Aβ amyloid deposition in the language system and how the brain responds

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Post-mortem measures of Aβ amyloid deposition correlate only weakly with cognitive dysfunction antemortem. We tested the hypothesis that functional reorganization forms a critical intermediary step between Aβ amyloid-associated brain injury and clinical disease expression. Fifteen patients with early-stage probable Alzheimer’s disease (AD) and 16 cognitively intact controls participated in this combined functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) study. The fMRI design had two factors: task (associative-semantic versus visuoperceptual judgement) and input-modality (written words versus pictures). We measured Aβ amyloid by means of Pittsburgh Compound B (11C-PIB). In the posterior third of the left superior temporal sulcus (STS), the fMRI response during the associative-semantic compared with the visuoperceptual task was lower in AD than in controls, in particular for words. Response amplitude correlated inversely with PIB uptake in this region. Contralaterally, the functional pattern differed substantially: the fMRI response in the right posterior STS during the associative-semantic versus the visuoperceptual task was higher in AD than in controls. Accuracy on the Boston Naming test correlated positively with the degree to which AD patients were able to recruit the right STS (r = 0.84, P_corrected = 0.014). PIB uptake did not correlate with naming accuracy. Functional reorganization of the language system in response to Aβ amyloid-related brain injury exists in early-stage AD and determines the degree of anomia more than Aβ amyloid load per se does.

Keywords: PIB; fMRI; Alzheimer; STS

Abbreviations: MCI = mild cognitive impairment; STS = superior temporal sulcus

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Amyloid aggregation is an attractive target for disease modification trials in Alzheimer’s disease (AD) (Klafki et al., 2006). It is important to understand in detail how Aβ amyloid load relates to brain dysfunction and to cognitive symptoms. Early studies in dementia in a nursing home showed a correlation between post-mortem measures of neuritic plaque load and severity of dementia prior to death (Roth et al., 1966; Blessed et al., 1968; Tomlinson et al., 1968; Tomlinson et al., 1970). Subsequent memory-clinic based autopsy studies in probable AD (Terry et al., 1991; Berg et al., 1993; Gomez-Isla et al., 1997) and one biopsy study (Neary et al., 1986), however, found only weak correlations between neuritic plaque load and psychometric indices. Brains from cognitively intact subjects may even show a neuritic plaque load indistinguishable from that seen in brains from patients who died with a diagnosis of dementia (Crystal et al., 1988; Katzman et al., 1988; Troncoso et al., 1996; Davis et al., 1999; Price and Morris, 1999; Neuprep. Group of the Medical Research Council Cognitive Function and Aging Study, 2001; Driscoll et al., 2006). We tested the hypothesis that functional reorganization forms a critical intermediary step between Aβ amyloid-related brain injury and cognitive dysfunction. We defined functional reorganization as activity increases in patients versus controls that correlate positively with off-line measures of cognitive performance. For the first time this hypothesis can be tested during lifetime by concurrent measurement of three processes in vivo: clinical expression, function of large-scale cognitive brain systems and Aβ amyloid load.

In order to measure functional changes, we used the same fMRI paradigm as we have used in amnestic mild
cognitive impairment (MCI) (Vandenbulcke et al., 2007): a modified version of the Pyramids and Palm Trees (PPT) test, a classical test of associative-semantic processing of words or pictures (Hodges et al., 1992; Howard and Patterson, 1992). Word and semantic processing are frequently impaired even in the earliest stage of AD (Appell et al., 1982; Bayles and Tomoeda, 1983; Huff et al., 1986; Chertkow and Bub, 1990; Hodges and Patterson, 1995; Hodges et al., 1996). In amnestic MCI, currently the best clinical approximation of a pre-dementia stage of AD (Morris et al., 2001; Petersen, 2004), the posterior third of the left superior temporal sulcus (STS) is less active during associative-semantic versus visuoperceptual processing of words compared with controls (Vandenbulcke et al., 2007). Activity levels correlate with subclinical impairment of single word processing (Vandenbulcke et al., 2007). In AD, the left posterior temporoparietal cortex is significantly less active than in age-matched controls when subjects perform a semantic tempoparietal cortex is significantly less active than in age-matched controls when subjects perform a semantic judgement about implement and animal nouns (Grossman et al., 2003a) compared with pseudowords. In mild-to-moderate stage AD, glucose metabolism in left posterior temporal and inferior parietal cortex correlates positively with performance of verbal semantic tests such as category verbal fluency (Desgranges et al., 1998). On the basis of these prior findings (Grossman et al., 2003a, b; Vandenbulcke et al., 2007), we hypothesized that in early-stage probable AD, activity in the left STS would be reduced.

Besides regions of reduced activity, we also searched for regions where activity during associative-semantic versus visuoperceptual processing was increased in patients versus controls and where these activity levels correlated positively with cognitive performance. Even during the initial stages of neurodegenerative disease, the brain retains a potential for plasticity (Hyman et al., 1987; Nathan et al., 1994; Becker et al., 1996; Arendt et al., 1997; Mesulam, 1999; Saykin et al., 1999; Grady et al., 2001; Grossman et al., 2003b). We hypothesized that functional reorganization might partially explain the lack of correlation between Aβ amyloid load and clinical symptoms. Activity increases in probable AD compared with controls have been demonstrated during episodic (Becker et al., 1996; Grady et al., 2003) and semantic memory retrieval (Saykin et al., 1999; Grady et al., 2003; Grossman et al., 2003a, b). These increases occurred mainly in prefrontal cortex (Becker et al., 1996; Saykin et al., 1999; Grady et al., 2003) and in left inferior temporal cortex and left middle temporal gyrus (Grossman et al., 2003a, b). Prefrontal response amplitude correlated positively with task performance (Becker et al., 1996; Saykin et al., 1999; Grady et al., 2003). The AD-related prefrontal increases generalized across episodic and semantic memory tasks (Grady et al., 2003) and may reflect adaptive strategic processes rather than language-specific reorganization (Grady et al., 2003).

