

Implicit memory and Alzheimer's disease neuropathology

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Explicit memory failure is the defining cognitive feature of Alzheimer's disease and relates to the hallmark neuropathological features (plaques and tangles) of this illness. However, a pattern of preserved and impaired implicit memory has been found in Alzheimer's disease patients that may be explained by the association between the processing demands of certain implicit tests and the level of regional Alzheimer's disease neuropathology. In this study, we tested the hypothesis that these neuropathological features are related to implicit memory—measured by repetition priming—in a test that emphasized conceptual (or meaning-based) cognitive processing, and that the pathological changes are not related to implicit memory in a repetition priming test that emphasized perceptual (or sensory-based) cognitive processing. Subjects were older nuns, priests and brothers participating in the Religious Orders Study who agreed to annual neurological and neuropsychological evaluation for Alzheimer's disease and common neurological conditions of ageing, and brain autopsy at time of death. Explicit memory was measured by seven tests of episodic recall and recognition and converted to a previously established summary measure. Implicit memory was measured by four repetition priming tests. One test, category exemplar priming, emphasized conceptual, or meaning-based cognitive processing. A second test, word-identification priming, emphasized perceptual, or sensory-based cognitive processing. Two additional priming tests, picture-naming and word-stem completion, invoke both conceptual and perceptual processes. Neuritic and diffuse plaques, and neurofibrillary tangles identified by Bielschowsky silver stain, were quantified from five regions separately (frontal, parietal, temporal, entorhinal cortex and the hippocampus) and converted to a previously established summary measure. In linear regression analyses—controlling for age, sex and education—higher levels of Alzheimer's disease neuropathology were related to lower levels of explicit memory proximate to death. Higher levels of neuropathology were also related to lower levels of priming on the category-exemplar test, but were not related to levels of priming on the word-identification, picture-naming, or word-stem completion tests. The results suggest that hallmark indices of Alzheimer's disease neuropathology are associated with performance on priming tests to the extent that conceptual, but not perceptual, processing resources are required.

Keywords: Alzheimer's disease; AD neuropathology; implicit memory; repetition priming; ageing

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Introduction

Memory is the recording, retention and retrieval of information. It accounts for all knowledge gained through experience. Memory is not a unitary process, but is composed of dissociable systems that mediate specific types of mnemonic function (Squire, 1987). Specific neurological disorders, such as global amnesia and Alzheimer's disease can affect some forms of memory while leaving others relatively intact.

One form of memory, referred to as explicit (e.g. Schacter and Tulving, 1994) or declarative (e.g. Squire, 1994), is the ability to consciously and directly recall or recognize recently processed information. Impairment of this form of memory is a defining feature of global amnesia secondary to bilateral medial-temporal and/or diencephalic damage (e.g. Milner *et al.*, 1968). It is also a defining feature of Alzheimer's

disease (Carlesimo and Oscar-Berman, 1992) and has been related to the classic neuropathological features (i.e. plaques, neurofibrillary tangles) that occur in medial-temporal regions early in the disease progression (e.g. Ghoshal *et al.*, 2002; Mitchell *et al.*, 2002).

Another form of memory, referred to as implicit (Schacter and Tulving, 1994) or nondeclarative (Squire, 1994), is the ability to improve task performance based on prior, but unconscious, experience. It is assessed indirectly by measuring facilitation in performance (i.e. decreased processing time or increased accuracy) due to previous exposure to identical or related information. Performance on many implicit memory tests is preserved in global amnesia (e.g. Warrington and Weiskrantz, 1968; Diamond and Rozin, 1984; Graf and Schacter, 1985; Cermak *et al.*, 1988; Gabrieli *et al.*, 1994) suggesting that medial-temporal and/or diencephalic regions are not critical to this form of memory. Likewise, some forms of implicit memory can be spared in Alzheimer's disease (reviewed in Meiran and Jelicic, 1995). One form of implicit memory, repetition priming, has yielded a complex pattern of preservation and compromise in this disease (reviewed in Fleischman and Gabrieli, 1998). One explanation for this pattern is that priming may be impaired in Alzheimer's disease to the extent that it draws upon conceptual processing (e.g. Salmon *et al.*, 1988; Monti *et al.*, 1996; Gabrieli *et al.*, 1999) mediated by cortical association regions (e.g. Blaxton *et al.*, 1996; Gabrieli *et al.*, 1996), whereas priming may be preserved to the extent that it draws upon perceptual processing (e.g. Buckner, 1995; Fleischman *et al.*, 1995; Gabrieli *et al.*, 1995; Keane *et al.*, 1995;) mediated by posterior, modality-specific cortical regions. *In vivo* metabolic imaging studies (e.g. Frackowiak *et al.*, 1981) and post-mortem studies of clinically-diagnosed Alzheimer's disease patients (Brun and England, 1981) find substantial damage to association cortices in the frontal, parietal, and temporal lobes, but relatively little compromise of primary perceptual (modality-specific) cortices. Thus, the pattern of impaired conceptual priming and spared perceptual priming may reflect the presence and regional distribution of hallmark neuropathological indices of the disease.

