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Semantic priming impairment in HIV

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Abstract

HIV+ subjects have shown impairment on tests of executive function including automatic attention and verbal tasks. Impairment of semantic priming in HIV patients would suggest a disruption of automatic semantic activation. We examined semantic priming in HIV+ individuals and HIV− control participants with no history of substance abuse, neurologic or psychiatric disorder unrelated to HIV. HIV+ participants were divided into cognitively normal and cognitively impaired subgroups on the basis of a neuropsychological battery of 15 tests. Participants were presented with English words and nonword letter strings and indicated if the stimulus was a word or nonword. The nonwords were orthographically and phonologically correct and were created by rearranging the letter sequence of words ("ulpit"). All words had an obvious antonym ("deep"); two-thirds were presented as sequential antonym pairs ("enter"–"exit"). There were no group differences in speed of response to nonwords, indicating no generalized reaction time deficit. While control and cognitively normal HIV+ participants showed an effect of priming on reaction time to correctly detected words, cognitively impaired HIV+ participants did not. The lack of semantic priming demonstrated by cognitively impaired HIV+ participants suggests that they have lessened activation of automatic semantic networks. (*JINS*, 1997, *3*, 348–358.)

Keywords: Human memory systems, Reaction time, Automatic processes

INTRODUCTION

Infection with the human immunodeficiency virus is sufficient to cause impairment of cognitive functioning in the absence of other cortical disease. The initial effects have been particularly noted in subcortical structures and in white matter, and involve microglia and macrophage infiltration rather than direct HIV effects on neurons (Navia et al., 1986; Ketzler et al., 1990; Everall et al., 1991; Wiley et al., 1991). Late in the disease, actual neuronal loss has been observed in frontal cortex, and may occur in other regions (Achim et al., 1993; Wesselingh et al., 1993; Pulliam et al., 1994). Reductions in caudate dopamine concentrations have been reported in HIV (Sardar et al., 1995); nonhuman primate studies suggest that reductions such as this may be associated with loss of frontal control attention (Brozoski et al., 1976; Sawaguchi & Goldman-Rakic, 1994). Reductions in N-acetylaspartate (NAA, a marker of neurons) have been observed in the supraventricular white matter of severely cognitively impaired patients, while basal ganglia show an increase in choline consistent with macrophage infiltration (Meyerhoff et al., 1994). Anatomical, biochemical, and functional imaging studies suggest that HIV dementia is particularly associated with basal ganglia damage (Rottenberg et al., 1987; Van Gorp et al., 1989; Kure et al., 1990; Aylward et al., 1993). The pattern of cognitive impairment associated with HIV includes deficits in executive function, attention and memory, and motor slowing (Navia et al., 1986; Grant et al., 1988). However, HIV related cognitive slowing is not a generalized deficit in speed of processing, but rather an impairment of discrete cognitive processes (Martin et al., 1993).

Frontal Processing Impairment in HIV

Early in their disease, HIV-positive subjects showed impairment on tests of executive function (Sahakian et al., 1995), long associated with the frontal lobe (Bianchi, 1895, Jacobsen, 1931). HIV-positive subjects showed disruption of reflexive orienting in a passive attention task (Sorensen et al., 1994). This effect that has also been observed in Parkin-

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son's disease (Kingstone et al., 1992), a neurological disorder characterized by disruption of the dopaminergic nigrostriatal pathway. Deficits in disengagement of attention in a divided attention and attention switching tasks have been reported in HIV (Grant et al., 1987; Miller et al., 1990; Sorensen et al., 1994) and in frontal cortical lesioned patients (Perret, 1974). Asymptomatic HIV+ subjects have also shown increased interference on a Stroop task (Saykin, 1988; Martin et al., 1992), a finding similar to that reported in Parkinson's patients (Brown & Marsden, 1988). PET studies in normal subjects show that the Stroop interference effect has been associated with activation of deep anterior cerebral structures (Pardo et al., 1990). These data support the model that frontal-mediated processes are impaired in HIV disease, and suggest that cognitive deficits seen in HIV may be associated with disruption of frontal–subcortical circuits.

Lexical Impairment and Subcortical Frontal Damage

There is evidence that frontal–subcortical circuits play a role in lexical processing. Subcortical ischemic lesions of the basal ganglia in humans has been shown to result in transient motor aphasia and paraphasia (Wallesch, 1985), and impairment of expressive language (McLean et al., 1985). Both Parkinson's disease (PD) and Huntington's disease (HD) have been associated with linguistic deficits. PD appears to be associated with a loss of motor control of language production (Darkins et al., 1988), while Huntington's disease, characterized by motor impairment and dementia associated with a loss of cholinergic and GABAergic neurons of the basal ganglia, is associated with impairment of both language generation and comprehension (Wallesch & Fehrenbach, 1988). Developmental disorders of language processing have been associated with dysfunction of the dopaminergic system of the basal ganglia (Kerbeshian et al., 1988). Patients with focal basal ganglia lesions showed aphasia associated with reductions in parietotemporal metabolism, suggesting that linguistic impairments in these patients may be associated with a disconnection of frontal and posterior language areas (Karbe et al., 1989).