As a measure of regional Aβ amyloid load, we used Pittsburgh Compound B ([11C-PIB] and PET. PIB is a derivative of thioflavin. In vitro studies have shown high affinity of PIB for insoluble Aβ amyloid in homogenates of AD brains (Mathis et al., 2003; Klunk et al., 2005). In vivo, at tracer levels, the signal probably mainly arises from high-affinity binding sites (Klunk et al., 2005), in particular fibrillar amyloid in plaques and cerebral amyloid angiopathy (Bacskai et al., 2003; Bacskai et al., 2007; Holtzman, 2007). AD patients show significantly increased cortical PIB uptake compared with controls (Klunk et al., 2004; Archer et al., 2006; Fagan et al., 2006; Mintun et al., 2006). PIB uptake correlates inversely with Aβ42 levels in cerebrospinal fluid (Fagan et al., 2006) and positively with rate of global atrophy (Archer et al., 2006). In probable AD, PIB uptake remains relatively stable throughout the disease course and until now no clear correlation has been found between PIB uptake and severity of cognitive dysfunction (Engler et al., 2006; Edison et al., 2007).

In our study we correlated fMRI activity and PIB uptake with an off-line measure of language dysfunction: accuracy on a common neuropsychological test, the Boston Naming test (BNT) (Kaplan et al., 1983). We predicted that picture naming accuracy in AD would be determined more by functional activity changes than by Aβ amyloid load per se. We also predicted that part of these changes would lie outside the normal activity pattern and would correlate positively with performance, reflecting functional reorganization.

**Subjects and methods**

**Subjects**

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. A consecutive series of 15 patients (six men, nine women) who fulfilled the diagnostic criteria for clinically probable Alzheimer’s disease (McKhann et al., 1984; American Psychiatric Association, 1994) and who were in an early disease stage, were recruited via the memory-clinic of the University Hospital Gasthuisberg (Table 1). The mean Mini Mental State Examination (MMSE) score (Folstein et al., 1975) was 24.6 (SD 2.7, range 19–28). Patients were on average 73.2 years of age (SD 6.8 years, range 65–87) and the mean educational level was 11.9 years (SD 2.4, range: 8–16). According to the modified Edinburgh Handedness Inventory, all patients were strongly right-handed (score = 100) except case 1 who was predominantly left-handed (score = 86.7). Eight of the patients were on a stable dosis of donepezil (5 or 10 mg/day), and seven on a stable dosis of galantamine (8 or 12 mg bid) for at least 3 months. Five patients were on a stable dose of a selective serotonin reuptake inhibitor (SSRI) [citalopram (case 2), escitalopram (cases 5, 15), sertraline (cases 9, 13)]. Two patients were on a stable dose of trazodone 100 mg once daily (cases 5, 7) and one patient (case 5) took lorazepam 1.25 mg before sleep. No other psychotropic drugs were taken.
Table 1 Neuropsychological data.

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Scores outside a 2 SD range of the control mean are marked in bold. Abbreviations: BNT: Boston Naming Test, AVF: Animal Verbal Fluency test, PALPA: verb-al association test of the Psycholinguistic Assessment of Language Processing in Aphasia, PPT: Pyramids and Palm Trees test, BORB-OD: Object Decision test of the Birmingham Object Recognition Battery, VOSP: number location test of the Visual Object and Space Perception battery, CPM: Raven’s Coloured Progressive Matrices, TMT: Trail Making Test; ‘/’ denotes the test was not administered.

Sixteen cognitively intact controls underwent the same protocol. They were matched for gender (7 men, 9 women), age (mean 70.9, SD 7.5, range 59–89 years), educational level (mean 12.9, SD 2.5, range 8–18 years) and handedness (modified Edinburgh Handedness Inventory score was —73 in one subject and 100 in all other subjects). The controls were selected from a cohort of elderly subjects recruited through an advertisement in a regional newspaper asking for volunteers above the age of 55 years for participation in a scientific study. Controls did not have any memory complaints nor a history of significant neurological or psychiatric illness. None of the controls took any psychotropic medication.

All subjects underwent an extensive standard neuropsychological evaluation of verbal [Rey Auditory Verbal Learning Test (Ivnik et al., 1990)] and non-verbal episodic memory [Rey Visual Design Learning Test (Rey, 1941) or Rey-Osterrieth figure recall (Osterrieh, 1941)], language [Aachen Aphasia Test (Gaets et al., 1992; Bastiaanse et al., 1995), Boston Naming test (Kaplan et al., 1983; Marien et al., 1998)], visuospatial [Object Decision test (Riddoch and Humphreys, 1993)] and visuospatial processing [Visual Object and Space Perception Battery (Warrington and James, 1991)] and executive function [Coloured Progressive Matrices (Raven et al., 1995)] (Table 1).

