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Retrograde Amnesia in Dementia: Comparison of HIV-Associated Dementia, Alzheimer's Disease, and Huntington's Disease

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Remote memory was assessed in persons with HIV-associated dementia (HIV-D), probable Alzheimer's disease (AD), and Huntington's disease (HD) and in healthy controls. The clinical groups were similar in overall dementia severity. Each clinical group exhibited impairments on remote memory tests relative to controls; however, temporally graded memory loss with selective preservation of older information was observed in the AD group but not the HD or HIV-D group. Analysis of cued retrieval indicated a preferential cuing benefit for the HIV-D and HD groups relative to the AD group. The similar pattern of remote memory performance demonstrated by the HIV-D and HD groups is a novel finding and suggests a subcortically mediated retrograde amnesia in HIV-D. The temporally graded pattern and the abnormal cued retrieval performance in the AD group are consistent with a consolidation deficit associated with extrahippocampal (cortical) and hippocampal damage.

HIV is known to cause disorders of the central nervous system that may lead to cognitive impairment and, in a minority of cases, dementia (American Academy of Neurology AIDS Task Force, 1991; Grant & Martin, 1994). HIV-associated dementia (HIV-D) occurs in 7% to 14% of patients with AIDS (Grant & Martin, 1994). The clinical neuropsychological profile of persons infected with HIV, whether they exhibit dementia or minor cognitive–motor disorder (American Academy of Neurology AIDS Task Force, 1991), includes impairments in attention–working memory (Grant et al., 1987, 1992; Stout et al., 1995; York, Franks, Henry, & Hamilton, 2001) and psychomotor speed (Grant & Heaton, 1990; Heaton et al., 1995; Martin, Sorensen, Edelstein, & Robertson, 1992), as well as a mild memory deficit characterized by impaired learning (i.e., accrual of information across learning trials) with relatively spared retention of information after a delay and spared recognition memory (Becker et al., 1997; Delis et al., 1995; Peavy et al., 1994; White et al., 1997).

This profile of neuropsychological deficits generally conforms to the "subcortical" dementia pattern (Cummings & Benson, 1988) described for a number of neurodegenerative diseases that primarily affect subcortical brain structures (Cummings, 1990). For example, this profile has been identified in persons with Huntington's disease (HD), a genetically transmitted disorder that results in degeneration of the basal ganglia. The subcortical dementia pattern differs from the pattern of frank amnesia, aphasia, and apraxia associated with Alzheimer's disease (AD), a disorder that primarily results in degeneration of medial temporal lobe structures and association cortices of the temporal, frontal, and parietal lobes (Braak & Braak, 1991).

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The general pattern of cognitive deficits associated with HIV-D is consistent with evidence that the disorder primarily involves subcortical pathology (Navia, Ho, Petito, & Price, 1986). However, the cerebral pathology underlying HIV-D may be quite diffuse (for a review, see McArthur, 1994), and both subcortical and cortical degeneration may contribute to the cognitive deficits associated with the disorder. Comparing the neuropsychological deficits of persons with HIV-D and those of persons with HD or AD may advance our understanding of the manifestation of neuropathology in HIV-D.

One aspect of cognitive functioning in HIV-D that has received little attention is the ability to recollect information from the past. An impairment in memory for information learned before the onset of an injury or disease (i.e., retrograde amnesia [RA]) has been shown to occur after circumscribed damage to medial temporal lobe structures (Scoville & Milner, 1957; Squire, Haist, & Shimamura, 1989); damage to diencephalic structures, as in alcoholic Korsakoff's syndrome (Albert, Butters, & Levin, 1979; Seltzer & Benson, 1974); and diffuse cortical or subcortical damage associated with various neurodegenerative diseases (e.g., Beatty, Salmon, Butters, Heindel, & Granholm, 1988; Green & Hodges, 1996; Wilson, Kaszniak, & Fox, 1981). A number of studies have shown that the RA associated with diencephalic or medial temporal lobe damage can extend years or decades into the past and often follows a temporal gradient in which information from the distant past is less affected than information from the more recent past. The temporal gradient of RA has been attributed to disruption of a long-term consolidation process that is dependent on a medial temporal–diencephalic memory system (Squire, 1987; Zola-Morgan & Squire, 1990).

Although some degree of RA is observed in most neurodegenerative diseases associated with dementia, dissociable patterns of RA have been found among groups that experience primarily cortical versus subcortical dysfunction (Albert, Butters, & Brandt, 1981; Beatty, Salmon, et al., 1988; Freedman, Rivoira, Butters, Sax, & Feldman, 1984; Hodges, Salmon, & Butters, 1993; Leplow et al., 1997). Several studies have shown, for example, that patients with probable AD exhibit a severe and temporally graded RA characterized by better memory for information from remote time periods than for information from recent time periods (Beatty, Salmon, et al., 1988; Hodges et al., 1993; Kopelman, 1989; Sagar, Cohen, Sullivan, Corkin, & Growdon, 1988). In contrast, patients with subcortical dysfunction due to HD (Albert et al., 1981; Beatty, Salmon, et al., 1988), Parkinson's disease (Freedman et al., 1984), or multiple sclerosis (Beatty, Goodkin, Monson, Beatty, & Herstgaard, 1988) have been shown to have a relatively mild RA that affects all time periods equally.

The disparate patterns of RA in AD and HD have been attributed to differences in the memory processes affected by the distinct pathology associated with the two disorders. The severe, temporally graded RA of AD is thought to reflect a consolidation deficit associated with medial temporal lobe dysfunction (Hodges, 1995; Nadel & Moscovitch, 1997) and a superimposed general loss of semantic knowledge arising from the deterioration of association cortices (Chan et al., 1993; Hodges, 1995; Hodges, Salmon, & Butters, 1992; Hodges et al., 1993; Salmon, Butters, & Chan, 1999). The mild, non–temporally graded RA associated with HD, in contrast, may reflect fronto-subcortical dysfunction that produces a general retrieval deficit affecting all memories equally, regardless of the age of the memory trace (Beatty, Salmon, et al., 1988).

