Journal of the International Neuropsychological Society (1999), **5**, 434–441.

Differential association of HIV-related neuropsychological impairment with semantic *versus* repetition priming

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(RECEIVED March 9, 1998; REVISED September 8, 1998; ACCEPTED September 17, 1998)

Abstract

There is evidence that the facilitating effects of stimulus repetition (repetition or identity priming) are mediated by visuoperceptual functions local to extrastriate cortex. Semantic or verbal–associative priming, on the other hand, is believed to be a function of more anterior brain systems. The present study finds evidence for disrupted semantic priming with intact repetition priming in a cognitively impaired HIV+ sample. These results are consistent with recent brain-imaging evidence for a subcortical and white-matter locus for HIV associated neuropathology resulting in effects on subcortical–frontal systems. (*JINS*, 1999, *5*, 434–441.)

Keywords: Presemantic systems, Extrastriate cortex, Semantic priming, Subcortical–frontal systems

INTRODUCTION

Priming occurs when previous experience with stimulus elements facilitates later performance with the same or related stimulus elements. Priming effects do not require that the stimuli be processed to the degree necessary for explicit verbal recall of the priming material (Tulving, 1985). Moreover, priming effects can be demonstrated in densely amnestic patients (Graf & Schacter, 1985; Heindel et al., 1993; Salmon et al., 1988; Shimamura & Squire, 1984; Warrington & Weiskrantz, 1968). This dissociation of priming from verbal recall has led to priming being classified as a type of "implicit" memory; that is, an effect of previous experience on later behavior that is distinct from explicit retrieval or report of the initial experience (Schacter, 1987). Two subclasses of priming have been studied: *repetition* or *perceptual* priming, and *semantic* or *verbal–associative* priming. Repetition priming, as its name indicates, involves repeating the exact same stimulus as both prime and target and is also referred to as *identity* priming. Semantic priming involves using different stimuli as prime and target, with the prime being linguistically related to the target. Schacter (1994) proposed that repetition priming is mediated by "presemantic" perceptual representation systems, which are domain-specific for stimulus form and structure, but not for stimulus meaning or other higher-order associative properties. Thus repetition priming with visual word stimuli would be mediated by a "visual–word–form" system dependent on the visual orthography of words, but independent of their meaning. Whether or not the semantic content of priming stimuli is processed has no influence on the magnitude of the identity priming effect.

Human brain imaging studies support the view that repetition and semantic priming are mediated by different cortical areas. Using positron emission tomography (PET), Petersen et al. (1988, 1990) found increased activation in extrastriate cortex when attention was focused on the form of visual word stimuli (upper *vs.* lower case), but they found increased activation in left inferior prefrontal cortex (LIPC) when volunteers had to generate word responses. Both Buckner et al. (1995) and Squire et al. (1992) found decreased PET activation in extrastriate cortex during identity primed word-stem completion relative to nonprimed baseline conditions. This suggests that the effect of visual word repetition is to decrease the necessary processing load in those brain areas that detect specific visual stimulus features. Raichle et al. (1994) found PET activation in prefrontal, pos-

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terior temporal, and anterior cingulate cortices during an associative word generation task. During repeated practice with the same task elements, this activation decreased to levels found with nongenerative single word repetition. Demb et al. (1995), using functional magnetic resonance imaging, found increased activation in LIPC during semantic encoding of visual word stimuli, with decreased LIPC activation over repeated presentations of the same words. This LIPC decrease in activation was process specific; it occurred when visual word stimuli were semantically reprocessed (i.e., studied for their meaning), but not when they were orthographically reprocessed (i.e., studied for their form). In summary, a consistent finding in brain imaging studies of semantic *versus* orthographic visual word stimulus processing has been that semantic processing involves anterior and possibly other widely spread brain regions, while orthographic encoding appears confined to posterior cortex, particularly the extrastriate region