Functional MRI

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, AR, USA).

The fMRI paradigm (Fig. 1A–D) has been described in detail before (Vandenbulcke et al., 2005, 2006, 2007). In summary, the experimental design was factorial (Vandenbergh et al., 1996). The first factor, task, had two levels: associative-semantic versus visuo-perceptual judgement. The second factor, input modality, also had two levels: pictures versus printed words. The associative-semantic condition was derived from the PPT test (Howard and Patterson, 1992). 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 interstimulus interval. Subjects had to press either a left- or right-hand key depending on which of the two lower stimuli matched the upper stimulus more closely, either in meaning (for A and B) or in size on the screen (for C and D). (Translation: bot: bone, hond: dog, konijn: rabbit). (E) Areas of significantly \( P_{\text{uncorrected}} < 0.001 \) increased fMRI activity during associative-semantic judgments compared with the visuoperceptual baseline in elderly controls. As a group, patients did not show significantly reduced fMRI responses compared with controls on a whole brain corrected cluster-level threshold of \( P < 0.05 \). The MNI coordinate (mm) of every slice is indicated in the upper left corner. Overlap with the left STS VOI is shown in blue. (F–G) fMRI activity, expressed as the mean percentage signal change (error bars: s.e.) at every time point, averaged over all voxels belonging to the left STS VOI, in controls (F) and patients (G) (sem: associative-semantic task, size: visuoperceptual task, with pictures (pict) or words (word) as input modality).

A given triplet was presented in either the picture (Fig. 1A) or the word format (Fig. 1B) and this was counterbalanced across subjects. In the visuoperceptual control condition, a picture (Fig. 1C) or word stimulus (Fig. 1D) was presented in three
Table 2 Performance on the fMRI task.

<table>
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<th>Accuracy (% correct)</th>
<th>Omissions (%)</th>
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</tr>
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<td>sem word</td>
<td>3290 (499)</td>
<td>2803 (366)</td>
</tr>
<tr>
<td>size pict</td>
<td>2984 (515)</td>
<td>2437 (504)</td>
</tr>
<tr>
<td>size word</td>
<td>2828 (560)</td>
<td>2169 (375)</td>
</tr>
</tbody>
</table>

Performance parameters obtained in the fMRI experiment (mean (SD)). Abbreviations: sem: associative-semantic task, size: visuoperceptual task, with pictures (pict) or words (word) as input modality.

different sizes (9% size difference). Subjects had to press a left- or right-hand key depending on whether the two test stimuli matched the sample stimulus more closely in size on the screen. An epoch, i.e. a block of trials belonging to the same condition, consisted of four trials (total duration 27 s). During each fMRI run, a series of 4 epochs, one of each type, was replicated 3 times.

Image acquisition

A 1.5 Tesla Siemens Sonata system (Siemens Medical Solutions, Erlangen, Germany) equipped with an 8-channel receive-only head coil (MRI Devices Corp., Waukesha, USA) provided a high-resolution T1-weighted structural image (MPRAGE, sagittal inversion recovery prepared 3D gradient echo images; inversion time 800 ms, TE/TR 3.93/1950 ms, flip angle 12°, 1 x 1 x 1 mm³ voxels) and T2⁺ echo-planar images (EPI) [42 sagittal slices, 3 x 3 x 3 mm³ voxels; TE/TR 40/3000 ms; GeneRalized Autocalibrating Partially Parallel Acquisitions (GRAPPA) (Griswold et al., 2002)]. A total of 108 volumes were acquired during each run. Subjects underwent 4 to 6 runs each.

Image analysis

Image analysis was performed using Statistical Parametric Mapping (SPM2, Welcome Department of Cognitive Neurology, London, UK. http://www.fil.ion.ucl.ac.uk/spm/).

EPI images of each subject were realigned to correct for head motion. Head motion parameters did not differ significantly between patients and controls (two-sample t tests, P > 0.15). The anatomical MR volume was coregistered to the average of the realigned EPI volumes and non-linearly normalized to a custom-made T1 brain template in Montreal Neurological Institute (MNI) space. This template was based on 34 elderly normal subjects, normalized to MNI space, modulated (Good et al., 2001), and smoothed with a 12 x 12 x 12 mm³ FWHM Gaussian kernel.

In order to evaluate the contribution of grey matter volume loss to decreases in fMRI response, we performed a voxel-based morphometry analysis (Baron et al., 2001): MPRAGE scans were segmented into grey matter (GM) (Van Leemput et al., 1999), normalized to MNI space, modulated (Good et al., 2001), masked and smoothed with a 12 x 12 x 12 mm³ FWHM Gaussian kernel.