Lexical Impairment in HIV

Evidence that the linguistic impairment seen in HIV may be mediated by frontal–subcortical circuits has been provided by a study of declarative verbal memory (Peavey et al., 1994). HIV patients showed impairment of explicit verbal retrieval similar to that seen in HD, suggesting that subcortical deficits found in HD may underlie the impairments in HIV disease as well. The patients were consistently impaired in both free and cued verbal recall memory at short and long recall delays, indicating that these patients are not showing increased forgetting in comparison to control subjects. Neither HD nor HIV patients showed evidence of using semantic strategies during free recall, nor did they benefit from semantic cues (Peavey et al., 1994; Becker et al., 1995). It is possible that in HD patients, with frontal–subcortical damage, and in HIV patients, in whom frontal and subcortical damage may be present, the reduced efficiency of strategies observed may be due to the failure of semantic cues to activate related semantic items.

Explicit and Implicit Tests of Verbal Memory

Tests of declarative memory involve explicit memory tasks in which the individual is aware of the need to remember and recall stimuli, and may use a variety of strategies to perform the memory task. Priming tests, conversely, utilize implicit memory tasks in which both the encoding and later recall of stimuli are incidental to the task the person is instructed to perform. Priming is the process by which prior exposure to perceptual stimuli facilitates the later detection or identification of related stimuli (Butters & Delis, 1995). Priming is indexed by decreases in reaction time and error rate to the incidentally learned, or primed, stimuli. There is considerable evidence that, while declarative memory systems may be dependent upon priming processes (Tulving & Schacter, 1990), the two processes can be dissociated both anatomically and functionally. For instance, priming can occur in amnestic subjects, in the absence of the mesial temporal lobe structures necessary to the declarative memory system (Warrington & Weiskrantz, 1970; Tulving et al., 1982; Shimamura & Squire, 1984; Squire & Cohen, 1984; Shimamura,1986; Schacter, 1987; Tulving, 1987). Priming processes may occur at the perceptual level, which depends upon the physical properties of the stimuli, or the conceptual level, which requires semantic processing (Tulving, 1987).

Electrophysiological studies in normal subjects showing free and cued recall performance, but not priming, to be associated with an enhanced posterior scalp positivity at encoding, suggest that the cortical processes associated with encoding strategies affect declarative but not priming memory (Paller, 1990). Both HD and PD patients are impaired in free recall. HD patients show normal lexical priming (Heindel et al., 1989), as do nondemented PD patients (Bondi & Kaszniak, 1991), while demented PD patients are impaired (Heindel et al., 1989).

Impairment of the use of semantic strategies reported in HIV may be due to the inability of the cue to prime related semantic items, or alternatively to impairment of the retrieval component of the declarative memory system. In the former case, both semantic priming and verbal memory would be impaired in HIV, while in the latter case verbal memory impairment in HIV would occur even though priming processes were intact. In order to test the hypothesis that the verbal impairment previously reported in HIV was associated with reduced semantic priming, we examined semantic priming of visually presented words in cognitively normal and cognitively impaired HIV patients and normal control participants.

METHODS

Research Participants

Thirty-nine HIV seropositive (HIV+) participants and 21 HIV seronegative (HIV−) control participants were recruited from the San Francisco Bay Area. Any individual reporting a history of drug or alcohol abuse, head injury with loss of consciousness over 30 min, or a history of neurologic or psychiatric disorder unrelated to HIV was excluded. All procedures were approved by the University of California, San Francisco Committees on Human Research, and signed consent was obtained from all participants prior to study.

