DOI: 10.1093/brain/awh075 *Brain* (2004), **127,** 628–649

What's in a name: voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration

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Summary

Confrontation naming is impaired in neurodegenerative conditions like Alzheimer's disease (AD), frontotemporal dementia (FTD) and corticobasal degeneration (CBD). Some behavioural observations suggest a common source of impaired naming across these patient groups, while others find partially unique patterns of naming difficulty. We hypothesized that a large-scale neural network underlies naming, and that patterns of impaired naming in AD, FTD and CBD reflect cortical atrophy that interrupts this network in a manner that is partially shared and partially unique across these patient groups. We tested this hypothesis by correlating naming impairments with voxel-based morphometric (VBM) analyses of cortical atrophy in structural MRIs of 50 patients. We found significant naming deficits in all patient groups. Naming also correlated with lexical retrieval in all patient groups, including subgroups of patients with FTD. VBM analyses showed significant cortical atrophy, which was shared across AD, FTD and CBD patients in the left lateral temporal cortex; this area correlated with naming accuracy in all groups. Left lateral temporal atrophy thus appears to interfere with a lexical retrieval component of naming in AD, FTD and CBD. Impaired naming also correlated with semantic memory and visual perceptual–spatial functioning in specific groups of patients and, correspondingly, naming correlated with cortical atrophy in partially distinct neuroanatomical distributions in AD, FTD, CBD and subgroups of patients with FTD. These partially unique correlation profiles appear to reflect selective interruption of other components of the naming process, including semantic and visual perceptual–spatial functioning. These findings are consistent with the hypothesis that a large-scale neural network supports naming, and that this network is interrupted in several distinct ways in patients with neurodegenerative diseases.

Keywords: Alzheimer's; frontotemporal; corticobasal; naming; cortical atrophy

Abbreviations: AD = probable Alzheimer's disease; CBD = corticobasal degeneration; FTD = frontotemporal dementia; MMSE = Mini-Mental State Examination; NON-APH = non-aphasic patients with frontotemporal dementia; ns = not significant; PNFA = progressive non-fluent aphasia; ROI = region of interest; SD = semantic dementia; VBM = voxel-based morphometry

Received June 23, 2003. Revised September 17, 2003. Second revision November 2, 2003. Accepted November 4, 2003. Advanced Access publication February 4, 2004

Introduction

Confrontation naming difficulty is impaired in patients suffering from neurodegenerative diseases such as probable Alzheimer's disease (AD) (Tippett and Farah, 1994; Hodges *et al*., 1996; Lambon Ralph *et al*., 1997), frontotemporal dementia (FTD) (Cappa *et al*., 1998; Lambon Ralph *et al*., 1998) and corticobasal degeneration (CBD) (Kompoliti *et al*.,

1998; Black, 2000; Kertesz *et al*., 2000). Behavioural studies have attempted to establish the sources of naming difficulty in these patient groups to help with differential diagnosis and severity staging, and to improve our fundamental understanding of the neural basis for this critical element of human communication. However, this body of work has not arrived at a definitive conclusion. While cognitive models of naming have pointed out the large variety of possible naming deficits (Garrett, 1992; Levelt, 1992), qualitative analyses of naming errors document a relatively limited number of possible errors. The kind of deficit that is the most common, i.e. no response, is the least informative. In this study, we examined naming difficulty from a different perspective, i.e. through comparative analyses of correlations between confrontation naming difficulty and grey matter atrophy using voxel-based morphometry (VBM) analyses of high-resolution structural MRI in patients with impaired naming.

Our model of confrontation naming includes several components: (i) a stimulus such as a visual line drawing must be interpreted; (ii) the concept corresponding to this stimulus must be identified in semantic memory; and then (iii) the name that corresponds to the stimulus must be retrieved and expressed (Garrett, 1992; Levelt, 1992). Each of these components is quite complex. Lexical retrieval, for example, may involve components such as: (i) selecting the best name from among several possible choices which label objects with overlapping features (e.g. 'collie' versus 'dog'); (ii) inhibiting alternate names that share many phonological features (e.g. 'collie' versus 'dolly'); (iii) translating an abstract, material-neutral representation of a name into a material-specific form; and (iv) assembling the phonological or graphemic elements so that they can be spoken or written (e.g. the written word 'collie').

Naming has been studied extensively in neurodegenerative diseases such as AD—partly because this crucial linguistic process is impaired frequently and early in these illnesses. Naming deficit is also prominent in the subgroup of FTD patients with a fluent form of progressive aphasia that is also known as semantic dementia (SD) and, for example, is considered a diagnostic feature of this condition (Snowden *et al*., 1989; Hodges *et al*., 1992*a*; Neary *et al*., 1998). In AD, naming difficulty has been associated with impairments in lexical retrieval (Hodges *et al*., 1991; Cronin-Golomb *et al*., 1992), semantic (Huff *et al*., 1986; Lambon Ralph *et al*., 1997; Hodges *et al*., 1996) and visual (Tippett and Farah, 1994; Silveri and Leggio, 1996) components of naming. There is partial overlap with the basis for naming difficulty in FTD, as the deficit in this group has also been associated with an interruption of lexical retrieval (Weintraub *et al*., 1990; Thompson *et al*., 1997; Lambon Ralph *et al*., 1998) and semantic (Hodges *et al*., 1995; Lambon Ralph *et al*., 2001) processes. Individual case studies and occasional group reports also describe impaired naming in CBD (Kompoliti *et al*., 1998; Kertesz *et al*., 2000; P. Moore, K. Dennis and M. Grossman, unpublished data). These authors have emphasized the contribution of lexical retrieval and visual perceptual–spatial limitations.

Given the partially shared basis for impaired naming in these neurodegenerative diseases, one hypothesis is that naming difficulty is due to a deficit in a single critical component of the naming process such as lexical retrieval. A deficit in this process is due to cortical dysfunction within a specific neuroanatomical distribution that is compromised across patient groups, according to this approach. Quantitative differences in naming accuracy between groups are due to the severity of disease in this crucial brain area. Evidence consistent with this 'single deficit' hypothesis comes from correlation studies that associate naming difficulty with impaired lexical retrieval in many groups of patients. For example, several studies have emphasized the importance of difficulty with lexical retrieval in mildly impaired patients with AD (Chertkow *et al*., 1992; Hodges *et al*., 1992*b*, 1996; Garrard *et al*., 1998, 2001) and CBD (P. Moore, K. Dennis and M. Grossman, unpublished data). Subgroups of patients with FTD have distinct clinical presentations (Neary *et al*., 1998; Grossman, 2002), yet SD patients, progressive non-fluent aphasia (PNFA) patients and non-aphasic patients with FTD (NON-APH) with a disorder of social and executive functioning appear to share naming difficulty and an impairment of lexical retrieval (Weintraub *et al*., 1990; Hodges and Patterson, 1996; Thompson *et al*., 1997; Croot *et al*., 1998; P. Moore, K. Dennis and M. Grossman, unpublished data).

Additional support for this 'single deficit' approach comes from MRI studies suggesting shared patterns of cortical atrophy in AD and FTD. Areas of atrophy common to these patients appear to include the temporal neocortex, the frontal neocortex and the hippocampus (Baron *et al*., 2001; Chan *et al*., 2001; Galton *et al*., 2001; Busatto *et al*., 2003; Karas *et al*., 2003). Assuming a single source of naming difficulty, a correlative MRI study related impaired lexical retrieval in confrontation naming and category naming fluency tests in a combined group of SD patients and patients with AD to atrophy in a single region—the left anterior temporal cortex (Galton *et al*., 2001).

An alternate hypothesis is based on the partially distinct profiles of impaired naming in AD, FTD and CBD. This approach suggests that naming difficulty in these patient groups is related in part to the unique anatomical distribution of the cortical atrophy seen in these patients. Consistent with this 'large-scale network' approach, patients with AD, FTD or CBD have deficits in partially distinct cognitive components of the naming process. For example, a semantic deficit appears to contribute more prominently to naming difficulty in AD and FTD compared with CBD (Huff *et al*., 1986; Hodges *et al*., 1995; Lambon Ralph *et al*., 1997, 2001), while a visual perceptual–spatial deficit plays a more important role in naming difficulty in AD and CBD compared with FTD (Tippett and Farah, 1994; Silveri and Leggio, 1996; P. Moore, K. Dennis and M. Grossman, unpublished

data). Although all FTD subgroups have lexical retrieval difficulty, careful comparisons suggest qualitative differences in the nature of their lexical retrieval deficit as well (Thompson *et al*., 1997; Lambon Ralph *et al*., 1998; P. Moore, K. Dennis and M. Grossman, unpublished data). From this perspective, even such components of naming as lexical retrieval and the associated downstream processes are multifactorial in nature and may be compromised in several different ways.

Additional support for this 'large-scale network' approach comes from MRI studies suggesting partially distinct patterns of cortical atrophy in AD and FTD. Although direct comparisons of the anatomical distribution of atrophy in AD and FTD have been rare, distributions of atrophy in the temporal lobe appear to be somewhat different in these conditions (Baron *et al*., 2001; Chan *et al*., 2001; Galton *et al*., 2001; Good *et al*., 2002; Boxer *et al*., 2003; Busatto *et al*., 2003; Karas *et al*., 2003). Each FTD subgroup also appears to have a partially distinct anatomical distribution of disease, according to *in vivo* measures such as single photon emission computed tomography (Jagust *et al*., 1989; Miller *et al*., 1997), PET (Grossman *et al*., 1996*b*; Turner *et al*., 1996) and quantitative analyses of atrophy in high resolution MRI studies. Patients with SD thus seem to have prominent left anterior temporal disease (Mummery *et al*., 2000; Chan *et al*., 2001; Galton *et al*., 2001), while inferior frontal regions of the left hemisphere appear to be most compromised in patients with PNFA (Grossman *et al*., 1996*b*; Rosen *et al*., 2002*b*; Nestor *et al*., 2003) and disease in NON-APH patients is said to be focused in frontal regions of the right hemisphere (Miller *et al*., 1993; Rosen *et al*., 2002*a*). Occasional non-quantitative neuroimaging studies of CBD suggest a distribution of disease primarily involving the parietal cortex, although the temporal and frontal cortical regions also may be atrophic (Caselli *et al*., 1992; Grisoli *et al*., 1995; Savoiardo *et al*., 2000).

Patients with AD, FTD and CBD have not been directly compared with respect to the neural basis for their naming deficit. In this study, we correlated VBM analyses of volumetric structural MRI with naming to assess the hypothesis that partially shared and partially unique patterns of cortical atrophy across patient groups account for the profiles of impaired naming seen in these patients.

Methods

Subjects

We studied 50 patients diagnosed with a neurodegenerative condition at the Department of Neurology at the University of Pennsylvania. Initial clinical diagnosis was established by an experienced neurologist (M.G.) using published criteria. Subsequently, at least two trained reviewers of a consensus committee confirmed the presence of specific diagnostic criteria based on an independent review of the semi-structured history, mental status examination and neurological examination. If the reviewers disagreed in their diagnosis (which occurred in 11% of 70 cases, including patients with other diagnoses not participating in this study), consensus was established through open discussion by the entire committee. These patients and their legal representatives participated in an informed consent procedure approved by the Institutional Review Board at the University of Pennsylvania.