Little data are available regarding the relation of performance on measures of implicit memory and the presence and regional distribution of Alzheimer's disease neuropathology. Existing knowledge is inferred by combining data from two types of studies, one of the patterns of intact and impaired memory ability in living groups of Alzheimer's disease patients (often early-stage patients who can perform the tasks) and the second from post-mortem studies of the distribution of neuropathology in groups of Alzheimer's disease patients (often late-stage patients who come to autopsy). The present study directly examined the relation between multiple forms of memory and Alzheimer's disease neuropathology.

We used data from older persons participating in the Religious Orders Study, a longitudinal clinical-pathological study of ageing and Alzheimer's disease, to test the hypothesis that conceptual, but not perceptual, forms of implicit

memory are related to traditional markers of Alzheimer's disease neuropathology. Two repetition priming tests, known to be either strongly conceptual (category-exemplar priming; Roediger and McDermott, 1993) and consistently impaired in studies of clinical Alzheimer's disease (reviewed in Fleischman and Gabrieli, 1998), or strongly perceptual (word-identification priming; Roediger and McDermott, 1993) and consistently intact in studies of clinical Alzheimer's disease (Fleischman and Gabrieli, 1998), were administered. Two additional priming tests, picture-naming and word-stem completion, which vary in the extent to which they invoke conceptual and perceptual processes in priming (Roediger and McDermott, 1993) and have been widely used in studies of clinically-diagnosed Alzheimer's disease with variable results (Fleischman and Gabrieli, 1998; Mitchell and Bruss, 2003), were also administered, along with an extensive battery of explicit memory tests.

Methods

Subjects

All subjects were recruited from a cohort of older Catholic nuns, priests, and brothers who agreed to an annual clinical evaluation and brain donation at the time of death. Subjects come from ~40 groups across the United States (see 'Acknowledgements'). Each subject signed an informed consent and an anatomic gift act donating his or her brain to investigators at the time of death. The study was approved by the Human Investigations Committee of Rush University Medical Center. Since January 1994, more than 1000 persons have enrolled in the study and have undergone annual clinical evaluation for Alzheimer's disease and other causes of cognitive impairment with an overall follow-up rate in survivors of >95%. A sub-sample of 178 persons from this cohort agreed to participate in a 4-year longitudinal examination of explicit and implicit memory. Of these 178 subjects, 53 have died and all 53 have undergone autopsy. Indices of Alzheimer's disease neuropathology were available on the first 43 subjects. Analyses were performed on 40 subjects (Table 1), after excluding three subjects with possible Alzheimer's disease or dementia due to another condition.

Clinical evaluation

Each subject underwent a uniform structured clinical evaluation that included a medical history, neurological examination, neuropsychological performance testing, and review of brain scan when available as previously reported (Bennett *et al.*, 2002). Cognitive performance tests were reviewed by a board-certified neuropsychologist. Subjects were evaluated in person by a board-certified or board-eligible neurologist or geriatrician with expertise in the evaluation of older persons with and without dementia. Based on this evaluation, subjects were classified with respect to Alzheimer's disease and other common neurological disorders. Details of the evaluation have been described previously (e.g. Bennett *et al.*, 2002; Schneider *et al.* 2004; Wilson *et al.*, 2002). Briefly, the diagnosis of dementia and Alzheimer's disease followed the recommendations of the joint working groups of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA; McKhann *et al.*, 1984). It required evidence of meaningful decline in cognitive

Table 1 Characteristics

Demographic	
<i>n</i>	40
Men (%)	20
White	100
Mean age at death (SD)	86.9 (6.5)
Mean education (SD)	18.3 (2.3)
Clinical—proximate to death	
Mean MMSE (SD) ^a	22.5 (7.6)
Mean explicit memory global (SD)	−0.97 (1.5)
Mean category exemplar (SD)	2.4 (3.0)
Mean word-identification (SD) ^b	16.7 (14.8)
Mean picture naming (SD) ^b	54.9 (216.6)
Mean word-stem completion (SD)	5.1 (3.9)
Mean interval explicit memory (SD) ^c	0.61 (0.34)
Mean interval implicit memory (SD) ^c	1.35 (1.1)
Pathological	
Mean Alzheimer's disease Neuropathology summary (SD)	0.79 (0.63)
Mean hippocampal summary (SD)	0.60 (0.65)
Mean entorhinal summary (SD)	0.98 (0.86)
Mean frontal summary (SD)	0.70 (0.71)
Mean parietal summary (SD)	0.74 (0.68)
Mean temporal summary (SD)	0.86 (0.74)

Notes: ^aMini-mental status examination, ^blatency in milliseconds and ^cyears from last clinical evaluation.

function from a previous level of performance and impairment on tests of memory and at least one other cognitive domain. 'Probable Alzheimer's disease' refers to persons with clinical disease and no other condition that is thought to be contributing to cognitive impairment; 'possible Alzheimer's disease' refers to persons with Alzheimer's disease and another condition (e.g. stroke) that is thought to be contributing to cognitive impairment. Follow-up evaluations, identical in all essential details, were performed annually by examiners blinded to previously collected data. At the time of death, all available clinical data were reviewed blinded to post-mortem data, and a summary diagnostic opinion was rendered regarding the most likely clinical diagnosis at the time of death.