We have reported that semantic priming in HIV+ individuals with neuropsychological impairment is reduced relative to both HIV+ individuals without neuropsychological impairment and HIV− controls (Nielsen-Bohlman et al., 1997). Using a lexical decision task in which participants had to quickly decide if visually presented letter strings were words or nonwords, cognitively normal HIV+ individuals and HIV− controls exhibited comparable reaction time decreases when accurately detected word stimuli were immediately preceded by their antonyms. However, HIV+ individuals with moderate to severe neuropsychological impairment did not evidence a response time reduction with antonym priming. We proposed (Nielsen-Bohlman et al., 1997) that the semantic priming deficit in the HIV+ sample with moderate to severe neuropsychological impairment was due to pathology of subcortical–frontal systems that may underlie semantic association (Posner et al., 1992). There is considerable evidence for subcortical and white matter brain involvement in HIV disease, including reduced caudate dopamine levels (Sardar et al., 1995), caudate atrophy (Jernigan et al., 1993), frontal white matter N-acetylaspartate decreases indicative of axonal–dendritic damage, and basal ganglia choline increases indicative of macrophage infiltration of the basal ganglia (Meyerhoff et al., 1993, 1996). If the neuropsychological sequelae of HIV are the result of disease processes affecting primarily subcortical structures and white matter, we predict that while semantic priming is affected in HIV+ individuals with moderate to severe neuropsychological impairment, repetition priming may be relatively spared in the same individuals because of its functional localization in extrastriate cortex distal to the primary brain disease process.

The purpose of the following study was to test for an interaction between participant group (HIV+ cognitively impaired *vs*. HIV+ cognitively intact *vs*. HIV−) and priming type (semantic *vs*. repetition). To this end we examined samples that included the individuals in whom we previously (Nielsen-Bohlman et al., 1997) demonstrated group differences in semantic priming.

METHODS

Volunteer Recruitment

Sixty-one HIV+ and 27 HIV− research volunteers were recruited from the San Francisco Bay Area. Any individual reporting a history of drug abuse, head injury with a loss of consciousness, or 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. Thirty-nine of the HIV+ and 21 of the HIV− volunteers in the present sample had also participated in our earlier study (Nielsen-Bohlman et al., 1997). Their semantic priming data are reincluded here for comparison with the repetition priming data.

Neuropsychological Assessment

All participants underwent a battery of neuropsychological tests administered over 2 days, with each day's assessment lasting about 1 hr. The first half of the battery was administered by a psychometrician and included the Grooved Pegboard (Kløve, 1963), Stroop (Golden, 1975), Shipley Institute of Living Scale (SILS; Shipley, 1940), Symbol Digit Modalities subtest (Smith, 1968), Trail Making Tests A and B (Reitan & Wolfson, 1985), Controlled Word Association Test (COWAT; Benton & Hamsher, 1983), Short Category Test (Wetzel, 1982) and Rey–Osterrieth Complex Figure Test (Osterrieth, 1944). The remainder of the battery consisted of the MicroCog Assessment of Cognitive Functioning (MC; Powell et al., 1993) administered on an IBM-compatible microcomputer in a sound attenuated chamber.

Age- and education-adjusted *z* scores (based on each test's above-cited normative data) were calculated for all tests (including the MicroCog subtests). *Z* scores were then averaged within the following cognitive domains: (1) *attention* (Numbers Forward, Numbers Reversed, MicroCog (MC) Alphabet and MC Word 1); (2) *verbal* (COWAT and Shipley vocabulary tests); (3) *abstraction* (Shipley abstract score, Short Categories Test, Stroop interference score, Trail Making Test B, MC Analogies and MC Object Match A and B); (4) *spatial processing* (MC Tic Tac and MC Clocks); (5) *psychomotor* (Trails A and Oral and Written Digit Symbol); (6) *immediate memory* (MC Story immediate 1 and 2, Rey immediate, and MC Word List 2); (7) *delayed memory* (MC Story delay 1 and 2, MC Address delay, and Rey delay recall); (8) *motor* (Grooved Pegboard), and (9) *reaction time* (MC Timers 1 and 2).

The normalized *z* scores for all tests within a domain were averaged and converted to a domain percentile score. Each domain percentile score was then assigned a Clinical Impairment Score from zero to 2. A score of zero was assigned to domain scores above the 15th percentile, a score of 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. The

https://doi.org/10.1017/S1355617799555057 Published online by Cambridge University Press

Table 1. Volunteer age and education

Group	*N*	Age (years) *M* (*SD*)	Education (years) *M* (*SD*)
HIV− controls (NC)	27	37.7 (7.7)	16.2 (2.2)
HIV+ cognitively normal (CN)	33	41.1 (5.4)	16.5 (2.3)
HIV+ cognitively impaired (CI)	28	39.5 (7.0)	15.2 (2.4)

clinical impairment scores for the nine cognitive domains were summed to yield a Global Clinical Impairment Score (GCIS), ranging from zero to 18.

