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Word Reading and Posterior Temporal Dysfunction in Amnestic Mild Cognitive Impairment

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Patient studies that combine functional magnetic resonance imaging with chronometric analysis of language dysfunction may reveal the critical contribution of brain areas to language processes as well as shed light on disease pathogenesis. In amnestic mild cognitive impairment (MCI), a prodromal stage of Alzheimer's disease, we examined whether the brain system for associative-semantic judgments with words or with pictures is affected and how this relates to off-line chronometric analysis of word reading and picture naming. A consecutive memory clinic–based series of 13 amnestic MCI patients as well as 13 matched controls participated. One area, the lower bank of the posterior third of the left superior temporal sulcus (STS), showed a significant group-by-task interaction: In controls, it was activated during the associative-semantic condition with words compared with the visuoperceptual control condition but not when the same tasks were compared with pictures as input. In MCI, this word-specific activation was significantly reduced. Response amplitude correlated ($r = 0.90$) with the steepness of the slope of the time-accuracy curve for word reading. Our data provide converging evidence for a critical contribution of the lower bank of the left posterior STS to mapping word form onto word meaning (lexical-semantic retrieval).

Keywords: alzheimer, fMRI, language, lexical, semantic

Introduction

In cognitive neuroscience, patient studies have an important place not only because they may provide insight into the pathogenesis of cognitive dysfunction but also because from the consequences of regional brain dysfunction, essential information can be derived about the critical nature of the contribution of specific brain regions to cognitive processes (Posner and Carr 1992). In this study of the brain substrate of language and semantic memory, we combined functional magnetic resonance imaging (fMRI) in healthy controls with fMRI in patients. We examined how pathological alterations of fMRI activity patterns related to chronometric measures of word reading and picture naming (Posner and Carr 1992).

We selected a patient population who did not show a clinical language or semantic memory deficit according to conventional neuropsychological testing at the moment of testing but were at risk for developing clinically evident language or semantic memory problems over the years to come. Recently, brain alterations that precede the dementia stage of Alzheimer's disease (AD) have evoked a lot of interest. In memory clinic–based cohorts, a valid clinical approximation of this predementia stage is "amnestic mild cognitive impairment" (MCI) (Morris and others 2001; Petersen 2004). Amnestic MCI is clinically defined by the presence of a subjective complaint of memory decline and corroborated by an informant, objective impairment of episodic memory on routine neuropsychological assessment, and minimal impact upon instrumental activities of daily living (IADL) (Petersen 2004). Other cognitive domains are relatively preserved or only mildly affected, in which case the designation "amnestic MCI multidomain" has been proposed (Petersen 2004). In memory clinic–based cohorts, when criteria are strictly applied and alternative causes are rigorously excluded, approximately 80% of patients clinically diagnosed with amnestic MCI convert to probable AD within 6 years (Petersen 2004). The clinical condition of amnestic MCI provides us with a time window to study AD-related changes of the language and semantic memory system that chronologically precede the dementia stage (Morris and others 2001). fMRI studies in amnestic MCI until now have principally focused on episodic memory and on medial temporal volumes of interest (Small and others 1999; Machulda and others 2003; Dickerson and others 2004, 2005; Johnson and others 2004).

Patients who are in the early stage of probable AD are frequently impaired on single-word–processing tasks, particularly naming (Bayles and Tomoeda 1983; Huff and others 1986; Nebes 1989; Welsh and others 1992; Locascio and others 1995; Emery 1996). Naming impairment cannot be fully explained by the object identification problems that exist in some AD patients (Done and Hajilou 2005). The naming deficit may originate from disturbances at the level of lexical-semantic processing, that is, a context-dependent impairment of access to, or inability to use, structurally intact semantic representations (Bayles and Tomoeda 1983; Nebes and Brady 1988, 1990; Nebes 1989; Bayles and others 1991). Alternatively, word-finding and word comprehension problems may emanate from an actual loss of semantic knowledge that gives rise to a deficit that is consistent for a given item across a variety of tasks (Martin and Fedio 1983; Huff and others 1986; Chertkow and Bub 1990; Hodges and Patterson 1995; Hodges and others 1996; Cuetos and others 2003). For instance, AD patients who fail to name a picture are also deficient in retrieval of knowledge about the picture, even when tested by nonverbal means (Martin and Fedio 1983; Chertkow and Bub 1990). This has been interpreted as evidence in favor of semantic memory loss rather than a lexical-semantic retrieval deficit (Martin and Fedio 1983; Chertkow and Bub 1990). Single-word oral reading may also be impaired in early stage AD, in particular, for low-frequency irregular words (Fromm and others 1991; Patterson and others 1994) and for nonwords (Friedman and others 1992; Patterson and others 1994; Caccapolo-van Vliet and others 2004; Colombo and others 2004). Visuoperceptual word identification problems

(Patterson and others 1994; Glosser and others 2002; Gilmore and others 2005), problems with grapheme-to-phoneme conversion (Friedman and others 1992), or semantic memory loss (Patterson and others 1994) all have been invoked to explain oral reading disturbances in early stage probable AD. Studies of a final task, single-word repetition, suggested that lexical-phonological processing is relatively spared in early stage AD (Emery 1996; Glosser and others 1997).

We addressed 2 questions: First, is the network for language and semantic memory altered in amnestic MCI despite apparent preservation clinically, and are word-specific regions mainly affected or components of the semantic memory system that are independent of input modality (words or pictures)? In the light of the evidence that has been advanced in favor of the hypothesis of a semantic memory loss in AD (Martin and Fedio 1983; Chertkow and Bub 1990; Hodges and Patterson 1995; Hodges and others 1996), we predicted that amnestic MCI would be associated with changes in input modality–independent, semantic-processing areas rather than word-specific–processing areas.

As our second research question, we asked how regional dysfunction measured using fMRI relates to off-line chronometric analysis of word reading and picture naming. Our chronometric analysis was based on a time-accuracy approach that allowed to decompose word reading and picture naming into different processes (Wickelgren 1977; Verhaeghen and others 1998). We varied word or picture exposure duration and determined accuracy as a function of stimulus duration. Three measures can be derived for each individual's time-accuracy curve: the time of onset of the rising phase, the steepness of the slope, and the accuracy asymptote (Wickelgren 1977; Verhaeghen and others 1998). These parameters reflect different processes. For example, a delay of the onset of the word-reading curve may arise from early visual identification problems that impair letter identification. At the other end, a lowering of the asymptote of the word-reading curve may arise from speech output problems, such as phonological output, phonetic, or articulatory deficits (Levelt 1999). When onset or asymptote of the time-accuracy curves do not differ between groups but the slope does, time-sensitive processes are impaired that facilitate word reading and lie in between the early visual identification processes and speech output processes. In a reading experiment with regular words, these time-sensitive facilitatory processes include lexical assembly (phoneme-to-grapheme conversion) and lexical retrieval processes (orthographic-lexical, lexical-semantic, and lexical-phonological retrieval) (Ellis and Young 1988; Posner and Carr 1992; Caramazza 1997; Levelt 1999). We correlated the parameters that define the time-accuracy curve with fMRI response amplitude in those areas that were affected in the patients.