The control group was divided on the basis of risk for sexual contraction of HIV into high and low HIV infection risk subgroups. Homosexual and bisexual control participants composed a high risk subgroup ($n = 8$, 1 woman), while male heterosexual control participants composed a low risk subgroup ($n = 13$). High and low risk control participants showed no differences in demographics or performance on the priming task, and were therefore pooled in all analyses. A neuropsychological battery was given to determine if a level of neuropsychological impairment that may be associated with previously undetected neuropathology was present. From this battery a global impairment score (GIS) was calculated as a rating of clinical neuropsychological impairment. Participants were divided into subgroups on the basis of their GIS (a detailed discussion of GIS calculation follows). Participants with a GIS of 0 or 1 showed no evidence of clinical neuropsychological impairment, and were classified as *cognitively normal* (21 controls, 16 HIV+). Those with a GIS of 2 or greater showed evidence of clinical neuropsychological impairment in at least one cognitive domain, and were classified as *cognitively impaired* (23 HIV+). Four control participants who scored 2 or greater were excluded, as this score indicated a level of neuropsychological impairment that may be associated with previously undetected neuropathology. Low and high risk control participants and cognitively normal and impaired HIV+ participants were comparable in age and education (see Table 1). The HIV+ participants were also classified into CDC clinical categories (Centers for Disease Control, 1992) without regard to cognitive impairment. Thus the CDC classification assigned to participants in this study represented the state of physical health affected by the advancement of the disease. GIS and CDC characteristics of the HIV+ participants are shown in Table 2. An analysis of GIS by CDC level showed a group effect [$F(3,58) = 8.39$, $p < .001$]. Cognitively normal HIV+ participants were not different from controls in GIS, but evidenced systemic disease as indexed by CDC scores, while cognitively impaired HIV+ participants showed greater levels of both systemic disease and cognitive impairment than control and cognitively normal HIV+ participants [GIS: control = 0.3 ± 0.5, cognitively normal HIV+ = 0.1 ± 0.3, $F(1,35) = 1.36$ *vs.* control participants, cognitively impaired HIV+ = 3.8 ± 2.1, $F(1,42) = 57.4$, $p < .0001$ *vs.* control participants, $F(1,37) = 48.8$, $p < .0001$ *vs.* cognitively normal HIV+; CDC (control and A1-A3 = 1, B1-B3 = 2, C1-C3 = 3) control = 1 ± 0, cognitively normal HIV+ = 2.1 ± 0.7, $F(1,35) = 27.7$, $p < .0001$ *vs.* control participants, cognitively impaired HIV+ = 2.5 ± 0.5, $F(1,42) = 98.3$, $p < .0001$ *vs.* control participants, $F(1,37) = 5.8$, $p < .05$ *vs.* cognitively normal HIV+].

Table 1. Participant age and education

Group	*n*	Age *M* ± *SD*	Years education *M* ± *SD*
Controls	21	39.6 ± 6.5	16.0 ± 2.4
High risk	8	42.5 ± 6.2	15.8 ± 2.5
Low risk	13	37.8 ± 6.7	16.1 ± 2.3
HIV+	39	40.1 ± 6.3	15.5 ± 2.2
Cognitively normal	16	38.8 ± 5.0	15.9 ± 2.4
Cognitively impaired	23	41.0 ± 6.9	15.3 ± 2.1

Table 2. Patient global impairment and CDC classification

Group	GIS	CDC Level A	B	C
Cognitively normal HIV+	0–1	3	9	4
Cognitively impaired HIV+	2–3	0	7	5
	4–5	0	2	4
	6–9	0	2	3

Neuropsychological Assessment

All participants underwent a battery of neuropsychological tests measuring a wide variety of cognitive skills including attention, concentration, memory, language and verbal fluency, problem solving, visual–motor and visual–spatial skills, and fine motor ability. The battery was administered on 2 days with each assessment lasting about 1 hr. The first half of the battery was administered by a psychometrician and included Beck Depression Scale (Beck et al., 1961), Stroop (Golden, 1975), Grooved Pegboard (Klove, 1963), Shipley Institute of Living Scale (SILS: Shipley, 1940), Symbol Digit Modalities subtest (Smith, 1968), Rey-Osterrieth Complex Figure (Osterrieth, 1944), Trail Making Tests A and B (Reitan & Wolfson, 1985), Short Category Test (Wetzel, 1982), and Controlled Oral Word Association (COWAT: Benton & Hamsher, 1983). The second half of the battery was administered on an IBM-compatible microcomputer in a sound-attenuated chamber, and was composed of the MicroCog Assessment of Cognitive Functioning (MC: Powell et al., 1993). Raw scores for the neuropsychological battery are shown in Table 3.

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Table 3. Neuropsychological test scores