Among the participants, 12 patients were given the diagnosis of AD based on National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria (McKhann *et al*., 1984). This included a progressive syndrome involving prominent episodic memory difficulty, associated with circumlocutory speech, a visual constructional impairment and/or an executive limitation.

Another 29 patients were given the diagnosis of FTD, according to published criteria (Lund and Manchester Groups, 1994; McKhann *et al*., 2001). We also used the consensus mechanism described above to establish subgroup diagnosis. The subgroups were based on published criteria (Neary *et al*., 1998), which have been modified to improve reliability (Davis *et al*., 2001; Price *et al*., 2001). We studied 15 FTD patients with a progressive form of aphasia and 14 FTD patients with a non-aphasic pattern of cognitive and social impairment. One aphasic subgroup consisted of patients presenting with a fluent form of progressive aphasia, also known as SD ($n = 8$). This was characterized by fluent and circumlocutory spontaneous speech, which may be empty in content, and is associated over time with difficulty understanding single words. Since these patients were relatively early in the course of their disease, they had a prominent naming deficit without widespread difficulty understanding single words. Another progressive aphasic subgroup of FTD patients consisted of those presenting with PNFA ($n = 7$). These patients had effortful speech, which may be associated with dysarthria and impaired grammatical comprehension, but relatively good single word comprehension. The NON-APH subgroup of FTD patients ($n = 14$) presented with social and behavioural difficulties, and a limitation of executive functioning.

Finally, nine patients were given the clinical diagnosis of CBD based on clinical-pathological studies reported in the literature and our own autopsy series (Rinne *et al*., 1994; Grimes *et al*., 1999; Riley and Lang 2000; Forman *et al*., 2002). These patients had progressive cortical sensory loss, apraxia and/or a lateralized extrapyramidal disorder (unilateral limb rigidity, myoclonus, dystonia, alien hand syndrome, gait difficulty and/or axial rigidity, but minimal resting tremor).

The initial clinical diagnosis of a neurodegenerative disease was consistent with the results of serum studies, structural imaging studies such as MRI or CT, studies of CSF (when available) and clinical functional neuroimaging studies such as single photon emissions computerized tomography (SPECT) or PET (these studies were not available to the consensus committee). Exclusion criteria included the presence of other neurological conditions such as stroke or hydrocephalus, primary psychiatric disorders such as depression or psychosis, or a systemic illness that can interfere with cognitive functioning. Most of these patients were taking a fixed dosage of an acetylcholinesterase inhibitor (e.g. donepezil, rivastigmine or galantamine). Some of these patients may have been medicated with a low dosage of a non-sedating anti-depressant (e.g. serotonin-specific re-uptake inhibitors such as sertraline) or an atypical neuroleptic agent (e.g quetiapine), as indicated clinically, but none of the patients demonstrated any evidence of sedation suggesting over-medication. Table 1 summarizes the demographical and

Table 1 *Demographic features and performance on measures of naming and related tasks in AD, FTD and CBD: mean (±SD)*

	AD	CBD	FTD	FTD subgroups		
				SD	PNFA	NON–APH
Age (years)	70.8 (±8.5)	64.0 (±7.0)	65.1 (±12.1)	65.5 (±13.0)	68.9 (±11.4)	63.07 (±12.2)
Education (years)	16.0 (±3.0)	13.6 (±3.1)	15.1 (±2.2)	15.4 (±2.3)	14.9 (±1.9)	15.07 (±2.3)
Duration (months)	51.1 (±18.4)	40.7 (±17.5)	41.3 (±31.8)	41.5 (±39.2)	39.0 (±22.5)	42.43 (±33.5)
MMSE (maximum = 30)	21.3 (±6.5)	18.8 (±7.4)	20.5 (±6.5)	23.8 (±4.6)	21.9 (±7.1)	18.00 (±6.5)
Naming (*Z*-score)	–3.03 (±2.37)	–3.77 (±3.67)	–3.94 (±3.12)	–4.87 (±2.6)	–3.67 (±4.3)	–3.55 (±2.8)
Retrieval (*Z*-score)	–3.19 (±0.66)	–2.99 (±1.05)	–3.22 (±1.04)	–2.92 (±0.9)	–3.56 (±0.7)	–3.21 (±1.0)
Semantic (*Z*-score)	–1.28 (±1.58)	–0.19 (±0.40)	–0.27 (±0.61)	–0.01 (±0.3)	–0.35 (±0.8)	–0.39 (±0.7)
Visual (*Z*-score)	–0.26 (±1.30)	–5.86 (±2.70)	–0.96 (±1.82)	–0.13 (±1.3)	–0.95 (±1.1)	–1.47 (±2.3)

clinical features of these patients. AD, FTD and CBD patient groups were selected to match in terms of age [$F(2,47) = 1.49$; not significant (ns)], education [$F(2,47) = 2.37$; ns), duration of disease [$F(2,47) = 0.61$; ns] and Mini-Mental State Examination (MMSE) score (Folstein *et al*., 1975) [$F(2,47) = 0.37$; ns]. Similarly, FTD patient subgroups were matched in terms of their age [$F(2,26) = 0.52$; ns], education [$F(2,26) = 0.10$; ns], duration of disease [$F(2,26) = 0.03$; ns] and MMSE score [$F(2,26) = 2.40$; ns].

Confrontation naming in these patients was compared with cohorts of 25 healthy older control subjects who were closely matched in age and education to each group of patients. The performance of each patient was converted to a *Z*-score based on each group's matched control subjects; we compare these normalized *Z*-scores statistically across the patient groups in Results below. It may be noted that the subgroups of control subjects did not differ statistically in their naming performance. The patients were participating in a longitudinal protocol. For the purpose of the present study, we selected the naming performance dataset closest in time to the MRI (naming data were obtained on the same day as the MRI in the overwhelming majority of patients) and these data were typically obtained early in the course of disease. Imaging data in these patients was compared with 12 right-handed, healthy, control subjects who were matched for age [mean (±SD) = 68.5 (±9.4) years]) and education [mean (±S.D.) = 15.4 (±1.8) years].

Cognitive materials and procedure

We administered several measures to assess confrontation naming and the major processes thought to contribute to naming. We selected a validated measure corresponding most closely to each component of naming that we hypothesized. The patients were offered rest breaks between tasks as necessary during the performance of these measures.

Confrontation naming

To assess confrontation naming (Morris *et al*., 1989), we used an abbreviated version of the Boston naming test (Kaplan *et al*., 1983), which was thought to be representative of the full protocol. Each subject was asked to name orally each test stimulus ($n = 15$). All visual stimuli were black-and-white line drawings, and target names were divided equally between high frequency, mid-frequency and low frequency items. Patients were given as much time as they needed to respond.

Lexical retrieval

To assess semantically-guided lexical search, retrieval and associated downstream processes such as phonological assembly and articulation, patients were asked to name orally as many different words as possible belonging to a target semantic category, i.e. ANIMALS (Mickanin *et al*., 1994). They were given 60 s to complete this task. We report the number of unique words meeting the category criterion in this time span. Two FTD patients (one SD patient and one NON-APH patient) did not complete this task.

Semantic category membership judgement

To assess semantic memory with a simple task that required little expression and minimized executive resource demands, patients were asked to judge the semantic category membership of 48 individually presented stimuli in response to a simple probe ('Is it an X?') (Grossman *et al*., 1996*a*). One target category was natural (VEGETABLES) and one manufactured (TOOLS); half of the stimuli in each category were targets and half foils, and half of each category of stimuli were printed words and half colour photos (matched for frequency, familiarity and visual complexity across categories). Stimuli were presented in a manner blocked by category and material. Patients were given as much time as they needed to complete the task. Performance on this task has been validated by behavioural and SPECT correlation studies in AD patients with impaired semantic memory (Grossman *et al*., 1997). Two FTD patients (both NON-APH patients) and one CBD patient did not complete this task.

Visual–spatial functioning

To assess visual perceptual–spatial functioning (Morris *et al*., 1989) in a manner involving a constructional element, patients were asked to copy four geometric designs graded according to their perceptual–spatial complexity. Performance was evaluated on an 11-point scale. One patient in each group (including one NON-APH FTD patient) did not complete this task.

Table 2 *Correlation of lexical retrieval, semantic and visual–spatial performance with confrontation naming in AD, CBD and FTD**

	Lexical retrieval	Semantic memory	Visual–spatial
AD	0.62	–	–
CBD	0.77	–	0.67
FTD	0.63	0.52	–
SD	0.97	–	–
PNFA	0.83	–	–
NON-APH	0.60	–	–

*All correlations are Pearson *r*-values significant at least at the $P < 0.05$ level of significance, according to Pearson correlations, except for the visual correlation in CBD patients which is significant at the $P < 0.07$ level.

Imaging procedure

All images were acquired by a GE Horizon Echospeed 1.5 T MRI scanner (GE Medical Systems, Milwaukee, WI, USA). Each study began with a rapid sagittal T1-weighted image to determine patient position. High resolution T1-weighted 3D spoiled gradient echo images were then acquired with TR (repetition time) = 35 ms, TE (echo time) = 6 ms, slice thickness = 1.3 mm, flip angle = 30°, matrix size = 128 × 256, and a rectangular FOV (field of view) giving an in-plane resolution of 0.9 × 0.9 mm. The brain volumes were normalized by registration to the T1 template (Evans *et al*., 1993) of 305 averaged brain volumes in SPM99 (Frackowiak *et al*., 1997) using 12-parameter affine registration, non-linear registration using 12 non-linear iterations and 7 × 8 × 7 basis functions. The brains were normalized to Talairach and Tournoux brain coordinates (Talairach and Tournoux, 1988). We examined the results of both unmodulated and modulated routines, but a comparison found no regional differences between these techniques. We report below the results from the unmodulated analysis.

We used VBM to analyse brain volumes (Ashburner and Friston, 2000). SPM99 was used to segment the brain volumes into four tissue types (grey matter, white matter, CSF and other). Based on *a priori* MRI information, the segmentation algorithm in SPM99 calculates a Bayesian probability for each voxel of each tissue group in the volume. We inspected each slice of each segmented volume to ensure that no voxels from the dural sinuses or other adjacent non-brain structures were misclassified as grey matter (Good *et al*., 2001; Karas *et al*., 2003). Lastly, using SPM99, the grey matter volume was smoothed with a 12 mm FWHM (full width at half maximum) Gaussian filter to minimize individual gyral variations.