PIB PET

All patients and controls underwent a Pittsburgh Compound B (PIB) PET scan. The PET tracer, N-methyl-[11C]2-(4’-methyl-aminophenyl)-6-hydroxybenzothiazole (Klunk et al., 2004), was injected intravenously as a bolus (mean dose 230 MBq, SD 77 MBq, range 70–379 MBq) in an antecubital vein. We acquired dynamic images during a 90-min period using a Siemens HR+ high resolution PET scanner (Siemens Medical Solutions, Erlangen, Germany) operated in 3D mode. Attenuation correction (based on a pre-injection transmission scan using 68Ge/68Ga rod sources), random and scatter correction were applied. Images were reconstructed as 4 x 15 s, 4 x 60 s, 2 x 150 s and 16 x 300 s frames and realigned (SPM2) to correct for head motion. Frames were smoothed with a 6 x 6 x 6 mm³ FWHM Gaussian kernel and entered in a Logan graphical analysis with cerebellar cortex as a reference region (Lopresti et al., 2005), resulting in parametric images of volume of distribution ratios (DVR). DVR was used as a measure of Aβ amyloid load (Price et al., 2005). For each individual, we summed the images from the first 3 min of acquisition and warped this summed image to the SPM2 PET template in MNI space using a non-linear transformation. The same normalization matrix was applied to the DVR images. Normalized DVR images (2 x 2 x 2 mm³ voxels) were masked with a brain mask to remove most extracerebral noise and smoothed with a 12 x 12 x 12 mm³ FWHM Gaussian kernel.

Primary statistical analyses

Behavioural data during the fMRI experiment (Table 2) were analysed using a three-factor repeated-measures Analysis of Variance (ANOVA) of reaction times, accuracies and omissions, with stimulus modality (two levels: pictures versus words) and task (two levels: associative-semantic versus visuoperceptual task) as within-subjects factors and group as between-subjects factor (two levels: AD versus controls) [STATISTICA, version 6, StatSoft, Inc. (2001), www.statsoft.com].

fMRI data were analysed using SPM2. For every subject, a t statistic for the parameter estimates was generated for the following fMRI 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
Before proceeding to the second level of analysis, we explicitly tested homogeneity of the sample subjects’ fMRI datasets by means of DISTANCE software (Kherif et al., 2003); the data did not show any outlier or clustering. It was therefore statistically sound to represent the group results through the mean using a random-effects analysis (Kherif et al., 2003).

In SPM2, we examined whether there were significant differences between AD patients and controls in fMRI response or PIB uptake (DVR maps) using a 2-sample t test. Within the AD group, we conducted a simple linear regression analysis with either fMRI response (contrast 1) or PIB uptake as the dependent variable and picture naming accuracy (BNT scores) as regressor.

We performed a whole brain search using a significance threshold of voxel-level $P_{uncorrected} < 0.001$ combined with a cluster-level $P_{corrected} < 0.05$ (Poline et al., 1997). We also probed a specific volume of interest (VOI) that was derived from our previous study in amnestic MCI (Vandenbulcke et al., 2007): The posterior third of the lower bank of the left superior temporal sulcus (82 3 3 mm$^3$ voxels (Fig. 2D). Within this VOI the significance threshold was set at a voxel-level $P < 0.05$ corrected for the VOI.

We also calculated the mean fMRI response (contrast 1) and mean PIB uptake in the VOI, and determined the correlation between these two parameters using a Pearson correlation coefficient.

Secondary statistical analyses

Re-classification of subjects

In an additional analysis we removed the PIB-negative AD patients (remaining AD subjects $n = 13$) as well as the PIB-positive controls (remaining control subjects $n = 13$) (Fig. 3B, C). In a separate analysis we removed the left-handed AD subject (remaining AD subjects $n = 14$) and the left-handed control (remaining control subjects $n = 15$). The statistical analyses were otherwise identical to those described above.

Effect of grey matter volume loss

In order to control for changes in grey matter volume, we included the GM volume map as a covariate using Biological Parametric Mapping (Casanova et al., 2007). The Biological Parametric Mapping (BPM) toolbox is an extension of SPM’s general linear model that allows for using a different design matrix in each voxel. This enables the combination of information from different imaging modalities on a voxel-by-voxel basis. We included the GM map as a covariate in our categorical comparison between fMRI responses during associative-semantic versus visuoperceptual processing in AD compared with controls.

Results

Behavioral performance

There was a significant main effect of group: AD patients responded more slowly ($P = 0.00099$) and less accurately ($P = 0.0061$) and tended to make more omissions ($P = 0.056$) than controls. The main effect of task was also significant: Subjects performed the associative-semantic task more slowly ($P = 0.000001$), less accurately ($P = 0.0015$) and with more omissions ($P = 0.0035$) compared with the visuoperceptual task. Finally, there was a significant main effect of stimulus modality: Subjects were slower ($P = 0.000044$) and less accurate ($P = 0.000003$), and made more omissions ($P = 0.0029$) with pictures than with words.

The 3-way repeated-measures ANOVA of reaction times, accuracies and omissions did not yield any significant interactions between group and task (mean reaction time: $P = 0.29$, accuracy: $P = 0.49$, omissions: $P = 0.058$), between group and modality (mean reaction time: $P = 0.46$, accuracy: $P = 0.15$, omissions: $P = 0.16$), between task and...
modality (mean reaction time: $P = 0.12$, accuracy: $P = 0.065$, omissions: $P = 0.98$) or between group, task and modality (mean reaction time: $P = 0.35$, accuracy: $P = 0.90$, omissions: $P = 0.070$).

**Whole brain search volume**

As our main finding, several AD subjects showed abnormally high activity in the right hemisphere in the
superior temporal sulcus during associative-semantic versus visuoperceptual processing. Activity levels in this region correlated positively with naming accuracy. Details are provided below. Corrected \( P \)-values reported in this section are corrected at the cluster level for the whole brain search volume (Poline et al., 1997).