Subjects and Methods

Subjects

A consecutive series of 13 patients (8 men, 5 women) who were recruited via the memory clinic, University Hospital Gasthuisberg, Leuven, participated. They fulfilled the clinical diagnostic criteria for amnestic MCI (Petersen 2004). Patients were between 55 and 76 years of age (mean 65.8, standard deviation [SD] 6.8 years), mean educational level was 12.7 years (SD 2.7), and mean modified Edinburgh inventory handedness score +88.7. Memory impairment was the primary reason for attending the memory clinic in all patients, and memory decline was confirmed by an informant and by a routine clinical neuropsychological evaluation. Other cognitive domains and IADL were relatively preserved, so that a diagnosis of clinically probable AD (McKhann and others 1984; American Psychiatric Association 1994) could not be made. Clinical dementia rating (CDR) scale (Morris and others 1997) was 0.5 in each of the patients, with a mean memory score of 0.58 (SD 0.18). We excluded patients who had significant vascular lesions on clinical fluid-attenuated recovery magnetic resonance imaging (MRI) sequences. All subjects were formally psychiatrically assessed to exclude mood or anxiety disorders as a cause of the memory complaint. All were free from cognitive enhancing or other psychotropic medication.

The MCI patients were compared with 13 cognitively intact controls, matched for gender (8 men, 5 women), age (mean age 65.9, SD 6.3, range 56–77 years), educational level (12.9 years, SD 2.6), handedness (modified Edinburgh inventory +87.4), and vascular risk factors. The controls were selected from a cohort of elderly cognitively intact subjects recruited through advertisement in a regional newspaper. Controls did not have any memory complaints and had no history of significant neurological or psychiatric illness.

After complete description of the study to the subjects, written informed consent was obtained in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethical Committee, University Hospital Gasthuisberg, Leuven.

After inclusion, MCI patients and controls underwent a standard neuropsychological research protocol (Table 1). Controls as well as all MCI patients except one (case 7) also underwent apolipoprotein E (apo E) genotyping after inclusion in the study. The MCI group comprised 5 apo E ε4 heterozygotes (41%) and 1 homozygote (8%), the control group 3 apo E ε4 heterozygotes (23%) and no homozygotes.

Neuropsychological Protocol

Language was assessed by means of the validated Dutch versions of the Aachen Aphasie test (Akense Afasie test [AAT]) (Graets and others 1992) and of the verbal association test of the psycholinguistic assessment of language processing in aphasia (Bastiaanse and others 1995). Episodic memory was tested by means of the auditory verbal learning test and the Rey visual design learning test. Other cognitive domains were tested by means of the trail-making test, the Raven's colored progressive matrices, the number location test of the visual object and space perception battery (Warrington and James 1991), and the object decision test of the Birmingham object recognition battery (Riddoch and Humphreys 1993). The functional activities questionnaire (Pfeffer and others 1992) and the CDR total score (Morris and others 1997) were also included.

fMRI Experiment: Stimuli and Tasks

Stimuli were projected from a Barco 6300 LCD projector (1280 × 1024 pixels) onto a screen 28 cm in front of the subjects' eyes. The experiment was conducted using Superlab for PC version 2.0 (Cedrus, Phoenix, AZ). The design of the fMRI experiment was factorial (Vandenberghe and others 1996). The first factor, task, had 2 levels: associative-semantic versus visuoperceptual judgment. The second factor, input modality, also had 2 levels: pictures versus printed words. The associative-semantic condition was derived from the pyramids and palm trees test (Howard and Patterson 1992) (Fig. 1*A*). During a trial, a triplet of stimuli was presented for 5250 ms, one stimulus on top (the sample stimulus) and one in each lower quadrant (the test stimuli), at 3.8 ° eccentricity, followed by a 1500-ms interval. Subjects had to press a left- or right-hand key depending on which of the 2 test stimuli matched the sample stimulus more closely in meaning. A given triplet was presented in either the picture (Fig. 1*A1*) or the word format (Fig. 1*A2*), and this was counterbalanced across subjects. In the visuoperceptual control condition, a picture (Fig. 1*A3*) or word stimulus (Fig. 1*A4*) was presented in 3 different sizes. Subjects had to press a left- or right-hand key depending on which of the 2 test stimuli matched the sample stimulus more closely in size on the screen.

Image Acquisition

A 1.5-T Siemens Sonata system (Siemens Medical Solutions, Erlangen, Germany) equipped with an 8-channel receive-only head coil (MRI Devices Corp., Waukesha, WI) provided a high-resolution magnetization-prepared rapid gradient echo T_1-weighted structural volume as well as T_2* echo-planar images (EPI) (42 sagittal slices, voxel size 3 × 3 × 3 mm^3, time echo/time repetition 40/3000 ms). Usage of the generalized

