Longitudinal Profiles of Semantic Impairment for Living and Nonliving Concepts in Dementia of Alzheimer's Type

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Abstract

■ Two types of theoretical account have been proposed to explain the phenomenon of category-specific impairment in tests of semantic memory: One stresses the importance of different cortical regions to the representation of living and nonliving categories, while the other emphasize the importance of statistical relationships among features of concepts belonging to these two broad semantic domains. Theories of the latter kind predict that the direction of a domain advantage will be determined in large part by the overall damage to the semantic system, and that the profiles of patients with progressive impairments of semantic memory are likely to include a point at which an advantage for one domain changes to an advantage for the other. The present series of three studies employed semantic test data from two separate cohorts of patients with probable dementia of Alzheimer's type (DAT) to look for evidence of such a crossover. In the first study, longitudinal test scores from a cohort of 58 patients were examined to confirm the presence of progressive semantic deterioration in this group. In the second study, Kaplan–Meier survival curves based on serial naming responses and plotted separately for items belonging to living and nonliving domains indicated that the representations of living concepts (as measured by naming) deteriorated at a consistently and significantly faster rate than those of nonliving concepts. A third study, carried out to look in detail at the performance of mildly affected patients, employed an additional cross-sectional cohort of 20 patients with mild DAT and utilized a graded naming assessment. This study also revealed no evidence for a crossover in the advantage of one domain over the other as a function of disease severity. Taken together with the model of anatomical progression in DAT based on the work of Braak and Braak (1991), these findings are interpreted as evidence for the importance of regional cerebral anatomy to the genesis of semantic domain effects in DAT. ■

INTRODUCTION

Semantic memory is the component of long-term, declarative memory that is concerned with the representation of world knowledge (Tulving, 1972, 1983). This critically important component of brain function encompasses factual knowledge, the ability to identify and interact appropriately with the objects of perception, and the understanding of words and their meanings. Along with phonology and syntax, therefore, semantic memory represents one of the cognitive functions critical to the production and comprehension of language.

Progressive impairment of semantic memory frequently occurs, alongside more widespread cognitive decline, in patients with dementia of Alzheimer's type (DAT) (Hodges & Patterson, 1995; Hodges, Salmon, & Butters, 1992; Chertkow & Bub, 1990; Martin & Fedio, 1983). Affected patients are clinically anomic and perform poorly on tests such as naming from pictures or verbal descriptions, word-to-picture matching, category fluency (generating exemplars from a given category), and the Pyramids and Palm Trees test—a test of associative knowledge (Howard & Patterson, 1992). Deficits on these tests tend to be consistent across sessions and across modalities (Hodges et al., 1992; Chertkow & Bub, 1990), and naming errors consist predominantly of semantic category coordinates (e.g., ''lion'' for tiger, or ''camel'' for giraffe) (Hodges, Salmon, & Butters, 1991; Huff, Corkin, & Growden, 1986). Moreover, the amount of information generated when the patient is asked to provide a definition for a word is closely related to the quality of the naming response given to a picture of the same item (Hodges, Patterson, Graham, & Dawson, 1996). Finally, a recent longitudinal study (Salmon, Heindel, & Lange, 1999) has shown that the rate of decline over time is significantly greater for category than for initial letter fluency tasks—two types of fluency test that place differing demands on the semantic system.

The distribution of neuropathological changes in DAT has been a rich source of information about the impor-

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tance of different brain structures in various cognitive domains. Several autopsy studies have suggested that the earliest changes in DAT selectively involve the transentorhinal zone, evolve to incorporate the temporal neocortex proper, and spread to inferior parietal regions still later in the disease (Braak & Braak, 1991; Hyman, 1990; Brun & Englund, 1981). This ordered sequence seems to fit the clinical profile that is most typical of the early stages of the disease—namely, deficits in new learning and (variably and often somewhat later) in semantic memory (Hodges & Patterson, 1995). The fact that some patients with DAT present with early visuospatial impairments and show predominantly biparietal changes at postmortem suggests that atypical patterns of progression may also occur (Galton, Patterson, Xuereb, & Hodges, 2000; Mackenzie-Ross et al., 1996).

There is, however, considerable disagreement about the importance of regional pathological changes in individuals whose semantic memory impairment differs in severity across broad groups of semantic categories. The phenomenon of category-differential semantic impairment has been described with advantages for both living and nonliving concepts (e.g., Sacchett & Humphreys, 1992; Warrington & Shallice, 1984), and double dissociations of this kind constitute strong evidence that separate neural systems underpin some aspect of processing for each of the two stimulus types (Shallice, 1988). The most straightforward interpretation would be that living and nonliving categories are represented by distinct neural systems (Caramazza & Shelton, 1998). Yet, because the living versus nonliving distinction does not always correctly define the sets of items that are lost and preserved in these cases, two other accounts, based on the fine-grained constituents of concept representations, have been proposed. These models fall into two groups.

One type of theory is characterized by the claim that knowledge about some items (dominated by living things) depends principally on perceptual features (size, shape, color, etc.), while functional attributes are more salient for another class of objects (mainly nonliving items such as manmade artifacts) (Warrington, 1982; Warrington & McCarthy, 1987). Cases with a relative advantage for nonliving categories would thus reflect the differential impairment of sensory knowledge, whereas greater impairment of functional knowledge would tend to produce the reverse pattern. This account, which has come to be known as the sensory–functional theory (SFT), emphasizes the importance of regional cerebral anatomy to the representation of different types of subordinate feature knowledge (Gainotti, Silveri, Daniele, & Giustolisi, 1995). It is supported by the observation that among the earliest cases reported to show disproportionate loss of knowledge about living things were a number of patients with well circumscribed temporal lobe lesions resulting from herpes simplex virus encephalitis (HSVE) (Sartori, Job, Miozzo, Zago, & Marchiori, 1993; Pietrini et al., 1988; Warrington & Shallice, 1984), while the complementary pattern has tended to occur in the context of damage to frontoparietal regions, following left middle cerebral artery (MCA) territory infarction (Sacchett & Humphreys, 1992; Warrington & McCarthy, 1983, 1987). A similar correlation between regional cerebral activation and semantic domain has been observed in normal volunteers using positron emission tomography (PET) activation and functional magnetic resonance imaging (fMRI) studies (Thompson-Schill, Aguirre, D'Esposito, & Farah, 1999; Cappa, Perani, Schnur, Tettamanti, & Fazio, 1998; Mummery, Hodges, Patterson, & Price, 1998), and an analogy with the distinction between dorsal and ventral streams of visual information proposed by Mishkin, Ungerleider, and Macko (1983) has also been noted.

Category-differential semantic impairment has also been reported in individual patients with DAT (Garrard, Patterson, Watson, & Hodges, 1998; Lambon Ralph, Howard, Nightingale, & Ellis, 1998; Gonnerman, Andersen, Devlin, Kempler, & Seidenberg, 1997; Montanes, Goldblum, & Boller, 1995; Silveri, Daniele, Giustolisi, & Gainotti, 1991), and the more diffuse neuropathological character of this condition makes such cognitive–anatomical correlations rather harder (though not impossible) to sustain. In a cross-sectional analysis of a large cohort of DAT patients, Garrard et al. (1998) demonstrated that category-related semantic impairments, with advantages in both directions, characterized the neuropsychological profiles of a small number of individual cases, and that such patterns tended to occur at relatively late stages of disease progression. It was argued that cases with the more commonly occurring advantage for nonliving categories were following the typical pattern of neuropathological progression in DAT, while the few instances of superior performance on living categories had suffered early biparietal involvement. The latter association was subsequently verified in a single case at postmortem.

The second type of account has attempted to explain how category-differential semantic impairments may arise from relatively nonfocal disease processes in a different fashion (Devlin, Gonnerman, Andersen, & Seidenberg, 1998; Moss, Tyler, & Jennings, 1997). Conceptual knowledge is assumed to be represented in a widely distributed network of low-level representational units (semantic features). Among these features are some that will usually occur in isolation, and others that will tend, statistically, to co-occur across exemplars. For instance, the properties of having body fur (lions, rabbits, horses, etc.) or a carnivorous diet (lions, sharks, eagles, etc.) delimit groups of concepts that may have little else in common with one another. If, on the other hand, ''has feathers'' is among a concept's features, then it will almost always also include the feature ''has a beak,'' and vice versa. Groups of features that cohere in this way are described as being ''intercorrelated,'' and the degree to which a concept includes such feature intercorrelations is believed to affect its vulnerability as

the general matrix of featural elements becomes degraded (Gonnerman et al., 1997). When damage is mild, concepts relying on intercorrelated features are predicted to survive longer because of the collateral activation that such features provide for one another. The same property, however, leads to the prediction that when damage is sufficiently severe, intercorrelated features will degrade en masse, rendering those concepts to which they contribute disproportionately vulnerable.