Given the distinct patterns of RA seen in neurodegenerative disorders that produce cortical and subcortical dementia syndromes, the purpose of the present study was to replicate and extend findings of RA among AD and HD patients by comparing the remote memory performance of these groups with that of a group of individuals with HIV-D. Because the clinical neuropsychological impairment associated with HIV-D generally conforms to a subcortical dementia pattern, it was hypothesized that the pattern of RA in HIV-D would resemble that of HD. Thus, individuals with HIV-D were expected to exhibit mild RA equally affecting all time periods from their past.

Method

Participants

Seventy people were recruited for this study: 7 with HIV-D, 12 with HD, 11 with probable AD, 17 young healthy control (YHC) participants similar in age and education to the participants with HIV-D and HD, and 23 older healthy control (OHC) participants similar in age and education to the participants with AD.

Participants with HIV-D were recruited from the University of California, San Diego (UCSD) HIV Neurobehavioral Research Center. They had been diagnosed with HIV-D according to the guidelines of the American Academy of Neurology AIDS Task Force (1991), including (a) deficits in at least two areas of cognitive functioning, (b) abnormal motor function, and (c) change in social, occupational, or emotional functioning. In addition, it was established that these abnormalities or changes were not related to an etiology other than HIV infection.

Participants with HD were recruited from the UCSD Huntington's Disease Clinical Research Program, where they had been diagnosed with the disease on the basis of (a) clinical symptoms of choreoathetosis, (b) positive family history of HD, and (c) dementia, defined according to the criteria of the revised third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM–III–R*; American Psychiatric Association, 1987). Participants with probable AD were recruited from the UCSD Alzheimer's Disease Research Center, where they had been diagnosed in accordance with *DSM–III–R* criteria for primary degenerative dementia (American Psychiatric Association, 1987) and in accordance with the criteria for probable AD developed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann et al., 1984).

The YHC and OHC participants were recruited through newspaper and other advertisements in the San Diego area community. Participants from all groups with a significant history of alcohol abuse, drug abuse, or neurological or psychiatric diagnosis unrelated to the primary grouping diagnosis were excluded from the study.

Demographic characteristics and Mattis Dementia Rating Scale (DRS; Mattis, 1976) scores for the five participant groups are shown in Table 1. The HIV-D, HD, and YHC groups were similar in age and education, as were the AD and OHC groups ($p > .10$ in all instances). All participants in the three groups with dementia were in the mildly to moderately impaired range (i.e., DRS score above 110), and the groups did not differ significantly in average DRS scores. As expected, the members of each group with dementia scored significantly lower on the DRS than their respective control group ($p < .05$ in all instances).

Materials

The Remote Memory Battery, originally developed by Albert et al. (1981) and updated by Beatty, Salmon, et al. (1988), was updated again to

Table 1
Means and Standard Deviations: Demographic and Dementia Information

Group	*n*	Age (years)		Education (years)		Sex ratio (male/female)	DRS score	
		M	*SD*	*M*	*SD*		*M*	*SD*
HIV-D	7	38.0	8.7	13.8	1.6	7/0	124.6	6.4
HD	12	46.8	13.2	13.2	1.8	6/6	129.6	7.5
YHC	17	40.0	7.5	14.1	1.6	10/7	142.4	0.9
AD	11	74.7	6.0	14.8	3.2	7/4	122.5	7.2
OHC	23	71.4	7.0	15.9	2.8	12/11	141.1	2.9

Note. DRS = Mattis Dementia Rating Scale; HIV-D = HIV-associated dementia; HD = Huntington's disease; YHC = young healthy control; AD = Alzheimer's disease; OHC = older healthy control.

include material through the early 1990s. The battery contained two sections: the Famous Faces Test and the Public Events Questionnaire. The Famous Faces Test comprised a total of 85 photographs of famous people, 15 from each decade from the 1940s through the 1980s and 10 from the early 1990s. The Public Events Questionnaire comprised a total of 85 questions regarding widely publicized events, again 15 from each decade from the 1940s through the 1980s and 10 from the early 1990s. The famous faces and public events used in the late 1980s/early 1990s update were chosen from a larger pool of items previously administered to a separate sample of healthy young and older participants. Items that were answered correctly by approximately 70% to 80% of the respondents were chosen for inclusion in the update to avoid floor and ceiling effects and to establish a baseline similar to that for previous decades.

Procedure

The Remote Memory Battery was administered to each participant individually by a trained psychometrist. Testing was conducted in a quiet, well-lit room at the participant's home or at one of the participating research centers. Participants younger than 60 years of age were not administered items from the 1940s and 1950s on the basis of the assumption that they had not been exposed to the information or had encoded it at a young age. Thus, only the AD and OHC groups were tested for remote memory from those two decades.

The photographs from the Famous Faces Test were shown one at a time in a fixed order (i.e., sequentially rotating through an item from the 1940s, 1950s, 1960s, 1970s, 1980s, and 1990s). Each participant was asked to name the person depicted (spontaneous free recall). If the participant was unable to correctly name the person, a standard set of semantic cues was provided (e.g., Ross Perot: billionaire businessman, ran independently for president, from Texas). If the participant was still unable to correctly name the person, a phonemic cue (i.e., the famous person's initials) was provided. The items from the Public Events Questionnaire were administered in the same manner as those of the Famous Faces Test, with semantic and then phonemic cues provided if free recall of the correct answer was unsuccessful (e.g., for Panama ["To what country did the U.S. cede control of an inter-oceanic canal?"], the cues were as follows: central American, Jimmy Carter, Pacific Ocean, and begins with "P").