Participant Grouping

HIV+ volunteers with a GCIS of zero or 1 were classified as *cognitively normal* (CN; $N = 33$). Twenty-eight HIV+ volunteers had a GCIS of 2 or greater and were classified as *cognitively impaired* (CI). Of the 27 HIV− controls (NC), 23 had GCIS scores of zero or 1, with the remaining 4 having a GCIS of 2. The grouping factor consists of three levels: HIV+ cognitively normal ($N = 33$), HIV+ cognitively impaired ($N = 29$), and HIV− controls ($N = 27$).

Age and education for the three groups are presented in Table 1. CDC classification of the clinical stage of systemic disease (specifically excluding neuropsychological indicators; DiSclafani et al., 1997) and mean CD4 cell counts (per cubic milliliter) for the two HIV+ groups are presented in Table 2. Mean cognitive domain percentile scores for the three groups are presented in Table 3.

APPARATUS AND PROCEDURE

Participants were relaxed, awake, and seated upright in a sound-attenuated chamber. They were asked to fixate on a 35-cm computer monitor and perform a two-choice reaction time task (lexical decision for semantic priming; stimulus categorization for identity priming, described below) by lifting as quickly as possible the index finger of one hand or the other. Hand assignment for each task was counterbalanced across groups, as was the order of the lexical decision and stimulus categorization tasks.

Stimuli were displayed by a 20-MHz Intel 80386 microcomputer slaved to the data acquisition computer. Response data were measured using a photo-diode system. The relaxed finger blocked a light beam. With a finger lift, the beam was allowed to connect and a response was detected. Responses occurring 1000 ms after stimulus onset were excluded as being unacceptably delayed. Responses occurring prior to 100 ms after stimulus onset were excluded as being possibly delayed responses to the previous stimulus. If a participant made more than one response during the 100 to 1000 ms poststimulus interval, only the first response was recorded.

Lexical Decision Task (Semantic Priming)

In the lexical decision task, participants were presented with 150 English words and 148 nonword letter strings (both ranged from 2 to 7 letters) and were asked to respond with one hand if the stimulus was a word, and the other hand if the stimulus was a nonword. Response accuracy and speed were equally stressed. The nonwords were orthographically and phonologically correct and were created from rearranging the letter sequence of legal English words (e.g., "ulpit," "aceep"). The actual words were matched with antonym pairs (e.g., "enter–exit") or words that had another obvious antonym but were unrelated (e.g., "deep–hire"). Eighty-two words were preceded by nonwords. Fifty-one words were preceded by their antonym. These 51 words comprised the *antonym primed* condition. Seventeen words pre-

Table 2. CDC classification* frequencies (number of volunteers) and mean CD4 counts (per cubic millimeter) by global impairment levels

Group	GIS	CDC–A	CDC–B	CDC–C	CD4	(*SD*)
CN	0–1	3	14	16	167	(147)
CI	2–3	1	7	5	109	(84)
CI	4–5	2	2	4	56	(73)
CI	6–9	0	2	3	238	(161)
CI	10–14	0	1	1	81	(106)
CI total	2–14	3	12	13	117	(113)

*Excluding neuropsychological dysfunction indicators.

https://doi.org/10.1017/S1355617799555057 Published online by Cambridge University Press

Table 3. Means and standard deviations of neuropsychological domain percentile scores

Domain	CI *M* (*SD*)	CN *M* (*SD*)	NC *M* (*SD*)
Abstraction	36 (21)	66 (17)	63 (18)
Attention	32 (17)	58 (18)	49 (22)
Memory (immediate)	27 (26)	56 (21)	51 (19)
Memory (delayed)	24 (26)	57 (26)	57 (24)
Motor	24 (31)	59 (24)	60 (24)
Psychomotor	17 (22)	53 (18)	50 (24)
Reaction Time	30 (23)	56 (20)	50 (17)
Spatial	38 (17)	50 (13)	46 (13)
Verbal	65 (26)	79 (18)	80 (18)

Note. CI = HIV+ cognitively impaired; CN = HIV+ cognitively normal; NC = HIV− controls.

ceded by an unrelated word served as the unrelated word comparison for the semantically antonym primed condition. A random ordering of presentations was created with the restriction that antonym pairs always occurred together. The stimuli were presented as white letters in the center of the otherwise black, blank 35-cm screen. The intertrial interval was 2800 ms with a random jitter of 200 ms. Stimulus duration was 200 ms.