There is some evidence that living and nonliving concepts differ systematically in the degree to which their component features participate in intercorrelations (Garrard, Lambon-Ralph, Hodges, & Patterson, 2001; McRae, de Sa, & Seidenberg, 1997), suggesting that the degree of damage to the semantic system alone (i.e., irrespective of the distribution of pathology) might be a powerful determinant of category-specific effects. Moreover, in a progressive degenerative condition such as DAT, the direction of this advantage would be expected to change with the progression of the disease. Such direction-by-severity interactions have been predicted by two theoretical models, though these make different assumptions about the distribution of feature intercorrelations in living and nonliving concepts, and opposing predictions about the effect of disease progression on the integrity of living and nonliving concepts.

One model, proposed by Devlin et al. (1998), rests on the assumption that there is a greater degree of intercorrelation among the features of living than nonliving items, an idea that has found support in the developmental (Keil, 1987, 1989) and normal adult experimental (Garrard et al., 2001; McRae et al., 1997) literatures. This model predicts an advantage for living things early in the course of the degenerative process, and an advantage for artifacts in the later stages (Figure 1A). In addition, another approach has emphasized the importance of intercorrelations between sensory and functional features, which, in general, characterize the relationships, evident in many artifacts, between form (e.g., the serrated edge of a saw or knife) and function (cutting) (Durrant-Peatfield, Tyler, Moss, & Levy, 1997; Moss et al., 1997; De Renzi & Lucchelli, 1994). This account also predicts a relationship between severity and the direction of the category advantage, but in the opposite direction to that of Devlin et al.: With mild degrees of damage, unique identification of a concept should be best-preserved for the nonliving things due to the presence of strong form–function intercorrelations among the distinctive features of these items. With more severe impairments, however, the category advantage is predicted to reverse because the living concepts are supported, to a greater degree, by the shared, intercorrelated attributes (Figure 1B).

While both of the above models have been supported by the behavior of corresponding connectionist simulations under varying conditions of damage (Devlin et al., 1998; Durrant-Peatfield et al., 1997), empirical evidence for a crossover in either direction in patients with progressive degenerative disease has been sparse. In a cross-sectional study of 15 patients with probable DAT, Gonnerman et al. (1997) noted a small interaction between disease severity and domain, but few of the differences were striking, and there was no explicit comparison with potential domain differences shown by normal controls (McKenna & Parry, 1994). Moreover, the interaction may have been exaggerated by the method of defining disease severity (degree of impairment in a naming test for living items). A similar cross-sectional survey was carried out by Garrard et al. (1998) on a rather larger cohort of 58 patients, together with a normal control group, using equal numbers of living and non-

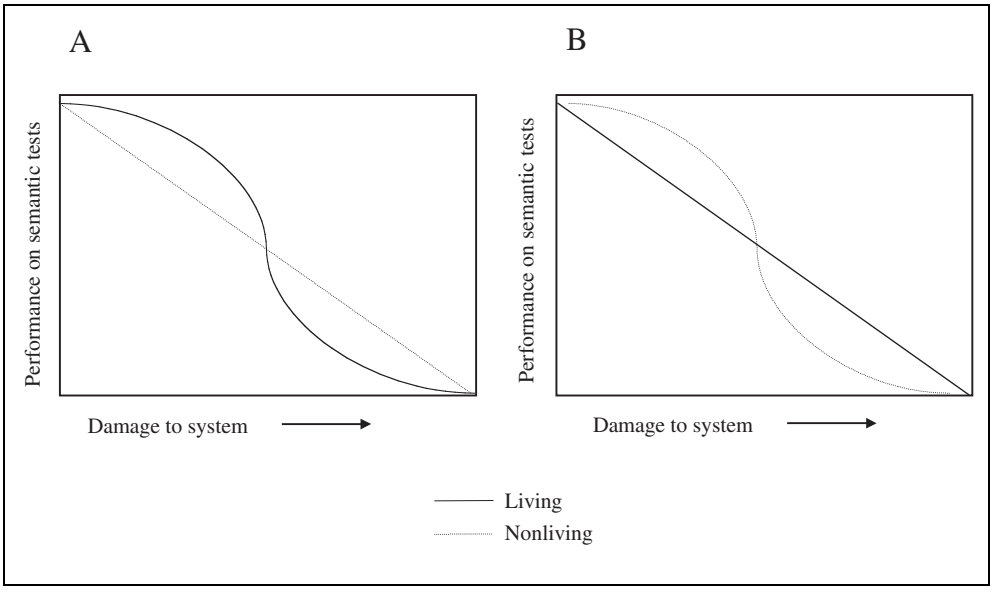

Figure 1. Hypothetical longitudinal profiles of changes in semantic knowledge for living and nonliving concepts, according to the models of (A) Gonnerman et al. (1997) and (B) Moss et al. (1997).

living items. The occurrence of several cases with significant advantages for either living or nonliving items has already been mentioned, but no interaction between the direction of the advantage and disease severity was detected despite the use of sensitive analytical techniques and a number of different methods of severity ranking.

Although cross-sectional analyses provide one way of examining the relationship between semantic domain and disease severity, longitudinal studies are clearly even more appropriate. All three of the accounts outlined above make predictions about longitudinal profiles in relation to category or feature knowledge. The anatomically based account predicts that visual knowledge will, in the majority of cases, be disproportionately disrupted in the early stages, as the pathology spreads from medial to lateral temporal areas. This should result in a persistently greater failure rate on stimuli from living categories fairly early in the disease process. There is no reason to expect a reversal of the direction of this difference with deterioration of the knowledge base, though the size of the advantage for nonliving things should inevitably diminish as all knowledge degrades. The two intercorrelational accounts predict complementary patterns: According to the model of Devlin et al., an early advantage for living categories should change, at some stage, into an advantage for nonliving things, while the model of Moss et al. predicts the reverse. Thus, the appearance of any form of interaction between severity and domain would favor some version of an intercorrelational account of category-differential semantic breakdown.

To date, very little such evidence has been reported. Gonnerman et al. (1997) described longitudinal analyses of two of the patients in their cohort: Although neither showed the critical ''crossover effect'' predicted by the model, in one case, there was a suggestive modulation in the size of an advantage for living things over time. The significance of these findings is, however, somewhat tempered by the composition of the stimulus list, with unequal numbers in the two domains and a set of living stimuli consisting entirely of fruit and vegetables. Predictions from the model of Moss et al. have been examined in one patient with a progressive aphasic syndrome, tested serially over two and a half years, whose success in naming reversed from a nonliving to a living advantage (Moss & Tyler, 1999).

Clearly, considerably more longitudinal data are required before any general conclusions can be reached about the validity of these approaches. Moreover, such data must meet a number of requirements in order usefully to address this particular theoretical debate. First, because the intercorrelation hypothesis was originally formulated to account for the phenomenon of category-differential impairment in patients with DAT, a group of patients with this condition would seem to be the most suitable study population. Secondly, because the profiles of cognitive decline in individual patients proceed at differing rates from a wide range of starting points, a longitudinal survey should ideally combine multiple within-subjects comparisons, in order to take account of such differences. Thirdly, in order to detect variations in the category-differential profile of semantic knowledge at all stages of disease progression, the population tested must include patients at the mildest end of the clinical spectrum, as well as those with more obvious semantic impairments. Finally, in the light of the importance of psycholinguistic variables such as familiarity and age of acquisition to performance on individual items in semantic tests, particularly naming (Lambon Ralph et al., 1998; Funnell & Sheridan, 1992), it is advantageous to control for these factors in such analyses.

We met all of the above requirements in a series of studies using two groups of patients with probable DAT: For the first two studies, we used data from a consecutive series of 58 patients who had undergone serial testing using a standard semantic battery over periods up to 6 years; for the third study, we used a smaller group with more mild disease, in whom semantic deficits were detectable only by using a set of graded materials (McKenna, 1997). These more difficult stimuli were administered to counteract the possibility of category differences being masked by ceiling effects on the standard items. The aims of the study were, first, to determine whether the general pattern of neuropsychological decline can be understood in terms of neuropathological accounts of progression in Alzheimer's disease (Braak & Braak, 1991; Hyman, 1990; Brun & Englund, 1981) and, secondly, to look for evidence, in detailed analyses of the rate of deterioration in individual living and nonliving concepts, that might support any of the competing accounts of category-differential semantic impairment.