One region, the right superior temporal sulcus, showed a stronger fMRI response during the associative-semantic versus visuoperceptual control condition in AD compared with controls (54, 9, –6, \( Z = 4.68 \), extent (ext.) 1647 mm\(^3\), corrected (corr.) \( P = 0.001 \)). In AD, response amplitude in the right STS during associative-semantic versus visuoperceptual processing correlated positively with accuracy on the BNT (51, –9, –15, \( Z = 4.53 \), \( r = 0.90 \), ext. 1134 mm\(^3\), corr. \( P = 0.001 \); 54, –24, 0, \( Z = 3.96 \), \( r = 0.84 \), ext. 702 mm\(^3\), corr. \( P = 0.014 \)) (Fig. 2A, B). In 6 AD individuals (cases 1, 4, 6–7, 11–12), the fMRI contrast value in the posterior right STS cluster was more than 2 SD above the mean of controls (Fig. 2B). All of these subjects scored within the normal range on the BNT. In case 13,
the fMRI contrast value was more than 2 SD below the mean of the controls. This subject had the lowest BNT score of all AD subjects.

Increased PIB uptake in AD compared with controls was widespread (−66, −52, −22, \(Z = 4.73\), ext. 539096 mm\(^3\), corr. \(P < 0.001\)) (Fig. 3A). Three out of 16 controls showed PIB uptake similar to AD patients and 2 out of 15 AD patients (case 2, 4) showed PIB uptake similar to controls (Fig. 3B, C). Nowhere did PIB uptake correlate with BNT scores in AD (uncorrected \(P > 0.001\)) (Fig. 2C).

**Left superior temporal sulcus**

In the left STS, our volume of a priori interest, fMRI activity was reduced in AD compared with controls. This region was homotopical to the right-sided STS region discussed above. Details are provided below.

In the left STS, the fMRI response during the associative-semantic compared with the visuoperceptual task was significantly reduced in AD patients compared with controls (−66, −39, −6, \(Z = 3.14\), corr. \(P = 0.031\)) (Fig. 1E-G). In controls, activity in the left STS was significantly higher during the associative-semantic compared with the visuoperceptual task (−54, −42, 0, \(Z = 4.50\), corr. \(P < 0.001\)) (Fig. 1F). In patients, activity did not differ between the associative-semantic and the visuoperceptual task (corr. \(P > 0.2\)) (Fig. 1G). We obtained similar findings when we used only the word conditions (group-by-task interaction: −63, −42, −6, \(Z = 2.89\), corr. \(P = 0.056\)). Controls significantly activated the left STS during associative-semantic compared with visuoperceptual processing of words (−60, −39, −3, \(Z = 3.87\), corr. \(P = 0.004\)) (Fig. 1F: red versus purple). In AD, this activation was less pronounced (−63, −39, 3, \(Z = 3.67\), corr. \(P = 0.009\)) (Fig. 1G: red versus purple). When we used only the picture conditions and compared the associative-semantic with the visuoperceptual task, no significant group-by-task interaction was obtained (corr. \(P > 0.1\)). In AD patients, fMRI response amplitude in the left STS during associative-semantic versus visuoperceptual processing did not correlate significantly with BNT scores (−54, −39, 0, \(Z = 2.99\), \(r = 0.71\), corr. \(P = 0.062\)) (Fig. 2E).

PIB uptake in the left STS was significantly higher in AD than in controls (−66, −26, −2, \(Z = 3.79\), corr. \(P = 0.001\)) (Fig. 3A). PIB uptake in AD did not correlate with BNT scores (corr. \(P > 0.6\)) (Fig. 2F). In AD patients, mean PIB uptake correlated inversely with mean fMRI response during associative-semantic versus visuoperceptual processing in the left STS (\(r = -0.56\), \(P = 0.029\)) (Fig. 4). The degree of PIB uptake in left STS was comparable to that in right STS (paired \(t\) test \(P = 0.23\)).

GM volume in the left STS was significantly lower in patients compared with controls (−66, −38, −6, \(Z = 3.02\), corr. \(P = 0.013\)) and correlated weakly with the mean fMRI response during associative-semantic versus visuoperceptual processing in left STS (\(P = 0.13\)).

**Re-classification of subjects**

If we removed the 3 PIB-positive controls and the 2 PIB-negative AD patients, we obtained similar results. PIB-positive AD patients showed significantly higher fMRI responses during associative-semantic versus visuoperceptual processing than PIB-negative healthy controls in the right STS (54, 9, −9, \(Z = 4.16\), ext. 891 mm\(^3\), corr. \(P = 0.022\)). In PIB-positive AD patients fMRI response during associative-semantic versus visuoperceptual processing correlated positively with BNT scores in the right STS (51, −9, −15, \(Z = 4.21\), ext. 1053 mm\(^3\), corr. \(P < 0.001\)). In the left STS, fMRI response during associative-semantic versus visuoperceptual processing was lower in PIB-positive AD patients compared with PIB-negative controls (−60, −39, −6, \(Z = 3.52\), corr. \(P = 0.011\)). It correlated negatively with DVR in the PIB-positive AD group (−66, −46, 4, \(Z = 3.09\), corr. \(P = 0.027\))