Memory testing

Materials, design, procedures, and scoring rules for the tests used in this study are published in detail elsewhere (Wilson *et al.*, 2002; Fleischman *et al.*, 2004).

Seven episodic memory tests served as the measures of explicit memory. Four of the tests involved story retention: immediate and delayed recall of the East Boston Story (Albert *et al.*, 1991) and of Story A from Logical Memory of the Wechsler Memory Scale—Revised (Wechsler, 1987). Three of the tests involved learning and retaining a 10-word list (Welsh *et al.*, 1994)—Word List Memory is the total number of words immediately recalled after each of three consecutive presentations of the list. Word List Recall is the number of words recalled after an ~3 min delay; and Word List Recognition is the number of words correctly recognized in a four-alternative, forced-choice format, administered after Word List Recall.

For the implicit memory study phase, words were read or pictures were named. Four priming tests were administered: category-exemplar, word-identification, picture-naming and word-stem completion. Category-exemplar is considered the quintessential conceptual priming task, drawing strongly on conceptual processing resources, and word-identification is considered the quintessential

perceptual priming task, drawing strongly on perceptual processing resources (Roediger and McDermott, 1993). The status of picture-naming priming and word-stem completion priming along the conceptual/perceptual processing distinction is less clear (Light *et al.*, 2000; Mitchell and Bruss, 2003), although both tasks are known to draw largely on perceptual processing (Roediger and McDermott, 1993), with contributions from lexical (word-stem completion; e.g. Rueckl and Mathew, 1999) and lexical and conceptual (picture-naming) processing resources (e.g. Park and Gabrieli, 1995).

In the test phase of the category-exemplar test, subjects were told that they would be given the name of a category (e.g. vegetables) and they were to produce eight items belonging to that category, (e.g. celery, carrot, or zucchini) as quickly as they could. Priming was measured as the increase in the probability of producing a studied versus an unstudied category exemplar.

In the test phase of the word-identification test, subjects were asked to visually identify words that were presented very briefly. For each trial, the target word was presented for 16.7 ms and was immediately masked with a row of ×10's. Following a correct identification, the experimenter advanced to the next trial. Following an incorrect identification, the exposure duration of the same word was increased in multiples of 16.7 ms until the word was correctly identified. Priming was the difference in the number of trials (measured in milliseconds) needed to identify studied versus unstudied words.

In the test phase of the picture-naming test, subjects were asked to name pictures as quickly and as accurately as possible. Priming was measured as the difference in milliseconds needed to name studied versus unstudied pictures.

In the test phase of the word-stem completion test, a three-letter word stem cue (e.g. GRA___) was given and subjects were asked to produce the first word that came to mind (e.g. GRAPE) that started with those three letters. Priming was measured as the increase in the probability of producing a studied versus an unstudied word in response to the stem cue.

The implicit memory session took place within 6 months of the clinical evaluation in which the explicit memory tests were administered (Table 1).

Neuropathological evaluation

Brains were removed in a standard fashion as described previously (e.g. Bennett *et al.*, 2003; Schneider *et al.*, 2004). After weighing, each brain was cut coronally using an acrylic plastic jig into 1 cm slabs. Either the left or right hemisphere was chosen for fixation and each slab was fixed for 3–14 days in 4% paraformaldehyde. Thus, tissue blocks within each case were taken from the same hemisphere, but both left and right hemispheres were represented across the group. Tissue from the midfrontal gyrus, the inferior parietal gyrus, the superior temporal gyrus, hippocampus, and the entorhinal cortex was paraffin embedded, sectioned at 6 μm, and stained with a modified Bielschowsky silver stain (Yamamoto and Hirano, 1986).

Neuritic plaques, diffuse plaques, and neurofibrillary tangles were counted separately in each of the five cortical regions, by a board-certified neuropathologist or a trained technician blinded to all clinical data, as previously described (Bennett *et al.*, 1993). Neuritic plaques were identified by a discrete brownish discoloration with thickened argyrophilic neurites, with and without central cores of amyloid. Diffuse plaques were identified by a diffuse blush, with or without a filamentous nature, but without thickened argyrophilic neurites. To determine the density of each pathological index, we first examined the entire slide under low power (total magnification of

$\times 20$ or $\times 40$) and identified the region that appeared to have the greatest density of neuritic plaques. Then, using a graticule to mark a 1 mm^2 area, the total number of neuritic plaques was counted at a magnification of $\times 100$. This procedure was followed for each of the three pathological indices (neuritic plaques, diffuse plaques and neurofibrillary tangles) in each of the five cortical regions (frontal, parietal, temporal, entorhinal, hippocampal), resulting in 15 individual measures of neuropathology for each person. The inter-rater reliability of counts of neuritic plaques, diffuse plaques and neurofibrillary tangles using this procedure ranges from 0.89 to 0.93 for the three indices, respectively (Bennett *et al.*, 2003).

