psychological distress, or estimated verbal IQ, since our groups were well matched on these variables. These findings are consistent with our previous report of spatial working memory deficits in HIV-seropositive participants (E. Martin et al., 1995), and indicate that the working memory deficit can be replicated when subjects are tested with a very different experimental task.

The question of selective impairment of particular aspects of working memory processing by HIV-1 requires further study, since the TOL–WM procedure did not completely separate delayed memory and storage from processing and planning mechanisms. Presumably, storage mechanisms were engaged selectively during the initial *memory* phase of each TOL–WM problem: Participants could not engage in planning during the delay interval, but could only encode and maintain an online memory representation of the goal position. However, it is likely that both planning and memory

https://doi.org/10.1017/S1355617797004517 Published online by Cambridge University Press

mechanisms were active during the problem-solving phase of each trial, because participants were required to continue to maintain an online representation of the correct solution while they planned and executed their moves.

Additional findings from this study do suggest, however, that the delayed memory component of the TOL–WM performance may have been more affected in the seropositive participants than the planning/processing component. First, there were no differences between seropositive and seronegative participants in planning ability as measured by performance of the modified Porteus Mazes, which does not engage delayed memory processing. Second, seropositive participants were significantly impaired on the delayed memory component (as indexed by the total number of TOL–WM problems solved correctly) compared to controls when TOL–WM scores were analyzed controlling for the corrected number of moves. Third, slightly more seropositive participants scored in the abnormal range compared to controls on the delayed memory component (13) than on the planning/memory component (8). Given these results, one might speculate that impairment of cognitive mechanisms responsible for forming and/or maintaining memory representations online may be a critical component of the working memory deficit in HIV. In this regard, Stout et al. (1995) recently speculated that their seropositive participants' impaired reading span performance appeared due primarily to deficits in holding information temporarily in short-term memory. Experiments designed to test this hypothesis are currently underway in our laboratory.

Investigators have reported inconsistent evidence concerning the performance of HIV-seropositive participants on the standard TOL. A. Martin (1994) reported that HIV-seropositive participants showed no deficit compared to seronegative controls on the standard TOL. Sahakian et al. (1995) reported that HIV-seropositive participants did show impaired performance of a computerized adaptation of the standard TOL, but the deficit was only evident on the most difficult TOL problems (e.g., those requiring the greatest minimum number of moves for correct performance). Notably, the standard TOL places much less stress than the TOL–WM on mechanisms responsible for maintaining memory representations over a time delay, because the goal position is always visible to participants. In this regard, Law et al. (1994) found no differences in performance when HIV-seropositive subjects and seronegative controls were tested using Baddeley's (1986) dual task working-memory paradigm, which similarly places less load than the TOL–WM on delayed memory mechanisms.

This is the second report from our laboratory, each using a different experimental task, that HIV-seropositive drug users can be discriminated meaningfully from matched seronegative controls on measures of working memory. An obvious next question concerns the generality of the working memory deficit. The DRST and TOL–WM studies indicate that visual and spatial working memory are impaired in HIV-seropositive individuals. One would predict that verbal working memory should be impaired in these individuals as well, since the nature of the deficit appears to involve memory mechanisms common to different working memory domains. Preliminary data from our laboratory and findings from a recent study of seropositive gay men (Stout et al., 1995) support this hypothesis (Farinpour et al., 1997; E. Martin et al., 1997).

Our finding of consistent working memory deficits in HIV-seropositive drug users is particularly significant given this population's inconsistent pattern of neuropsychological performance across studies (e.g., Stern, 1994) and the frequency of impaired neuropsychological performance in substance abusers, regardless of serostatus (e.g., Grant et al., 1978). In a previous paper (E. Martin et al., 1995), we emphasized the limits of employing neuropsychological assessment strategies derived from the literature on gay men to the population of seropositive drug users. The current study reinforces our earlier conclusion that the literature on cognition in basal ganglia disease indeed provides a consistent and theoretically meaningful framework for the evaluation of diverse HIV-seropositive groups.

ACKNOWLEDGMENTS

Portions of this paper were presented at the 24th Annual Meeting of the International Neuropsychological Society, February 14–17, 1996, Chicago. We thank Roxanna Farinpour for assistance with data collection; and Pat Goldman-Rakic, Tom Jobe and two anonymous reviewers for helpful comments and discussion of earlier drafts of the manuscript. Supported by a Department of Veterans Affairs Merit Review grant to Eileen M. Martin.

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