RESULTS

Study 1: Longitudinal Neuropsychological Profile of a DAT Cohort

General Neuropsychological Measures

Although the long duration of follow-up on the patients from this cohort provided the ideal conditions in which to look for longitudinal trends in the indices of cognitive impairment, the data revealed few measures showing a significant decline in the group means over time. The absence of these expected trends is, however, difficult to interpret because the patients who withdraw or become untestable part-way through the study tend to be those at the more severe end of the spectrum of cognitive dysfunction, who contribute most to a change in the average test scores. The interval between consecutive testing rounds may also have been too short to detect a decline in individual patients on some of the less sensitive measures. To reveal such trends as may be present in these data, therefore, results from Rounds 1, 3, 5, and 7 only were considered, allowing results to be

compared at intervals of approximately 1 year. Eighteen patients reached Round 7, and comparisons of scores across time were restricted to data from these individuals. Missing values in any round were replaced with the series mean. The subject group means were analyzed using repeated-measures analysis of variance, with one four-level within-subjects factor (testing round).

The results of these analyses are shown in Table 1, where it can be seen that in eight of the 11 tests, the patient group scored significantly worse (> 2 SD lower) than controls at one or more of the assessments. Moreover, five of the 11 tests are associated with a significant change over the assessment period. Although this change is not a consistent downward trend in all cases, post hoc *t* tests confirm that scores dropped significantly between Rounds 1 and 7 in all but one. In general, the measures on which patients deteriorated over time were those that depend on multiple cognitive domains (Mini-Mental State Examination [MMSE]), or on episodic memory (RMT, Logical memory), which would be expected to show a progressive decline in almost all patients with DAT. Although delayed recall (another measure of episodic memory) does not show a significant decline over time, the patients were already per-

Table 1. Mean Scores, at Yearly Test Intervals, of the 18 Patients from the DAT Cohort Who Reached Testing Round 7, on a Series of Standardized Neuropsychological Tests

Test		*Testing Round*					*ANOVA*[a]	*Post Hoc t Test (1 vs. 7)*
		Controls	*1*	*3*	*5*	*7*		
MMSE	Mean	29.2	21.9[b]	21.6[b]	20.7[b]	17.6[b]	$F(3,51) = 16.1$, $p < .001$	3.3, $p < .01$
	SD	1.0	5.6	5.9	5.0	6.5		
Logical memory (immediate recall)	Mean	11.6	4.1	3.4[b]	3.8[b]	2.9[b]	$F(3,51) = 8.4$, $p < .01$	2.4, $p < .05$
	SD	3.9	1.9	1.7	2.1	1.9		
Logical memory (delayed recall)	Mean	8.5	0.74[b]	0.44[b]	0.42[b]	0.14[b]	$F(3,51) = 2.4$, *ns*	
	SD	3.4	1.0	0.8	0.8	0.3		
Recognition Memory Test (words)	Mean	47.3	31.9[b]	32.9[b]	32[b]	22.5[b]	$F(3,51) = 32.9$, $p < .001$	6.5, $p < .001$
	SD	2.8	6.2	4.8	5.5	4.9		
Recognition Memory Test (faces)	Mean	43.7	36[b]	39.5	40.0	34.4[b]	$F(3,51) = 6.3$, $p < .01$	1.5, *ns*
	SD	3.8	7.9	6.4	4.9	9.0		
Rey complex figure (copy)	Mean	34.0	23.1[b]	29.1	23.8[b]	23.1[b]	$F(3,51) = 2.3$, *ns*	
	SD	2.9	6.8	11.8	11.1	10.7		
Backward digit span	Mean	4.8	4.0	4.0	3.8	4.2	$F(3,51) < 1$	
	SD	1.2	1.4	1.8	1.4	1.5		
Judgement of Line Orientation	Mean	27.4	25.0	22.3	26.8	22.5	$F(3,51) = 2.4$, *ns*	
	SD	3.9	11.2	4.8	9.1	2.0		
Object matching	Mean	37.3	33.8	34.8	34.2	30.6[b]	$F(3,51) = 5.03$, $p < .01$	2.4, $p < .05$
	SD	3.1	4.1	5.5	6.6	8.1		
FAS fluency	Mean	14.9	9.5	10.2	9.5	8.9	$F(3,51) < 1$	
	SD	3.4	4.3	4.3	4.1	5.2		
Token test	Mean	35.7	30.0[b]	31.6[b]	32.1[b]	31.4[b]	$F(3,51) < 1$	
	SD	0.5	6.3	4.2	4.6	5.3		

[a]Four-way repeated-measures analysis of variance with testing round as within-subjects variable.

[b]Value at least 2 standard deviations below control mean.

forming near floor level at Round 1, making further decline virtually impossible to demonstrate. The longitudinal pattern of impairment in tests of semantic memory was analyzed separately.

Tests of Semantic Memory

Performance of the 18 patients who reached Round 7 on tests from the semantic battery (with sampling of test results at intervals of 12 months) are shown in Table 2. The patients' performance fell significantly (> 2 *SD*) below control values, on at least one testing round, on all measures, and there were significant effects of testing round on four of the seven semantic tests, in all of which post hoc *t* tests showed a significant decline between the first testing round and the last. The exceptions to this pattern were: (i) naming to description, on which the patients performed at the same level of impairment throughout the assessment period; and (ii) sorting at Levels 1 and 2, relatively undemanding tests on which the patients performed at or close to normal levels. When data from all three levels of sorting were analyzed using a 3 (Level) × 4 (Test round) analysis of variance, in addition to the expected main effect of Level [$F(2,16) = 597.2$ ($p < .001$)], there was a trend towards an effect of Test round [$F(3,24) = 2.8$ ($p = .06$)], and a significant interaction between Test round and Level [$F(6,24) = 3.1$ ($p = .01$)].

Longitudinal neuropsychological test data for this cohort are therefore consistent with the notion that both episodic and semantic memory were progressively compromised by the disease process. The pattern of performance on the three levels of sorting was, moreover, consistent with the idea that the more specific aspects of conceptual knowledge are somewhat more vulnerable to semantic disintegration than those aspects that are common to many category members (Hodges, Graham, & Patterson, 1995; Warrington, 1975).

Further evidence of progressive semantic impairment in this population was provided by a replication of Salmon et al.'s (1999) demonstration of differential impairment in the rate of decline for semantic category versus phonological (FAS) fluency tests. Mean *z* scores for the group on these two tests at Years 1–4 of testing are displayed in Figure 2. A 2 (Phonological vs. Category fluency) × 4 (Testing round) repeated-measures analysis

Table 2. Mean Scores, at Yearly Test Intervals, of the 18 Patients from the DAT Cohort Who Reached Testing Round 7, on Tests from the Semantic Battery

Test		*Testing Round*					*ANOVA*[a]	*Post Hoc t Test (1 vs. 7)*
		Controls	*1*	*3*	*5*	*7*		
Category fluency (mean of eight categories)	Mean	14.2	7.5[b]	6.9[b]	6.2[b]	5.7[b]	$F(3,51) = 6.6$, $p < .01$	3.3, $p < .01$
	SD	2.4	2.5	3.0	2.9	2.6		
Picture naming	Mean	43.3	35.3[b]	34.7[b]	35.3[b]	31.1[b]	$F(3,51) = 7.4$, $p < .001$	3.0, $p < .01$
	SD	2.2	8.8	12.5	12.4	13.2		
Naming to verbal description	Mean	22.5	17.6[b]	17.5[b]	17.3[b]	16.9[b]	$F(3,51) = 0.17$	
	SD	1.3	6.8	6.6	5.9	5.1		
Word–picture matching	Mean	47.4	45.2[b]	45.2[b]	43.9[b]	39.3[b]	$F(3,51) = 9.89$, $p < .001$	3.1, $p < .01$
	SD	1.0	4.1	3.7	5.4	10.1		
Sorting—level 1	Mean	47.9	47.5[b]	47.8	46.9[b]	47.6	$F(3,51) = 1.04$, *ns*	
	SD	0.2	6.7	2.5	2.4	1.3		
Sorting—level 2	Mean	46.9	44.2[b]	45.5	44.8[b]	45.2	$F(3,51) = 1.5$, *ns*	
	SD	0.9	6.6	3.9	2.9	2.2		
Sorting—level 3	Mean	68.8	66.8	66.3	64.4[b]	64.8	$F(3,51) = 4.07$, $p < .05$	3.0, $p < .05$
	SD	2.2	2.4	3.8	4.2	4.0		

[a]Four-way repeated-measures analysis of variance with testing round as within-subjects variable.

[b]Value at least 2 standard deviations below control mean.