In the case of both components of the Remote Memory Battery, total numbers of correct responses for items within each decade in the free recall condition, after semantic cues, and after phonemic cues were recorded. The order of administration of the Famous Faces Test and Public Events Questionnaire was counterbalanced within each participant group.

Scoring and Statistical Analyses

First, because patterns of performance did not differ overall for the Famous Faces Test and the Public Events Questionnaire, the number of correct responses achieved on the two tests was combined to create a total score for each decade. The number of correct responses for each decade was then divided by the total number of possible responses for that decade, and the result multiplied by 100, to obtain a percentage correct score.

Second, because test items are referenced to calendar years but participant groups were from different generations, scores on the Remote Memory Battery were collapsed across "life epochs" to allow a direct comparison of temporal patterns of performance among the older and younger patient and control groups. This approach has been shown to be sensitive to temporal gradients (Brown, 2002). For the older groups, numbers of correct responses for the 1940s and 1950s were summed to form the early life epoch, numbers of correct responses for the 1960s and 1970s formed the middle life epoch, and numbers of correct responses for the 1980s and 1990s formed the recent life epoch. For the younger groups, items from the 1960s composed the early life epoch, items from the 1970s represented the middle life epoch, and items from the 1980s and 1990s were summed to form the recent life epoch. The score for each life epoch was then divided by the total number of possible responses for that epoch, and the result multiplied by 100, to obtain a percentage correct score.

To examine the integrity of remote memory across epochs while ameliorating floor effects that might obscure subtle differences (Beatty, Salmon, et al., 1988), we also divided the number of correct responses within each life epoch by the total number of *correct* responses across all epochs. This proportion score provided a measure of the distribution of correct responses across the life epochs. The composition of the life epochs was the same as that just described except that when more than one decade contributed to a life epoch, the proportions were averaged (e.g., for the older groups, the early life epoch was the average of the proportion correct scores for the 1940s and 1950s). Proportions from the younger groups (HD, HIV-D, and YHC) were multiplied by a scaling factor (120/180) to allow direct comparisons across groups and across time periods, because the older groups (AD and OHC) were administered more items (180) than the younger groups (120) and because the older and younger groups were administered different numbers of items in the life epochs (e.g., 30 items in the early life epoch for younger participants and 60 for older participants). As a result, we label the proportion scores "adjusted proportions" because they are not true proportion scores. As a means of stabilizing variance, the adjusted proportion scores underwent a square root transformation before the data analysis.

Finally, the effect of cuing was examined by calculating percentage correct scores achieved spontaneously, after semantic cues, and after phonemic cues. These scores were calculated after collapsing across decades because there was no significant interaction between cuing and decade for any group.

Percentage correct scores, adjusted proportion scores, and cuing scores were examined with analyses of variance (ANOVAs) in which group was the between-subjects factor and life epoch (or decade) was the within-subject factor. Although corrections for nonsphericity (Huynh–Feldt epsi-

lon) were applied when the assumption of sphericity was not met, uncorrected parameters are reported here for simplicity, because the pattern of results did not change when corrections were applied. Least significant difference tests focusing on marginal means or paired samples *t* tests (when comparing across decades within a single group) were used for comparisons in post hoc analyses.

Results

Percentage Correct

The percentages of correct responses (spontaneous plus cued) achieved by each group are presented by decade in Table 2. ANOVAs focusing on scores from the younger groups (HIV-D, HD, and YHC) revealed significant main effects of group, $F(2, 33) = 12.80$, $p < .001$, and decade, $F(3, 99) = 9.70$, $p < .001$, but no significant Group × Decade interaction, $F(6, 99) = 0.82$, $p > .50$. Post hoc comparisons showed that the YHC group performed better overall than either of the two younger dementia groups ($p < .01$ in all instances) and that the HD and HIV-D groups did not differ from each other ($p > .50$). In addition, performance was better for recent decades than for distant decades (e.g., 1960s vs. 1990s, $p < .01$; 1970s vs. 1990s, $p < .01$; 1960s vs. 1970s, $p > .30$; and 1980s vs. 1990s, $p > .10$) across all groups.

ANOVAs focusing on percentage correct scores from the older groups (AD and OHC) revealed significant main effects of group, $F(1, 32) = 68.62$, $p < .001$, and decade, $F(5, 160) = 6.97$, $p < .001$, and a significant Group × Decade interaction, $F(5, 160) = 4.14$, $p < .01$. Post hoc paired samples *t* tests indicated that, in general, the OHC group performed similarly for most decades, although performance was slightly poorer for the 1960s than for other decades ($p < .04$ in all instances) and slightly better for the 1990s ($p < .09$ in all instances). In contrast, the AD group performed worse than the OHC group overall ($p < .001$) and performed worse for recent decades than for more remote decades (e.g., 1940s vs. 1980s, $p < .03$; 1950s vs. 1990s, $p < .04$).

To allow a direct comparison of the temporal patterns of performance across older and younger groups, the percentages of correct responses (spontaneous plus cued) achieved by each group are presented by life epoch in Figure 1. ANOVAs indicated that there were main effects of group, $F(4, 65) = 25.87$, $p < .001$, and life epoch, $F(2, 130) = 9.61$, $p < .001$, and a significant interaction between group and life epoch, $F(8, 130) = 4.55$, $p < .001$. Post hoc comparisons indicated that the AD group performed worse than all other groups ($p < .001$ in all instances). The HD and HIV-D groups performed similarly to each other ($p = .70$) but worse than other groups ($p < .005$ in all instances except HIV-D vs. OHC, where $p = .07$); the YHC group performed best ($p < .04$ in all instances). Overall, there was slightly better recall in the recent life epoch (1980s and 1990s) than in the middle and early epochs ($p < .04$ in all instances). The interaction between group and life epoch was due to the OHC and YHC groups' better performance in the early life epoch ($p < .03$ in all instances), whereas in the middle and recent life epochs the YHC performed better than the OHC group ($p < .07$ for middle and $p < .01$ for recent). The OHC group was not significantly different from the HIV-D group ($p > .10$ in all instances).