Table 1
Neuropsychological individual and group data

	Case													MCI Mean (SD)	Controls Mean (SD)	*t*
	1	2	3	4	5	6	7	8	9	10	11	12	13			
Age (years)	55	55	60	62	68	68	70	76	63	64	67	73	75	65.8 (6.8)	65.9 (6.3)	0.0
Education (years)	17	14	9	12	14	16	17	12	11	12	9	10	12	12.7 (2.7)	12.9 (2.6)	0.0
FAQ (/7)	**2**	**2**	**2**	**2**	**3**	**2**	**2**	**2**	**3**	**2**	**2**	**2**	**3**	**2.2** (0.4)	1.0 (0.0)	−9.8
CDR																
Global CDR (/3)	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	**0.5** (0)	0 (0)	−14.0
Sum of the boxes (/18)	**2.5**	**0.5**	**1**	**0.5**	**2.5**	**1**	**1.5**	**0.5**	**3**	**2**	**1.5**	**1.5**	**1**	**1.5** (0.85)	0 (0)	−5.2
Auditory verbal learning test																
Learning (/75)	**33**	48	**35**	43	**31**	**34**	49	**36**	**31**	**23**	**29**	**27**	**17**	**33.7** (9.2)	50.1 (6.5)	5.4
Recall (/15)	**5**	8	**4**	**6**	**0**	**5**	9	**2**	**5**	**1**	**6**	**1**	**0**	**4.2** (3.3)	11.2 (1.7)	6.6
% Recall	**71**	**61**	**50**	**50**	**0**	**55**	**75**	**28**	**71**	**20**	**75**	**20**	**0**	**47.3** (31.4)	90.1 (7.4)	4.7
Recognition (/15)	**8**	14	**12**	**13**	14	**12**	14	**13**	14	**4**	15	**7**	**6**	**11.3** (3.7)	14.6 (0.6)	3.0
Rey visual design learning test																
Recognition (/15)	**9**	14	**11**	13	**5**	14	13	13	12	**9**	14	**8**	13	**11.4** (2.9)	14.0 (1.4)	3.1
Aachen Aphasie test																
Naming (/120)	119	116	117	115	117	119	120	109	114	110	116	115	**105**	114.7 (4.3)	117.2 (4.4)	1.6
Comprehension (/120)	116	119	105	117	112	117	111	112	111	109	112	115	109	112.7 (3.9)	113.6 (5.4)	1.4
Auditory word–picture matching (/30)	29	30	24	30	27	30	28	**25**	26	30	23	30	26	27.5 (2.5)	28.7 (1.8)	1.4
Auditory sentence–picture matching (/30)	30	30	28	30	27	30	27	30	27	26	29	27	30	27.8 (2.8)	28.7 (1.8)	1.1
Visual word–picture matching (/30)	30	29	**26**	29	29	30	30	27	28	28	30	29	27	28.6 (1.3)	28.8 (1.0)	0.5
Visual sentence–picture matching (/30)	27	30	27	28	29	27	26	30	30	25	30	29	26	28.0 (1.8)	27.8 (2.1)	−0.3
Spontaneous speech (/30)	30	30	30	30	30	30	30	29	30	30	29	30	29	29.7 (0.4)	29.8 (0.4)	0.5
Communicative behavior (/5)	5	5	5	5	5	5	5	5	5	5	5	5	5	5.0 (0.0)	5.0 (0.0)	0.0
Articulation (/5)	5	5	5	5	5	5	5	5	5	5	5	5	5	5.0 (0.0)	5.0 (0.0)	0.0
Automatized language (/5)	5	5	5	5	5	5	5	5	5	5	5	5	5	5.0 (0.0)	5.0 (0.0)	0.0
Semantic structure (/5)	5	5	5	5	5	5	5	**4**	5	5	5	5	**4**	4.8 (0.4)	4.9 (0.3)	0.6
Phonological structure (/5)	5	5	5	5	5	5	5	5	5	5	5	5	5	5.0 (0.0)	5.0 (0.0)	0.0
Syntactic structure (/5)	5	5	5	5	5	5	5	5	5	5	**4**	5	5	4.9 (0.3)	4.9 (0.3)	0.0
Reading (/30)	30	30	30	30	30	30	30	30	30	30	30	30	30	30 (0.0)	30 (0.0)	0.0
Writing (/30)	30	30	30	29	30	30	28	30	30	30	28	28	30	29.4 (0.8)	29.5 (0.8)	0.8
PALPA (/30)	30	29	29	29	29	27	30	29	30	28	27	29	25	28.5 (1.4)	28.4 (1.7)	−0.2
TMT	2.0	2.6	3.2	1.8	3.2	2.7	1.7	2.3	2.7	2.6	3.0	**4.2**	3.2	2.71 (0.68)	2.55 (0.63)	−2.2
CPM (/36)	36	36	27	36	29	34	35	33	30	30	**23**	**19**	29	30.5 (5.3)	32.4 (2.7)	1.8
Number location (/10)	8	10	10	9	10	10	7	9	9	8	9	10	10	9.1 (0.9)	9.4 (0.7)	1.2
Object decision (/64)	58	57	57	57	55	56	57	55	**47**	**51**	57	55	**47**	54.5 (3.8)	57.8 (2.0)	2.3

Note: Individual data—Bold, 2 SDs lower than average of our age- and education-matched controls. Group data—Bold, $P < 0.05$ corrected for multiple comparisons. CPM, colored progressive matrices; FAQ, functional activities questionnaire; PALPA, psycholinguistic assessment of language processing in aphasia; TMT, trail-making test.

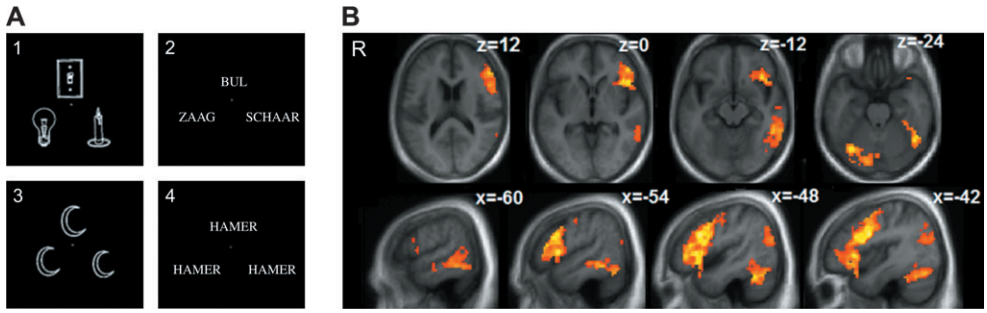

Figure 1. (*A*) Stimuli and tasks. (*1*, *2*) Associative-semantic task with pictures (*1*) and with words (*2*) (translation: Sample stimulus, Axe; Test stimuli, Saw and scissors). (*3*, *4*) Visuoperceptual task with pictures (*3*) or words (*4*) (translation: Hammer). (*B*) Search volume obtained from the subtraction associative-semantic minus visuoperceptual conditions across groups (contrast 1). Threshold: uncorrected $P < 0.001$. *x* and *z*: Talairach coordinates (in mm).

autocalibrating partially parallel acquisitions method together with sagittal acquisition maximized sensitivity for anterior temporal activity changes and minimized susceptibility artifacts (Griswold and others 2002). A total of 108 volumes were acquired during each run. Each run consisted of 3 replications of each of the 4 conditions. Each epoch, that is, a block of trials of the same type, consisted of 4 trials (total duration 27 s). Subjects underwent 4–6 runs each.

Image Analysis

We used Statistical Parametric Mapping 2002. Head motion parameters did not differ between groups ($P > 0.9$). After realignment, reslicing, and normalization (Friston and others 1995), the EPI volumes were spatially smoothed using a 6-mm full width half maximum (FWHM) isotropic Gaussian kernel. A high-pass filter with a FWHM of 216 s was applied and a low-pass filter consisting of a canonical hemodynamic response function (HRF). The epoch-related response was modeled by a canonical HRF convolved with a boxcar.

A *t*-statistic for the parameter estimates was generated for each subject for the following contrasts:

1. (Associative-semantic task with words + Associative-semantic task with pictures) – (Visuoperceptual task with words + Visuoperceptual task with pictures).
2. Associative-semantic task with words – Visuoperceptual task with words.
3. Associative-semantic task with pictures – Visuoperceptual task with pictures.
4. (Associative-semantic task with words + Visuoperceptual task with words) – (Associative-semantic task with pictures + visuoperceptual task with pictures) and inversely.

5. (Associative-semantic task with words – Visuoperceptual task with words) – (Associative-semantic task with pictures – visuoperceptual task with pictures) and inversely.