Test	Control $n = 21$		Cognitively normal HIV+ $n = 16$		Cognitively impaired HIV+ $n = 23$		Between-groups difference		Tukey test, $\alpha = .01$*
	M	*SD*	*M*	*SD*	*M*	*SD*	*F*	*p*	
Shipley Full IQ	114.29	8.25	112.56	3.54	104.52	95.17	8.91	.001	C, N> I
Shipley AQ	102.76	7.94	105.44	7.91	95.17	9.16	8.10	.001	N > I
Shipley CQ	97.10	22.26	103.94	7.83	89.87	11.43	3.94	.05	—
BECK Depression Inventory	4.90	5.11	12.94	5.17	13.87	7.00	14.45	.001	C < N, I
Shipley Abstraction	33.90	5.23	38.88	3.42	27.22	7.62	10.32	.001	C, N > I
Short Categories	17.81	10.90	17.56	10.06	31.96	12.7	11.03	.001	C, N < I
Stroop Interference	−0.24	1.29	−0.09	0.75	−0.39	0.35	ns	ns	—
Trail Making Test B	60.71	18.48	50.75	12.62	81.47	27.30	10.92	.001	C, N < I
Microcog Analogies	8.95	1.56	8.88	1.41	7.22	2.15	6.49	.005	C > I
Microcog Object Match	11.26	0.68	11.59	0.49	10.61	0.85	9.87	.001	C, N > I
Numbers forward	33.57	13.37	35.00	9.81	27.09	9.23	ns	ns	—
Numbers reversed	26.71	9.83	31.39	8.17	23.43	9.29	3.34	.05	—
Microcog Alphabet	44.90	0.30	44.81	0.40	43.74	3.05	ns	ns	—
Microcog Wordlist 1	15.67	0.91	15.88	0.34	15.13	1.71	ns	ns	—
Microcog Story Immediate	9.71	1.23	9.88	0.89	8.57	1.50	6.62	.005	N > I
Figural Memory Immediate	45.0	13.87	51.19	8.60	33.35	16.71	8.42	.001	N > I
Microcog Wordlist 2	13.90	4.67	15.38	1.09	14.26	3.02	ns	ns	—
Microcog Story Delay	21.67	3.21	22.19	2.81	18.70	4.53	5.41	.01	—
Figural Memory Delay	44.90	12.76	50.31	9.51	33.04	16.31	8.51	.001	N > I
Grooved Pegs, dominant	60.81	6.81	60.69	6.42	79.48	15.31	21.15	.001	C, N < I
Grooved Pegs, nondominant	66.90	10.15	67.69	8.63	83.57	14.42	13.91	.001	C, N < I
Trail Making Test A	28.29	8.21	26.81	7.41	34.09	9.59	4.12	.05	—
Symbol Digit, Oral	64.38	9.89	63.50	8.36	52.30	8.71	11.87	.001	C, N > I
Symbol Digit, Written	55.95	8.88	55.25	6.24	45.04	8.39	12.29	.001	C, N > I
Microcog Simple Timers	392.1	52.5	431.7	93.3	596.0	225.7	11.11	.001	C, N < I
Microcog Cued Timers	346.9	59.4	367.7	119.9	433.8	137.2	3.67	.05	—
Microcog Clocks	6.86	0.36	6.81	0.40	6.91	0.29	ns	ns	—
Microcog TicTac	47.90	16.39	51.31	23.05	31.35	19.55	5.98	.005	N > I
COWAT	50.05	11.07	47.94	9.34	39.22	10.67	6.53	.005	C > I
Shipley Vocabulary	36.05	2.75	35.88	2.47	34.26	4.06	ns	ns	—

*C = Control, N = Cognitively Normal HIV+, I = Cognitively Impaired HIV+.

Age- and education-normalized scores were obtained for each test. The normalized scores were pooled into nine cognitive domains as follows: (1) *attention* (Numbers Forward, Numbers Reversed, MC Alphabet, MC Word List 1), (2) *verbal* (COWAT, Shipley vocabulary tests), (3) *abstraction* (Shipley abstract score, Short Categories, Stroop interference score, Trail Making Test B, MC Analogies, MC Object Match A & B), (4) *spatial processing* (MC Tic Tac, MC Clocks), (5) *psychomotor* (Trails A, oral and written Digit Symbol), (6) *memory* (Story delay 1 & 2, MC Address delay, Rey delay recall), (7) *learning* (MC Story immediate 1 & 2, Rey immediate, MC Word List 2), (8) *motor* (Grooved Pegboard), and (9) *reaction time* (MC Timers 1 & 2). Cognitively normal HIV+ participants were comparable to controls in all domains, while cognitively impaired HIV+ participants showed widespread clinical and subclinical reductions (see Table 4).

The normalized *z* scores for all tests within a domain were averaged and converted to a domain percentile score. Each domain percentile score was ranked on a scale from 0 to 2. A rank of 0 was assigned to domain scores falling above the 15th percentile, 1 was assigned to domain scores falling at or below the 15th and above the 5th percentile, and a rank of 2 was assigned to domain scores falling at or below the 5th percentile. These nine rank domain scores were summed to give a global impairment score ranging from 0 to 18.