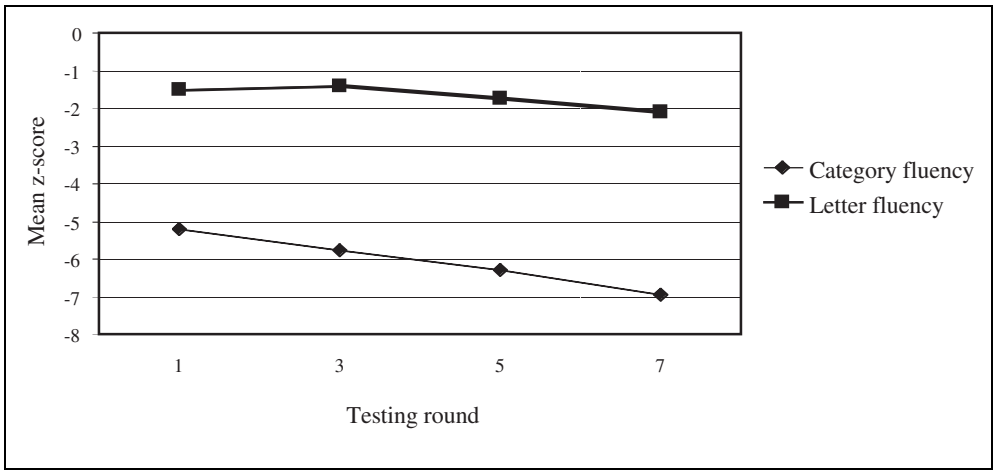

Figure 2. Comparative longitudinal profiles on phonological and category fluency tests of the 18 patients who reached testing Round 7. Yearly observations are used in order to enhance differences.

of variance confirmed significant main effects of Fluency type [$F(1,17) = 151.1$ ($p < .001$)] and Testing round [$F(3,51) = 5.52$ ($p < .05$)], as well as a significant Fluency type × Testing round interaction [$F(3,51) = 4.78$ ($p < .01$)].

Category-Differential Effects

Scores at each testing round on category fluency, picture naming, naming to description, and word–picture matching for the living and nonliving item subsets are presented separately in Table 3. Because of the anomalous findings that have been reported when considering the category of musical instruments within the domain of artifacts (e.g., Farah, Meyer, & McMullen, 1996; Basso, Captiani, & Laiacona, 1988; Warrington & Shallice, 1984), scores relating to this group of stimulus items were excluded from the totals for this domain. The category of water creatures was excluded from the natural kinds set to preserve the numerical balance.

At no time and on none of the four measures was there a statistically significant difference between scores on the living and nonliving subsets. Such minor differences as did emerge all showed higher scores for items in the nonliving domain, and there was no evidence of any temporal modulation of this trend [interaction

Table 3. Mean Scores, at Yearly Test Intervals, of the 18 Patients from the DAT Cohort who Reached Testing Round 7, on Living and Nonliving Stimuli from the Semantic Battery

		Testing Round				
Test		*Controls*	*1*	*3*	*5*	*7*
Category fluency	Living	61.7 (10.9)	27 (19.9)	26.6 (19.4)	24.6 (19.6)	21.1 (10.3)
	Nonliving	57.9 (7.4)	26.9 (18.0)	27 (18.6)	26.1 (17.8)	24.4 (11.2)
	Sig.[a]	*ns*	*ns*	*ns*	*ns*	*ns*
Picture naming	Living	16.3 (1.5)	13.5 (3.2)	13.4 (4.7)	13.7 (4.8)	11.8 (5.1)
	Nonliving	16.8 (1.5)	14.4 (3.7)	13.6 (5.1)	13.9 (4.9)	12.9 (5.3)
	Sig.	*ns*	*ns*	*ns*	*ns*	*ns*
Naming to verbal description	Living	7.8 (0.4)	5 (2.5)	5.6 (2.5)	5.8 (2.2)	5.7 (1.8)
	Nonliving	7.7 (0.7)	5.7 (2.4)	5.9 (2.1)	5.9 (2.0)	6.2 (2.2)
	Sig.	*ns*	*ns*	*ns*	*ns*	*ns*
Word–picture matching	Living	17.8 (0.7)	16.7 (1.9)	16.3 (2.9)	16.4 (2.5)	15.1 (3.4)
	Nonliving	17.9 (0.3)	16.7 (1.7)	16.6 (2.3)	16.7 (2.5)	15.3 (3.9)
	Sig.	*ns*	*ns*	*ns*	*ns*	*ns*

[a]Significance values are calculated using paired *t* tests corrected for multiple comparisons using Bonferroni's method.

between testing round and domain: $F(3,102) = 1.05$, $p > .1$].

Comment. The above analyses have confirmed the presence of significant decline in a longitudinally studied DAT cohort on a variety of neuropsychological measures, notably those that depend on either episodic memory, semantic memory, or a combination of cognitive domains. Evidence for decline of semantic memory over time was also found in the significant difference between the longitudinal patterns associated with the category and letter fluency tests. These results would be predicted by the neuroanatomical pattern of progression proposed on the basis of neuropathological studies (Braak & Braak, 1991; Hyman, 1990; Brun & Englund, 1981).

Comparisons between semantic domains failed to show any significant group advantage for either living or nonliving categories on any test over 4 years of testing. In the few instances where a small (nonsignificant) domain advantage was evident, it always favored the nonliving categories. This predominantly negative finding is consistent with most previously reported group studies of DAT (Hodges et al., 1992; Gonnerman et al., 1997), including an earlier report of cross-sectional data from this cohort (Garrard et al., 1998), but inconsistent with the prediction that relative performance on living and nonliving items should change over time. A more statistically powerful test of this hypothesis could, however, be achieved by considering longitudinal semantic performance in an item-by-item fashion.

Study 2: Patterns of Concept ''Loss'' Over Time

Concept Survival Over Time

Concept survival over time is presented in Figure 3 using a Kaplan–Meier model, with cumulative survival plotted against testing round number, and separate lines for the living and nonliving concepts. Definition of completed cases was based on a lenient criterion (Figure 3A) and stringent criterion (Figure 3B) of concept ''loss'' (defined below under Methods), and both definitions resulted in the emergence of a more rapid dropout rate for the concepts in the living domain. This difference was consistent throughout the period of observation. The difference between the survival distributions for the two semantic domains was statistically significant using the lenient definition of concept ''loss'' [Log Rank test $(1\ df) = 7.59, p < .01$], but not when the more stringent definition was used [Log Rank test $(1\ df) = 2.06$, $p > .05$].

To examine the role played by other theoretically important variables in the different rates of concept ''loss,'' survival times for each item (using the lenient criterion) were predicted using a series of Cox regressions (Kalbfleisch & Prentice, 1980). With age of acquisition and domain as predictors, there were significant effects of both variables [domain: Wald $(1\ df) = 50.8$, $p < .001$; age of acquisition: Wald $(1\ df) = 9.4, p < .01$]. With familiarity and domain as predictors, the effect of familiarity was highly significant [Wald $(1\ df) = 21.2$, $p < .001$], but domain no longer reached significant levels [Wald $(1\ df) = 0.39, p > .5$]. An analysis with all three predictors entered simultaneously showed age of acquisition to be the most significant (with earlier acquired items persisting longer) [Wald $(1\ df) = 21.1$, $p < .0001$], while familiarity [Wald $(1\ df) = 2.9, p > .05$] and domain [Wald $(1\ df) = 2.6, p > .05$] both fell short of statistical significance.

Because the categories of musical instruments and water creatures were excluded in the previous longitudinal analysis of domain differences, the survival analyses were repeated after exclusion of these categories from the data. All results were similar: The difference between the two survival curves remained significant in the Kaplan–Meier analysis using the lenient definition of concept ''loss'' [Log Rank $(1\ df) = 5.34, p < .05$] and age of acquisition remained the only significant predictor of concept survival in the Cox regression [Wald $(1\ df) = 17.3, p < .0001$].

Comment. Using longitudinal naming accuracy as the dependent measure, the above analyses have shown that the rate of concept dropout from semantic memory (as defined by the onset of a persistent inability to name the item) in a population of patients suffering from progressive degenerative disease was marginally greater for nonliving than for living concepts. This difference can be interpreted largely by the greater resilience of familiar concepts, insofar as the domain effect was not statistically significant once this variable was taken into account. All analyses demonstrated consistent effects of age of acquisition, with early acquired items exhibiting greater preservation. The patterns of concept ''loss'' remained consistent throughout the period of observation, and there was no crossover of the patterns for the two domains. Varying the criterion for defining concept ''loss'' and excluding the atypical category of musical instruments led to no qualitative differences in the patterns of results achieved.