Statistical analysis

Measures

We constructed a summary measure of explicit memory, as previously described (Wilson *et al.*, 2002). The summary explicit memory measure was formed by converting raw scores on component tests to Z-scores, using the baseline mean and SD, and computing the average. Because factor analyses indicated that the four individual priming tests loaded on four separate factors, as previously described (Fleischman *et al.*, 2004), we examined each test separately rather than forming a composite measure.

A summary neuropathology measure was constructed for analyses, as previously described (Bennett *et al.*, 2003). Briefly, we first converted the raw counts for each neuropathological index (e.g. neuritic plaques, diffuse plaques, and neurofibrillary tangles) in each region to a standard distribution. We did this by dividing the count by the SD for that particular count in that region in all persons. For example, to derive the neuritic plaque standard score in the frontal region in one individual, the number of neuritic plaques in the frontal cortex of that person was divided by the SD for the frontal cortex neuritic plaques from all subjects in the sample. Next, we formed summary measures of neuritic plaques, diffuse plaques, and neurofibrillary tangles by averaging the scaled scores for each pathologic index from the five cortical regions. Finally, we constructed the global measure of Alzheimer's disease neuropathology by averaging the summary measures of neuritic plaques, diffuse plaques, and neurofibrillary tangles.

Models

We used linear regression models to examine the association of the summary Alzheimer's disease neuropathology measure to the summary measure of explicit memory and to the four repetition priming memory measures, proximate to death (Fig. 1). In secondary analyses, we used linear regression models to examine the association of global Alzheimer's disease neuropathology in each of the five brain regions separately to the summary measure of explicit memory and to the four repetition priming memory measures. All regression models controlled for the potentially confounding variables of age, sex and education. A probability level of 0.05, two-tailed, was adopted for all analyses. Models were validated graphically and analytically. All analyses were carried out in SAS[®] statistical software (SAS Institute, 2000).

Results

Scores on the summary explicit memory measure ranged from -3.7 to $+1.1$. Higher scores indicated better explicit

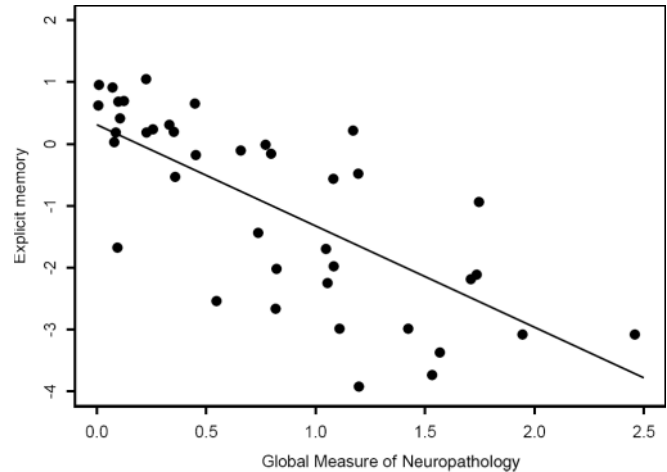


Fig. 1 Association of global Alzheimer's disease neuropathology and explicit memory.

memory. Ten percent of the sample had scores < -2.9 and 10% had scores > 0.72 . For each of the individual priming tests, higher scores indicated greater priming. Scores on the category-exemplar test ranged from -3.0 to 10.0 ; 10% of the sample did not prime. Scores on the word-identification test ranged from -17 to 57 ms; 5% of the sample did not prime. Scores on the picture-naming test ranged from -461 to 741 ms; 25% of the sample did not prime. Scores on the word-stem completion test ranged from -1.0 to 15.0 ; 1% of the sample did not prime. Scores on the summary Alzheimer's disease neuropathology measure ranged from 0.22 to 2.5 . Higher scores indicated the presence of more neuropathology. Ten percent of the sample had scores < 0.08 and 10% of the sample had scores > 1.7 . Score distributions are given in Table 1.

Associations between global Alzheimer's disease neuropathology and memory measures

Prior to examining the relation of Alzheimer's disease neuropathology to measures of implicit memory, we first established that our measure of these neuropathological features was related to episodic memory in the subset of subjects participating in these analyses. Using linear regression models that were adjusted for age, sex and education (Table 2), we found that higher levels of global neuropathology were related to lower levels of explicit memory proximate to death. Each 1 unit increase in the global neuropathology score was associated with a 1.6 unit decrease in explicit memory score ($P < 0.001$). Global Alzheimer's disease neuropathology contributed $\sim 55\%$ of the variance (based on the adjusted R^2 measure) to the explicit memory measure.

We then applied this analytic procedure to each of the individual priming tests. The first model measured the association between Alzheimer's disease neuropathology and scores on the conceptual implicit memory test,

Table 2 Relation of summary measure of Alzheimer’s disease neuropathology to measures of explicit and implicit memory*

Measure	Estimate	SE	P-value
Explicit memory	−1.636	0.286	<0.001
Category-exemplar priming	−1.740	0.846	0.047
Word-identification priming	1.143	3.474	0.967
Picture-naming priming	−85.560	60.625	0.167
Word-stem completion priming	−1.588	1.123	0.166

*From linear regression models adjusted for age, sex, and education.