Stimuli

In this lexical decision task, participants were presented with 150 English words and 148 nonword letter strings (both ranged from two to seven letters) and were asked to respond with one hand if the stimulus was a word, the other hand if the stimulus was a nonword. The nonwords were orthographically and phonologically correct and were created from rearranging the letter sequence of words (e.g., "ulpit," "aceep"). Eighty-four nonwords were preceded by words, and 64 nonwords were preceded by nonwords. The

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Table 4. Cognitive domain percentile scores

	Control		Cognitively normal HIV+		Cognitively impaired HIV+	
Domain	*M* ± *SD*	≤15th %ile	*M* ± *SD*	≤15th %ile	*M* ± *SD*	≤15th %ile
Abstraction	62 ± 19	0%	67 ± 13	0%	38 ± 20*	9%
Attention	51 ± 20	0%	57 ± 13	0%	39 ± 17*	0%
Learning	51 ± 19	5%	61 ± 16	0%	29 ± 24*	48%
Memory	57 ± 22	10%	63 ± 20	0%	29 ± 30*	57%
Motor	57 ± 25	5%	55 ± 24	6%	18 ± 24*	65%
Psychomotor	52 ± 25	5%	50 ± 20	0%	23 ± 22*	48%
Reaction time	54 ± 12	0%	50 ± 18	0%	35 ± 27*	39%
Spatial processing	47 ± 14	0%	47 ± 17	0%	39 ± 15	0%
Verbal	82 ± 16	0%	81 ± 13	0%	64 ± 24*	4%

*Difference from control subjects, $p < .05$.

words were matching antonym pairs (e.g., "enter–exit") or words that had an obvious antonym that was not presented as a stimulus (e.g., "deep–hire"). Eighty-two words were preceded by nonwords, 17 words were preceded by an unrelated word, and 51 words were preceded by a related word. A random ordering of presentations was created with the three following restrictions: the antonym pairs were always presented together, always preceded by a nonword, and always directly followed by a nonword.

The stimuli were displayed by a 20-MHz Intel 80386 microcomputer that was slaved to present stimuli only when a command bit pulse was received from the data acquisition computer. The stimuli were presented as white letters in the center of a black, otherwise blank, 14″ screen. The intertrial interval was 2800 ± 200 ms. Similarly to prior reports, stimulus duration was 200 ms (Rugg, 1984; Paller et al., 1987).

Procedure

Participants were relaxed, awake, and seated upright in a sound attenuated chamber. They were asked to fixate on the center of the screen and perform the lexical decision task as quickly as possible while still responding accurately, lifting a finger of one hand when they saw a word or a finger of the other hand when they saw a nonword. They were not given any additional information about the stimuli. Hand assignment was counterbalanced across groups, and participants could not choose which hand was used for words or nonwords.

Response data were measured using a beam detection system. Participants rested their fingers on a response pad that provided a beam of light. The relaxed finger rested naturally in a position that blocked the beam. When participants responded by lifting their finger, the beam was allowed to connect and a response was detected. This method provided accurate reaction time data, as participants did not have to apply a minimum force for detection to occur. All responses occurring prior to 100 or over 1000 ms after stimulus onset were excluded. If a participant made more than one response during a trial, only the first response was recorded. Thirty-channel EEG was recorded throughout this procedure; those data will be presented elsewhere.

Analysis

Repeated measures analysis of variance (RmANOVA) was performed on the reaction time and reaction time variance to correctly detected stimuli, percent correct responses, percent incorrect responses and percent nonresponse errors. Additionally, the percentage of priming was calculated for reaction time [− (unrelated word RT − primed word RT)/unrelated word RT) × 100] and accuracy [(unrelated word % correct response − primed word % correct response)/unrelated word % correct response) × 100]. Each stimulus was classified on the basis of its immediately preceding stimulus: nonwords preceded by nonwords, unrelated words preceded by unrelated words, and words preceded by antonyms (prime–target pairs). For the RmANOVA, the stimulus classifications were the repeated measures and participant group was the between-subject factor. Correlations and regressions were run between percent priming and the nine GIS domain percentile scores.

RESULTS

Accuracy

Accuracy was affected by stimulus type [% correctly detected stimuli, $F(2,56) = 30.0$, $p < .001$; see Table 5]. All groups showed an increase in accuracy to primed words [unrelated words *vs.* primed words, control $F(1,20) = 12.1$, $p < .005$; cognitively normal HIV+ $F(1,16) = 13.5$, $p < .005$; cognitively impaired HIV+ $F(1,21) = 9.3$, $p < .01$]. Cognitively impaired HIV+ participants showed less accurate responses to the primed words than the control subjects [$F(1,42) = 4.9$, $p < .05$], although no Group × Stimulus interactions were found. Ceiling effects were apparent, especially to the primed words in the control group. Erroneous response and nonresponse rates were affected by stimulus type [false response, stimulus effect, $F(2,56) = 22.2$, $p < .001$;

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Table 5. Accuracy and reaction time to correctly detected words

	Percent correct			Reaction time (ms)		
Group	Nonwords	Unrelated words	Primed words	Nonwords	Unrelated words	Primed words
Control	87 ± 11	89 ± 10	96 ± 4	632 ± 75	556 ± 64	515 ± 77
Cognitively normal HIV+	88 ± 8	89 ± 7	94 ± 8	630 ± 85	586 ± 69	535 ± 73
Cognitively impaired HIV+	80 ± 16	86 ± 12	91 ± 9*	636 ± 70	568 ± 57	562 ± 73*

*Difference from control subjects, $p < .05$.

nonresponse, stimulus effect, $F(2,56) = 15.8$, $p < .001$]. As shown in Table 6, both types of erroneous responses were reduced to the primed words [unrelated *vs*. primed words: false response, $F(1,57) = 25.5$, $p < .001$; nonresponse, $F(1,57) = 11.1$, $p < .005$], and nonresponses were increased to the nonwords [$F(1,57) = 6.7$, $p < .05$ *vs*. unrelated words]. There were no effects of group on errors. As average error rates were well below 20% for each group in each condition, a signal detection analysis was not performed.