Concept Survival at Different Stages of Semantic Impairment

Although no evidence emerged from the above analyses to suggest that degenerative brain disease has any qualitatively different effects on the probability of ''loss'' of living and nonliving concepts, there are two possible ways in which such differences might have been concealed. First, testing rounds provided a convenient way of plotting observations at roughly equal time steps, but the wide variation in both disease stage and rate of disease progression evident in the patient population raises doubts about the legitimacy of collapsing across subjects in this fashion. Specifically, the rate of survival

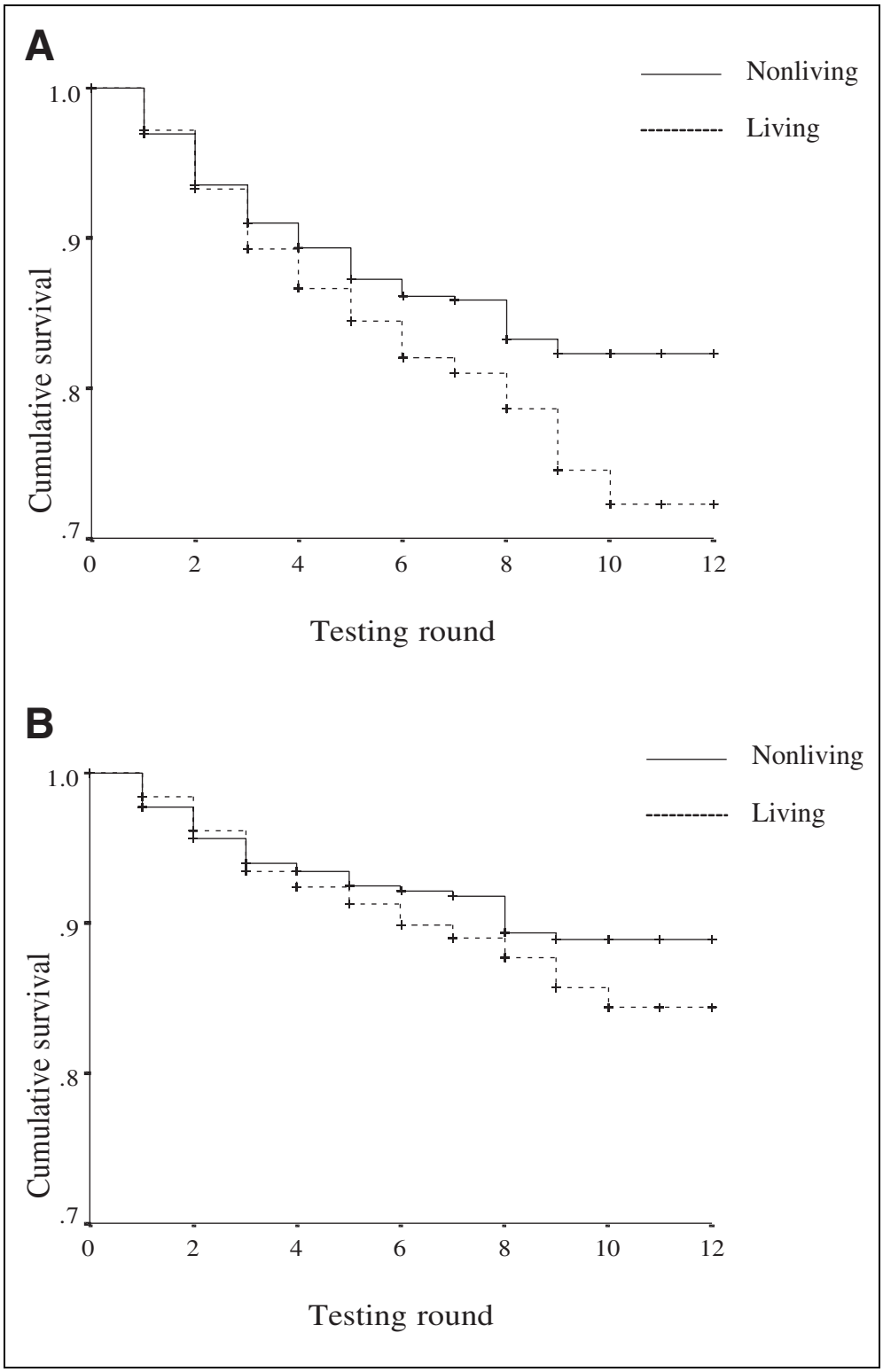

Figure 3. Kaplan–Meier plot showing cumulative proportion of surviving concepts at each round of testing, with separate lines for the living and nonliving subsets. Censored cases have been defined according to (A) a lenient criterion (item unnamed on at least the last two testing rounds) and (B) a stringent criterion (item unnamed on at least the last three testing rounds).

among concepts that had been ''lost'' by some of the more severely affected patients before entry into the study may have provided evidence in support of the intercorrelational hypothesis. Secondly, although the patients' mean overall level of cerebral damage may reasonably be expected to have increased over the course of the study, it has been suggested that the predictions of the intercorrelational hypothesis are based specifically on levels of damage to the semantic system (Devlin et al., 1998).

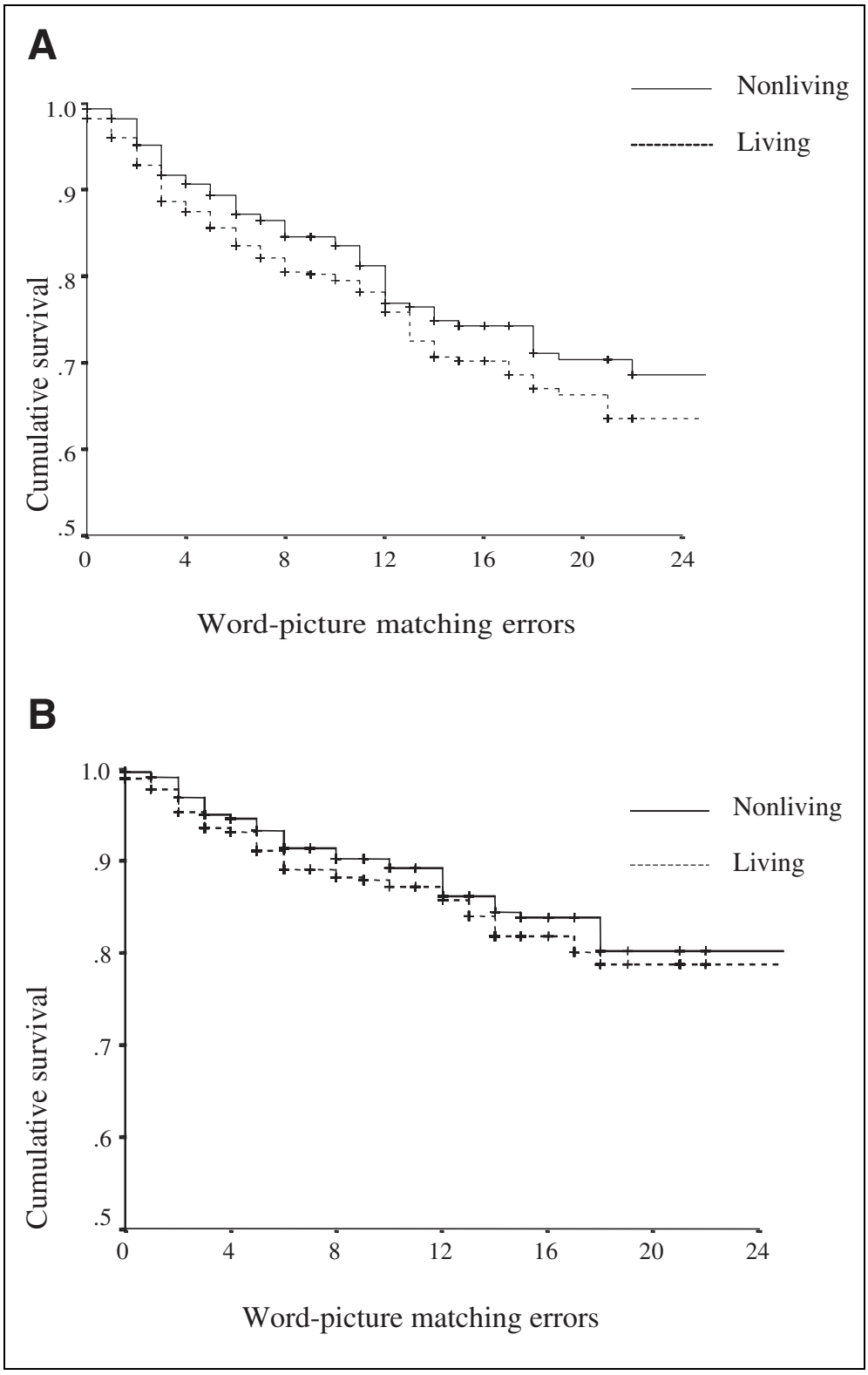

Figure 4. Kaplan–Meier plot showing cumulative proportion of surviving concepts at each level of global semantic impairment (as defined by the score obtained on the word–picture matching test), with separate lines for the living and nonliving subsets. Censored cases have been defined according to (A) lenient and (B) stringent criteria as before.