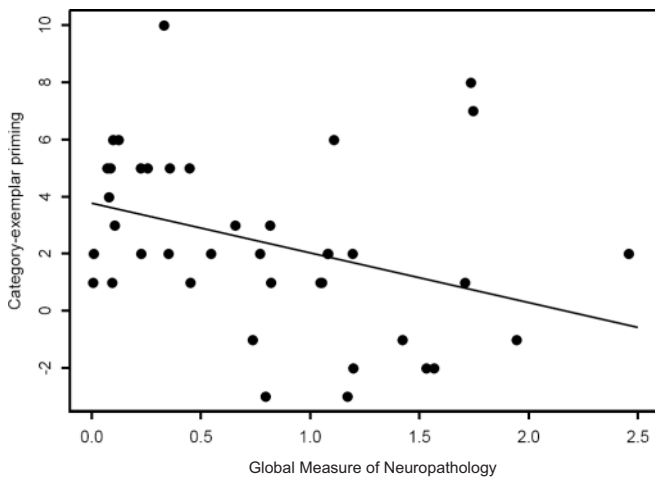


Fig. 2 Association of global Alzheimer’s disease neuropathology and category-exemplar priming.

category-exemplar priming (Fig. 2). Each 1 unit increase in the global neuropathology score was associated with a 1.7 unit decrease in category-exemplar priming score ($P=0.047$), with the global neuropathology measure contributing ~3% of the variance to the priming measure. Next, we measured the association between global neuropathology and scores on the perceptual implicit memory test, word-identification priming (Fig. 3). Levels of neuropathology were not related to priming scores on the word-identification test ($P=0.967$). Finally, we examined the association of the summary measures of Alzheimer’s disease neuropathology to picture-naming and word-stem completion priming scores. Levels of neuropathology were not related significantly to priming scores on either test ($P=0.167$ and 0.166 , respectively), although the modest trend towards a relation appear to lie between the strong association for category-exemplar priming and the absence of any relation with word-identification priming.

Associations between regional Alzheimer’s disease neuropathology and memory measures

Neuropsychological studies have shown that explicit memory is dependent on the integrity of medial-temporal and cortical

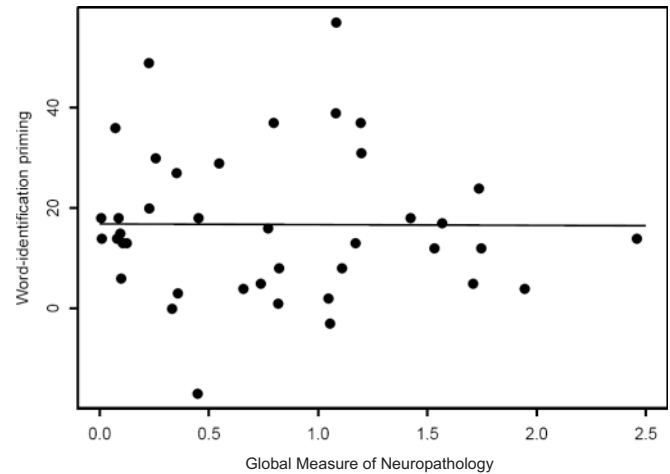


Fig. 3 Association of global Alzheimer’s disease neuropathology and word-identification priming.

Table 3 Relation of summary measure of Alzheimer’s disease neuropathology, separately in five regions, to measures of explicit and implicit memory*

Measure	Region	Estimate (SE)	P-value
Explicit memory	Hippocampal	−0.771 (0.365)	0.043
	Entorhinal	−1.015 (0.229)	<0.001
	Frontal	−1.179 (0.307)	<0.001
	Parietal	−1.157 (0.263)	<0.001
	Temporal	−1.347 (0.260)	<0.001
Category-exemplar priming	Hippocampal	−1.237 (0.923)	0.190
	Entorhinal	−1.442 (0.603)	0.023
	Frontal	−1.021 (0.805)	0.213
	Parietal	−1.452 (0.805)	0.080
	Temporal	−1.157 (0.752)	0.133
Word-identification priming	Hippocampal	−2.417 (3.635)	0.511
	Entorhinal	0.037 (2.376)	0.988
	Frontal	1.365 (3.184)	0.671
	Parietal	0.412 (3.263)	0.900
	Temporal	−1.366 (3.004)	0.652
Picture-naming priming	Hippocampal	45.724 (55.597)	0.417
	Entorhinal	−34.507 (44.959)	0.448
	Frontal	−104.998 (54.462)	0.062
	Parietal	−126.089 (54.544)	0.027
	Temporal	−87.235 (52.017)	0.102
Word-stem completion priming	Hippocampal	−1.466 (1.123)	0.202
	Entorhinal	−0.707 (0.791)	0.378
	Frontal	−0.896 (1.050)	0.400
	Parietal	−1.357 (1.060)	0.209
	Temporal	−1.519 (0.968)	0.126