SPM99 was used for all statistical analyses. This included a two sample *t*-test routine to compare the grey matter volume of each patient group to the control group of 12 healthy seniors, and to assess relative grey matter atrophy across patient groups by comparing pairs of contrasts involving each patient group and the healthy seniors. A proportional analysis threshold was used to include only voxels with ⩾40% of the grand mean value. Implicit masking was used to ignore zeros and global calculation was based on the mean voxel value. We set our statistical threshold for the atrophy studies of each patient group relative to control subjects at a value of $P < 0.0001$. We did not correct for multiple comparisons in this and other analyses due to the hypothesis-driven nature of the statistical tests. Moreover, the small size of the voxels would have made a Bonferroni-like statistical correction too conservative. Instead, for all analyses, we accepted only clusters comprised of ⩾100 adjacent voxels because this would also demonstrate a consistent effect in a particular neuroanatomical distribution (Forman *et al*., 1995). The between group comparisons of grey matter atrophy derived from pairs of patient–control contrasts were set at a statistical threshold of $P < 0.001$. The correlation analyses involved a regression of the confrontation naming *Z*-score on grey matter atrophy derived from the contrast of each patient group with the elderly control subjects. We set a statistical threshold for these analyses at $P < 0.001$. We focused on the significant correlations of naming and cortical volume that correspond to areas of significant grey matter atrophy. These correlations occur in demonstrably abnormal brain regions, and it is these correlated voxels that are likely to reflect interruptions of the large-scale neural network underlying naming. In comparison, naming–cortical correlations involving brain regions without significant grey matter atrophy are difficult to interpret unequivocally as these correlations are in regions where the large-scale neural network for naming is less likely to be compromised.

Results

Behavioural analyses of naming performance

Confrontation naming accuracy is summarized in Table 1. As can be seen, the average naming deficit in AD, FTD and CBD patient groups differed significantly from older control subjects' performance, using a criterion of $Z < -1.96$ (significant at the $P < 0.05$ level). However, an analysis of variance (ANOVA) did not reveal a difference in naming accuracy across patient groups [$F(2,47) = 0.38$; ns]. All three FTD subgroups were significantly impaired in their confrontation naming relative to the performance of healthy seniors as well (at least at the $P < 0.05$ level, according to *Z*-score distributions). Although there was no statistical difference between FTD patient subgroups in their confrontation naming [$F(2,26) = 0.48$; ns], Table 1 shows that SD patients were the most impaired FTD subgroup. SD patients were also more impaired than AD patients and CBD patients. An evaluation of individual patient performance profiles revealed that 32 (64%) of the patients differed significantly from older control subjects in their naming accuracy at the $P < 0.05$ level ($Z < -1.96$). This included seven (58%) of the AD patients, four (44%) of the CBD patients and 21 (72%) of the FTD patients [including seven (88%) of the SD patients, four (56%) of the PNFA patients and 10 (71%) of the NON-APH patients]. These findings confirm previous observations that confrontation naming is widely compromised in patients with these neurodegenerative diseases and that confrontation naming is particularly impaired in the SD subgroup of patients with FTD.

Table 1 also summarizes the performance of the patient groups with regard to measures of each of the major cognitive components thought to contribute to confrontation naming. All patient groups differed from control subjects in their lexical retrieval performance at the $P < 0.01$ level (according to *Z*-score distributions),

including each of the FTD patient subgroups. However, lexical retrieval performance did not differ between the patient groups [F(2,47) = 0.20; ns] nor between subgroups of patients with FTD [F(2,26) = 0.65; ns]. Inspection of individual patient performance profiles revealed that 42 (88%) of the patients differed significantly from older control subjects in their lexical retrieval performance at the $P < 0.05$ level ($Z < -1.96$). This included all 12 (100%) of the AD patients, seven (78%) of the CBD patients and 23 (85%) of the 27 FTD patients who performed this task (including six (86%) of the seven SD patients, seven (100%) of the PNFA patients and 10 (77%) of the 13 NON-APH patients). None of the patient groups differed significantly from the older control subjects in their performance on the simple measure of semantic memory we administered (including each of the FTD patient subgroups). Nevertheless, an ANOVA revealed a difference between groups [F(2,46) = 5.44; $P < 0.01$]. AD patients (33% of whom were impaired according to individual *Z*-score analyses) differed significantly from FTD patients and CBD patients in their semantic memory performance at the $P < 0.05$ level according to a Newman–Keuls procedure. CBD patients differed significantly from older control subjects in their visual–spatial performance at the $P < 0.01$ level (according to the *Z*-score distribution), although AD patients and FTD patients (and each of the FTD patient subgroups) did not differ from control subjects. We also found a difference between groups on the visual–spatial measure [F(2,46) = 24.69; $P < 0.001$]. CBD patients (seven of whom were impaired according to individual *Z*-score analyses) differed significantly from AD patients and FTD patients in their visual–spatial performance at least at the $P < 0.05$ level according to a Newman–Keuls procedure.

A correlation analysis is summarized in Table 2. As can be seen, confrontation naming accuracy correlated with lexical retrieval performance in AD, FTD and CBD. We also saw a correlation between naming accuracy and lexical retrieval in each of the FTD subgroups. We also found that CBD patients show a correlation between confrontation naming and visual–spatial functioning. In FTD, confrontation naming accuracy also correlated with semantic memory performance.

These findings confirmed significant naming difficulty in mildly-to-moderately demented patients with AD, CBD and FTD. Moreover, lexical retrieval was significantly impaired across all patient groups and correlated with impaired confrontation naming in each patient group. These observations emphasize the importance of lexical retrieval in these patients and suggest that impaired naming may be due to the disruption of a single component of the naming process across groups of patients with different neurodegenerative diseases. However, semantic memory appeared to play a role in naming difficulty in FTD and visual–spatial functioning contributed to the naming deficits of CBD patients. These findings are more consistent with the hypothesis that various components of the naming process may be disrupted differentially in neurodegenerative diseases; this may result in partially distinct patterns of impaired naming across these groups of patients. Indeed, the lexical retrieval component of naming and associated downstream processes can be compromised in many ways.

VBM analyses of cortical atrophy

The anatomical loci of peak grey matter atrophy in patients with AD, FTD and CBD, and the extent of the associated clusters are summarized in Table 3. These findings showed partially overlapping distributions of cortical atrophy across the patient groups. AD patients demonstrated significant grey matter atrophy in the bilateral temporal, left frontal and right parietal regions. FTD patients also showed cortical atrophy in the bilateral temporal and frontal brain regions. CBD patients showed grey matter atrophy in the bilateral temporal and frontal regions as well as the bilateral parietal regions. As illustrated in Fig. 1A, patients with AD, FTD and CBD showed overlapping distributions of significant cortical atrophy in the lateral temporal cortex of the left hemisphere. There was also a very small area of overlapping significant atrophy in the right inferolateral temporal cortex (11 voxels). An area of cortical atrophy common to AD, FTD and CBD suggests the possibility that the basis for impaired naming may be shared in part across these patient groups.

We also examined cortical atrophy in AD, FTD and CBD patient groups compared with each of the other patient groups. These group-by-group contrasts, summarized in Table 3 and illustrated in Fig. 1, emphasized differences in the distribution of grey matter atrophy across these patient groups. Consider first the pattern of atrophy in AD compared with FTD and CBD. Relative to FTD, AD patients have significantly greater atrophy in the bilateral posterolateral temporal-parietal and lateral occipital regions (Fig. 1B). We also observed significantly greater atrophy in the left hippocampus in AD relative to FTD (not shown). Relative to CBD, AD patients have greater atrophy in a left anterior and ventral temporal distribution (Fig. 1C). AD patients also have greater atrophy than CBD patients in the left anterior cingulate cortex (not shown). Atrophy in FTD also differed from that seen in AD and CBD. FTD patients have relatively greater atrophy in the right prefrontal (Fig. 1D) and left medial frontal (not shown) regions compared with AD patients. Relative to CBD, FTD patients have greater atrophy in the left anterior temporal (Fig. 1E) and the left anterior cingulate (not shown) regions. CBD patients showed greater atrophy in bilateral parietal and right frontal and temporal regions compared with AD patients (Fig. 1F). Compared with FTD patients, CBD patients have greater atrophy in bilateral temporal-parietal regions (Fig. 1G), including the medial parietal cortex (not shown). These partially distinct patterns of cortical atrophy are consistent with the hypothesis that the neural basis for impaired naming may differ in part across these patient groups.

Table 3 *Grey matter atrophy in AD, FTD and CBD relative to healthy seniors and relative grey matter atrophy in each patient group compared with other groups of patients*

	Anatomical locus (Brodmann area)	Coordinates			No. of voxels	*Z*-score
		x	*y*	*z*		
AD	Left anterior–lateral temporal (21, 39)	–62	–24	–2	70 061	5.24
	Left medial temporal/hippocampus (36)	–30	–36	–2	70 061	5.10
	Left dorsolateral prefrontal (46)	–52	36	18	456	4.26
	Left dorsolateral prefrontal (8)	–40	22	48	131	3.87
	Left prefrontal (6)	–58	0	36	204	3.89
	Right temporal/hippocampus (36, 21)	30	–32	–2	1406	4.91
	Right inferior parietal (40)	52	–52	32	285	4.17
FTD	Left anterior–lateral temporal (20)	–44	6	–36	4778	4.75
	Left ventral temporal (20)	–42	–30	–18	236	3.94
	Left dorsolateral prefrontal (8)	–44	8	38	758	4.36
	Left anterior prefrontal (10)	–42	58	–2	717	4.08
	Left superior frontal (6)	–22	18	50	205	4.08
	Left superior parietal (7)	–20	–46	58	274	4.37
	Left striatum	–18	0	–6	4778	4.91
	Right anterior temporal (21)	48	2	–28	141	4.26
	Right ventral temporal (20)	48	–36	–28	173	3.84
	Right frontal (47)	42	16	12	110	3.78
	Right striatum	20	2	–4	481	4.29
CBD	Left anterior–lateral temporal (21)	–58	–12	–16	449	3.97
	Left medial temporal (35)	–26	–42	–4	425	4.03
	Left dorsolateral prefrontal (8)	–42	12	38	210	4.99
	Left lateral and medial parietal (7)	–10	–54	56	8640	5.02
	Left thalamus	–8	–20	–8	1199	4.28
	Right inferior temporal (37)	44	–42	–26	753	4.21
	Right dorsolateral prefrontal (8)	32	20	44	115	3.86
	Right lateral and medial parietal (7)	2	–54	58	8640	4.78
	Right parietal operculum (40)	46	–26	2	157	3.70
Atrophy in AD relative to FTD	Left hippocampus, medial temporal	–34	–34	2	1092	3.38
	Left posterolateral temporal–parietal (37)	–44	–68	–4	285	3.12
	Left posterolateral temporal–parietal (22)	–64	–42	12	405	3.02
	Left lateral occipital (18)	–36	–88	10	302	3.39
	Right posterolateral temporal–occipital (22)	34	–20	22	779	3.23
	Right lateral occipital (19)	42	–82	–2	753	3.32
	Bilateral brainstem	0	–58	–50	724	4.12
Atrophy in AD relative to CBD	Left ventral–anterior temporal (20)	–46	–12	–44	617	3.77
	Left anterior temporal (21)	–54	4	–32	732	3.06
	Left anterior cingulate (24)	–10	22	20	100	3.23
Atrophy in FTD relative to AD	Left medial frontal (6)	–2	4	54	2170	3.43
	Left striatum	–16	–2	0	200	3.47
	Right superior prefrontal (6)	16	–10	56	2170	3.62
	Right dorsolateral prefrontal (46)	36	16	28	137	3.30
	Bilateral brainstem	–6	–24	–38	899	3.25
Atrophy in FTD relative to CBD	Left anterior temporal (21)	–48	6	–30	326	3.17
	Left anterior cingulate (24)	–10	36	16	194	3.08
Atrophy in CBD relative to AD	Left inferior parietal (39)	–42	–60	22	137	3.14
	Right ventral temporal (28)	10	–26	–10	1270	3.61
	Right temporal–occipital (19)	40	–66	–16	553	3.29
	Right dorsolateral prefrontal (46)	28	42	4	118	3.42
	Right dorsolateral prefrontal (8)	38	6	36	523	3.03
	Right parietal–temporal–occipital (19)	24	–76	28	9253	4.47
	Right superior parietal (7)	42	–40	44	9253	4.05
	Right anterior parietal–frontal (43)	54	–8	8	810	3.43