Stimulus Categorization Task (Repetition Priming)

In the stimulus categorization task, participants were presented with 250 English words, 250 line drawings of objects selected from the Snodgrass and Vanderwart (1980) set of pictures, and computer pixel-shuffled scrambles of words and object pictures (50 each). In this task, volunteers were asked to respond with one hand if a stimulus was a recognizable word, and with the other hand if the stimulus was a recognizable picture. If the stimulus was a scrambled word or picture, they were to make no response. Response accuracy and speed were equally stressed. The stimuli were presented in pseudorandom order with the following constraints. For 60 trials during the task the exact same word stimulus was repeated twice in a row. The second stimulus of each such pair constituted the repetition primed or *word same* condition. For another 60 trials, word stimuli were immediately preceded by other semantically unrelated word stimuli. The second stimulus of these pairs constituted the *word different* comparison for the identity primed word same condition. For the remaining 480 trials of the stimulus categorization task, 130 other word stimuli were preceded by either images or scrambles. All stimuli were presented in white on a black background at the center of the 35-cm computer monitor. All stimuli were approximately 10 cm in height and width, subtending a visual angle of 5° to 6°. The intertrial interval was 2800 ms with a random jitter of 200 ms. Stimulus duration was 200 ms.

Data Analysis

Only reaction times from trials with correct responses were considered for analysis. For each participant, for each condition, median reaction times (RT) across correct response trials were computed. We note that this is a change from the analyses reported in the earlier semantic priming manuscript (Nielsen-Bohlman et al., 1997) where mean reaction times within each condition were computed. Since individual reaction time distributions are often skewed towards shorter response latencies, median RTs are a more accurate representation of central tendency and thus more likely to detect priming effects.

The RT data were analyzed using a repeated-measures analysis of variance (ANOVA). The ANOVA had a three-level between-participants group factor [HIV+ cognitively normal (CN) *vs*. HIV+ cognitively impaired (CI) *vs*. HIV− control (CN)], and within-participants factors of priming condition (primed *vs*. not-primed word stimuli) and priming type (semantic *vs*. repetition priming). The primary *F* test of interest is the three-way interaction of Group × Priming Condition × Priming Type. If this *F* value is significant, the null hypothesis that there is no difference in the effect of HIV-related cognitive status upon the two types of priming may be rejected.

RESULTS

Demographic and Clinical Variables (Tables 1 and 2)

There were no significant differences among the three groups on age [$F(2,85) = 1.9$, $p = .1553$]. There was a trend toward a difference among the groups in education [$F(2,85) = 2.48$, $p = .09$], with the HIV+ cognitively impaired volunteers tending to be less educated than both the HIV− controls and the HIV+ cognitively normal volunteers.

There was no significant association within the HIV+ samples between the CDC clinical stage (derived excluding neuropsychological function indicators) and the severity of cognitive impairments [$\chi^2 = .055$, $p = .973$). There also was no significant difference in CD4 counts between the HIV+ cognitively normal and HIV+ cognitively impaired groups [$F(1,58) = 2.06$, $p = .1564$].

Roughly half of the cognitively normal (16/33) and cognitively impaired (14/28) HIV+ samples were on prescribed psychoactive medications. These were typically either an antidepressant or a combination of antidepressant and a minor tranquilizer. (Only 2 individuals in each of the HIV+ groups were on a minor tranquilizer alone.) This is in contrast to the low rate of psychiatric medication in the HIV− control group (2/27).

Priming Effects

Response accuracy was 85% or greater in all three groups for the semantic antonym primed and unrelated word con-

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Table 4. Reaction times in milliseconds

Priming task	Word type	Cognitively impaired HIV+ group *M* (*SD*)	Cognitively normal HIV+ group *M* (*SD*)	HIV− control group *M* (*SD*)
Semantic				
	Antonym	570 (56)	519 (82)	496 (86)
	Unrelated	568 (57)	570 (87)	545 (62)
Repetition				
	Same	564 (66)	531 (68)	536 (83)
	Different	613 (69)	582 (79)	579 (87)

ditions as well as for the repetition primed word same and word different conditions. The reaction time data for the correct trials from these four stimulus conditions are presented in Table 4. In light of the marginally significant effect of the grouping factor on education level, the reaction time data were analyzed by analysis of covariance with years of education as a covariate (with covariate adjustments made by the method of partial sums of squares; Searle, 1971). The three-way interaction of Group × Priming Condition × Priming Type was significant [$F(2,84) = 6.01$, $p = .0036$] as was the interaction of Group × Priming Condition [$F(2,84) = 7.65$, $p = .0009$]. The main effect of group approached significance [$F(2,84) = 2.78$, $p = .0677$]. The source of the three-way interaction can be seen in Figure 1. All three groups show comparable reaction-time decreases following word stimulus repetition when compared to nonrepeating word stimuli (repetition priming). Both the HIV+ cognitively normal and HIV− groups show comparable reaction time decreases when word stimuli are preceded by antonyms as opposed to unrelated words (semantic priming), while the HIV+ cognitively impaired group does not show this semantic priming effect. That the antonym primed word condition is the source of the three-way interaction was borne out by *post-hoc t* tests between education-adjusted cell means (Table 5). For the antonym primed word condition, the HIV+ cognitively impaired