The *t*-map was subsequently transformed to a *Z* map. The data did not show any outlier or clustering (Kherif and others 2003). We weighted the individuals' contrast images for the total number of runs per subject and entered the significance maps into a second-level analysis. Using a 1-sample *t*-test, we first defined our search volume: we determined where the associative-semantic condition yielded higher activity than the visuoperceptual condition (contrast 1) across subjects at an uncorrected $P < 0.001$. Within this search volume, we determined where the images for each of the above contrasts (contrasts 1–5) differed between controls and MCI patients. We used a 2-sample *t*-test with a voxel-level significance threshold set at $P < 0.05$ corrected for the search volume.

We wanted to exclude that between-group differences in gray matter volume contributed to functional activity differences. We conducted an optimized voxel-based morphometric (VBM) analysis (Ashburner and Friston 2000). Using a 2-sample *t*-test, we examined where gray matter volume differed between the patient group and the MCI group.

Chronometric Experiment

In order to assess word or picture processing with higher sensitivity, we conducted a chronometric study. A trial consisted of a forward mask (200-ms duration), followed by a test stimulus (a word or a picture), which was immediately followed by a backward mask (200-ms duration). Word size was 1.5° and picture size 5.7°. Only regular words were used. Test stimulus presentation duration varied between 30, 45, 60, 90, 150, 200, 500, or 800 ms. Subjects were instructed to read the word or name the picture. Subjects received 320 trials in total. Each concept was presented once as a word and once as a picture in a counterbalanced order. All pictures were drawn from the standardized Snodgrass and Vanderwart picture set (Snodgrass and Vanderwart 1980). Name agreement for the picture's most common ("dominant") name in English was 90.9% (SD 9.7, range 60–100%) (Snodgrass and Vanderwart 1980) and in Dutch 90.7% (SD 13.4, range 60–100%), as determined in an independent sample of Dutch-speaking controls. Word frequency was 1.36 (SD 0.60) (Baayen and others 1993). Answers were considered correct if they were the picture's dominant name, a synonym, or the name of a subordinate to the entity designated by the dominant name. For the word-reading task, only well-articulated fully pronounced words were qualified as correct.

For each individual, onset, slope, and asymptote of the time-accuracy function for words and pictures were calculated by means of the following equation (Wickelgren 1977; Verhaeghen and others 1998):

$$p = \begin{cases} c^*(1 - e^{(a-\Delta t)/b}) & \text{if } \Delta t \geq a \\ 0 & \text{if } 0 \leq \Delta t < a \end{cases}. \quad (1)$$

In this equation, p stands for the percentage of correctly answered items, which is a function of presentation time Δt. The curve described by equation (1) is negatively accelerating, that is, it remains at zero up to a certain point in time (parameter a), where it starts to rise steeply, and it becomes less and less steep with advancing presentation time, flattening toward a horizontal asymptote (parameter c) (Verhaeghen and others 1998). The parameter a (the onset) represents the point on the time axis where performance starts to rise above zero. The parameter c (the asymptote) represents the level of performance a participant would reach if an unlimited amount of time were available. The parameter b (the rate of approach) represents the rate at which performance goes to the asymptote. Higher values of b indicate that the time-accuracy function is less steep, that is, participants with higher b values are slower in reaching the asymptotic level of performance than participants with lower b values. The parameter b presumably reflects the speed of deployment of the elaboration process, that is, the rate at which associations can be generated to the stimulus (Verhaeghen and others 1998). Goodness of fit was estimated as the sum of squared differences between the measured and calculated values (sum of the squared errors).

Ten MCI patients (cases 1–3, 5, 6, 8–10, 12, 13) and 10 matched controls participated in the chronometric study.

We carried out a multiple linear regression analysis with fMRI response amplitude as outcome variable and the psychophysical word and picture identification parameters a, b, and c as regressors. This analysis was restricted to a spherical volume of interest (radius 3 voxels) surrounding the voxels of peak differential activation between MCI and controls. The analysis was carried out on the data of the MCI patients only and was therefore independent of the voxel selection criterion. The significance map was thresholded at a voxel-level inference of $P < 0.05$ corrected for the spherical volume of interest.

Follow Up

During the first year of follow up, case 7 (Table 1) died from an unrelated cause and case 11 (Table 1) withdrew consent. After 1 year, the 11 remaining patients and 11 matched controls underwent a clinical and neuropsychological reevaluation and a repeat structural and functional MRI. Subjects were also reevaluated clinically and neuropsychologically after the second year.

For the follow-up scans, we determined where the difference between the associative-semantic and the visuoperceptual conditions (contrast 1) differed between patients and controls at the second time point (2-sample *t*-test, significance threshold $P < 0.05$ corrected for the search volume).

Results

Neuropsychological Data

As a group, patients performed significantly worse than controls on all measures of episodic memory performance (Student's *t*-test for independent samples: $P < 0.05$, Table 1) but not in other cognitive domains. In each of the MCI individuals, the score of at least 1 episodic memory task fell 2 SDs below the mean of our age- and education-matched controls (Table 1). In 8 subjects, performance in cognitive domains other than episodic memory was strictly preserved neuropsychologically. The remaining 5 subjects scored more than 2 SDs lower than our controls on one (case 9–11) or more nonepisodic memory measures (case 12, 13). These patients could be classified as amnestic MCI multidomain (Petersen 2004). One patient (case 13) scored within the range of published age- and education-based norms on all subtests of the Akense Afasie test (Graets and others 1992) but just below 2 SD compared with our own matched controls for naming and repetition. Scores on the AAT reading task were at ceiling in all subjects.

Performance of the fMRI Experiment

We conducted a 3-factor repeated-measures analysis of variance of reaction times, accuracies, and omissions, with stimulus modality and task as within-subject factors (2 levels: pictures vs. words and semantic vs. visuoperceptual, respectively) and with group as between-subject factor (2 levels: MCI vs. controls) (Table 2).

Subjects performed the visuoperceptual task faster than the semantic task ($F_{1,24} = 132$, $P < 0.00001$), more accurately ($F_{1,24} = 61.5$, $P < 0.00001$) and with fewer omissions ($F_{1,24} = 7.8$, $P < 0.01$). Subjects responded faster during the word compared with the picture conditions ($F_{1,24} = 22.7$, $P < 0.0001$) and more accurately ($F_{1,24} = 11.7$, $P < 0.01$). The number of omissions did not differ significantly between word and picture conditions ($F_{1,24} = 2.9$, $P = 0.1$).

Reaction times ($F_{1,24} = 0.8$, $P = 0.3$), accuracies ($F_{1,24} = 2.5$, $P = 0.1$), or omissions ($F_{1,24} = 1.8$, $P = 0.2$) did not differ significantly between groups, although the MCI patients tended to be slower and less accurate and omit more responses than the control group (Table 2). There were no significant interactions between group and task, between group and modality, or between group, task, and modality.

fMRI Data

Across groups, the contrast between the associative-semantic conditions and the visuoperceptual conditions (contrast 1) activated a distributed left hemispheric system (Fig. 1*B*), replicating previous results (Vandenberghe and others 1996). This activity map was used as our search volume to detect between-group differences for contrasts 1–5.