Table 2
Percentage of Correct Scores by Decade on the Remote Memory Battery (Combined Spontaneous and Cued Recall)

Group	1940s	1950s	1960s	1970s	1980s	1990s
YHC						
M			82.9	81.2	89.8	92.1
SD			12.7	12.4	8.4	10.2
HIV-D						
M			54.8	58.1	61.9	69.3
SD			23.2	21.9	24.1	23.4
HD						
M			52.8	55.6	59.4	59.2
SD			23.3	21.1	26.3	21.3
OHC						
M	73.5	75.7	67.2	70.6	72.8	78.9
SD	16.4	11.9	15.9	17.1	14.2	16.9
AD						
M	29.1	29.4	19.1	20.3	19.1	19.1
SD	21.5	23.3	23.2	23.4	18.4	24.4

Note. YHC = young healthy control; HIV-D = HIV-associated dementia; HD = Huntington's disease; OHC = older healthy control; AD = Alzheimer's disease.

Adjusted Proportion Correct

Adjusted proportions of correct responses from each life epoch (spontaneous plus cued recall) relative to all correct responses are shown in Figure 2. This analysis revealed a significant interaction between group and life epoch, $F(8, 130) = 8.47$, $p < .001$. Post hoc analyses indicated that the performance of the AD group explained the interaction entirely. Whereas the proportion of correct responses for the HIV-D, HD, YHC, and OHC groups was evenly distributed across the three life epochs, the AD group produced a higher proportion of correct responses from the early life epoch than the other groups ($p < .001$ in all instances) but produced lower proportions of correct responses from the middle ($p < .03$ in all instances) and recent ($p < .001$ in all instances) life epochs. Thus, only patients with AD exhibited a temporal gradient in performance, one that consisted of a disproportionate amount of information recalled from the early life epoch.

Effect of Cuing on Retrieval

The percentages of correct responses produced by each group spontaneously, after semantic cues, and after phonemic cues are shown in Figure 3. Percentage correct scores were collapsed across decades, because ANOVAs revealed no interaction between group and decade for either type of cue ($p > .15$ in all instances). Analyses revealed a main effect for group, $F(4, 65) = 5.26$, $p < .01$, but no main effect for cuing type (semantic vs. phonemic), $F(1, 65) = 0.53$, $p = .50$, and no interaction between group and cuing type, $F(4, 65) = 1.67$, $p > .10$. Post hoc comparisons involving the main effect of group indicated that the AD group benefited least from cuing overall ($p < .05$ in all instances except for the HIV-D group comparison, where $p = .085$).

Because cuing occurred only in the case of items for which responses were incorrect after spontaneous recall, the relative benefit of cuing may also be examined by calculating the number of correct responses with cuing as a percentage of items that were available for cuing (i.e., number correct following cue/[total number of items − number of spontaneous correct responses] × 100). According to these cuing benefit scores, the YHC group re-

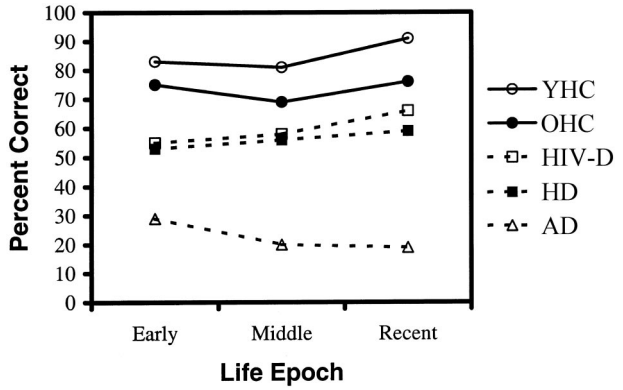

Figure 1. Percentages of correct responses (combined spontaneous and cued recall) for each life epoch on the Remote Memory Battery (combining the famous faces and public events tests). YHC = young healthy control; OHC = older healthy control; HIV-D = HIV-associated dementia; HD = Huntington's disease; AD = Alzheimer's disease.

called 56.3% of cued items, the OHC group recalled 44.8%, the HD group recalled 36.6%, the HIV-D group recalled 32.9%, and the AD group recalled only 13.2%, $F(4, 65) = 12.71$, $p < .001$. Post hoc comparisons confirmed that the YHC group benefited significantly more from cuing than did all other groups ($p < .05$) and that the OHC, HD, and HIV-D groups performed similarly ($p > .09$ in all instances). As before, the AD group benefited significantly less from cuing than all other groups ($p < .05$ in all instances).

Discussion

The results of the present study demonstrate that individuals with HIV-D have a mild RA that is similar in severity to that of

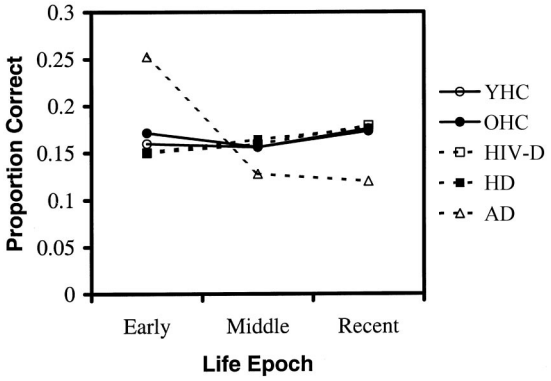

Figure 2. Adjusted proportion of correct responses (combined spontaneous and cued recall) for each life epoch on the Remote Memory Battery (combining the famous faces and public events tests). Adjusted proportions were calculated as number correct for each epoch divided by number correct across all epochs. These proportions reflect a correction for the different numbers of items in life epochs across groups (see text). YHC = young healthy control; OHC = older healthy control; HIV-D = HIV-associated dementia; HD = Huntington's disease; AD = Alzheimer's disease.