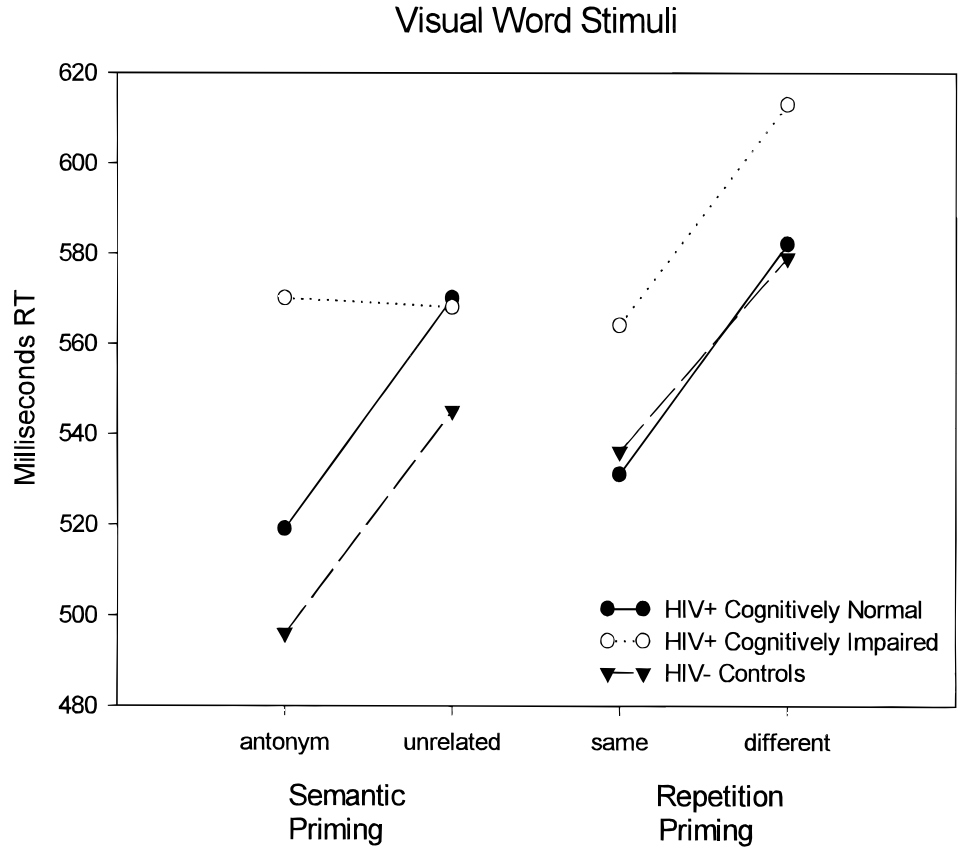

Fig. 1. Group mean reaction times by word stimulus condition.

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Table 5. *Post-hoc t* tests between education-adjusted* cell means

Priming task	Word type	CI *versus* CN *df* = 59	CI *versus* NC *df* = 53	CN *versus* NC *df* = 58
Semantic				
	Antonym	$t = 2.697$	$t = 3.659$	$t = 1.107$
		$p = .0084$**	$p = .0004$**	$p = .2716$
	Unrelated	$t = 0.033$	$t = 1.282$	$t = 1.314$
		$p = .9736$	$p = .2032$	$p = .1924$
Repetition				
	Same	$t = 1.862$	$t = 1.497$	$t = -0.317$
		$p = .0660$	$p = .1380$	$p = .7517$
	Different	$t = 1.553$	$t = 1.609$	$t = 0.114$
		$p = .1240$	$p = .1112$	$p = .9096$

Note. CI = HIV+ cognitively impaired; CN = HIV+ cognitively normal; NC = HIV− controls.
*Least-squares estimates of marginal means (Searle et al., 1980).
**Significant at less than the .01 level.

group's mean was significantly different beyond the .01 level from both the HIV+ cognitively normal and HIV− control group means. There were no other significant differences at the .05 level or better between group means at any other of the Priming Task × Word Type conditions.