Table 3 *Continued*

	Anatomical locus (Brodmann area)	Coordinates			No. of voxels	*Z*-score
		x	*y*	*z*		
Atrophy in CBD relative to FTD	Left temporal–occipital (19)	–42	–70	–6	380	3.12
	Left medial parietal (7)	–6	–56	58	22 165	5.67
	Left inferior parietal–occipital (40)	–50	–22	32	185	3.70
	Right parietal–temporal–occipital (39)	46	–70	18	22 165	5.02
	Right medial parietal (7)	4	–70	44	22 165	5.10

We performed similar analyses of grey matter atrophy in subgroups of patients with FTD. These findings are summarized in Table 4. As can be seen, significant grey matter atrophy was evident in several areas of the left temporal cortex in SD. Patients with PNFA also showed significant cortical atrophy in portions of the left temporal lobe, as well as significant grey matter atrophy in several left frontal regions. NON-APH patients with FTD also demonstrated some left temporal grey matter atrophy, as well as cortical atrophy in a right frontal distribution. Figure 2A illustrates the distribution of grey matter atrophy in these FTD subgroups. An area of significant cortical atrophy shared across all FTD patients was seen in the left anterior temporal cortex; this is consistent with the possibility that disruption of a single component of the naming process may explain naming difficulty in all subgroups of patients with FTD.

Areas of significant cortical atrophy that differed across subgroups of FTD patients are summarized in Table 4. For example, Fig. 2B shows that SD patients have significant grey matter atrophy in the left posterolateral temporal cortex relative to PNFA patients. Figure 2D illustrates the distribution of significant grey matter atrophy in PNFA relative to SD in the frontal cortex of the right hemisphere. Other pairwise FTD subgroup comparisons are shown in Fig. 2. These differences suggest that confrontation naming difficulty in subgroups of FTD patients may be due to partially distinct sources of impairment.

Correlations between confrontation naming accuracy and cortical volume

Table 5 summarizes the coordinates of the peak foci of significant correlations between confrontation naming performance and grey matter volume in patients with AD, FTD and CBD. In AD, significant correlations between cortical volume and confrontation naming were found in the left lateral temporal cortex and the left anterior cingulate cortex. Fig. 3 shows the distribution of areas of significant correlation between naming and cortical volume, which overlap with areas of significant cortical atrophy. The correlations between naming performance and grey matter volume corresponded to areas of significant cortical atrophy in an anterior-lateral temporal distribution of the left hemisphere, as well as a small inferolateral temporal area in the right hemisphere (Fig 3A).

Table 5 shows that patients with FTD have significant correlations between confrontation naming accuracy and grey matter volume in the bilateral anterior temporal and bilateral frontal regions. The correlation between naming and cortical volume in FTD corresponds to the area of significant cortical atrophy in the left anterior-lateral temporal cortex, as well as small areas in the right temporal cortex and left frontal cortex (Fig. 3B).

Table 5 also shows that naming performance correlated with grey matter volume in CBD in the bilateral frontal and temporal cortices. These naming-cortical correlations correspond to areas of significant cortical atrophy in CBD in small areas of the frontal and temporal cortex bilaterally (Fig. 3C). These observations are consistent with the hypothesis that the neural basis for impaired naming partially overlaps in lateral aspects of the left temporal cortex across patients with AD, FTD and CBD. Unique correlations in each patient group also appear to provide evidence consistent with the claim that partially distinct components of the large-scale neural network for naming are interrupted in patients with neurodegenerative diseases.

We also examined patterns of correlation between confrontation naming performance and cortical volume in subgroups of patients with FTD. Table 5 summarizes the coordinates of the peak foci of significant correlation between confrontation naming and grey matter volume in these patients. In SD, significant correlations were seen in bilateral temporal cortex. Fig 4A shows the area of correlation between naming and cortical volume in SD that overlaps with significant cortical atrophy. This was in the left lateral temporal region. Table 5 indicates that the anatomical distribution of significant naming-volume correlation in PNFA was in the frontal and temporal areas bilaterally. The naming-volume correlations overlapping with areas of significant grey matter atrophy in PNFA were in the left anterior temporal cortex, as well as the inferior, orbital, dorsolateral prefrontal and premotor portions of the left frontal lobe (Fig. 4B). In NON-APH patients, significant naming-volume correlations were seen in bilateral frontal cortex extending to the anterior cingulate cortex and in the left temporal and

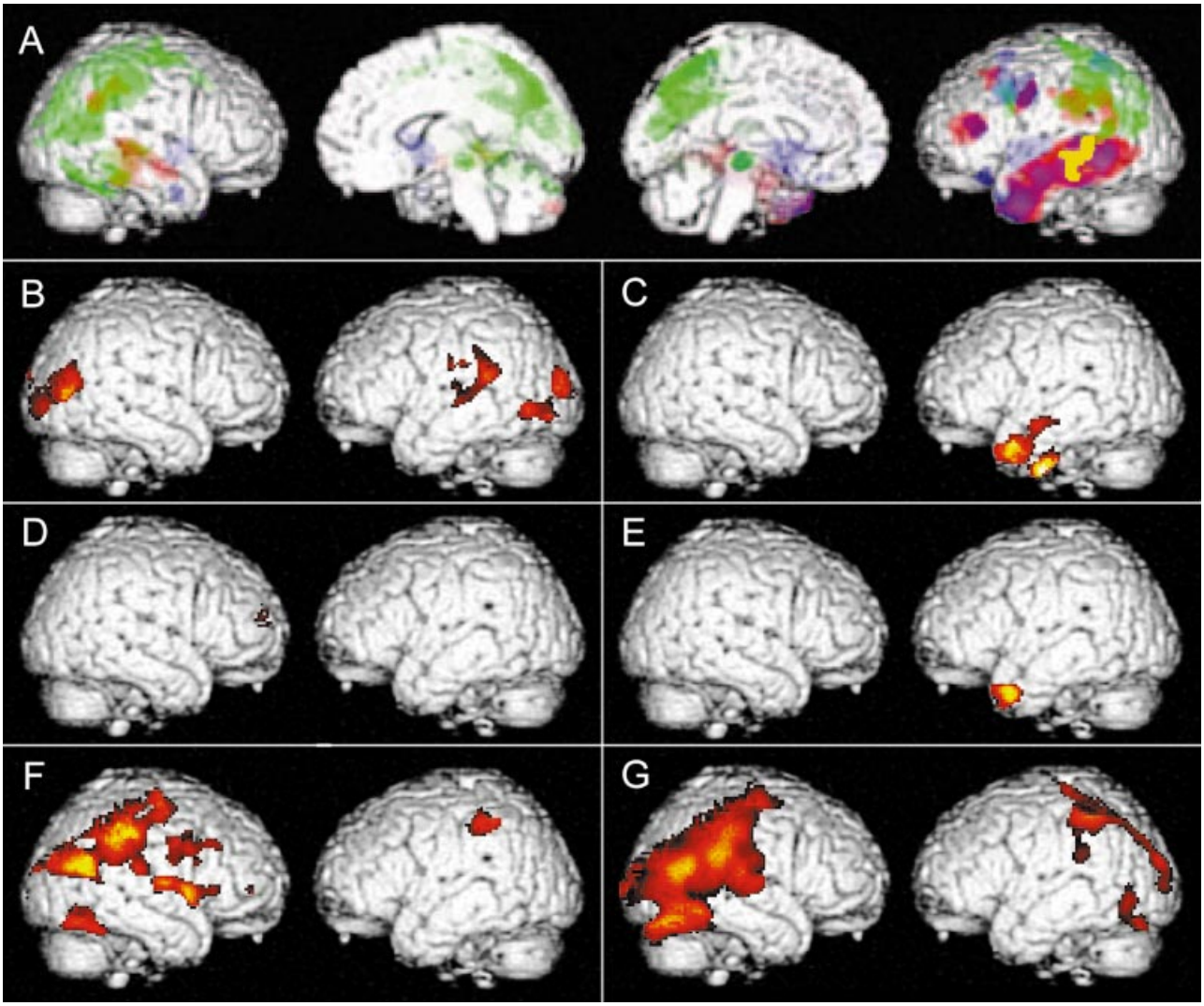

Fig. 1 Grey matter atrophy in AD, FTD and CBD. The yellow area in the left lateral temporal cortex indicates the distribution of significant cortical atrophy common to all groups. (**A**) Atrophy in each patient group relative to healthy seniors (pink: AD; blue: FTD; green: CBD). (**B**) Atrophy in AD disease relative to FTD. (**C**) Atrophy in AD relative to CBD. (**D**) Atrophy in FTD relative to AD. (**E**) Atrophy in FTD relative to CBD. (**F**) Atrophy in CBD relative to AD. (**G**) Atrophy in CBD relative to FTD.

parietal regions (Table 5). Significant naming-volume correlations overlapping with regions of significant cortical atrophy in NON-APH (Fig. 4C) were in the left anterior temporal cortex and the right dorsolateral prefrontal cortex. These distinct naming-cortical correlations are consistent with the hypothesis that a large-scale neural network for naming is interrupted in several unique ways in subgroups of patients with FTD.