*From linear regression models adjusted for age, sex and education.

association areas, whereas implicit memory, measured by repetition priming, appears to be exclusively cortically-based (reviewed in Gabrieli, 1998). In a series of exploratory secondary analyses, we examined the regional bases of the associations between Alzheimer’s disease neuropathology and scores on the explicit memory and implicit memory measures (Table 3). The exploratory nature of these analyses

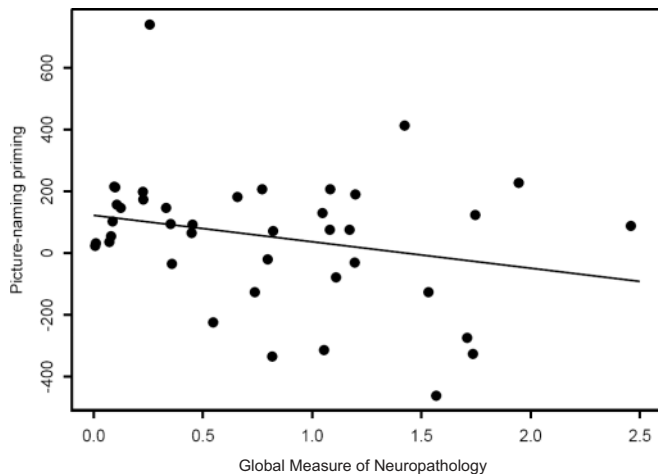


Fig. 4 Association of global Alzheimer's disease neuropathology and picture-naming priming.

is stressed given that neuropathology was highly intercorrelated across specific regions (most $P < 0.001$).

Alzheimer's disease neuropathology was measured in two medial-temporal regions (entorhinal cortex and hippocampus) and three cortical regions (frontal, parietal, and temporal). We first conducted a series of linear regression analyses adjusted for age, sex, and education to examine the association of neuropathology to explicit memory. We found that higher levels of neuropathology in all regions were related to lower scores on explicit memory measured proximate to death (all P values < 0.001).

We next conducted a series of linear regression analyses, adjusted for age, sex, and education, to examine the relation of regional Alzheimer's disease neuropathology to implicit memory (Table 3). Higher levels of neuropathology in entorhinal cortex were related to lower scores on the conceptual implicit memory test, category-exemplar priming, with trends occurring for temporal and parietal cortices. By contrast, the level of neuropathology was not related to scores on the perceptual implicit memory test, word-identification priming, in any region. A higher level of Alzheimer's disease neuropathology in parietal cortex was related to lower scores on the picture-naming priming test, with trends occurring for temporal and frontal cortices (Fig. 4). Finally, levels of neuropathology in all regions were not related to scores on the word-stem completion priming test, although there was a trend toward an association with temporal cortex (Fig. 5).

Discussion

The goal of this study was to examine the association between traditional markers of Alzheimer's disease neuropathology and implicit memory, measured by repetition priming. After documenting the expected negative association between explicit memory proximate to death and traditional markers in Alzheimer's disease neuropathology in this sample of

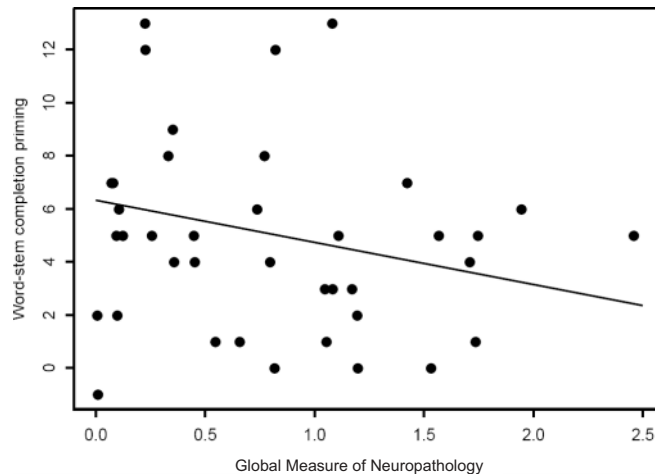


Fig. 5 Association of global Alzheimer's disease neuropathology and word-stem completion priming.

aged Religious Orders' Study subjects, we found that higher levels of global neuropathology were related to lower levels of implicit memory proximate to death on the category-exemplar priming test, but that levels of global neuropathology were not related to implicit memory on the word-identification priming test. The results parallel the findings from behavioural studies of clinically-diagnosed Alzheimer's disease that document a consistent pattern of compromised and preserved performance, respectively, on these two tests.

Behavioural studies of clinically-diagnosed Alzheimer's disease have shown a reliable reduction in priming on the category-exemplar test (e.g. Maki and Knopman, 1996; Monti *et al.*, 1996; Gabrieli *et al.*, 1999), and the findings of the current study link that reduction to the global presence of Alzheimer's disease neuropathology. A reliable preservation of priming on the word-identification test is similarly documented in studies of the disease (e.g., Keane *et al.*, 1991, 1994; Fleischman *et al.*, 1995; Koivisto *et al.*, 1996), and the current findings indicate that this form of priming is unrelated to presence of global neuropathology in Alzheimer's disease. Behavioural studies of picture-naming priming and word-stem completion priming have produced more variable findings in Alzheimer's disease (for reviews see Meiran and Jelicic, 1995; Fleischman and Gabrieli, 1998; Mitchell and Bruss, 2003), and in this study, these forms of priming were marginally unrelated to global Alzheimer's disease neuropathology. Thus, the pattern of associations between performance on the four priming tests administered in this study, and the presence of global neuropathology, supports the widely documented heterogeneity of priming findings.