Reaction Time

Reaction time was affected by stimulus type [$F(2,56) = 87.2$, $p < .001$], and a Group × Stimulus interaction was found [$F(4,112) = 3.7$, $p < .01$, Table 5]. Nonwords and unrelated words showed no group difference, with nonwords generating slower reaction times overall [stimulus effect, nonwords *vs*. unrelated words, $F(1,57) = 92.3$, $p < .001$]. Cognitively impaired HIV+ participants showed reduced priming in comparison to control participants [Group × Stimulus interaction, unrelated *vs*. primed words, $F(1,42) = 5.8$, $p < .05$; see Figure 1], and to cognitively normal HIV+ participants [$F(1,37) = 15.6$, $p < .001$]. Reaction time to primed words was comparable in the cognitively normal HIV+ and control groups, while the impaired HIV+ participants made slower responses to the primed words than controls [$F(1,42) = 4.2$, $p < .05$]. Control and cognitively normal HIV+ participants showed decreased reaction times to correctly detected primed words, but cognitively impaired HIV+ participants did not [unrelated words *vs*. primed words, control $F(1,20) = 11.7$, $p < .005$; cognitively normal HIV+ $F(1,16) = 23.8$, $p < .0005$; cognitively impaired HIV+ $F(1,21) = 1.6$, $p = .22$]. Percent reaction time priming was comparable and significantly greater than 0 in the control and cognitively normal HIV+ groups [control = 7% ± 10%, $t(20) = 3.3$, $p < .005$; cognitively normal HIV+ = 9% ± 5%, $t(15) = 7.1$, $p < .001$] but was not significantly different from zero in the cognitively impaired HIV+ group [1% ± 7%, $t(22) = 0.9$, $p = .4$; impaired *vs*. control: $F(1,42) = 5.1$, $p < .05$, impaired *vs*. cognitively normal HIV+: $F(1,37) = 12.8$, $p < .005$; see Figure 2].

To investigate the possibility that differences in reaction time priming were associated with specific neurocognitive deficits, correlations between percent priming and each of the nine cognitive domain percentiles were examined. The abstraction and verbal domains were correlated to percent reaction time priming for all subjects [Abstraction: $F(1,58) = 11.3$, $p < .005$, $r^2 = .16$; verbal: $F(1,58) = 5.8$, $p < .05$, $r^2 = .09$]. However, these correlations were not additive, suggesting that they may reflect a single underlying process [multiple regression, abstraction and verbal, $F(2,57) = 6.2$, $p < .05$, $r^2 = .18$]. Of the tests that comprised the abstraction domain, the Shipley Abstraction and Trail Making Test B were correlated to reaction time priming [Shipley Abstraction: $F(1,58) = 8.7$, $p < .01$, $r^2 = .13$; Trail Making Test B: $F(1,58) = 10.0$, $p < .01$, $r^2 = .15$]. Within the verbal domain, the COWAT was correlated with percent reaction time priming [$F(1,58) = 14.6$, $p < .0005$, $r^2 = .20$]. There was a Group × Domain interaction only in the psychomotor domain [$F(2,54) = 5.0$, $p < .05$] between all three subject groups. The cognitively impaired HIV+ participants displayed a significant correlation between priming and the psychomotor domain ($r^2 = 0.45$, $p < .001$), while the cognitively normal HIV+ and control subjects did not. Of the three tests that comprised the psychomotor domain, a Group × Score effect on percent reaction time prim-

Table 6. Error responses

	Percent false responses			Percent nonresponses		
Group	Nonwords	Unrelated words	Primed words	Nonwords	Unrelated words	Primed words
Control	2.8 ± 3.0	3.9 ± 4.7	1.7 ± 2.9	9.7 ± 10.8	7.3 ± 8.9	2.5 ± 3.2
Cognitively normal HIV+	3.6 ± 3.4	5.4 ± 5.6	1.3 ± 1.6	8.6 ± 9.3	4.8 ± 7.2	4.6 ± 6.7
Cognitively impaired HIV+	6.3 ± 7.0	5.9 ± 4.8	3.0 ± 3.5	13.2 ± 14.2	8.9 ± 10.0	5.8 ± 7.8