Discussion

Naming is a complex process involving components such as interpreting a visual stimulus, identifying the corresponding concept in semantic memory, and selecting and expressing the name that best labels this concept. Since naming is so complex, a neurobiologically valid model of naming is likely to require converging evidence from multiple sources. This may include: neuroanatomical observations based on studies of stroke patients (Hillis *et al*., 2001); functional neuroimaging studies of healthy subjects using PET (Howard *et al*., 1992; Whatmough *et al*., 2002) or functional MRI (Smith *et al*., 2001; Simon *et al*., 2002); fine-grained temporal observations of the naming process with electrocortical studies of naming during the presurgical evaluation of epilepsy patients (Ojemann and Schoenfield-McNeill, 1999; Crone *et al*., 2001); and event-related scalp potential studies of healthy subjects (Indefrey and Levelt, 2000). The present study examines the nature of naming difficulty in patients with AD, FTD and CBD, and the relationship between these naming deficits and the patterns of cortical atrophy seen in these patients. We argue below that naming is supported by a large-scale neural network involving multiple cortical regions. Our observations are consistent with the hypothesis that this network is interrupted in a manner which is partially

Table 4 *Grey matter atrophy in FTD subgroups relative to healthy seniors and relative grey matter atrophy in each frontotemporal subgroup compared with other subgroups*

	Anatomical locus (Brodmann area)	Coordinates			No. of voxels	*Z*-score
		x	*y*	*z*		
SD	Left ventral temporal (20)	–44	–34	–22	954	4.49
	Left anterior temporal (21)	–44	6	–36	424	4.01
	Left posterolateral temporal (39)	–52	–52	4	311	3.88
	Left parahippocampal (34)	–16	0	–8	187	4.06
PNFA	Left dorsolateral prefrontal (8, 9)	–38	16	38	155	3.79
	Left inferior frontal (10, 47)	–46	56	2	285	4.29
	Left anterior insula	–20	4	–4	333	3.99
	Left premotor (6, 4)	–38	–22	60	150	4.35
	Left anterior temporal (21)	–52	4	–34	139	3.79
	Left ventral temporal (19)	–22	–62	–16	109	4.16
NON-APH	Left anterior insula	–20	2	–4	209	3.68
	Left anterior temporal (21)	–44	6	–36	312	4.07
	Left parahippocampal (28)	–6	–24	–8	150	3.90
	Right dorsolateral prefrontal (8)	32	22	42	1075	4.03
	Right anterior prefrontal (10)	6	70	–4	124	3.93
Atrophy in SD relative to PNFA	Left posterolateral temporal (39)	–38	–60	20	103	3.47
Atrophy in SD relative to NON-APH	Left ventral temporal (20)	–48	–20	–20	1459	4.35
	Left ventral temporal (20)	–20	–2	–36	253	3.16
	Right occipital (18)	30	–96	–24	137	3.23
Atrophy in PNFA relative to SD	Right dorsolateral prefrontal (9)	56	16	38	4283	4.42
	Right inferior frontal (47)	40	30	–24	256	3.55
Atrophy in PNFA relative to NON-APH	Left inferior temporal (37)	–50	–62	–10	292	3.52
	Left ventral temporal-occipital (19)	–26	–68	–18	117	3.33
	Left occipital (18)	–4	–96	–16	379	3.39
Atrophy in NON-APH relative to SD	Right dorsolateral prefrontal (8)	26	30	52	10 011	3.58
	Bilateral anterior cingulate (6)	–2	16	64	10 011	3.64
	Right anterior insula	24	16	12	1420	3.35
Atrophy in NON-APH relative to PNFA	Right posterolateral temporal (39)	38	–60	26	116	3.12

shared across these patient groups and in a manner that is partially unique to each patient group. This yields a pattern of naming difficulty that includes a component common to all groups, namely lexical retrieval, as well as components distinct to each patient group involving specific aspects of retrieval as well as impairments of semantic memory and visual perceptual–spatial functioning.

Behavioural observations of impaired naming: partially shared and partially distinct patterns of naming difficulty

We found that naming difficulty is significantly compromised in AD, FTD and CBD. This is consistent with many previous observations of naming performance in these patient groups. Moreover, the level of naming difficulty was quantitatively equivalent across groups. One factor appeared to contribute to naming difficulty across all three patient groups: consistent with previous observations, naming accuracy correlated with lexical retrieval in AD (Hodges *et al*., 1991; Cronin-Golomb *et al*., 1992), in FTD (Thompson *et al*., 1997; Lambon Ralph *et al*., 1998) and in CBD (P. Moore, K. Dennis and M. Grossman, unpublished data). This suggests that a single component, i.e. lexical retrieval, may play a role in naming difficulty shared across patient groups.

It is also apparent in our data and in previously published work that these patients demonstrate some qualitatively distinct features in their impaired naming. Consider first patients with AD. Only lexical retrieval showed a statistically significant correlation with naming difficulty in the AD patients participating in this study. This differed from the pattern seen in FTD and CBD, where additional factors appeared to contribute to their naming deficit. Although some work has related semantic memory to impaired naming in AD

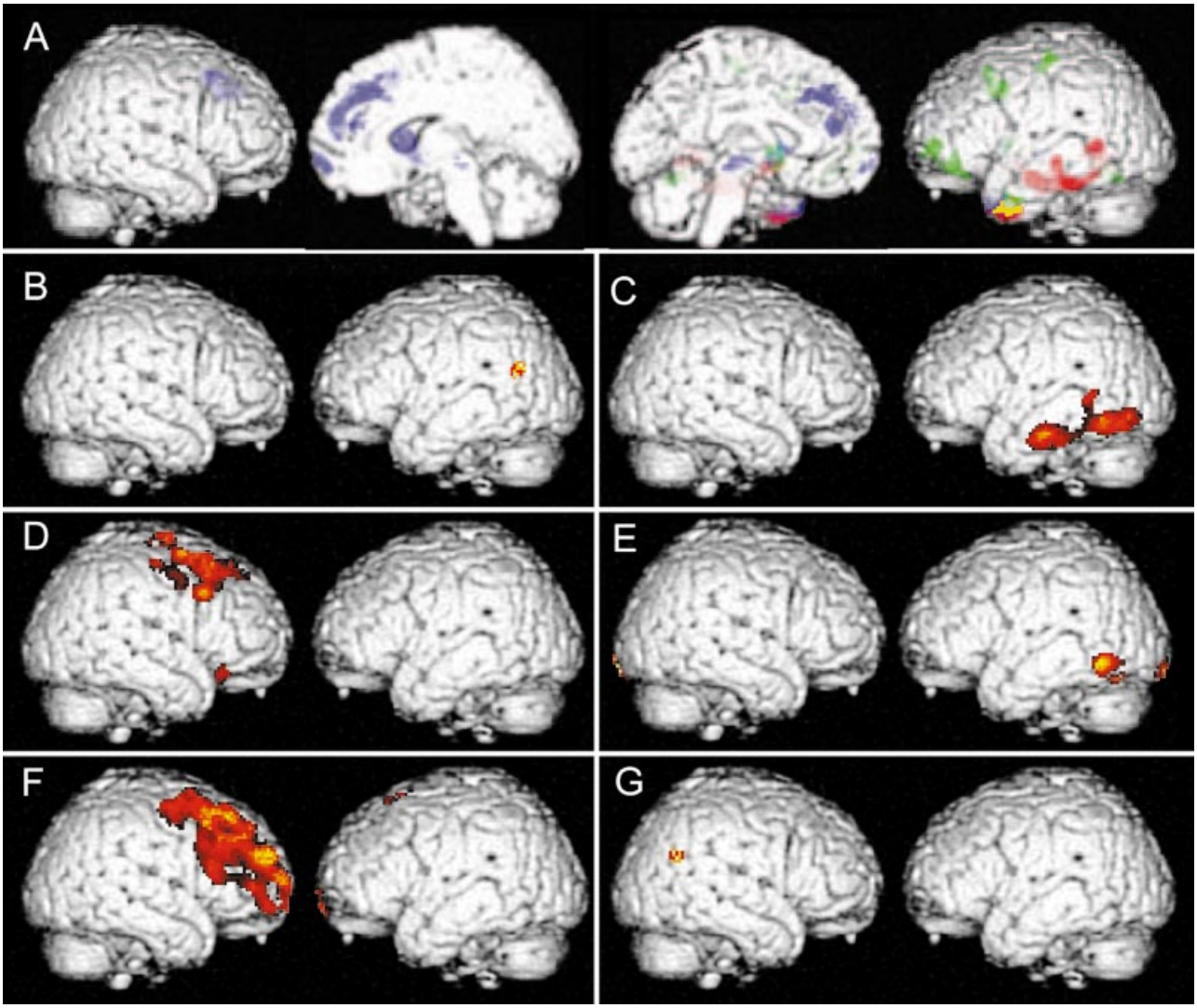

Fig. 2 Grey matter atrophy in SD, PNFA and NON-APH patients with FTD. The yellow area in the left anterior temporal cortex indicates the distribution of significant cortical atrophy common to all groups. (**A**) Atrophy in each subgroup of frontotemporal dementia relative to healthy seniors (pink: SD; green: PNFA; blue: NON-APH).(**B**) Atrophy in SD relative to PNFA. (**C**) Atrophy in SD relative to NON-APH. (**D**) Atrophy in PNFA relative to SD. (**E**) Atrophy in PNFA relative to NON-APH. (**F**) Atrophy in NON-APH relative to SD. (**G**) Atrophy in NON-APH relative to PNFA.

(Huff *et al*., 1986; Hodges *et al*., 1996; Lambon Ralph *et al*., 1997), we may not have observed a naming-semantic correlation in these AD patients because of their degree of dementia and heterogeneity in semantic functioning within the AD group (Grossman *et al*., 1996*a*, 1997). We adopted the strategy of studying AD patients with mild-to-moderate dementia—even though this limits the ability to generalize our findings across the entire spectrum of AD severity—to allow matching for severity with groups of FTD and CBD patients. With this measure of semantic memory, we also minimize the potential confounds associated with task-related resource demands. In FTD, by comparison, naming accuracy appeared to correlate with lexical retrieval as well as with the semantic component of naming. This has been seen in other work (Hodges *et al*., 1995; Lambon Ralph *et al*., 2001; P. Moore, K. Dennis and M. Grossman, unpublished data). Naming in CBD correlated with lexical retrieval and performance on a measure of visual perceptual–spatial functioning (P. Moore, K. Dennis and M. Grossman, unpublished data). These findings suggest that impaired naming may have qualitatively distinct features in AD, FTD and CBD. While the measures of lexical retrieval, semantic and visual perceptual–spatial functioning were selected to reflect each of these components of naming, our observations may be limited by the fact that each was assessed by a single measure and thus may not capture its full scope in the naming process. Moreover, the numbers of patients we examined in each group was relatively small. This limits the statistical treatments of the data, suggests caution in generalizing our findings and emphasizes the importance of additional work with larger and more varied groups of these patients. With these caveats in mind, our observations are consistent with

Table 5 *Correlations of grey matter atrophy with confrontation naming in AD, FTD and CBD and in subgroups of patients with FTD*