The findings of this study suggest that some forms of repetition priming are more vulnerable to the global accumulation of Alzheimer's disease neuropathology than are others. One potential explanation lies in the functional dissociation between conceptual versus perceptual processes in priming that has been established in young normal

persons (Roediger and Blaxton, 1987*a, b*; Blaxton, 1989; Weldon, 1991) and has been widely applied to results of studies in persons with clinically diagnosed Alzheimer's disease (see Fleischman and Gabrieli, 1998). Conceptual priming requires processing the meaning of stimuli, and is often impaired in this illness (e.g. Brandt *et al.*, 1988; Salmon *et al.*, 1988; Carlesimo *et al.*, 1995; Monti *et al.*, 1996; Gabrieli *et al.*, 1999). We found an association between global Alzheimer's disease neuropathology and category-exemplar priming, widely considered to be the quintessential conceptual priming test (Roediger and McDermott, 1993). By contrast, perceptual priming requires processing the sensory form of stimuli, and is often preserved in Alzheimer's disease (e.g. Ober *et al.*, 1991; Fleischman *et al.*, 1995; Postle *et al.*, 1996; Park *et al.*, 1998; Gabrieli *et al.*, 1999). We did not find an association between global Alzheimer's disease neuropathology and word-identification priming, widely considered to be the quintessential perceptual priming task (Roediger and McDermott, 1993).

The status of the picture-naming priming and word-stem completion priming tests along the conceptual-perceptual processing distinction is currently unclear (e.g. Mitchell and Bruss, 2003). Previously believed to be strongly perceptual tests, recent studies have shown that, in addition to drawing on perceptual processes, word-stem completion priming invokes lexical/phonetic processing (e.g. Rueckl and Mathew, 1999) and picture-naming priming invokes lexical and conceptual processing (e.g. Park and Gabrieli, 1995). In this study, global Alzheimer's disease neuropathology was not significantly related to performance on either of these priming tests. However, unlike the robust lack of association of global neuropathology with perceptual word-identification priming, or the robust association with conceptual category-exemplar priming, the findings for picture-naming priming and word-stem completion were marginal, perhaps reflecting the multi-componential processing demands of these two tasks. According to this viewpoint, perceptual components of priming may be spared, and lexical and/or conceptual components may be compromised, so that the overall status of task performance reflects the mixture of spared and compromised cognitive processes. The strength of the relationship between global Alzheimer's disease neuropathology and priming may then depend on the extent that a test draws upon conceptual, and not perceptual, processing.

Alternatively, other cognitive processes, such as stimulus production and stimulus identification, have been linked to the success or failure of both perceptual (e.g. Gabrieli *et al.*, 1999; Fleischman *et al.*, 2000) and conceptual (e.g. Vaidya *et al.*, 1997; Gabrieli *et al.*, 1999) priming in studies of clinically diagnosed Alzheimer's disease. The category-exemplar priming test requires the selection and the production of exemplars of semantic categories, whereas the word-identification test requires the perception and identification of visual events. Thus, another explanation for the current findings is that the presence of global Alzheimer's disease neuropathology is related to the extent that a priming test

requires production, rather than identification processes. Both perceptual production (word-stem completion) and perceptual identification (word-identification) priming tests were administered in this study, and the association of word-identification with global neuropathology was strongly non-significant, but the association with word-stem completion was marginally non-significant. This finding hints that production processes in perceptual priming may be linked to global neuropathological markers of Alzheimer's disease. A conceptual production priming test (category-exemplar production) was included in this study, but a conceptual identification test, such as category-exemplar verification (e.g. Gabrieli *et al.*, 1999) was not. Thus, the findings cannot address the association between production and identification processes and global Alzheimer's disease neuropathology within the realm of conceptual priming.

It is well-established that the earliest cognitive symptom of Alzheimer's disease is a profound explicit memory deficit, and the earliest site of neuropathology is in the mesial-temporal lobe (e.g. Small *et al.*, 1997; Dickerson *et al.*, 2001; Kordower *et al.*, 2001; Marquis *et al.*, 2002). As the disease progresses, neuropathological changes spread outside the mesial-temporal lobe and into multimodal association areas (e.g. Hyman *et al.*, 1984). Modality-specific cortices in far posterior regions remain relatively preserved until the later stages of the disease (e.g. Damasio *et al.*, 1990). It is thought that implicit memory, measured by repetition priming, is a cortically-based phenomenon (reviewed in Gabrieli, 1998). Neuroimaging activation studies have implicated multimodal association neocortex in conceptual priming (Blaxton *et al.*, 1996; Gabrieli *et al.*, 1996), and lesion (e.g. Fleischman *et al.*, 1995; Gabrieli *et al.*, 1995; Keane *et al.*, 1995) and neuroimaging studies (e.g. Squire, 1994; Schacter and Tulving, 1994; Buckner *et al.*, 1995; Blaxton *et al.*, 1996) have implicated posterior modality-specific cortical regions in visual perceptual priming. Based on these studies, we undertook exploratory analyses to examine the association of regional neuropathology to the pattern of priming compromise and preservation found in this study. Because these were qualitative analyses, and because many of the findings were marginal, we caution that they should be considered suggestive patterns in need of further investigation.