The activity map obtained by the contrast of the associative-semantic conditions minus the visuoperceptual conditions (contrast 1) differed between controls and patients in one region: the posterior third of the lower bank of the left superior temporal sulcus (STS) (Figs 2*A* and 3*A*). The group-by-task interaction was significant (–60, –42, 0, extent (ext.) 21, $Z = 4.32$, corrected $P < 0.05$). When we restricted the analysis to the word conditions only (contrast 2), the group-by-task interaction remained significant (–63, –39, 0, ext. 18, $Z = 4.10$, corrected $P = 0.05$) (Fig. 3*C* vs. *D*, red vs. magenta) but not when the analysis was restricted to the picture conditions only (contrast 3, uncorrected $P > 0.01$) (Fig. 3*C* vs. *D*, blue vs. cyan).

In controls, this region was activated during the associative-semantic condition with words in comparison with the visuoperceptual condition with words (–60, –42, 0, $Z = 4.58$, uncorrected $P < 0.00001$; Fig. 3*C*, red vs. magenta) but not when the same tasks were compared with pictures as input (uncorrected $P > 0.01$, Fig. 3*C*, blue vs. cyan). The posterior STS voxels that showed a modality-by-task interaction at uncorrected $P < 0.001$ are shown in Figure 3*B* in blue. These word-specific voxels partially overlapped with the voxels that showed a group-by-task interaction (Fig. 3*B*, blue vs. red). The overlap is indicated by the blue outline.

Table 2
Performance parameters obtained in the fMRI experiment (mean [SD])

	Reaction time (ms)		Accuracy (% correct)		Omissions (%)	
	MCI	Controls	MCI	Controls	MCI	Controls
Semantic (P)	3028 (493)	2962 (464)	80.1 (7.5)	81.4 (8.3)	5.9 (6.1)	6.4 (5.7)
Semantic (W)	2947 (694)	2819 (406)	84.6 (9.3)	87.6 (6.8)	7.3 (9.3)	2.4 (6.8)
Visuoperceptual (P)	2692 (673)	2475 (529)	87.4 (9.0)	91.0 (6.5)	6.0 (8.2)	2.4 (6.1)
Visuoperceptual (W)	2381 (406)	2136 (446)	88.0 (10.0)	92.4 (7.2)	5.1 (6.1)	1.3 (4.6)

Note: Semantic (P), associative-semantic task with pictures; Semantic (W), associative-semantic task with words; Visuoperceptual (P), visuoperceptual task with pictures; Visuoperceptual (W), visuoperceptual task with words.

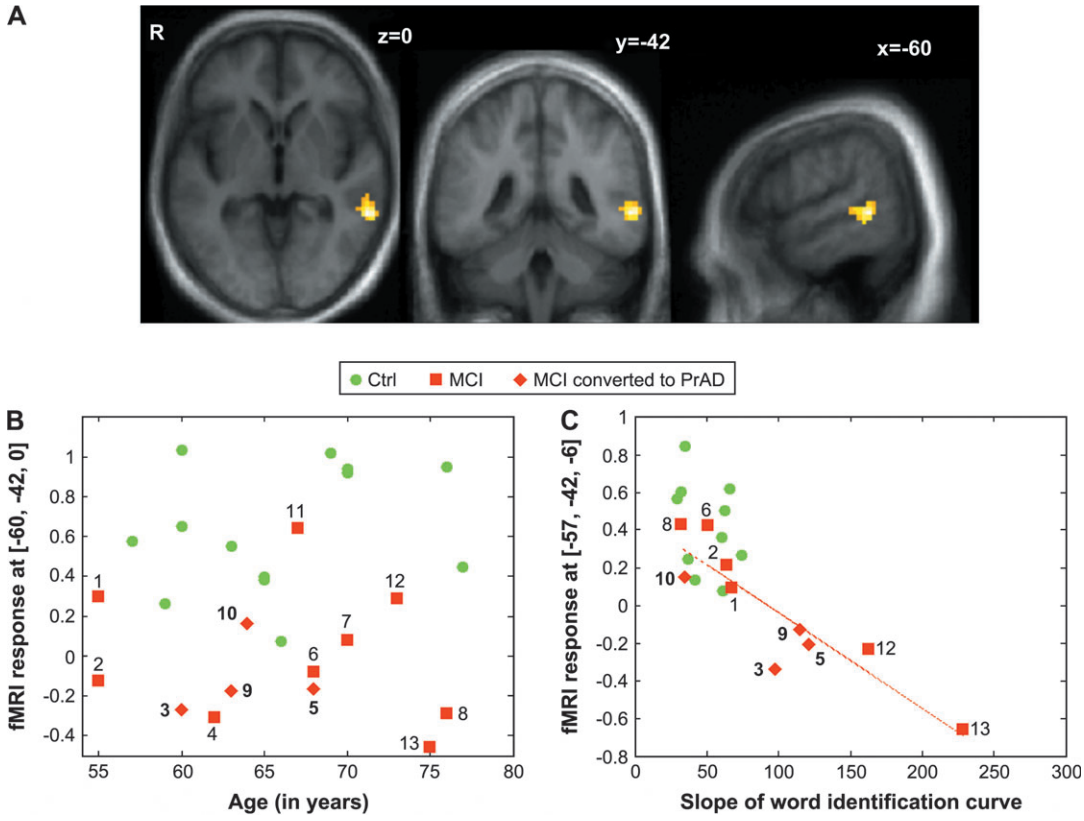

Figure 2. (*A*) Map of higher activity in controls compared with MCI during the associative-semantic conditions compared with the visuoperceptual conditions (group-by-task interaction). Superposition onto the group-averaged structural brain MRI. Uncorrected $P < 0.001$. (*B*) Individual fMRI responses in the peak of the cluster depicted in Figure 2A. *x* axis: age; *y* axis: percentage signal change in the peak voxel of the cluster depicted in Figure 2*A*. Each data point corresponds to one individual. Green, controls; Red, MCI; Diamonds, converters. Indices correspond to those used in Table 1. (*C*) Correlation between the slope (psychophysical parameter *b*) of the word identification curve (Fig. 4*A*) and the fMRI response amplitude (percentage of BOLD signal change) in posterior STS (Fig. 2*A*). Same conventions as in (*A*).