Both of these objections can be addressed by adopting an index of overall semantic impairment in place of the time variable, to ensure that all patients had reached an equivalent stage of progression at each observation point. The survival analyses were therefore repeated using the scores obtained on the word–picture matching

test to represent progressive stages of semantic degradation.

Figure 4 displays the rate of ''loss'' of living and nonliving concepts using the same lenient (Figure 4A) and stringent (Figure 4B) criteria as before. The two survival functions are plotted against degree of semantic impairment, as defined by the number of errors made on the word–picture matching test. Analyses of the patterns of concept survival produced similar results to those based on testing rounds: The difference between the two survival curves was significant under the lenient but not the stringent criterion of concept ''loss'' [Log Rank ($1\ df$) = 7.61, $p < .01$ and Log Rank ($1\ df$) = 2.05, $p > .05$, respectively]. In a Cox regression using the lenient criterion of concept ''loss,'' there was a significant effect of age of acquisition [Wald ($1\ df$) = 37.6, $p < .0001$] and a trend towards an effect of domain [Wald ($1\ df$) = 3.78, $p = .05$] but no independent effect of familiarity [Wald ($1\ df$) = 0.23, $p > .5$] as significant predictors of concept survival.

Comment. The earlier finding that living concepts were ''lost'' from semantic memory at a faster rate than

Table 4. Scores on General Neuropsychological Tests, Tests from the Semantic Battery, and the Category-Specific Names Test Achieved by the 20 Subjects in the Mild DAT Cohort

				Semantic Battery (/64)				*Category-Specific Names Test*	*RMT*	*RMT*	*Rey*	*Rey*
Patient	*Age*	*Sex*	*MMSE*	*Naming*	*W–PM*	*CCT*	*GNT*	*(Total)*	*(Words)*	*(Faces)*	*Copy*	*Recall*
JP	52	F	26	64	63	60	25	100	17[a]	25	32	8
BC	65	M	24[a]	63	64	59	22	97	18[a]	19[a]	24[a]	1.5[a]
PP	79	F	23[a]	62	64	60	21	94	NT	NT	33	0.5[a]
JM	52	F	25[a]	64	64	59	23	91	NT	20[a]	24[a]	3[a]
HP	76	F	24[a]	64	64	58	21	86	17[a]	20[a]	36	5[a]
IH	74	F	23[a]	64	61[a]	54	16	80	21[a]	25	25[a]	2[a]
HB	57	F	25[a]	64	64	62	20	79[a]	NT	NT	35	24
AD	57	F	24[a]	64	64	57	25	78[a]	19[a]	24	36	0[a]
DB	58	F	21[a]	NT	63	46	18	72[a]	NT	NT	26[a]	1[a]
RW	68	M	20[a]	62	63	53	6[a]	69[a]	14[a]	23[a]	31	7[a]
JW	63	M	26	64	62[a]	58	14	67[a]	17[a]	25	27[a]	9[a]
JJ	80	M	22[a]	64	63	57	20	63[a]	NT	NT	34	4[a]
AD	75	M	22[a]	54[a]	62[a]	57	21	60[a]	18[a]	17[a]	33	7[a]
CG	74	M	24[a]	64	64	53	21	58[a]	21[a]	21[a]	28	7.5[a]
GC	60	M	24[a]	61	64	53	16	56[a]	12[a]	21[a]	32	3[a]
PL	79	M	24[a]	61	64	52	23	50[a]	15[a]	22[a]	29	NT
HL	69	M	22[a]	60	64	58	20	49[a]	17[a]	18[a]	31	0[a]
BK	66	M	26	62	62[a]	56	20	43[a]	21[a]	20[a]	34	14
VJ	75	M	26	49[a]	60[a]	51	12[a]	32[a]	17[a]	19[a]	35	NT
MC	84	F	19[a]	46[a]	62[a]	41[a]	11[a]	9[a]	15[a]	17[a]	NT	NT
Control mean[b]	72		28.9	62.1	63.8	56.9	20.4[c]	87.5[c]	24.5	24.4	34	18.3
Control *SD*	9		1.3	1.9	0.4	7.3	4.1[c]	4.3[c]	1.2	0.63	2.9	5.2

MMSE = Mini-Mental State Examination; W–PM = Word–picture matching; CCT = Camel and Cactus test; GNT = Graded naming test; RMT = Recognition Memory Test; NT= not tested.

[a]Denotes a score more than 2 standard deviations below the control mean.

[b]Nonpublished values were obtained from a second group of controls ($n = 25$).

[c]Denotes values obtained from published means.

nonliving persisted when the temporal variable was modified to reflect progressive stages in the disintegration of semantic knowledge. As in the earlier analysis, the rates of concept ''loss'' in the two domains showed no crossover at any stage of semantic impairment. Although age of acquisition emerged as the major determinant of concept ''loss'' in both analyses, domain itself was found to be independently predictive in this analysis. If semantic deterioration can be regarded as reflecting the accumulation of pathological change in temporal neocortical regions (Braak Stages III and IV), then these findings would imply that such regions are somewhat more crucial to knowledge about living things.

For two reasons, however, the findings do not invite this interpretation unequivocally. The first is that, with the exception of the marginally significant effect of semantic domain in predicting the higher rate of ''loss'' of living than nonliving concepts, the only consistently demonstrated determinant of this difference has been age of acquisition. The interpretation of the relative positions of the survival curves at low values of the time variable must also be viewed with some caution, as it is clear that the performances on both sets of materials are close to ceiling. More specifically, a reversal of the domain advantage at a very early stage of disease progression may have gone undetected because of the insensitivity of the semantic battery to very mild impairments. To answer the first of these criticisms would require a replication of the present data using a larger and more closely matched series of items. The second, however, can be addressed by focusing on a subset of patients with very mild semantic impairment, and using a more difficult test of semantic knowledge to probe for differences between performance on the two domains.

Study 3: Category-Differential Effects in the Mild DAT Group

The scores achieved by the set of 20 mild DAT patients on various semantic and nonsemantic measures are displayed in Table 4, together with control values.

From Table 4, it can be seen that, while all patients were impaired relative to controls on tests of either episodic memory or visuo-spatial function, or both, their scores on the naming, word–picture matching, and visual association subtests of the semantic battery largely fell within the control ranges. By contrast, the scores achieved on the Category-Specific Names test, ranged from five patients who were at or just above the control mean to one showing severe impairment (below the fifth percentile).

Separate scores for each patient on the living and nonliving item subsets are shown in Figure 5, with individuals ranked in descending order of total naming score. While individual patients clearly differed in terms of whether living or nonliving items were more successfully named, few, if any, of the domain differences were striking. Moreover, there is no clear relationship between the direction of the domain difference and the degree of semantic impairment as measured by the total naming score.

To permit a formal examination of the relationship between semantic impairment and domain discrepancy, the observed domain differences were converted to discrepancy scores (total living items named minus total nonliving items named). When these are compared to the discrepancy scores observed in the normal control population (McKenna, 1997, p. 12), it is clear that only two cases fall outside the 5% confidence intervals of that distribution (Figure 6). Since 5% of cases would be

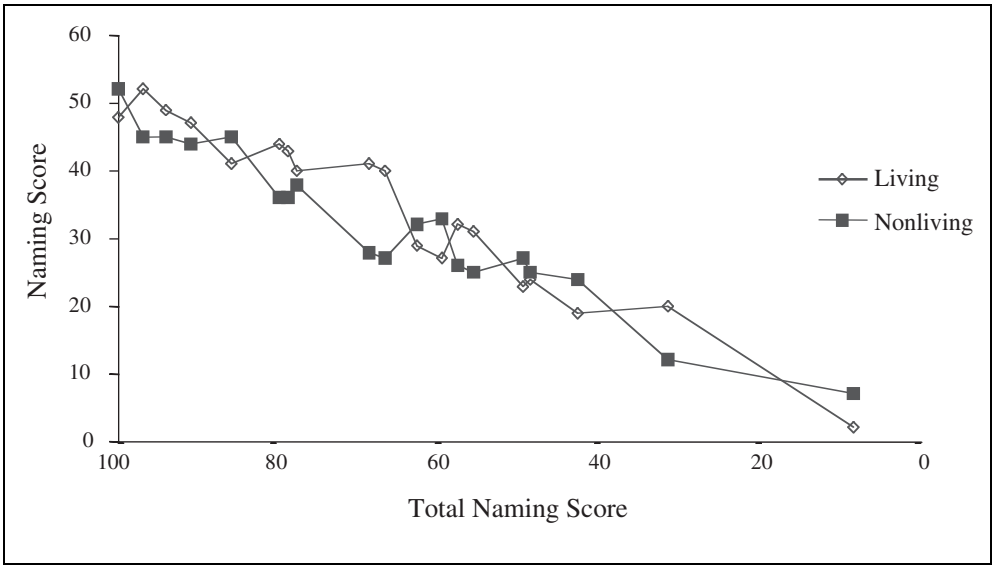

Figure 5. Total naming scores achieved by each of the subjects in the mild DAT cohort using the graded-difficulty category-specific naming test. Scores on the living (open diamonds) and nonliving (filled squares) subsets are shown separately, and the cases are arranged in descending order of total naming ability.