The presence of Alzheimer's disease neuropathology in the hippocampus was associated with explicit memory, and was not associated with implicit memory on any priming measure. This was an expected dissociation based on a well-established literature documenting impaired explicit, and preserved implicit, memory in amnesic patients with bilateral mesial-temporal lobe lesions (see Gabrieli, 2001 for a review). The presence of neuropathology in entorhinal cortex, a mesial-temporal lobe structure, was also associated with explicit memory, as expected based on clinicopathological studies (for reviews see Ghoshal *et al.*, 2002; Mitchell *et al.*, 2002). An unexpected finding was that category-exemplar priming was significantly related to Alzheimer's disease neuropathology in entorhinal cortex. This is unexpected

because amnesic patients with bilateral lesions encompassing the entorhinal cortex exhibit intact category-exemplar priming (Gabrieli, 2001). It is unlikely that explicit contamination of category-exemplar priming explains the finding because hippocampal neuropathology was not related to implicit memory on this, or any other priming task, used in the study. However, both explicit recognition memory and category-exemplar priming are strongly driven by conceptual processing and, indeed, in this study, recognition memory performance was correlated with category-exemplar priming performance ($P < 0.01$), but was not correlated with word-identification priming performance ($P = 0.57$). The findings thus suggest that performance on memory tests that strongly demand conceptual processing resources may be especially vulnerable to the presence of Alzheimer's disease neuropathology, particularly in entorhinal cortex.

The findings of this study have implications for the early diagnosis of Alzheimer's disease. It has been demonstrated in longitudinal studies (Hultsch *et al.*, 1992; Christensen *et al.*, 1997; Davis *et al.*, 2001; Fleischman *et al.*, 2004) that priming remains robust in old age, even in the face of significantly declining explicit memory. It has been speculated that when a priming deficit exists along with an explicit memory deficit, this could signal that Alzheimer's disease neuropathology is present and that a diagnosis of clinical Alzheimer's disease is imminent (e.g. Fleischman *et al.*, 1999, 2004). The current findings show that, indeed, the presence of Alzheimer's disease neuropathology in entorhinal cortex, the earliest site of devastating pathological change in Alzheimer's disease, is associated with reductions in both explicit memory and conceptual priming. It has recently been reported (Bennett *et al.*, 2005) that mild cognitive impairment, a transitional state between normal cognition and clinical Alzheimer's disease (e.g. Petersen *et al.*, 2001; Bennett *et al.*, 2002) is related to the presence of these neuropathological changes. However, not all persons with mild cognitive impairment develop clinical Alzheimer's disease (e.g. Marquis *et al.*, 2002; Palmer *et al.*, 2002). Thus, it is reasonable to speculate, based on the current findings, that those persons with mild cognitive impairment characterized by both an explicit memory deficit and a conceptual priming deficit, may be those who are particularly at risk for developing clinical Alzheimer's disease. Studies are needed that examine the status of priming in persons with mild cognitive impairment.

The findings of this study should be interpreted within the context of some limitations. First, the subjects were religious orders' members and thus do not represent the US population in terms of education and lifestyle. Second, our autopsy sample size was similar to that of the typical behavioural priming study in clinical Alzheimer's disease; however, it was small and may have limited power to detect effects. Third, we did not sample Alzheimer's disease neuropathology from far posterior modality-specific regions, such as the calcarine cortex, which are more involved in visual perceptual priming. Fourth, we used silver stained sections rather than antibody specific staining techniques, to identify amyloid deposition and tau

tangles, and used crude counts, sampled from a single hemisphere, rather than more unbiased counting techniques.

Despite these caveats, the present study finds within-subject evidence that directly relates multiple forms of memory, explicit and implicit, to the presence of Alzheimer's disease neuropathology. Explicit memory, as previously documented in clinicopathological studies, was related to neuropathology in medial temporal and neocortical regions. Implicit memory, which has not previously been examined in clinicopathological studies, was differentially related to Alzheimer's disease neuropathology depending upon the processes invoked by specific tests. Memory performance on the most purely conceptual priming test was related to Alzheimer's disease neuropathology. Memory performance on the most purely perceptual task was unrelated to the in Alzheimer's disease neuropathology. These findings support the view that memory ability in Alzheimer's disease may be impaired or intact to the extent that the processes underlying particular forms of memory are mediated by regions that are more or less affected by the presence of Alzheimer's disease neuropathology.

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