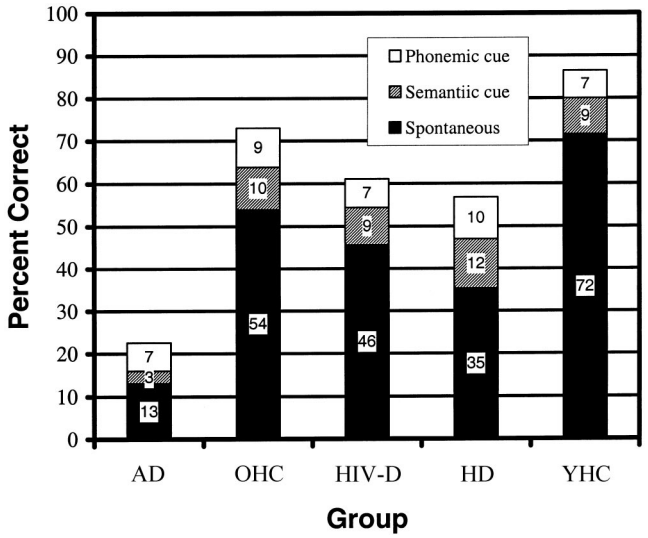

Figure 3. Percentages of correct spontaneous responses and correct responses after semantic and phonemic cues, collapsed across life epochs. Stacked bars represent the additive effects of semantic and phonemic cues, with actual percentages of correct responses indicated in respective sections of the column. AD = Alzheimer's disease; OHC = older healthy control; HIV-D = HIV-associated dementia; HD = Huntington's disease; YHC = young healthy control.

HD and less severe than that of AD. Despite similar levels of dementia (as measured by the Mattis DRS; Mattis, 1976), individuals with HIV-D and HD were able to correctly answer approximately 60% of the items from the Remote Memory Battery. Individuals with AD, however, could answer only about 25% of the items.

Furthermore, the temporal pattern of mild RA in individuals with HIV-D was similar to that in individuals with HD in that the two groups were equally impaired in recall of information from each of the previous decades and from each of the life epochs. This temporal pattern was distinct from that of persons with AD, which was characterized by more severe RA for information from the more recent past than for information from the distant past. These differences in the temporal gradient of remote memory loss among individuals with HD and AD replicate previous findings (Beatty, Salmon, et al., 1988) and extend them to show that a similar discrepancy exists between persons with AD and those with HIV-D.

The disparate patterns of RA exhibited by individuals with HIV-D and HD, on the one hand, and individuals with AD, on the other hand, suggest that the remote memory deficits of these groups may be mediated by different neuropsychological processes. The relatively mild, non–temporally graded RA associated with HIV-D and HD may be indicative of a general retrieval deficit that equally affects recall of information from any past time period. Such a retrieval deficit has been postulated as a contributory factor in the anterograde memory deficit observed with HIV-D or HD (Becker et al., 1997; Butters, Wolfe, Martone, Granholm, & Cermak, 1985; White et al., 1997; for a review, see Paulsen & Robinson, 2001) and has been attributed to the frontostriatal dysfunction that characterizes these disorders.

In contrast, the severe and temporally graded RA associated with AD may reflect the interruption of a long-term consolidation process that is dependent on medial temporal lobe structures such as the hippocampus. According to this view, the medial temporal lobe damage that occurs in AD interrupts a hippocampal-dependent process by which memories become gradually instantiated in a relatively permanent form in cortical regions outside of the hippocampus (e.g., temporal, frontal, or parietal association cortices). When hippocampal damage occurs, there is a relative preservation of older, more cortically instantiated memories (but see Nadel & Moscovitch, 1997, for an explanation of the temporal gradient in RA mediated by hippocampal lesion size). When there is little hippocampal damage but significant cortical damage, as is thought to be the case with semantic dementia, the reverse pattern has been observed (e.g., newer, hippocampally mediated memories are preserved and older, cortically mediated memories are lost; Nestor, Graham, Bozeat, Simons, & Hodges, 2001).

The particularly severe RA exhibited by individuals with AD, even for information from the most remote time periods, may result from a combination of the episodic and semantic memory deficits they experience (for a review, see Salmon, 2000). Some investigators have conceptualized the long-term consolidation of remote memories as a shift from a hippocampally mediated episodic form to a cortically mediated semantic form (e.g., Cermak, 1984; Hodges, 1995; Kapur, 1999; Nadel & Moscovitch, 1997; Schmidtke & Vollmer, 1997; but see Tulving, 2001, for an alternate view that semantic memory does not depend on a shift from episodic memory). Persons with a relatively circumscribed episodic memory impairment associated with alcoholic Korsakoff's syndrome (Albert et al., 1979) or restricted medial temporal lobe damage (Haist, Shimamura, & Squire, 1992) often exhibit temporally graded RA with normal or near normal recall of information from the distant past (reflecting intact semantic memory). This temporal gradient is also evident in the RA associated with AD, presumably owing to medial temporal lobe damage. However, the temporal gradient is superimposed on a general semantic memory deficit (for a review, see Salmon, 2000), arising from damage to cortical association areas, that severely affects the ability of individuals with AD to recall information from all time periods. Further research is certainly warranted in this area, however, given that the relationship between retrograde amnesia in AD and other measures of semantic memory has been questioned (Green & Hodges, 1996).