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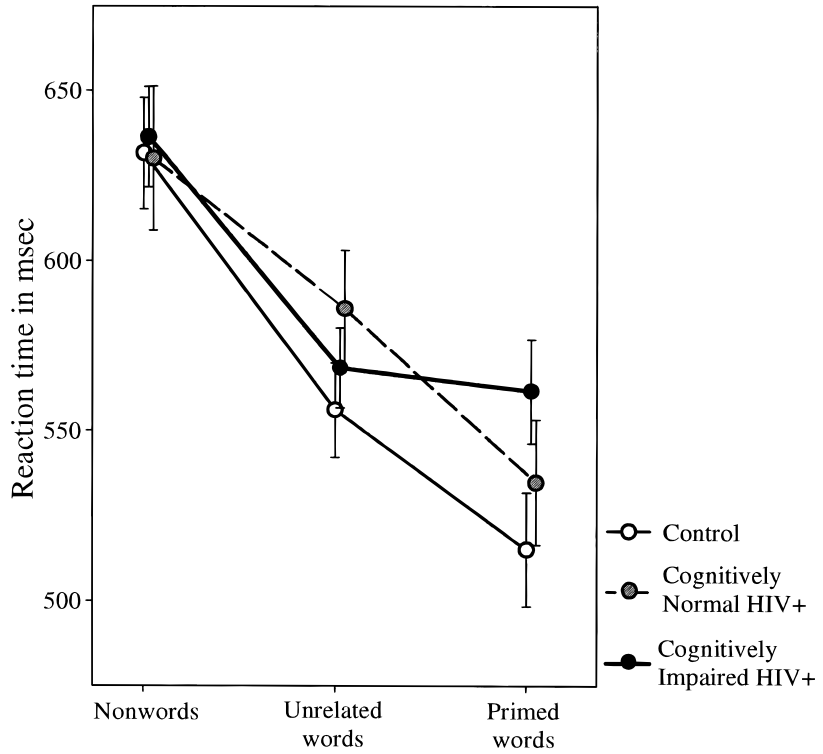

Fig. 1. Reaction time of control participants (white circles & thin line), cognitively normal HIV+ participants (grey circles & dashed line) and cognitively impaired HIV+ participants (black circles and thick line) to nonwords, unrelated words and primed words. Error bars show standard error. Although all groups show comparable reaction time to nonwords and unrelated words, cognitively impaired HIV+ individuals show no savings in reaction time due to priming.

ing was found only for the written Symbol Digit Test [$F(2,54) = 3.3$, $p < .05$]. Regression analysis showed that while the written Symbol Digit score was correlated with percent reaction time priming in the cognitively impaired HIV+ participants [$F(1,21) = 9.0$, $p < .01$, $r^2 = .30$], the two measures were not correlated in the control or cognitively normal HIV+ participants.

There was no effect of systemic disease level (as indexed by CDC score) on percent priming, nor was any group by CDC level interaction observed between cognitively normal and cognitively impaired HIV+ participants for overall reaction time, accuracy, or priming measures, suggesting that priming effects were independent of systemic disease level. No primed or unprimed word accuracy by group interaction was observed in the cognitively normal and impaired HIV+ groups, suggesting that there were no differences in speed–accuracy tradeoff. In order to further examine any association of priming with impairment of simple response processes in the HIV+ participants, we examined the covariance of simple visual reaction time (MicroCog visual timer test of Timers 1 & 2) with reaction time to primed and unprimed words. No Group × Visual RT nor Group × Stimulus × Visual RT interactions were observed, suggesting that priming effects are not dependent upon simple response processes.

DISCUSSION

This study provides evidence that cognitive impairment in HIV is associated with reduced semantic priming. This impairment was associated with the degree of cognitive impairment, but was not associated with clinical disease stage. The dissociation of the effects of cognitive impairment from the effects of systemic disease supports prior results in this laboratory (DiSclafani et al., 1997). Responses to nonwords were consistently slower than responses to unrelated words, suggesting that the speeding of reaction time to primed words was not due to a facilitory effect of word primes on all subsequent stimuli (Neeley, 1977). It also suggests that postlexical checking did not produce inhibition to unrelated words (Lorch et al., 1986; Shelton & Martin, 1992), consistent with this paradigm assessing automatic rather than controlled processes. The data support the notion that, unlike controls or cognitively normal HIV+ individuals, cognitively impaired HIV+ participants do not differentially activate neural pathways associated with word processing in primed and unprimed conditions (Shelton & Martin, 1992). This finding is consistent with other research showing impairments in semantic strategies and/or semantic activation in cognitively impaired HIV+ subjects (Peavy et al., 1994).