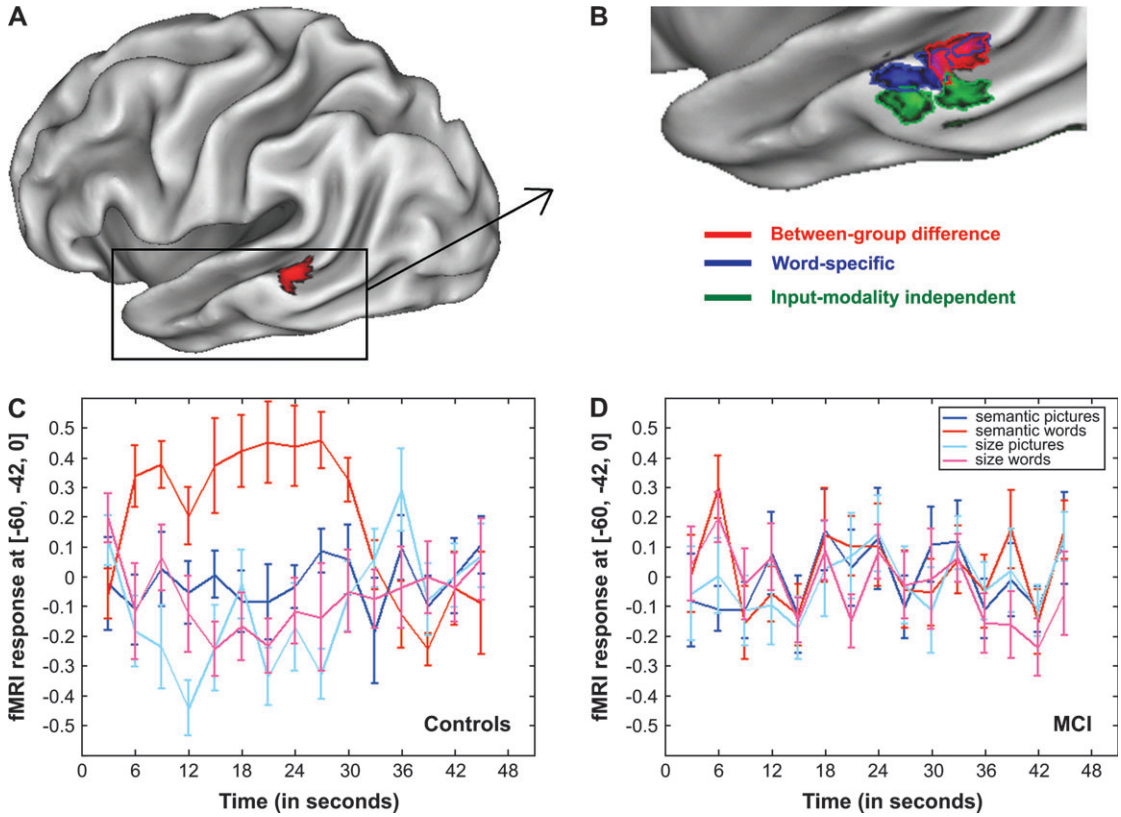

Figure 3. (*A*) Map of higher activity in controls compared with MCI during the associative-semantic conditions compared with the visuoperceptual conditions (group-by-task interaction). Uncorrected $P < 0.001$. Superposition onto a standard brain using computerized anatomical reconstruction and editing toolkit software (lateral view) (Washington University School of Medicine, Department of Anatomy and Neurobiology, http://brainmap.wustl.edu). (*B*) Superposition of 3 activity maps. Red, Group-by-task interaction: Higher activity in controls than in MCI during the associative-semantic compared with the visuoperceptual tasks. Blue, Control subjects: Task-by-modality interaction (contrast 5): Higher activity during the associative-semantic compared with the visuoperceptual task with words than with pictures. Green, Control subjects—Conjunction analysis: Higher activity during the associative-semantic compared with the visuoperceptual task with words (contrast 2) as well as with pictures (contrast 3). Uncorrected $P < 0.001$. (*C*) Activity time course averaged over the control subjects in the peak voxel of the cluster depicted in Figure 3*A* during the 4 types of epoch (epoch duration 27 s). Red: associative-semantic judgment with words. Blue: associative-semantic judgment with pictures. Magenta: visuoperceptual judgment with words. Cyan: visuoperceptual judgment with pictures. *x* axis: time in s; *y* axis: percentage of BOLD signal change. (*D*) Activity time course averaged over the MCI subjects in the peak voxel of the cluster depicted in Figure 3*A*. Same conventions as in (*C*).

Inferior to the voxels that showed word-specific activation (Fig. 3*B*, blue), a cluster of voxels showed input modality–independent activation during the associative-semantic minus the visuoperceptual conditions regardless of input modality, words or pictures (Fig. 3*B*, green) (conjunction analysis –63, –39, –6, $Z = 4.87$, corrected $P < 0.05$ [Nichols and others 2005]). This replicates our previous findings in the left posterior middle temporal gyrus (Vandenberghe and others 1996). These input modality–independent voxels are shown in Figure 3*B* in green.

Apart from the posterior STS, no other brain areas showed a between-group difference of activity for any of the contrasts tested (contrasts 1–5) (uncorrected $P > 0.005$). We did not find any regions where activity was higher in MCI compared with controls in the current study. VBM did not reveal any differences in gray matter volume between patients and normal persons in posterior temporal cortex (uncorrected $P > 0.05$). There was no correlation between performance of the fMRI task and blood oxygen level–dependent (BOLD) activity in the posterior temporal cortex (uncorrected $P > 0.01$).

Chronometric Data versus fMRI

The slope (parameter *b*) of the time-accuracy function for words was significantly steeper in controls than in MCI ($F_{1,18} = 5.3$, $P < 0.05$) (Fig. 4*A* and Table 3). The slope for picture identification did not differ significantly between groups ($F_{1,18} = 1.6$, $P = 0.2$) (Fig. 4*B* and Table 3). Onset (parameter *a*) ($F_{1,18} = 0.7$, $P = 0.4$) or plateau (parameter *c*) ($F_{1,18} = 3.8$, $P = 0.07$) of the word-reading curve and onset or plateau for picture identification ($F_{1,18} = 2.8$, $P = 0.1$ and $F_{1,18} = 0.6$, $P = 0.4$, respectively) did not differ significantly between groups. Cases 5, 12, and 13 did not perform at ceiling at stimulus durations of 800 ms. Errors at 500 and 800 ms in these 3 cases consisted of visual–phonological word errors (50%) (i.e., production of a different word that resembles the target word visually and/or phonologically) (Strain and others 1998), omissions of part of the word (20%), omissions of a response (15%), visual–phonological nonword errors (11%), and, rarely, production of a nonword that was visually and phonologically dissimilar (4%).

In order to evaluate whether case 13 (Fig. 4*A*) disproportionately influenced the group differences, we removed it from analysis: The difference of the steepness of the slope of the time-accuracy curve for word reading between MCI and controls remained significant ($F_{1,17} = 4.6$, $P < 0.05$).