The severity as well as the temporal pattern of RA exhibited by individuals with HIV-D is similar to that of individuals with HD and generally consistent with a deficit in retrieval arising from frontostriatal dysfunction. When provided with retrieval assistance in the form of semantic and phonemic cues, both the HIV-D and HD groups demonstrated greater benefit than the AD group. The AD group recalled only 13.2% of available items with cued retrieval, whereas the HD and HIV-D groups correctly recalled 36.6% and 32.9%, respectively, of the available items. Thus, the consolidation deficit exhibited by individuals with AD is reflected not only in the temporally graded nature of RA, as discussed earlier, but also in the abnormally low benefit they glean from cued retrieval (Hodges et al., 1993). This failure to benefit from retrieval cues is consistent with a loss of remote memory rather than an inability to effectively retrieve such memories.

Individuals with HD and HIV-D, in contrast, are able to benefit from retrieval cues during remote memory testing better than are individuals with AD, although a normal or greater than normal benefit might be expected if RA were solely a function of impaired retrieval processes. The similarity between HIV-D and HD in benefits from retrieval cues suggests that the remote memory impairment involved is due in part to a retrieval deficit and, furthermore, that remote memory impairment in HIV-D may be largely mediated by subcortical pathology (Navia et al., 1986), as appears to be the case in HD (Becker et al., 1997; Peavy et al., 1994; White et al., 1997). However, the inability of the HIV-D and HD groups to benefit from cuing to the same degree as the YHC group suggests that another factor, such as loss of remote memory, may also contribute to the RA pattern. Loss of remote memory in HD and HIV-D might reflect the diffuse cortical changes that occur in conjunction with subcortical gray and white matter pathology (de la Monte, Vonsattel, & Richardson, 1988; Jackson et al., 1995; Jernigan, Salmon, Butters, & Hesselink, 1991; McArthur, 1994; Navia et al., 1986; Rosas et al., 2002).

Several limitations of the present study should be noted. First, the participants with HIV-D and HD were younger than the participants with AD, and this may have contributed to the differences observed in the temporal gradient of RA. Piolino and colleagues (Piolino, Desgranges, Benali, & Eustache, 2002) have shown that age has a detrimental effect on remote memory that is greater for episodic than for semantic remote autobiographical memory, and this could have affected the nature and severity of the temporal gradient exhibited across the patient groups.

Furthermore, the time line of life experiences was compressed in the HIV-D and HD groups relative to the AD group, so they had less opportunity to exhibit a gradual temporal gradient in their remote memory loss. This is not to say, however, that temporally graded RA cannot be observed in middle-aged patients similar to those in the present HIV-D and HD groups, given that the gradient is often seen in the RA of middle-aged patients with Korsakoff's syndrome (Albert et al., 1979) or circumscribed medial temporal lobe damage (Squire et al., 1989). Thus, although the relative preservation of old memories in the present AD group was seen in distant time periods not measured in the younger groups (1940s and 1950s), other studies have revealed temporal gradients in newer memories (e.g., the past 30 years; Albert et al., 1979; Kopelman, Stanhope, & Kingsley, 1999), suggesting that age differences between groups do not explain differences in temporal gradients. It should also be noted that the temporally graded RA uniquely exhibited by patients with AD in the present study was apparent in relation to age-matched neurologically healthy controls. This indicates that the steepness of the temporal gradient in the RA of AD patients is above and beyond that expected from normal aging.

Second, interpretation of the temporal gradient of RA in individuals with AD is somewhat clouded by the insidious nature of the anterograde memory deficit associated with the disease. It may be the case that information from the most recent decade (or decades) before the diagnosis of AD is not learned as well as more remote information because of a "preclinical" anterograde memory impairment that often occurs before development of the full dementia syndrome (Albert, Moss, Tanzi, & Jones, 2001; Lange et al., 2003). Although this anterograde memory deficit may account, in part, for the particularly severe memory loss for information

from the 1980s and 1990s (or from the late life epoch), it is less likely to explain the discrepancy between the AD-associated RA for information from the 1940s and 1950s (early life epoch) and that for information from the 1960s and 1970s (middle life epoch).

Finally, the results of the present study were based on relatively small samples of participants with HIV-D, HD, and AD and should be replicated with larger samples. It should be noted, however, that despite our small sample sizes, significant deficits in RA were detected among each of the dementia groups. Furthermore, we were able to discern significant differences in the temporal patterns of RA exhibited by the AD group and the HIV-D and HD groups.

In summary, individuals with HIV-D exhibited a mild RA similar in severity and temporal pattern to that observed among individuals with HD. The non–temporally graded nature of RA across decades or life epochs and the benefit from cued retrieval are consistent with a frontostriatally mediated general retrieval deficit that equally affects the ability to recall information from any predisease time period. Additional research examining the neuropsychological underpinnings of RA in HIV-D is clearly warranted.

References

Albert, M. S., Butters, N., & Brandt, J. (1981). Patterns of remote memory in amnesic and demented patients. *Archives of Neurology, 38,* 495–500.

Albert, M. S., Butters, N., & Levin, J. (1979). Temporal gradients in the retrograde amnesia of patients with alcoholic Korsakoff's disease. *Archives of Neurology, 36,* 211–216.

Albert, M. S., Moss, M. B., Tanzi, R., & Jones, K. (2001). Preclinical prediction of AD using neuropsychological tests. *Journal of the International Neuropsychological Society, 7,* 631–639.

American Academy of Neurology AIDS Task Force. (1991). Nomenclature and research case definitions for neurologic manifestations of human immunodeficiency virus-type 1 (HIV-1) infection. *Neurology, 41,* 778–785.