	Anatomical locus (Brodmann area)	Coordinates			No. of vowels	*Z*-score
		x	*y*	*z*		
AD	Left anterior-lateral temporal (22)	–40	6	–12	1683	3.20
	Left anterior cingulate (24)	–16	–14	50	192	3.22
FTD	Left anterior-ventral temporal (20)	–52	–30	–20	18 934	4.41
	Left prefrontal (6)	–22	10	44	203	3.82
	Right ventral temporal (38)	26	14	–46	2990	3.56
	Right prefrontal (6)	28	28	10	1302	4.01
CBD	Left ventral temporal (36)	–20	0	–36	11 138	3.59
	Left anterior temporal-inferior frontal (44)	–40	12	8	11 138	3.19
	Right inferior frontal-anterior temporal (6)	48	–2	10	11 138	5.15
	Right dorsolateral prefrontal (10)	44	56	2	992	3.04
	Right cerebellum	14	–42	–40	2701	3.75
SD	Left ventral temporal (20)	–48	–34	–26	498	3.63
	Left ventral temporal (19, 37)	–50	–64	–24	118	4.68
	Right posterolateral temporal (22)	46	–52	16	126	3.43
	Bilateral occipital (18)	2	–92	–26	271	3.73
PNFA	Left prefrontal (6)	–24	12	48	119	3.06
	Left inferior parietal (40)	–48	–30	26	13 477	4.72
	Left lateral temporal (21)	–54	–14	–10	13 477	5.33
	Left inferior temporal (20)	–46	–4	–36	13 477	5.24
	Right dorsolateral prefrontal (8)	26	16	44	4385	3.91
	Right inferior temporal (20)	22	–4	–40	4385	3.78
	Right posterolateral temporal (22)	42	–58	12	159	3.24
	Right inferior temporal (37)	62	–60	–22	132	3.17
NON-APH	Left anterior prefrontal (10)	–40	60	–6	39 643	4.16
	Left anterior cingulate	–2	20	16	39 643	4.06
	Left parietal (7)	–36	–68	54	140	3.27
	Right dorsolateral prefrontal (8)	32	18	32	178	3.33
	Right lateral temporal (22)	70	–12	16	135	3.18
	Right cerebellum	10	–76	–50	458	3.28

the hypothesis that a deficit in lexical retrieval and associated downstream processes is common to all patients suffering from AD, FTD or CBD, and that this component of naming may play a role in the naming difficulty that is shared by these patients. Further, the behavioural findings suggest some unique aspects of impaired naming in each of these neurodegenerative diseases, consistent with the hypothesis that a large-scale neural network for naming is interrupted in several distinct ways in these patients.

Our observations also confirm a statistically significant naming deficit in SD, PNFA and NON-APH subgroups of patients with FTD. While clinical observations and empirical studies emphasize the profound naming impairment in patients with SD (Snowden *et al*., 1989; Hodges *et al*., 1992*a*; Neary *et al*., 1998), naming difficulty is also evident in PNFA and NON-APH patients (Weintraub *et al*., 1990; Hodges and Patterson, 1996; Thompson *et al*., 1997; Croot *et al*., 1998; P. Moore, K. Dennis and M. Grossman, unpublished data). SD patients showed the greatest naming impairment and almost all the individual SD patients had a significant naming deficit. However, we were not able to confirm a statistically greater deficit in SD than other patients with FTD due to the relatively small number of patients participating in this study.

We also examined whether the naming deficit in FTD subgroups is due to an impairment of a single critical component of the naming process or to the interruption of different components of a large-scale neural network underlying naming. SD, PNFA and NON-APH patients all showed a correlation with lexical retrieval, suggesting that a single component of naming is compromised across all three FTD subgroups. Previous work has also emphasized the contribution of other cognitive components to impaired naming in FTD subgroups. For example, patients with SD have semantic memory impairments that appear to play a role in their naming deficit (Hodges *et al*., 1995; Lambon Ralph *et al*., 1998, 2001; P. Moore, K. Dennis and M. Grossman, unpublished data). We may not have observed this because

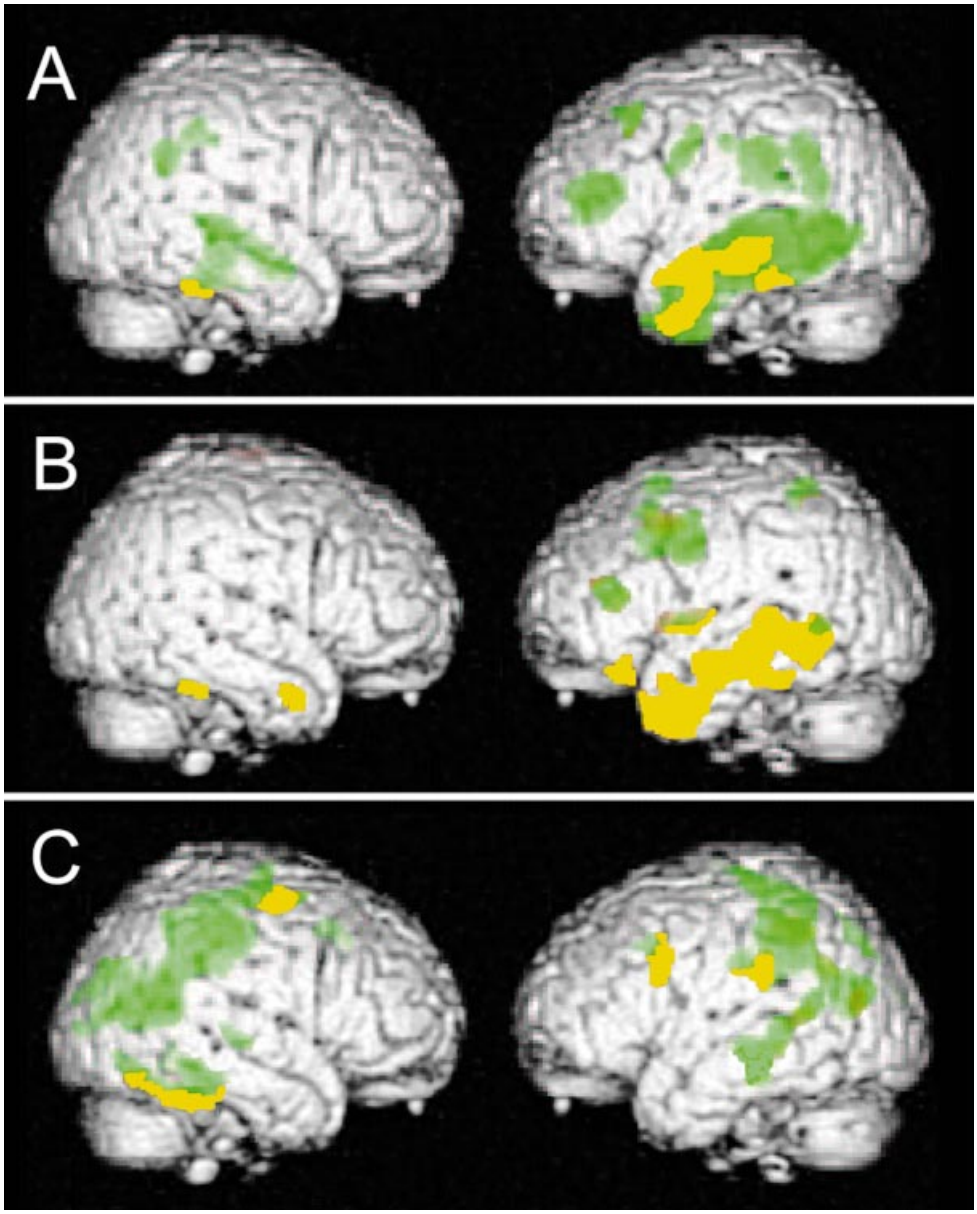

Fig. 3 Correlations between confrontation naming and cortical atrophy in AD, FTD and CBD. The yellow areas indicate the anatomical distribution of the significant correlations between naming and cortical volume that correspond to the regions of significant cortical atrophy shown in green. Correlations between naming and cortical volume that correspond to the regions of significant cortical atrophy in (**A**) AD, (**B**) FTD and (**C**) CBD.

the SD patients participating in the present study were early in the course of their disease and had a deficit in understanding occasional words that was not sufficiently extensive to be detected by a standard, group-based, semantic protocol (Lambon Ralph *et al*., 2001). Semantic difficulty may also be present in PNFA and NON-APH patients—as manifested in their respective deficits in verb knowledge and social knowledge (Bak *et al*., 2001; Grossman *et al*., 2003; Wood and Grafman, 2003; P. Moore, K. Dennis and M. Grossman, unpublished data). In this context, we may have seen a correlation of naming with semantic memory across all FTD patients, but not in each subgroup either due to the relatively small number of participants in each subgroup or because of the different kinds of semantic memory that may be compromised in these subgroups. The deficit in NON-APH patients may depend to some extent on their pattern of non-aphasic cognitive impairment, such as the presence of distractibility and other non-specific test-taking issues unrelated to the naming process *per se* (Rahman *et al*., 1999; Perry and Hodges, 2000; Rosen *et al*., 2002*a*). PNFA patients also appear to have some executive deficits that may limit their naming (Rhee *et al*., 2001). Finally, it is important to