Within a volume of interest centered around the activity peak in the posterior STS, a significant and strong correlation existed between fMRI response amplitude and the steepness of the

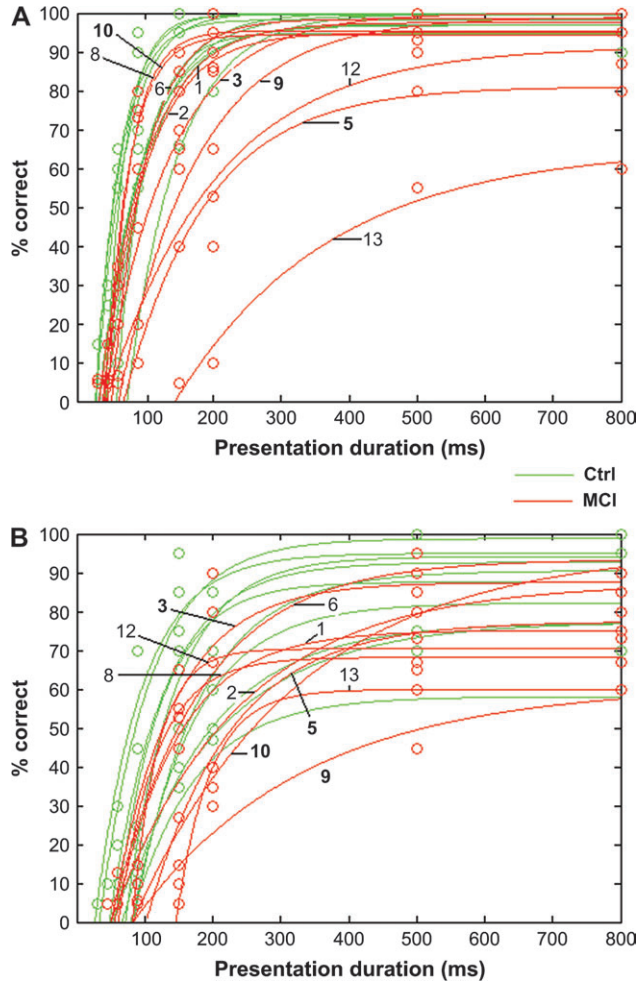

Figure 4. Chronometric experiment. (*A*) Time-accuracy curve for word reading. *x* axis: word presentation duration. *y* axis: percentage of correct responses. Each circle corresponds to an individual's mean accuracy at a given stimulus duration. Red: MCI. The indices identify the MCI individual and correspond to those used in Table 1. Green: controls. Bold: converter. (*B*) Time-accuracy curve for picture naming. *x* axis: picture presentation duration. Same conventions as in (*A*).

slope of the time-accuracy curve for word reading (–57, –42, –6, $Z = 3.57$, $r = -0.90$, corrected $P < 0.05$) (Fig. 2*C*). No correlation was found within this volume with the other parameters of this curve or with psychophysical parameters of the time-accuracy curve for picture identification (–57, –39, –3, $Z = 1.31$, $r = -0.44$, uncorrected $P > 0.05$).

In order to test the neuroanatomical specificity of the correlation between the word identification slope and BOLD response amplitude, we looked for correlations in other parts of the semantic-processing network in MCI using the same method as that applied for STS: We defined spherical volumes of interest (radius 3 voxels) surrounding the voxels of peak activity obtained in the contrast of associative-semantic conditions minus visuoperceptual conditions in healthy controls (–36, 27, –12; –33, 6, 54; –66, –39, –6; –39, –39, –27; –45, –53, –21; 30, –78, –45). Within these volumes, we determined the correlation between the psychophysical word identification parameters and BOLD response amplitude in the MCI group using a multiple linear regression analysis at $P < 0.05$ corrected for each volume separately. None of the volumes of interest contained voxels that significantly correlated with word identification parameters.

Table 3
Psychophysical experiment

	Words				Pictures			
	MCI		Controls		MCI		Controls	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Onset	55.8	32.2	39.7	14.8	75.6	30.3	59.7	19.9
Slope	**97.5**	61.9	**50.8**	15.4	125.5	76.5	92.1	27.5
Asymptote	91.8	10.7	98.6	1.9	77.7	12.9	85.3	12.3

Note: Parameters *a* (onset), *b* (steepness of slope), and *c* (asymptote) of the time-accuracy curves (mean [SD]). Lower values of *b* mean that the slope is steeper. Bold, significant between-group difference at $P < 0.05$.

Follow-Up Data

Within the first year, 3 patients (case 5, 9, 10) converted from CDR 0.5 to CDR 1 and fulfilled criteria for probable AD after the first year. One additional patient (case 3) converted within the second year. Three of the converters (cases 3, 5, 9) had a word identification slope at initial evaluation that was less steep than any of the controls (Fig. 4*A*), as well as posterior STS activity below that seen in controls at initial scanning (Fig. 2*B*,*C*).

The fMRI data collected after the first year confirmed that the left posterior STS was significantly less active during the associative-semantic compared with the visuoperceptual condition in the patients (converters and nonconverters) compared with the controls (Fig. 5, yellow). Again, the task-by-group interaction was significant in the lower bank of the left posterior STS (–63, –42, 3, ext. 55, $Z = 4.03$, corrected $P = 0.05$) (Fig. 5, yellow). A conjunction analysis (Nichols and others 2005) confirmed that the between-group differences overlapped between the 2 time points (–60, –39, 0, ext. 30, $Z = 3.91$, uncorrected $P < 0.0001$) (Fig. 5, yellow vs. red).

Discussion

Using fMRI, we dissected left posterior temporal cortex and discerned 2 functionally distinct but juxtaposed regions (Fig. 3*B*): The lower bank of the posterior STS, which is activated during associative-semantic judgments with words specifically (Fig. 3*B*, blue), and the middle temporal gyrus, which is activated during associative-semantic judgments regardless of input modality, words or pictures (Fig. 3*B*, green). Using a time-accuracy approach, we decomposed the reading process in a group of patients with amnestic MCI and demonstrated a change in the slope of the time-accuracy curve for written word identification. Amnestic MCI was also associated with dysfunction of the left posterior STS, the word-specific–processing region (Fig. 3*B*, red). Hypoactivity of left posterior STS correlated inversely with the steepness of the slope of the time-accuracy curve for word reading (Fig. 2*C*).

The associative-semantic condition with words differed between groups not only in comparison with the visuoperceptual conditions but also in comparison with the associative-semantic condition with pictures (Fig. 3*C*,*D*). The most parsimonious explanation is a change during the associative-semantic condition with words rather than activity increases in the 3 other conditions of our factorial design. We did not include a low-level resting state condition as a reference because even the simplest baseline condition is associated with organized functional brain

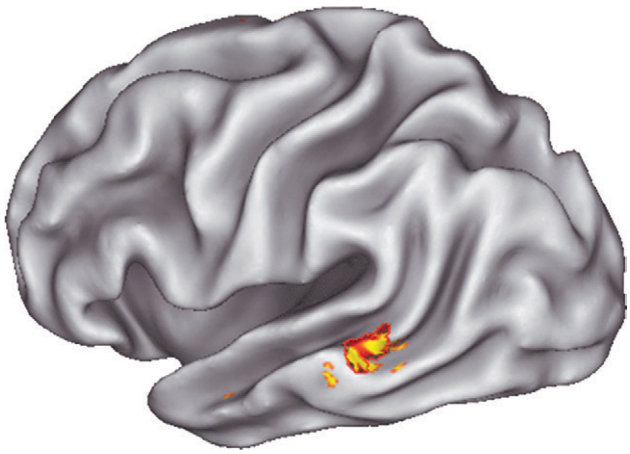

Figure 5. Map of higher activity in controls compared with MCI during the associative-semantic compared with visuoperceptual conditions after 1-year follow up (yellow) (group-by-task interaction). This map is superimposed onto the map obtained at the initial assessment (red). Uncorrected $P < 0.001$.

activity (Binder and others 1999), which may itself be affected by disease (Lustig and others 2003).