Removing the two left-handed subjects also did not alter the results. fMRI activity during associative-semantic versus visuoperceptual processing was increased in patients compared with controls in the right STS (57, 9, −9, \(Z = 4.45\), ext. 1026 mm\(^3\), corr. \(P = 0.016\)). In the AD group, fMRI response during associative-semantic versus visuoperceptual processing in the right STS correlated positively with BNT scores (51, −9, −15, \(Z = 4.46\), ext. 918 mm\(^3\), corr. \(P = 0.002\); 54, −24, 0, \(Z = 3.83\), ext. 675 mm\(^3\), corr. \(P = 0.012\)). The left STS response during associative-semantic versus visuoperceptual processing was significantly lower in patients than in controls (−66, −39, −6, \(Z = 3.20\), corr. \(P = 0.027\)) and correlated negatively with DVR (−66, −48, 2, \(Z = 3.40\), corr. \(P = 0.010\)).

**Effect of grey matter volume loss**

The results reported in this section were obtained with inclusion of grey matter volume map as a covariate. They essentially confirmed the results obtained in our primary analyses: fMRI activity during associative-semantic versus visuoperceptual processing in the right STS remained significantly higher in AD compared with controls (54, 9, −6, \(Z = 4.46\), ext. 1512 mm\(^3\), corr. \(P = 0.001\) and correlated positively with BNT scores in the AD group (51, −9, −15, \(Z = 4.34\), ext. 1026 mm\(^3\), corr. \(P = 0.001\); 60, −21, 0, \(Z = 3.90\), ext. 594 mm\(^3\), corr. \(P = 0.018\)). In the left STS the response during associative-semantic versus visuoperceptual processing tended to be lower in AD than in controls (−63, −39, −3, \(Z = 2.67\), corr. \(P = 0.106\)). In the left STS the partial volume corrected DVR correlated inversely with the fMRI response during associative-semantic versus visuoperceptual processing, even when the grey matter volume map was included as an additional regressor (−66, −45, 3, \(Z = 3.34\), corr. \(P = 0.028\)). The partial volume corrected PIB data did not correlate with BNT scores in AD in left STS or anywhere else in the brain.
Effect of accuracy during the fMRI task

The results reported in this section were obtained with inclusion of accuracy during the fMRI tasks as a covariate. They essentially confirmed the results obtained in our primary analyses: When we used accuracy on the fMRI task as a covariate, the fMRI response during associative-semantic versus visuoperceptual processing in the right STS was still significantly higher in AD than in controls (57, 0, –15, $Z = 4.34$, ext. 918 mm$^3$, corr. $P = 0.027$). In AD fMRI responses during the associative-semantic versus visuoperceptual task in the right STS correlated positively with BNT scores, even when accuracy during the fMRI tasks was included as an additional regressor (54, –9, –15, $Z = 4.46$, ext. 864 mm$^3$, corr. $P = 0.003$; 54, 24, 0, $Z = 4.08$, ext. 513 mm$^3$, corr. $P = 0.050$). The left STS tended to be less active during associative-semantic versus visuoperceptual processing in patients compared with controls (–66, –39, 6, $Z = 2.73$, corr. $P = 0.088$). In the left STS the fMRI response during associative-semantic versus visuoperceptual processing correlated negatively with DVR in the AD group (–66, –48, 3, $Z = 3.44$, corr. $P = 0.021$).

Discussion

As our main finding, the right superior temporal sulcus showed abnormally high activity during associative-semantic versus visuoperceptual processing in a subset of early-stage AD patients. This activity correlated positively with naming accuracy, fulfilling our two criteria for functional reorganisation (Fig. 2B). The right-sided area lay symmetrically to an area in the posterior third of the lower bank of the left STS where activity during associative-semantic versus visuoperceptual processing was reduced in AD compared with controls (Fig. 2A, D; Fig. 1F, G). Left-sided STS dysfunction correlated with the local Aβ amyloid load (Fig. 4A).

Patients performed all 4 conditions more slowly and less accurately than controls but the group-by-task interactions remained below significance. Since our fMRI results are based on a contrast between associative-semantic and visuoperceptual conditions, aspecific effects of task difficulty are subtracted out. Furthermore, when we entered accuracy as a covariate of no interest, results remained essentially the same.

A lower fMRI response during associative-semantic versus visuoperceptual processing in AD compared with controls may theoretically result from either lower activity per unit volume (dysfunction of remaining neuronal populations) or a loss of grey matter volume (decrease in number of neurons). Our left STS region showed a certain degree of atrophy in patients versus controls. The correlation between grey matter volume loss and the fMRI response during associative-semantic versus visuoperceptual processing remained below the significance threshold but strictly speaking a formal partial volume correction would be required to tease out the contribution of these two effects. To our knowledge no validated methods of partial volume correction exist for fMRI. fMRI hypo-activity during the associative-semantic versus visuoperceptual

![Fig. 4](http://brain.oxfordjournals.org/)
task may therefore reflect either a loss of grey matter volume in this region or hypo-activity of the remaining neuronal populations or, more probably, a combination of both. In amnestic MCI we found similar decreases in responses during associative-semantic versus visuoperceptual processing in patients versus controls in the absence of any measurable grey matter volume loss (Vandenbulcke et al., 2007). Our findings demonstrate that a key node of the typical language network is structurally or functionally damaged in amnestic MCI (Vandenbulcke et al., 2007) and early-stage AD while other nodes of the language network appear to be relatively spared.