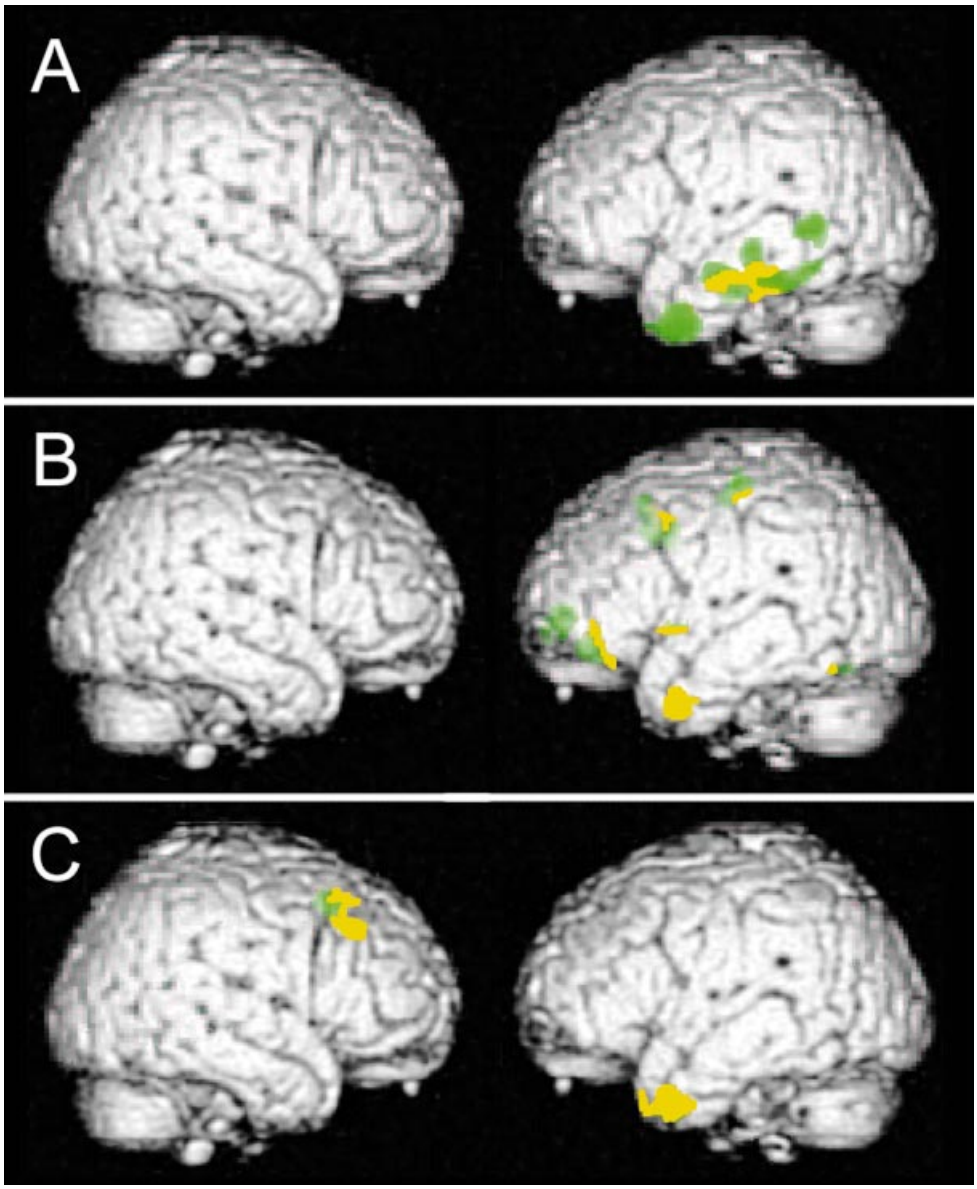

Fig. 4 Correlations between cortical atrophy and confrontation naming in SD, PNFA and NON-APH patients. The yellow areas indicate the distribution of the significant correlations between naming and cortical volume that correspond to the regions of significant cortical atrophy shown in green. Correlations between naming and cortical volume that correspond to regions of significant cortical atrophy in (**A**) SD, (**B**) PNFA and (**C**) NON-APH.

emphasize that lexical retrieval itself is a complex process involving multiple components. Despite the overwhelmingly common occurrence of a specific kind of naming deficit, i.e. failure to retrieve a word, which superficially appears to be identical in all groups of patients, the neurodegenerative process may interrupt different aspects of retrieval and expression in a large-scale neural network for naming in subgroups of FTD patients. This possibility can be examined by looking for different cognitive-cortical correlative patterns in patients with superficially similar profiles of impaired naming. We discuss below cortical atrophy in neurodegenerative diseases and the relationship of this atrophy to their naming deficit.

Correlations of naming difficulty with cortical atrophy: a single component of naming compromised across all patient groups

The present study sought to take advantage of partially shared and partially distinct patterns of naming difficulty across neurodegenerative diseases to learn about the neural basis for

confrontation naming. In particular, we tested the hypothesis that qualitative similarities in language and cognition related to naming are due in part to patterns of cortical atrophy shared across AD and FTD, while qualitative differences in the language and cognitive components of naming are also associated with the partially distinct patterns of cortical atrophy seen in AD and FTD. We add to these observations the first quantitative study of grey matter atrophy in CBD. While an important advantage of this approach is the prominent anomia in these patients, one shortcoming is the absence of histopathologically confirmed diagnosis. Clinical diagnosis is a marker for regional cortical abnormality that interferes with the naming process, and additional work will be needed in the future to relate naming deficits more directly to histopathological abnormalities.

We used VBM analyses of structural MRI to identify the neuroanatomical distribution of grey matter atrophy in neurodegenerative diseases. Although other techniques are available, imaging studies of regional cortical atrophy have generally adopted one of two approaches: (i) a region-of-interest (ROI) analysis; or (ii) VBM. Few direct comparisons of VBM and ROI approaches have been published (Good *et al*., 2002), and discrepancies may be due to several differences between techniques that emphasize their relative advantages and disadvantages. The VBM technique does not allow the careful preservation of gyral and sulcal patterns of individual patients which can be achieved with an ROI approach, even though there is significant variability in the sulcal patterns across individuals that may be difficult to interpret with the ROI approach (Steinmetz and Seitz, 1991). Careful histological analyses also underline the poor correspondence between gross sulcal anatomy and microscopically-defined architectonic boundaries (Amunts *et al*., 1999). These individual anatomical features are blurred in VBM analyses that normalize each brain to a template and smooth the images in preparation for statistical analysis of group data. Although labour-intensive and time-consuming, the ROI technique is less reliable than a computer-based, fully-automated VBM approach. There are potential problems associated with the automatic identification of tissue types during extraction of the brain from the skull prior to segmentation (Good *et al*., 2001; Karas *et al*., 2003). The brain to which experimental subjects are normalized can be vexing: since the most widely used average brain uses young adults (Evans *et al*., 1993), greater deformation is required when studying the brains of elderly subjects. Potential solutions include using a 'local' template composed of the participants in a study, normalizing with a high dimensional algorithm, or implementing a deformation-based approach to normalization (Gee and Haynor, 1999; Good *et al*., 2001; Karas *et al*., 2003)—although these are not problem-free,. Other shortcomings of VBM have been detailed elsewhere (Ashburner and Friston, 2000; Baron *et al*., 2001; Good *et al*., 2001; Karas *et al*., 2003). We attempted to minimize some of these issues by: (i) using age-matched seniors as a reference group; (ii) by inspecting each slice of each segmented image of each patient for inaccurately labelled voxels; and (iii) by performing direct comparisons of cortical atrophy across age-matched patient groups that take into account a common reference group. A final issue is that cortical atrophy may not always reflect the full extent of functional cortical disease identified by other techniques such as PET (Chételat *et al*., 2003). Additional work is needed to determine whether discrepancies between techniques reflect equally necessary components of a large-scale neural network supporting a cognitive function.

With these caveats in mind, the results of the present study are consistent with the claim that naming difficulty is due in part to the interruption of a single neural component across all groups of patients. For example, we found an area of cortical atrophy that is common to AD, FTD and CBD, i.e. the lateral temporal cortex in the left hemisphere. A very small area of the right inferolateral temporal cortex also shared atrophy across groups. Dorsolateral prefrontal regions of the left hemisphere of these patient groups with cortical atrophy were adjacent to each other, although there was no overlap across all three groups.

The observation of significant atrophy on its own permits only very limited inferences about brain–behaviour relationships in neurodegenerative diseases. Demented patients have many different kinds of cognitive deficits, and any of these may be related to an area of cortical atrophy. We therefore performed direct correlations between naming performance and cortical volume. We found that confrontation naming correlates with cortical volume in the left lateral temporal lobe of patients with AD, FTD and CBD. This is somewhat consistent with previous work showing a correlation between confrontation naming and the left anterior temporal cortex in a combined group of AD patients and SD patients (Galton *et al*., 2001). To confirm that a specific anatomical distribution of correlation between naming and cortical volume contributes to the naming impairment of these patients, we constrained our inferential reasoning further by requiring that the correlation correspond to a region of significant cortical atrophy. With this constraint, we observed naming-cortical volume correlations in a left lateral temporal distribution in each patient group which was also significantly atrophic. Based on the observations that (i) naming difficulty correlated with impaired lexical retrieval in groups of patients with AD, FTD and CBD, (ii) there was a correlation between naming and cortical volume in left lateral temporal cortex in all three groups of patients and (iii) left temporal cortex was atrophic in the area of significant correlation in all of these patients, it seems reasonable to infer that this left lateral temporal region contributes to naming in AD, FTD and CBD. Since lexical retrieval appears to be the only component associated with naming in all three patient groups, it is likely that left lateral temporal cortex plays a role in the lexical retrieval component of naming.

Much work has associated naming with the left temporal lobe. Naming difficulty has been observed following focal ischaemic insult to the left temporal lobe (Benson, 1979;

Kohn and Goodglass, 1985; Goodglass, 1993). Functional neuroimaging studies in healthy adults have shown activation of the left temporal cortex during naming (Howard *et al*., 1992; Mummery *et al*., 1998; van Turennout *et al*., 2000; Whatmough *et al*., 2002; Burgund *et al*., 2003). One PET study demonstrated activation in healthy subjects during naming of the left lateral temporal cortex, which was in the same anatomical distribution as patients with structural insult causing a lexical retrieval deficit during naming (Damasio *et al*., 1996). Based on the observation that semantic memory was preserved in their patients, these investigators hypothesized that the left lateral temporal cortex serves as an interface between the neural representation of a concept and the abstract representation of its name. The left lateral temporal area in this study is very similar to the anatomical distribution of the correlation we observed. It is also possible to speculate that the inferolateral temporal cortex of the right hemisphere contributed to the lexical retrieval component of naming difficulty across these patients, although the very small volume of tissue implicated in this region should be borne in mind. The right temporal cortex has been associated with sparse representations of word meaning (Beeman *et al*., 1994) and may contribute to retrieval by helping to limit the scope of the search for a target concept. Regardless of the contribution to naming played by lateral temporal cortex, these findings suggest that the impairment of one component of naming is likely to be shared across patients with AD, FTD and CBD.

Correlations between naming and cortical atrophy: multiple interruptions of a large-scale neural network result in partially distinct patterns of impaired naming in AD, FTD and CBD

While the observations described above lend support to the 'single component' hypothesis of impaired naming, several findings suggest that this may not fully explain naming difficulty in these patients. Consider in more detail AD patients, where impaired naming correlated only with lexical retrieval. We found a significant correlation between naming and cortical volume in the left lateral temporal cortex in AD as well as in FTD, and a direct comparison showed that AD patients have significantly greater atrophy in the left lateral temporal cortex than FTD patients. Other imaging and autopsy work has shown significant atrophy in this anatomical distribution in AD as well (Grady *et al*., 1988; Arnold *et al*., 1991; Haxby *et al*., 1990; Johnson *et al*., 1993; Karbe *et al*., 1994; Alsop *et al*., 2000; Baron *et al*., 2001; Busatto *et al*., 2003). The 'single component' hypothesis would predict that naming should be more impaired in AD than FTD since left lateral temporal atrophy is greater in AD than in FTD. In fact, this was not found: naming difficulty was statistically equivalent in AD and FTD. Similarly, the lexical retrieval deficit was equivalent statistically across these patient groups. While the left lateral temporal cortex may contribute to the lexical retrieval component of naming, the severity of disease in this area does not appear to predict the relative severity of the impairment in naming or lexical retrieval.