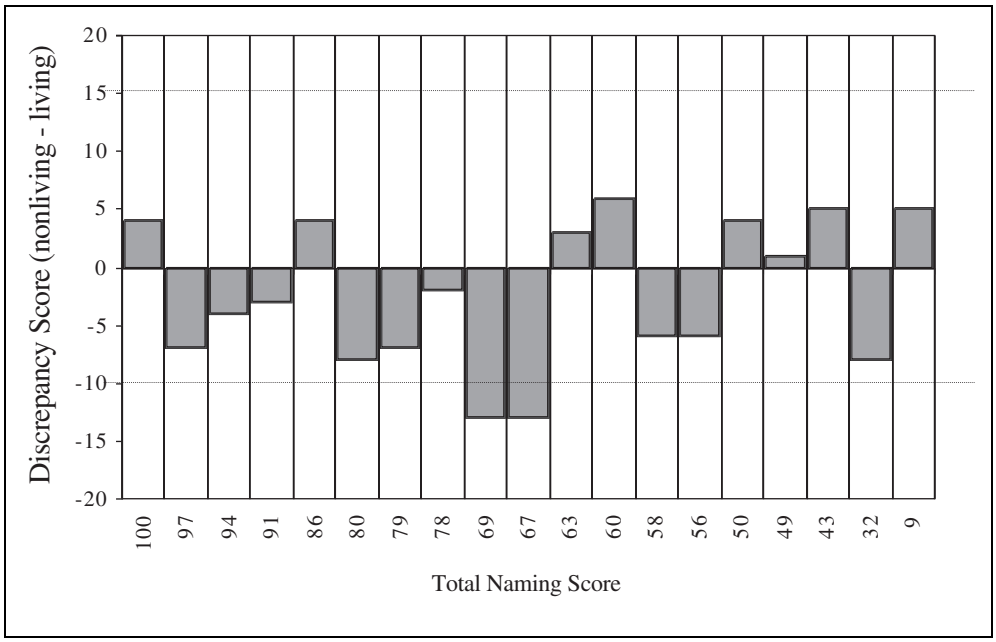

Figure 6. Discrepancy scores, calculated by subtracting the total score on the living subset from the total score on the nonliving subset, for each of the subjects in the mild DAT cohort, arranged in descending order of total naming ability. The reference lines indicate the 95% limits of the discrepancies observed in a normal sample of 400 individuals.

expected to fall outside this distribution by chance alone, this result cannot be interpreted as supporting the prediction that mildly affected individuals are more likely to demonstrate a discrepancy in favor of living items.

DISCUSSION

The three studies reported here have analyzed two groups of patients to address a current controversy in the cognitive neuropsychology of DAT. In the first two studies, data from a large serially examined cohort of patients with probable DAT were used to examine longitudinal patterns of concept ''loss'' from semantic memory over periods of up to 6 years. Study 1 used conventional statistical methods, while Study 2 employed the novel technique of survival analysis to compare the rates at which knowledge of living and nonliving concepts deteriorated over time. To our knowledge, this is the first time that such an approach has been taken using data of this kind. In the third study, a group of patients with mild DAT and little evidence of established semantic impairment were tested on a graded set of materials as a rigorous assessment of the presence of category differences in mildly affected individuals.

With regard to the overall cognitive profile, both sets of data were consistent with earlier findings that the course of the disease is characterized, in an appreciable number of patients, by progressive impairment of semantic memory (Hodges & Patterson, 1995). With respect to the issue of specific interest here, the results of the first analysis revealed modest but statistically significant differences in the rates at which concepts from the living and nonliving domains became consistently unnameable by patients over repeated testing sessions, with a larger and faster negative impact on living concepts. This difference was apparent when progression was represented not only by the time between consecutive testing rounds, but also by a specific index of semantic impairment. Although a Cox regression analysis revealed that age of concept acquisition was the most powerful predictor of concept ''loss'' in both series of data, semantic domain also emerged as an independently predictive factor, with borderline significance, in the second analysis. Most critical to the theoretical debate about the origin of domain differences in degenerative disease, however, was the fact that at no point in any of the survival analyses did the relative positions of the functions representing living and nonliving concept survival crossover.

If, as is now generally agreed, the failure to name an object or concept in DAT indicates that semantic knowledge about that item has become degraded, the small but statistically significant difference in the vulnerability of living relative to nonliving concepts in these analyses points to differences between these two conceptual domains at the level of representation. We would argue that this difference is most plausibly related to changes in the regional distribution of pathology with progression of the disease, in the manner observed by, among others, Braak and Braak (1991). There are two reasons for favoring this interpretation.

In the first place, as we have pointed out before (Garrard et al., 1998), the majority of previously reported cases demonstrating marked category effects

have occurred in the context of relatively well-circumscribed damage (often from HSVE), and thus lend themselves to an explanation that emphasizes the importance of regional cerebral anatomy. The anatomical account seems the most parsimonious explanation for the occurrence of the same phenomenon in the context of a progressive degenerative condition, unless and until there are the sorts of compelling reasons for a different account that are thus far totally lacking.

Secondly, there are now both theoretical and empirical criticisms of the intercorrelational account. Perry (1999) performed further simulations based on the model of Devlin et al. (1998) and pointed out a number of weaknesses at a computational level. These were as follows: (i) the model's performance when damaged was sensitive to subtle changes in its architecture (variation in the numbers of clean-up units); (ii) the model was not capable of generalizing to novel exemplars; (iii) performance changed when the model was trained on a new set of exemplars; and (iv) the learning algorithm caused the network to behave in a biologically implausible fashion.

To these theoretical arguments can now be added the empirical findings of the present study. Both of the alternative explanations of category-differential semantic impairment in the context of progressive neurodegenerative disease predict that the direction of the advantage should change at some stage in the course of the disease. The model of Devlin et al. (1998) predicts that an initial advantage for living categories will be replaced by an advantage for nonliving concepts at later stages, while that of Moss et al. (1998) predicts the reverse pattern. Although profiles suggestive of each of these predictions have been described in connectionist models (Devlin et al., 1998; Durrant-Peatfield et al., 1997), and in serial observations of one or two single cases with DAT (Gonnerman et al., 1997) or progressive aphasia (Moss and Tyler, 1999), the present study is the first to examine the hypotheses longitudinally in a large population of patients. Even with the additional statistical power that such an approach confers, however, neither of the predicted crossover patterns emerged as a feature of the present data. Instead, the discrepancy between the two survival curves, while increasing in magnitude with disease progression, consistently favored the nonliving items over the living. Although age of acquisition emerged as the most powerful predictor of concept ''loss'' in regression analyses, there was also the suggestion of an independent contribution of semantic domain when progression was defined by means of a measure of semantic impairment. This method of grouping includes, at each point, patients at equivalent levels of semantic impairment (as measured by word–picture matching), thus eliminating the impact of individual differences in both degree of impairment at the initial testing round and subsequent rate of deterioration.

One interpretation of these findings, and the one that we favor, is that the temporal neocortical regions, which are most subject to degenerative damage in DAT, are also differentially important in the representation of living concepts. An alternative interpretation of these longitudinal data is that ceiling effects masked an underlying advantage for living items among the more mildly affected patients. However, while the finding of an appropriate domain advantage in such a group, taken together with the results of the present study, might be consistent with the model of Devlin et al., there seems to be no additional finding that would yield the longitudinal profile predicted by Moss et al.

The Devlin et al. prediction was addressed by testing a sample of patients with mild DAT using suitably matched items of graded difficulty. This second cohort incorporated patients at all points in the range of naming abilities, from within the normal range (five cases) to floor level (seven cases). Only two evinced a significant difference between living and nonliving items, and neither of their overall naming scores fell at the extremes of the distribution. Thus, the prediction, from the model of Devlin et al. (1998), that a separate group of minimally affected patients would show a naming advantage for natural kinds, was not upheld by our results.