In principle, a change in the difference between the associative-semantic and the visuoperceptual condition can result from alterations either during the associative-semantic or during the visuoperceptual condition. The ‘control’ condition may also be affected by AD-related disease processes. Even a resting state condition is (Lustig et al., 2003). The correlation with behavioral measures of language performance and prior knowledge about the neuroanatomy of the language system allowed us to narrow down the possible interpretations of the left and right STS effects. The lower bank of the posterior third of the left STS is a well-known key node within the language network (Mesulam, 1998; Wise et al., 2001; Hillis et al., 2001). Furthermore, if one attributes the fMRI effect exclusively to changes that occur during the visuoperceptual condition, it is relatively hard to account for the positive correlations between language measures and fMRI responses during associative-semantic versus visuoperceptual processing.

In our study, three out of 16 healthy controls showed increased cortical PIB uptake (Fig. 3C). This proportion is comparable to that reported by others (Fagan et al., 2006; Mintun et al., 2006). PIB-positive controls showed an fMRI activity pattern very similar to that seen in PIB-negative controls, in both left and right STS (Fig. 4).

Two out of 15 probable AD patients did not show increased PIB uptake (Fig. 3B). According to prospective academic memory-clinic based autopsy series, diagnostic accuracy of a clinical AD diagnosis is 85–90% (Chui and Lee, 2003). The ‘PIB-negative’ rate may reflect false-positive clinical diagnoses at our centre. Alternatively, the PIB-negative cases may be related to the sensitivity of PIB. Only autopsy can discriminate between these two possibilities. Case 2 showed an encoding and retrieval deficit, both on verbal and non-verbal memory tests, as well as language dysfunction (Fig. 3B; Table 1). He had the lowest PIB uptake of all participants. Case 4 had a clinical and neuropsychological profile that was in full agreement with what one would expect in clinically probable AD (Fig. 3B; Table 1). Critically, if we excluded these 2 subjects from our analysis we obtained essentially the same results.

Five AD patients (cases 2, 5, 9, 13, 15) were on a stable dose of an SSRI. In a double-blind cross-over placebo-controlled trial in 8 patients with pure motor hemiparesis, single administration of fluoxetine led to significant hyperactivation of the ipsilesional motor cortex, together with improvement of motor skills (Pariente et al., 2001). An SSRI effect upon right-hemispheric STS activity can be excluded as an explanation for our findings since right-sided activity increases also occurred in patients who did not take an SSRI (Fig. 2).

Our data are not suggestive of a direct toxic effect of the PIB binding substance upon regional brain function: PIB-positive cognitively intact controls showed left posterior temporal fMRI responses during associative-semantic versus visuoperceptual processing that were well within the normal range (Fig. 4). Furthermore, in AD patients, levels of PIB uptake were identical between left and right STS and, nevertheless, right-sided STS responses during associative-semantic versus visuoperceptual processing were enhanced rather than diminished compared with controls (Fig. 2B, C, E, F). If the PIB binding substance does not have a direct toxic effect upon brain responses, then how can we explain the negative correlation between PIB uptake in left STS and the amplitude of response during associative-semantic versus visuoperceptual processing? Possibly, in patients with clinically probable AD, amyloid angiopathy reduces blood supply and diminishes the amplitude of left STS responses during tasks that normally strongly activate the left STS (Vandenberghe et al., 1996; Vandenbulcke et al., 2007). The right STS, which is not activated in normal circumstances during the tasks we studied (Vandenberghe et al., 1996; Vandenbulcke et al., 2007), may still retain a reserve for adaptive activity increases in the face of reduced left temporal perfusion during task performance. According to this hypothesis, the areas recruited during functional reorganisation depend on task context, for instance the degree to which a given function is left or right lateralised in normal subjects.

The absence of a correlation between cortical Aβ amyloid load and cognitive dysfunction has sometimes been attributed to the fact that already at the initial clinical stage the density of plaques is high (Berg et al., 1993). According to retrospective memory-clinic based autopsy series in AD, neocortical neurofibrillary tangles correlate better with disease severity than neocortical Aβ amyloid load does (Neary et al., 1986; Braak and Braak, 1991; Arriagada et al., 1992; Bancher et al., 1993; Berg et al., 1993; Gomez-Isla et al., 1997). Soluble Aβ amyloid in homogenized brain tissue also correlates more strongly with cognitive dysfunction than aggregated Aβ amyloid (Naslund et al., 2000). The most robust correlations with global measures of disease severity in AD are seen with neuronal (Neary et al., 1986; Gomez-Isla et al., 1997) and synapse loss (Terry et al., 1991). In that respect, Alzheimer’s disease has been termed a ‘neuronal perikaryal disorder’ (Neary et al., 1986) rather than brain amyloidosis. Cognitive dysfunction may be tightly linked with loss of neuronal function and loss of connectivity (Terry et al., 1991). Neuronal dysfunction and disconnection and neuronal loss may lead to alterations of brain activity
patterns and this may be one explanation why fMRI activity correlates better with cognitive dysfunction than Aβ amyloid load per se does (Fig. 2).