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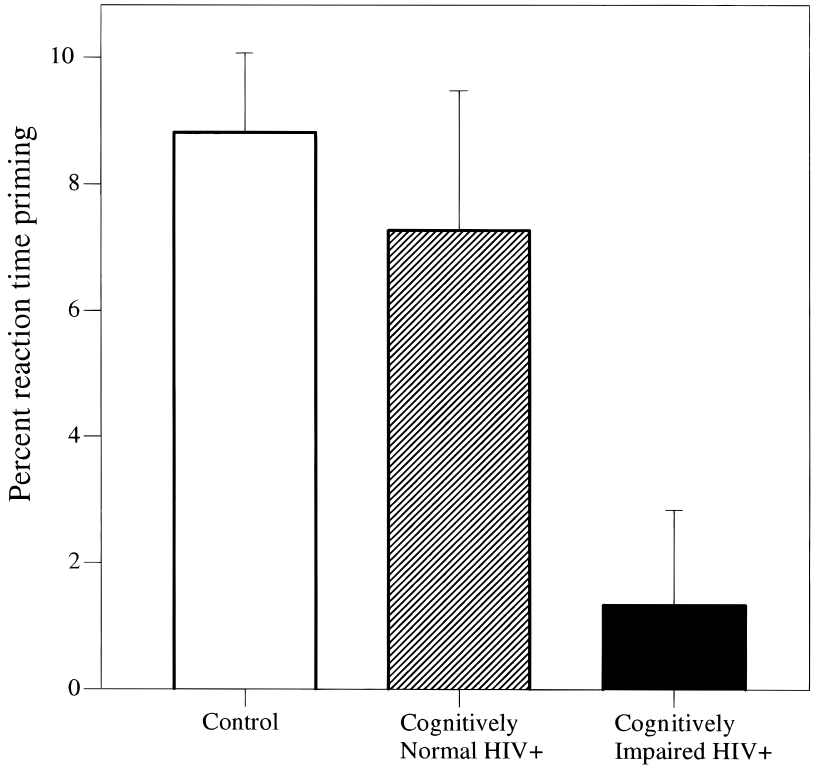

Fig. 2. Percent priming [(unrelated word RT − primed word RT) / unrelated word RT) × 100] for control participants (white bar), cognitively normal HIV+ participants (striped bar) and cognitively impaired HIV+ participants (black bar). Error bars show standard error. While control and cognitively normal HIV+ individuals show comparable priming effects, cognitively impaired HIV+ participants show no priming effect.

Reduced semantic priming in cognitively impaired HIV+ subjects was not associated with motor impairment. These participants' reaction times were comparable to those of the cognitively normal HIV+ and control groups to both nonwords and unrelated words. However, reduced priming was correlated with verbal and abstraction impairment across all groups, and with psychomotor impairment in only the HIV+ cognitively impaired group. The reduction in priming may represent one result of an underlying deficit that affects frontally mediated processes such as reflexive orienting, attentional switching, and Stroop phenomena (Grant et al., 1987; Saykin, 1988; Miller et al., 1990; Martin et al., 1992; Sorensen et al., 1994).

Reductions of NAA in frontal and periventricular white matter in the brains of HIV-infected subjects suggests that these regions may be implicated in a functional disconnection in HIV disease (Meyerhoff et al., 1996). Semantic processes have been postulated to activate a distributed circuit that includes a network of excitatory and inhibitory connections between anterior and posterior cortical structures and subcortical structures (Crosson, 1985). That frontal cortex is involved in an anterior–posterior semantic network is supported by human PET and lesion studies (Posner et al., 1992; Swick & Knight, 1996). Studies of Parkinson's disease, Huntington's disease, and patients with focal basal ganglia lesions show that basal ganglia damage impairs semantic processes, including the generation of expressive language (McLean et al., 1985; Wallesch, 1985; Darkins et al., 1988; Kerbeshian et al., 1988; Wallesch & Fehrenbach, 1988). However, frontal cortical lesions alone are insufficient to cause impairment in word priming (Shimamura et al., 1992; Swick & Knight, 1994, 1996).

The linguistic deficits associated with basal ganglia damage may involve a disconnection of frontal and posterior language areas (Karbe et al., 1989). Evidence suggesting that posterior cortex is critical to word priming has been provided by lesion studies. Behavioral response priming of lexical processes is associated with a positive shift in central and parietal scalp-recorded potentials that extends from 250 to 600 ms after presentation of the primed word (Bentin et al., 1985). Right temporal–occipital lesions abolish this shift bilaterally, with associated reductions in performance (Swick & Knight, 1995), and both left and right temporal–occipital lesions impair word priming (Nielsen-Bohlman et al., 1995).

Behavioral, lesion, and functional imaging studies provide converging evidence to support the notion that semantic priming involves a distributed cortical and subcortical network. HIV has been shown to damage subcortical structures (Navia et al., 1986) and white matter tracts (Meyerhoff, 1996). The inability of cognitively impaired HIV+ subjects to differentially activate semantic pathways during

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priming may be due to damage or disconnection of the frontal component of this system.

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