Epidemiological studies based on primary care settings have suggested that MCI is a heterogeneous and unstable construct with poor predictive value (Larrieu and others 2002). Key differences between the study of Larrieu and others (2002) and ours study are the rigorous and prospective application of the criteria of amnestic MCI of Petersen (2004), strict exclusion criteria as well as patient recruitment via a memory clinic. Under these conditions, amnestic MCI constitutes a reasonable clinical approximation of incipient AD (Morris and others 2001; Petersen 2004). The homogeneity of our subject sample is testified by the between-subject consistency of our random-effects fMRI results (Fig. 2*B*). Following inclusion, we characterized our MCI sample genetically. Our MCI group contained more apo E ε4 allele heterozygotes and homozygotes than the control group did, as one would expect in an AD risk group. During the first 2 years, 30.8% of the MCI group (cases 3, 5, 9, 10) converted to probable AD, but none of the controls, confirming that AD risk was substantially higher in our amnestic MCI patients than in controls (Petersen 2004). Five out of 13 MCI patients showed subtle changes in cognitive domains other than episodic memory. This subtype of amnestic MCI has sometimes been designated amnestic MCI multidomain (Petersen 2004). This condition may carry a higher risk of conversion to AD than purely amnestic MCI (Bozoki and others 2001). In our experiments, this subgroup behaved similarly to the purely amnestic group.

In the psychophysical experiment, cases 5, 12, and 13 did not perform at ceiling at 800-ms stimulus durations (Fig. 4*A*). Errors in these 3 cases consisted of visual–phonological word or nonword errors and partial and total omissions that are still compatible with pathological slowing of word identification. A data point at a longer stimulus duration, for example, 2000 ms, might have provided a better estimate of time-unconstrained reading capabilities in these subjects. In tests such as the AAT oral reading test, which does not have time constraints, all 3 cases performed at ceiling (Table 1).

In a previous reaction-time study of written word identification in MCI (Massoud and others 2002), slowing of word identification speed predicted conversion to probable AD (Massoud and others 2002). Our data provide an anatomical substrate for the word identification deficit in MCI (Massoud and others 2002): the lower bank of the left posterior STS (Fig. 2*A*,*C*). This localization is compatible with the distribution of pathological depositions in Alzheimer's disease: The STS is among the areas that show the highest density of neuritic plaques and neurofibrillary tangles in mild AD compared with normal controls (Tiraboschi and others 2004).

In healthy controls, the left posterior STS is active during word reading in comparison with picture naming (Bookheimer and others 1995; Price and Mechelli 2005) or in comparison with rest (Cohen and others 2000). According to a seminal paper on word comprehension and retrieval (Wise and others 1991), the left posterior and middle STS showed higher activity not only when subjects compared the meaning of auditorily presented words but also when they generated verbs that were semantically appropriate to a presented concrete noun (Wise and others 1991). Its role in word comprehension as well as word generation was subsequently confirmed in several follow-up experiments (Mummery and others 1999; Wise and others 2001). Our patient study complements these studies by demonstrating the critical nature of the contribution of the left posterior STS to word reading (Fig. 2*C*). Two possible explanations for STS activation as well as the change of steepness of slope are lexical-semantic or lexical-phonological processing (Posner and Carr 1992; Caramazza 1997; Levelt 1999). In our opinion, a lexical-semantic deficit is the more likely cause: Posterior STS is active when subjects carry out an associative-semantic task with words but not with pictures (Fig. 3*C*,*D*). This fits with a role in mapping word form onto word meaning (lexical-semantic retrieval) (Butterworth and others 1984). Lexical-semantic retrieval also facilitates written word identification (Posner and Carr 1992), as tested in our psychophysical experiment. Our interpretation is in line with previous patient lesion studies that implicate the posterior temporal cortex in the 2-way mapping between word form and word meaning (Gainotti 1987; Hart and Gordon 1990; Chertkow and others 1997; Mesulam 2000; Hillis and others 2001). It also fits with the activation of posterior STS seen in healthy volunteers when they attend to semantic relationships between semantically related written words compared with phonological relationships between rhyming words (McDermott and others 2003). In MCI, connections between orthographic word forms and their meaning may have undergone de-differentiation, diminishing the speed of written word identification. De-differentiation has been put forward as one of the mechanisms underlying age-related slowing of perceptual speed (Park and others 2004). Strictly speaking, our psychophysical and neuroimaging findings only pertain to the mapping of "orthographic" word form onto meaning. The same or a nearby posterior STS region also responds to auditorily presented words (Binder and others 2000; Kotz and others 2002; Rissman and others 2003). Similar findings might be expected if words were presented in the auditory modality but this remains to be investigated. An alternative account of the left posterior STS findings lies at the level of lexical-phonological rather than lexical-semantic processing (Binder and others 2000; Levelt and Indefrey 2000; Price and Mechelli 2005). Strictly speaking, this possibility cannot be excluded because phonological and lexical-semantic processing may closely interact with each other and both may have a facilitatory effect on word identification as well as on associative-semantic tasks with words.

In probable AD, single-word–reading problems have been principally attributed to a lexical-semantic retrieval deficit (Bayles and Tomoeda 1983; Nebes and Brady 1988, 1990; Nebes 1989) or a degradation of semantic representations (Huff and others 1986; Chertkow and Bub 1990; Chertkow and others 1992; Hodges and others 1992; Hodges and Patterson 1995; Cuetos and others 2003). We presented converging evidence for a word-specific role of STS. Our findings therefore strongly support an account in terms of a lexical retrieval problem rather than semantic degradation. On the basis of the current study in MCI and previous studies of semantic memory in probable AD (Grady and others 2003; Grossman and others 2003), we propose that, as the disease progresses to the stage of clinically probable AD, damage extends from word-specific–processing regions, such as the posterior STS, into modality-independent, semantic-processing areas such as the posterior middle temporal gyrus (Fig. 3*B*).

To conclude, left posterior temporal cortex contains 2 juxtaposed but functionally distinct regions, one in the lower bank of the STS that is word-specific and the other in the posterior middle temporal gyrus that is involved in semantic processing regardless of input modality (Fig. 3*B*, blue and green). Amnestic MCI is associated with dysfunction of the former area (Fig. 3*B*, blue and red) leading to subclinical impairment of written word identification (Fig. 2*C*).

Notes

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