The right STS profile fulfilled two criteria for functional reorganisation: Activity lay outside the normal activity pattern and correlated positively with performance levels (Fig. 2B). In Wernicke aphasia due to stroke, hyperactivity in the right superior temporal sulcus during word comprehension correlated positively with training-induced improvement of performance (Musso et al., 1999). The right-sided temporal area of increased activity in Wernicke aphasics (60, –14, –6) (Musso et al., 1999) lay very close to that seen in our study (54, 9, –6). A positive correlation between fMRI activity in the right STS and picture naming is compatible with a compensatory effect but this must be tested further, e.g. by means of repetitive transcranial magnetic stimulation (rTMS) (Coslett and Monsul, 1994; Thiel et al., 2005; Cotelli et al., 2006; Thiel et al., 2006; Devlin and Watkins, 2007). In patients with mild-to-moderate stage Alzheimer’s disease, TMS of the right dorsolateral prefrontal cortex improves picture naming performance whereas it does not have any effect in normals (Cotelli et al., 2006). From our findings, one would predict that in probable AD, stimulation of the right posterior superior temporal sulcus would affect naming performance. Right-sided activity increases during a language task versus a visuo perceptual control task bears resemblance to what we have seen in primary progressive aphasia (PPA) in the anterior temporal cortex using an identical functional imaging protocol (Vandenbulcke et al., 2005). In both PPA and AD, the right-hemispheric activity increase is homotopical to affected left-sided language areas in anterior or posterior temporal cortex, respectively (Fig. 2). But there are also clear differences between what we have seen in PPA and the current data in AD. The right-sided activity in early-stage AD correlated positively with language performance whereas in PPA the correlation was negative (Vandenbulcke et al., 2005). Second, in PPA the strongest right-sided responses were found in those subjects who activated the left anterior temporal cortex the least (Vandenbulcke et al., 2005), resulting in a net laterality shift. In AD, increased activity in the right STS occurred mainly in those subjects who also activated the left STS relatively well (Fig. 2B,E). These functional differences may relate to the differences between the two patient populations. Neuropathologically, the majority of PPA patients do not have AD pathology (Mesulam, 2000). In our PPA study 7 out of 19 patients fulfilled criteria for semantic dementia. The likelihood of Alzheimer pathology in semantic dementia is only 11% (Davies et al., 2005). A significant portion of our PPA sample had non-fluent progressive aphasia, which is more suggestive of a tauopathy than of AD (Knibb et al., 2006). One of our PPA cases (case 5 (Vandenbulcke et al., 2005)) had a progranulin mutation and corresponds to patient DR 119 described by Cruts et al. (2006) (Cruts et al., 2006) which leads to frontotemporal lobar degeneration with ubiquitine-positive tau-negative inclusions (Pirici et al., 2006). The differences between patient populations, PPA versus AD, may explain the different results in these 2 studies but there are also differences between the cognitive functions attributed to the left anterior temporal pole (Saffran and Sholl, 1999; Vandenberge et al., 2002) and the left posterior STS (Levell and Indefrey, 2000; Price and Mechelli, 2005; Vandenbulcke et al., 2007). Each of these factors may contribute to the different characteristics of the right-hemispheric responses between PPA versus AD.

Right-hemispheric recruitment has been described before in AD during semantic memory retrieval (Saykin et al., 1999; Grady et al., 2003) but these changes were restricted to prefrontal cortex. Furthermore, prefrontal recruitment in AD generalized across different tasks tapping semantic or episodic memory retrieval (Grady et al., 2003). In contrast, the changes we describe in AD occurred in posterior temporal cortex, homotopical to a typical left-sided language area (Wise et al., 2001). While prefrontal recruitment may be related to more general strategic processes, the right-sided posterior temporal change is probably more tightly linked with word-specific processes. Functional reorganisation may arise through different mechanisms. Due to the disease, latent capacities of the right hemisphere may be recruited (Hillis, 2005). These latent capacities may consist of semantically mediated reading (Cossett and Monsul, 1994) and single word comprehension (Gazzaniga and Sperry, 1967; Zaidel, 1976; Kertesz, 1979; Knopman et al., 1983; Selnes et al., 1983). At a microscopic structural level, there may be terminal sprouting, growth of collateral branches of axons and dendritic remodelling (Cotman and Nieto-Sampedro, 1982; Nathan et al., 1994; Arendt et al., 1997; Mesulam, 1999). These neuronal mechanisms are capable of causing effects even at a distance from a lesion site (Cotman and Nieto-Sampedro, 1982; Hyman et al., 1987). Transcallosal disinhibition seems less likely as an explanation for the pattern in AD since under such conditions we would expect the highest right-sided activity levels in those patients who activate the left side the least, i.e. opposite to what we observed (Fig. 2B,E).

Our findings have implications for interventional studies in AD. Enhancement of functional reorganisation may be part of a strategy to counteract cognitive decline in AD. Potential methods to stimulate plasticity may be cholinergic (Hyman et al., 1987; Mesulam, 1999) or serotonergic stimulation (Pariente et al., 2001), behavioral intervention (Musso et al., 1999) or rTMS (Naeser et al., 2005; Devlin and Watkins, 2007).

To conclude, in accordance with our a priori hypothesis, cognitive performance in AD depends at least as much on the capacity for functional reorganisation as on Aβ amyloid load per se. As has been suggested previously by post-mortem studies (Hyman et al., 1987), the brain’s
own responsiveness to Aβ amyloid-related injury may constitute a valid target for therapeutic intervention.

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