DISCUSSION

A significant interaction was found between HIV-related cognitive status and the type of priming facilitation of motor response to lexical stimuli. This interaction resulted from comparable repetition priming across groups, but absent semantic priming specific to the HIV+ cognitively impaired group.

There is a growing body of evidence that visual patterns and the orthographic forms of words are encoded by posterior cortical functions that are relatively spared in diseases that affect subcortical and frontal brain systems. Huntington's disease, a basal ganglia disorder, impairs motor skill learning as measured by the pursuit-rotor task (Heindel et al., 1988) yet seems to have no effect on repetition priming as measured by word-stem completion (Shimamura et al., 1987). Shimamura et al. (1992) found that patients with dorsolateral prefrontal cortical lesions from middle cerebral artery occlusion were still capable of word-stem completion priming comparable to age-matched controls. Unlike Huntington's patients, patients with Alzheimer's disease are impaired on the word-stem completion test (Salmon et al., 1988). However, it has been reported that Alzheimer's patients can show word repetition priming effects for perceptual identification (Keane et al., 1991) and lexical decision (Ober & Shenaut, 1988). Even though the same word stimulus acts as both prime and primed stimuli during repetition priming, semantic or conceptual priming could conceivably contribute to repetition task performance since word meaning must still presumably be activated. In a task like word-stem completion, in which word generation is involved, such semantic coactivation may play a greater role than in tasks not involving word generation, such as perceptual identification or lexical decision. Thus impaired semantic activation may have contributed to the reduced word-stem completion reported by Salmon et al. (1988) for Alzheimer's patients. In the current study we can conclude that it was highly unlikely that semantic coactivation contributed to response speeding in the repetition priming condition for the HIV+ cognitively impaired volunteers because those volunteers did not evidence semantic priming in the semantic priming paradigm.

Gabrieli et al. (1994) reported a semantic *versus* repetition priming differential in Alzheimer's disease patients, similar to our finding in HIV+ cognitively impaired volunteers. Gabrieli et al.'s (1994) Alzheimer's patients evidenced impaired word-completion priming, but intact picture-completion priming. Gabrieli et al. (1994) suggested that a perceptual–structural system located in extrastriate cortex mediates picture-completion priming, while word-completion priming is mediated by a more anteriorly located semantic system. In their discussion, Gabrieli et al. (1994) note that, in brain imaging studies, Alzheimer's patients have exhibited discontinuity between near-normal levels of metabolism in occipital cortex and greatly reduced metabolism in temporoparietal cortex. They suggest that a posterior brain perceptual–structural system may be relatively spared in Alzheimer's disease. The results of Gabrieli et al. (1994) are consistent with the present study in showing that conceptual and perceptual priming can be functionally dissociated by specific neurological diseases.

An important limitation of the current study is that we only assessed immediate repetition priming where the primed stimulus followed directly after its prime. Repetition priming has also been demonstrated over longer intervals, and it is possible that under such conditions repetition priming deficits may be present in HIV+ cognitively impaired samples. Repetition priming effects can be found following either a hundred intervening trials or delays of up to 2 weeks after presentation of the initial priming material (Feustal et al.,

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1983; Sloman et al., 1988; Tulving et al., 1991). However, such remarkably long-latency effects for word stimuli may be dependent on instructional set and amount of exposure to the test material, possibly implicating mediation in part by explicit or declarative memory (Cave & Squire, 1992; Squire et al., 1987). The word-stem completion task is one of the most frequently used tests in studies of repetition priming for word stimuli. It typically involves separate phases 2 to 15 min apart for exposure to and test of implicitly retained material (Schacter, 1987). As noted above, word-stem completion tasks can potentially confound semantic processes with repetition priming effects.

Finally, it should be pointed out that the HIV related deficit in semantic priming appears to be independent of whether individuals are receiving psychoactive medication. The HIV+ cognitively normal and HIV+ cognitively impaired groups had similar proportions of individuals receiving psychoactive medication (roughly one-half each), yet the HIV+ cognitively normal sample showed an antonym priming effect significantly greater than the HIV+ cognitively impaired group but not significantly different from the largely nonmedicated HIV− controls.

In conclusion, immediate repetition priming is intact while semantic priming is impaired in cognitively impaired HIV+ volunteers. It is suggested that visuostructural encoding mediated by extrastriate cortex is relatively spared in HIV-related brain pathology. Semantic and conceptual association processes that involve subcortical–frontal brain systems appear to be more susceptible to the effects of HIV disease.

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