American Psychiatric Association. (1987). *Diagnostic and statistical manual of mental disorders* (3rd ed., rev.). Washington, DC: Author.

Beatty, W. W., Goodkin, D. E., Monson, N., Beatty, P. A., & Herstgaard, D. (1988). Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis. *Archives of Neurology, 45,* 611–619.

Beatty, W. W., Salmon, D. P., Butters, N., Heindel, W. C., & Granholm, E. L. (1988). Retrograde amnesia in patients with Alzheimer's disease or Huntington's disease. *Neurobiology of Aging, 9,* 181–186.

Becker, J. T., Caldararo, R., Lopez, O. L., Dew, M. A., Dorst, S. K., & Banks, G. (1997). Qualitative features of the memory deficit associated with HIV infection and AIDS: Cross-validation of a discriminant function classification scheme. *Journal of Clinical and Experimental Neuropsychology, 17,* 134–142.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82,* 239–259.

Brown, A. S. (2002). Consolidation theory and retrograde amnesia in humans. *Psychonomic Bulletin & Review, 9,* 403–425.

Butters, N., Wolfe, J., Martone, M., Granholm, E., & Cermak, L. S. (1985). Memory disorders associated with Huntington's disease: Verbal recall, verbal recognition and procedural memory. *Neuropsychologia, 23,* 729–743.

Cermak, L. S. (1984). The episodic/semantic distinction in amnesia. In L. R. Squire & N. Butters (Eds.), *The neuropsychology of memory* (pp. 52–62). New York: Guilford Press.

Chan, A. S., Butters, N., Paulsen, J. S., Salmon, D. P., Swenson, M. R., & Maloney, L. T. (1993). An assessment of the semantic network in patients with Alzheimer's disease. *Journal of Cognitive Neuroscience, 5,* 254–261.

Cummings, J. L. (1990). *Subcortical dementia*. London: Oxford University Press.

Cummings, J. L., & Benson, D. F. (1988). Psychological dysfunction accompanying subcortical dementias. *Annual Review of Medicine, 39,* 53–61.

de la Monte, S. M., Vonsattel, J. P., & Richardson, E. P. (1988). Morphometric demonstration of atrophic changes in the cerebral cortex, white matter, and neostriatum in Huntington's disease. *Journal of Neuropathology and Experimental Neurology, 47,* 516–525.

Delis, D. C., Peavy, G., Heaton, R., Butters, N., Salmon, D. P., Taylor, M., et al. (1995). Do patients with HIV-associated minor cognitive/motor disorder exhibit a "subcortical" memory profile? Evidence using the California Verbal Learning Test. *Assessment, 2,* 151–165.

Freedman, M., Rivoira, P., Butters, N., Sax, D. S., & Feldman, R. G. (1984). Retrograde amnesia in Parkinson's disease. *Canadian Journal of Neurological Sciences, 11,* 297–301.

Grant, I., Atkinson, J. H., Hesselink, J. R., Kennedy, C. J., Richman, D. D., Spector, S. A., & McCutchan, J. A. (1987). Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections: Studies with neuropsychologic testing and magnetic resonance imaging. *Annals of Internal Medicine, 107,* 828–836.

Grant, I., Caun, K., Kingsley, D. P. E., Winter, J., Trimble, M. R., & Pinching, A. J. (1992). Neuropsychological and NMR abnormalities in HIV infection: The St. Mary's-Queen Square study. *Neuropsychiatry, Neuropsychology, and Behavioral Neurology, 5,* 185–193.

Grant, I., & Heaton, R. K. (1990). Human immunodeficiency virus-type 1 (HIV-1) and the brain. *Journal of Consulting and Clinical Psychology, 58,* 22–30.

Grant, I., & Martin, A. (1994). Introduction: Neurocognitive disorders associated with HIV-1 infection. In I. Grant & A. Martin (Eds.), *Neuropsychology of HIV infection* (pp. 3–19). New York: Oxford University Press.

Green, J. D. W., & Hodges, J. R. (1996). Identification of famous faces and famous names in early Alzheimer's disease: Relationship to anterograde episodic and general semantic memory. *Brain, 119,* 111–128.

Haist, F., Shimamura, A. P., & Squire, L. R. (1992). On the relationship between recall and recognition memory. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 18,* 691–702.

Heaton, R. K., Grant, I., Butters, N., White, D. A., Kirson, D., Atkinson, J. H., et al. (1995). The HNRC 500—Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society, 1,* 231–251.

Hodges, J. R. (1995). Retrograde amnesia. In A. D. Baddeley, B. A. Wilson, & F. N. Watts (Eds.), *Handbook of memory disorders* (pp. 81–107). New York: Wiley.

Hodges, J. R., Salmon, D. P., & Butters, N. (1992). Semantic memory impairment in Alzheimer's disease: Failure of access or degraded knowledge? *Neuropsychologia, 30,* 301–314.

Hodges, J. R., Salmon, D. P., & Butters, N. (1993). Recognition and naming of famous faces in Alzheimer's disease: A cognitive analysis. *Neuropsychologia, 31,* 775–788.

Jackson, M., Gentleman, S., Lennox, G., Ward, L., Gray, T., Randall, K., et al. (1995). The cortical neuritic pathology of Huntington's disease. *Neuropathology and Applied Neurobiology, 21,* 18–26.

Jernigan, T. L., Salmon, D. P., Butters, N., & Hesselink, J. R. (1991). Cerebral structure on MRI, Part II: Specific changes in Alzheimer's and Huntington's diseases. *Biological Psychiatry, 29,* 68–81.

Kapur, N. (1999). Syndromes of retrograde amnesia: A conceptual and empirical synthesis. *Psychological Review, 125,* 800–825.