Although these data provide some evidence for a differential importance of temporal regions in the representation of concepts from living categories, they do not reveal the reasons for such an association. In particular, the proposal that the visual aspects of these items are particularly salient to the task of distinguishing among category members remains hypothetical. The data could thus equally well be interpreted as evidence in favor of ''... evolutionarily adapted domain-specific knowledge systems subserved by distinct neural mechanisms'' (Caramazza & Shelton, 1998). This alternative position, however, makes no predictions about the location of such neural mechanisms: A system specialized for the recognition of animals might depend on ventral or dorsal cortical regions with equal likelihood. Yet, the finding that a more rapid ''loss'' of concepts from the living domain is seen in parallel with global semantic impairment suggests that these two phenomena are associated in a nonrandom fashion. Moreover, it is well established that the inferior temporal lobe is critical to higher order visual processing (Goodale, Milner, Jacobson, & Carey, 1991; Mishkin et al., 1983) and the importance of the inferior parietal lobe in crossmodal sensory integration suggests a possible role in the representation of functional information.

The occurrence of anatomical variants of DAT offers the possibility of systematically exploring the differential effects of progressive temporal and parietal degeneration on conceptual knowledge, but such studies await the development of techniques that allow reliable distinctions to be made sufficiently early in the disease process.

METHODS

Study 1

Data were obtained from (i) a longitudinal cohort, consisting of 58 patients with probable DAT, drawn from an unselected consecutive series diagnosed in a memory disorders clinic at Addenbrooke's Hospital in 1991–1992, and willing to be enrolled into a longitudinal study of semantic memory and related cognitive deficits, and (ii) 46 normal control subjects. The sex distribution, mean age, educational level, and MMSE scores of these groups are displayed in Table 5.

All patients underwent CT or MRI scanning together with the usual battery of screening blood tests to exclude treatable causes of dementia, but quantitative imaging was available in only a few of the patients studied. Written informed consent had been obtained from all subjects or the caregivers where appropriate.

All patients had agreed to participate at approximately 6-monthly intervals in regular testing sessions involving a wide range of neuropsychological measures. As well as those described in detail below, these included the following standard clinical tests: MMSE (Folstein, Folstein, & McHugh, 1975), Dementia rating scale (Mattis, 1992), Recognition Memory Test for words and faces (Warrington, 1984), Judgement of Line Orientation (Benton, DesHamsher, Varney, & Spreen, 1983), Complex Figure Test (Lezak, 1983), object matching (unusual views) (Humphreys & Riddoch, 1984), and digit span. All patients had completed between 1 and 12 rounds of testing, with a mean interval between testing rounds of 30.6 weeks (SD = 11.4). Withdrawal from the study was due to a variety of factors including patient choice, inability to cooperate with testing due to advancing disease, or death. Of the 16 patients known to have died since the study commenced, pathological examination has been performed in 11, and has confirmed the diagnosis of Alzheimer's disease in all cases.

Semantic Memory Test Battery

This battery of tests, employing one consistent set of stimulus items, and designed to assess input to and output from conceptual knowledge about the same group of items via different sensory and response modalities, has been described in detail elsewhere (Hodges et al., 1992). It contains 48 items from three categories of natural kinds (12 land animals, 6 sea creatures, and 6 birds) and three categories of artifacts (12 household items, 6 vehicles, and 6 musical instruments) matched for category prototypicality and word frequency. The items were chosen from the corpus of line drawings by Snodgrass and Vanderwart (1980). The following tests were used for the present analyses:

1. Category fluency for each of the six categories, with 1 min allowed per category.
2. Naming of all 48 line drawings without cueing.
3. Naming in response to verbal description (e.g., "What do we call the small green animal that leaps around ponds?") for 24 of the 48 items (four from each of the six categories).
4. Word–picture matching in response to a spoken word for all 48 items. Subjects were presented with picture arrays consisting of eight items from the same category (e.g., land animals) and asked to point to the item named by the examiner .
5. Sorting of all 48 line drawings according to three criteria, of increasing levels of specificity: Level 1—domain (i.e., living vs. nonliving); Level 2—basic level category (e.g., animals vs. birds vs. sea creatures); and Level 3—subordinate property (e.g., larger than a dog vs. smaller than a dog).

Study 2

The data used for this study were the responses (correct or incorrect) given by the 58 DAT patients described above on each item of the picture-naming test at each round of testing. This information was used to examine the rate at which semantic memory for individual concepts degraded using a Kaplan–Meier survival analysis, a method of estimating time-to-event in the presence of cases for which the event is not recorded (Kaplan & Meier, 1958). For the purposes of the present analysis,

Table 5. Characteristics of the Control Group and the Two DAT Groups Used in the Study

	Studies 1 and 2		*Study 3*
	DAT (Longitudinal)	*Controls*	*DAT (Mild)*
Number	58	46	20
Sex (f, m)	31, 27	34, 12	8, 12
Mean age (*SD*)	68.0 (8.8)	72.9 (9.0)	67.6 (11.2)
Mean years of education (*SD*)	11.6 (3.3)	10.4 (2.0)	11.85 (3.01)
Mean MMSE (*SD*)	19.9 (7.3)	28.9 (1.3)	23.6 (1.9)

Table 6. Incidence of Fluctuations in Naming Performance of Increasing Magnitudes

Size of Fluctuation	*n*	*Percent of Total Possible*
Concept correctly named after at least . . .		
. . . 1 naming failure	673	28.6
. . . 2 consecutive naming failures	240	10.4
. . . 3 consecutive naming failures	101	5.0
. . . 4 consecutive naming failures	34	2.1
. . . 5 consecutive naming failures	16	1.2

each subject provided a series of observations (one per concept), equal in length to the number of testing rounds that he/she completed. There was a total of 2,784 observations, with a mean duration of 5.4 testing rounds (range 1–12).

To describe a concept as having become ''lost from semantic memory'' may appear to be at odds with the idea that individual concept representations consist of overlapping patterns of activation within a distributed semantic network, and as such are subject to variable degrees of degradation with damage to the network. We use this phrase, however, simply as a convenient label for the point at which the concept in question has become so degraded that it is no longer able to support successful naming in a consistent fashion. This sense of the word is indicated by the use of quotation marks.

A concept was regarded as having been ''lost'' if the patient's naming response changed from correct to incorrect, and remained incorrect during all subsequent testing sessions. Incomplete (censored) cases therefore included those in which the concept was never named (16.6% of observations) and those in which the concept was named at the last recorded session (60.8% of observations). For the remainder, however, it was less clear how many consecutive naming failures should be required before an item could be regarded as permanently ''lost,'' because some patients' naming accuracy was found to vary from round to round (as a result of fluctuating attention or other unstable factors that can affect performance). Table 6 displays the numbers and proportions of observations in which variations of different kinds occurred.

Table 6 shows that the number of cases in which an item was successfully named following one or more consecutive naming failures accounted for 28.6% of all concept observation times. Counting as ''lost'' all concepts that were unnamed only at a patient's last testing session would have resulted in a sizeable false-positive rate, while counting only those unnamed for at least the last four sessions would almost certainly have underestimated the true rate of concept ''loss.'' The survival analyses were therefore performed on data between these two extremes: A relatively stringent criterion of concept ''loss'' required incorrect responses in at least the final three, and a somewhat more lenient criterion in at least the final two testing sessions.

Study 3

Subjects, Materials, and Methods

Data for this study were obtained from a mildly affected cohort (MMSE 19–26), consisting of 20 patients with probable DAT, whose performance on the semantic battery was relatively well preserved despite established deficits in other cognitive domains. Demographic data relating to this group were displayed in Table 1.

The semantic tests reported here are based on a modified corpus of 64 items, which has been used in place of the 48-item set as our standard semantic memory assessment instrument since 1997. The tests of picture naming and word–picture matching, as well the nonverbal test of associative semantics (the Camel and Cactus test: described in detail in Bozeat et al., 2000) were all based on this 64-item set.

Graded test of living and nonliving item naming and comprehension. The Category-Specific Names test (McKenna, 1997) is a demanding assessment of knowledge of items from four semantic categories, of which two (animals and fruit/vegetables) are drawn from the living domain, and two (manipulable and nonmanipulable objects) from the nonliving domain. The test items are ordered by difficulty according to standardization studies demonstrating that the 30 items in each category were correctly named by varying proportions of a normal population (n = 400) aged between 20 and 70 (McKenna, 1997). For instance, the category of manipulable objects begins with the items passport, calendar, and thermometer (all named by at least 99.5% of the population), and ends with the items jardiniere, topi, and tantalus (which could be named by less than 25% of controls). The four sets are matched for mean item familiarity.

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