Kopelman, M. D. (1989). Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. *Neuropsychologia, 27,* 437–460.

Kopelman, M. D., Stanhope, N., & Kingsley, D. (1999). Retrograde amnesia in patients with diencephalic, temporal lobe, or frontal lesions. *Neuropsychologia, 37,* 939–958.

Lange, K. L., Bondi, M. W., Salmon, D. P., Galasko, D., Delis, D. C., Thomas, R. G., & Thal, L. J. (2003). Decline in verbal memory during preclinical Alzheimer's disease: Examination of the effect of APOE genotype. *Journal of the International Neuropsychological Society, 8,* 943–955.

Leplow, B., Dierks, C., Herrmann, P., Pieper, N., Annecke, R., & Ulm, G. (1997). Remote memory in Parkinson's disease and senile dementia. *Neuropsychologia, 35,* 547–557.

Martin, E. M., Sorensen, D. J., Edelstein, H. E., & Robertson, L. C. (1992). Decision-making speed in HIV-1 infection: A preliminary report. *AIDS, 6,* 109–113.

Mattis, S. (1976). Mental status examination for organic mental syndrome in the elderly patient. In L. Bellack & T. B. Karasu (Eds.), *Geriatric psychiatry* (pp. 77–121). New York: Grune & Stratton.

McArthur, J. (1994). Neurological and neuropathological manifestations of HIV infection. In I. Grant & A. Martin (Eds.), *Neuropsychology of HIV infection* (pp. 56–107). New York: Oxford University Press.

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984). Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, 34,* 939–944.

Nadel, L., & Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. *Current Opinions in Neurobiology, 7,* 217–227.

Navia, B. A., Ho, E., Petito, C. K., & Price, R. W. (1986). The AIDS dementia complex: II. Neuropathology. *Annals of Neurology, 19,* 525–535.

Nestor, P. J., Graham, K. S., Bozeat, S., Simons, J. S., & Hodges, J. R. (2001). Memory consolidation and the hippocampus: Further evidence from studies of autobiographical memory in semantic dementia and frontal variant frontotemporal dementia. *Neuropsychologia, 40,* 633–654.

Paulsen, J. S., & Robinson, R. G. (2001). Huntington's disease. In J. R. Hodges (Ed.), *Early-onset dementia: A multidisciplinary approach* (pp. 338–366). New York: Oxford University Press.

Peavy, G., Jacobs, D., Salmon, D. P., Butters, N., Delis, D. C., Taylor, M., et al. (1994). Verbal memory performance of patients with human immunodeficiency virus infection: Evidence of subcortical dysfunction. *Journal of Clinical and Experimental Neuropsychology, 16,* 508–523.

Piolino, P., Desgranges, B., Benali, K., & Eustache, F. (2002). Episodic and semantic remote autobiographical memory in ageing. *Memory, 10,* 239–257.

Rosas, H. D., Liu, A. K., Hersch, S., Glessner, M., Ferrante, R. J., Salat, D. H., et al. (2002). Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology, 58,* 695–701.

Sagar, H. J., Cohen, J. J., Sullivan, E. V., Corkin, S., & Growdon, J. H. (1988). Remote memory function in Alzheimer's disease and Parkinson's disease. *Brain, 111,* 185–206.

Salmon, D. P. (2000). Disorders of memory in Alzheimer's disease. In L. S. Cermak (Ed.), *Handbook of neuropsychology: Vol. 2. Memory and its disorders* (2nd ed., pp. 155–195). Amsterdam: Elsevier.

Salmon, D. P., Butters, N., & Chan, A. S. (1999). The deterioration of semantic memory in Alzheimer's disease. *Canadian Journal of Experimental Psychology, 53,* 108–116.

Schmidtke, K., & Vollmer, H. (1997). Retrograde amnesia: A study of its relation to anterograde amnesia and semantic memory deficits. *Neuropsychologia, 35,* 505–518.

Scoville, W. B., & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry, 20,* 11–21.

Seltzer, B., & Benson, D. F. (1974). The temporal gradient of retrograde amnesia in Korsakoff's disease. *Neurology, 24,* 527–530.

Squire, L. R. (1987). *Memory and brain.* New York: Oxford University Press.

Squire, L. R., Haist, F., & Shimamura, A. P. (1989). The neurology of memory: Quantitative assessment of retrograde amnesia in two groups of amnesic patients. *Journal of Neuroscience, 9,* 828–839.

Stout, J. C., Salmon, D. P., Butters, N., Taylor, M., Peavy, G., Heindel, W. C., et al. (1995). Decline in working memory associated with HIV infection. *Psychological Medicine, 25,* 1221–1232.

Tulving, E. (2001). Episodic memory and common sense: How far apart? In A. Baddeley, J. P. Aggleton, & M. A. Conway (Eds.), *Episodic memory: New directions in research* (pp. 269–287). New York: Oxford University Press.

White, D. A., Taylor, M. J., Butters, N., Mack, C., Salmon, D. P., Peavy, G., et al. (1997). Memory for verbal information in individuals with HIV-associated dementia complex. *Journal of Clinical and Experimental Neuropsychology, 19,* 357–366.

Wilson, R. S., Kaszniak, A. W., & Fox, J. H. (1981). Remote memory in senile dementia. *Cortex, 17,* 41–48.

York, M. K., Franks, J. J., Henry, R. R., & Hamilton, W. J. (2001). Verbal working memory storage and processing deficits in HIV-1 asymptomatic and symptomatic individuals. *Psychological Medicine, 31,* 1279–1291.

Zola-Morgan, S., & Squire, L. R. (1990, October 12). The primate hippocampal formation: Evidence for a time-limited role in memory storage. *Science, 250,* 288–290.

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