Additional evidence for a multifactorial approach to naming comes from the observation of different behavioural correlation profiles in FTD and CBD, and the distinct patterns of significant cortical atrophy across these patient groups. Consider in this context patients with FTD. The pattern of correlations between naming and cortical atrophy appears to reflect a combination of the profiles seen across FTD subgroups. SD, PNFA and NON-APH patients all showed a significant correlation between confrontation naming accuracy and lexical retrieval, although correlations between naming and cortical volume showed a distinct profile in each subgroup. This observation suggests that a single neural locus for all aspects of lexical retrieval and its associated phonological assembly and articulatory processes is unlikely. Instead, different parts of a large-scale neural network appear to be implicated in different aspects of lexical retrieval during naming. The lexical retrieval component of naming is known to be quite complex. Retrieval may involve selecting the correct name from among many possible choices in semantic memory that are equally accurate because they label objects with overlapping features. This appears to be a component of retrieval associated with the left lateral temporal cortex that is compromised across AD, FTD and CBD groups (as noted above). Other components of retrieval include, but are not limited to, inhibiting names that share many phonological features but do not name the target object, translating a material-neutral representation of the name into a material-specific form that can be expressed in a specific modality, and assembling phonological or graphemic components into a specific word that can be expressed. An impairment in any of these subcomponents could interfere with the retrieval component of naming.

Consider in this context the SD subgroup of patients with FTD. In the present study, a direct correlation between confrontation naming difficulty and cortical volume suggested that a lateral region of the left temporal lobe contributes to naming difficulty in SD. This left lateral temporal area also had statistically significant cortical atrophy, so it is reasonable to infer that the correlation between naming difficulty and cortical volume involving this area reflects an interruption of a large-scale neural network for naming, and particularly the lexical retrieval component of naming. While we observed cortical atrophy in the left anterior temporal region in SD similar to previous studies (Laakso *et al*., 2000; Mummery *et al*., 2000; Chan *et al*., 2001; Galton *et al*., 2001; Rosen *et al*., 2002*a*), we did not find a direct correlation between confrontation naming and grey matter volume in this region of the left temporal lobe. This differs from other work that has implicated the left anterior temporal area in naming difficulty. One correlation study related left anterior temporal cortical atrophy to naming

difficulty in a combined group of patients with SD and AD (Galton *et al*., 2001), but correlation data in each individual group were not reported. A longitudinal study related retrieval to left temporal atrophy in SD (Lambon Ralph *et al*., 2001), but anatomically detailed correlative data were not provided. In a functional neuroimaging study of lexical comprehension in patients with SD, limited activation was observed in lateral portions of left temporal cortex (Mummery *et al*., 1999). The authors attributed the comprehension difficulty in SD to a disconnection within the left temporal lobe between the anterior temporal and lateral temporal structures. In the present study, we cannot rule out that atrophy in the left anterior temporal cortex makes an indirect contribution to the compromised naming process in SD through interruption of connectivity in the left temporal lobe. Indeed, the left anterior temporal region was implicated in the naming deficits of the larger group of FTD patients that includes this SD subgroup, and it may be that we failed to find a left anterior temporal correlation in the SD subgroup of this study because of the small number of participants. We also observed a correlation between naming and the right lateral temporal cortex, although this portion of the right temporal cortex was not significantly atrophic in SD. The right temporal cortex has been implicated in the semantic component of naming (Lambon Ralph *et al*., 2001), but in patients who are more severely impaired than the SD patients in the present study. In sum, a retrieval component of naming associated with left lateral temporal cortex appears to be interrupted in patients with SD, and this may involve selection of a target from semantic memory.

Patients with PNFA also have confrontation naming difficulty (Grossman *et al*., 1996*b*; Hodges and Patterson, 1996; Thompson *et al*., 1997). Observations in this study are consistent with previous work associating the naming impairment in PNFA with limited lexical retrieval (P. Moore, K. Dennis and M. Grossman, unpublished data). In the present study, PNFA patients showed a unique correlation between naming and cortical volume in several left frontal brain regions. Since these regions correspond to areas of statistically significant grey matter atrophy, we suspect that these areas play a role in the naming difficulty of PNFA patients. Despite the association of these anatomical regions with lexical retrieval in PNFA, these correlations do not involve the same anatomical distribution as in SD and NON-APH subgroups. Left frontal correlations between naming and cortical volume in areas of significant left frontal cortical atrophy in PNFA are thus likely to reflect the fact that several distinct components of lexical retrieval can be interrupted during confrontation naming in neurodegenerative diseases. Consistent with previous work (Grossman *et al*., 1996*b*, 1998), areas of naming-cortical correlation that also showed statistically significant cortical atrophy in the present study were in the inferior and orbital frontal cortex of the left hemisphere. The left inferior frontal cortex has been implicated in confrontation naming in functional neuroimaging studies of healthy adults (Simon *et al*., 2002; Whatmough *et al*., 2002; Burgund *et al*., 2003). Several functional neuroimaging studies have hypothesized that the left inferior frontal cortex plays a role in the retrieval process (Kapur *et al*., 1994; Tulving *et al*., 1994; Demb *et al*., 1995; Poldrack *et al*., 1999), although the precise nature of this role is a subject of debate. Some studies suggest that the inferior frontal cortex is important for resolving competition between equally probable candidate targets during lexical retrieval (Thompson-Schill *et al*., 1997), while others emphasize the controlled nature of lexical retrieval (Wagner *et al*., 2001). Studies of brain-damaged patients (Freedman *et al*., 1998) and functional neuroimaging studies of healthy adults (Taylor *et al*., 1997; Jonides *et al*., 1998; Nobre *et al*., 1999; Rogers *et al*., 1999) suggest that these areas play an important role in inhibitory control. Neuropsychological studies suggest that PNFA patients have some difficulty with measures such as the Stroop test that depend in part on inhibitory control (Grossman *et al*., 1996*b*; Grossman *et al*., in press). Another approach associates the left inferior frontal cortex with phonemic discrimination (Zatorre *et al*., 1996; Poldrack *et al*., 1999, 2001). It is possible to speculate that left inferior frontal regions contribute to naming by helping to select among candidate names that are phonologically and/or semantically similar to the target.

We also found naming-volume correlations in premotor and dorsolateral prefrontal regions of the left frontal lobe in PNFA. Behavioural studies of brain-damaged patients (Perry and Hodges, 1999; Thompson-Schill *et al*., 1999) and functional neuroimaging studies of healthy adults (Braver *et al*., 1997; Jonides *et al*., 1997; Sylvester *et al*., 2003) emphasize the contribution of these regions to executive resources such as verbal working memory and the development of strategies to augment lexical search. Neuropsychological studies have shown that PNFA patients also have working memory limitations (Grossman *et al*., 1996*b*; Hodges and Patterson, 1996; Rhee *et al*., 2001). It is possible that working memory contributes to confrontation naming during the extended process of searching the mental lexicon for a target word.

In NON-APH patients, a correlation between naming and cortical volume in an area of statistically significant cortical atrophy was found in the right dorsolateral prefrontal cortex. This distribution of disease has been seen in previous imaging studies of these patients (Miller *et al*., 1993; Rosen *et al*., 2002*a*). The role of this brain region in naming is not clear. Activation studies of healthy adults have also recruited the right prefrontal cortex during spatial working memory challenges (Jonides *et al*., 1993; Courtney *et al*., 1996; Smith *et al*., 1996; Braver *et al*., 1997; Grady *et al*., 1998; Reuter-Lorenz *et al*., 2000) and this may work together with the right temporal cortex to limit the scope of the search for a target.

PNFA and NON-APH patients also showed a correlation between grey matter volume and naming difficulty in the left anterior temporal cortex. The precise role of the left anterior temporal cortex in confrontation naming is unclear. Previous

observations of left anterior temporal atrophy in SD suggested that this brain region may contribute to semantic memory (Mummery *et al*., 2000; Chan *et al*., 2001; Galton *et al*., 2001). Although mild PNFA patients are not known to have significant semantic difficulty for nouns and objects (Croot *et al*., 1998; Grossman *et al*., 1996*b*; Hodges and Patterson, 1996), they appear to be impaired in their comprehension of verbs—a deficit associated with disease in inferior frontal cortex (Bak *et al*., 2001; Rhee *et al*., 2001). NON-APH patients may have difficulty with the comprehension of social knowledge (Wood and Grafman, 2003). We cannot rule out the possibility that the left anterior temporal cortex plays an indirect role in lexical retrieval—mediated in part by a disconnection of reciprocal projections in the uncinate fasciculus between the inferior frontal cortex and the anterior temporal cortex. Although we may not be able to specify the precise components of lexical retrieval and associated processes that are compromised in each subgroup of patients with FTD, the association of impaired lexical retrieval with different neuroanatomical distributions of cortical atrophy across these subgroups suggests that a large-scale neural network for naming is interrupted in several different ways that can compromise different facets of lexical retrieval and associated downstream processes during naming.

We are not aware of previous VBM studies of atrophy in CBD. Relative to healthy seniors, CBD patients showed extensive cortical atrophy in a parietal distribution bilaterally. We also observed frontal and temporal cortical atrophy in CBD. CBD is reported to be difficult to diagnose accurately (Litvan *et al*., 1997) and the great variety of clinical manifestations seen in these patients may be due to the widely distributed disease evident at autopsy in CBD (Bergeron *et al*., 1996; Boeve *et al*., 1999; Forman *et al*., 2002).

We noted above the association of the lexical retrieval component of naming difficulty with left lateral temporal atrophy found in all patients, including patients with CBD. A significant naming-cortical correlation in CBD was also seen in the left frontal cortex. The left frontal cortex in this distribution is often associated with verbal working memory and other measures of executive functioning, as noted above in our discussion about PNFA. Although we did not assess this cognitive domain in the present study, executive difficulties such as limited working memory have been demonstrated in patients with CBD (Pillon *et al*., 1995; Pillon and Dubois, 2000). It is conceivable that verbal working memory plays a role in mental search aspects of the lexical retrieval component of naming that is compromised in CBD.

The naming deficit in CBD also correlated uniquely with impaired performance on a measure of visual perceptual–spatial functioning. At least two cortical areas may play a role in the visual perceptual–spatial component of impaired naming in CBD. First, we observed a naming-volume correlation in the right temporal cortex in CBD that corresponded to an area of significant cortical atrophy in these patients. The right ventral temporal cortex may also contribute to a visual perceptual–spatial component of naming in CBD, particularly given the association of this brain region with the ventral stream of visual–perceptual processing (Ungerleider and Mishkin, 1982; Haxby *et al*., 1991; Grady *et al*., 1992; Horwitz *et al*., 1992). Secondly, our visual perceptual–spatial measure also involved a considerable organizational element, corresponding to an executive component of visual functioning. Previous work has also demonstrated the contribution of the right frontal cortex to visual–perceptual processing. For example, studies of stroke patients and functional MRI studies of healthy subjects have associated the right frontal cortex with executive resources such as visual working memory (Butters *et al*., 1970; Jonides *et al*., 1993; Courtney *et al*., 1996; Smith *et al*., 1996; Braver *et al*., 1997; Grady *et al*., 1998; Reuter-Lorenz *et al*., 2000) and selective attention (Corbetta *et al*., 1993; Coull *et al*., 1996). In the present study, we also observed a significant correlation between confrontation naming and cortical volume in the right frontal cortex in CBD, which corresponded to an area of significant cortical atrophy in these patients. This may contribute to the working memory needed to appreciate a visual stimulus.

Conclusion

These evaluations suggest that a large-scale neural network underlies naming, and that interruption of this large-scale network occurs in a manner that is partially shared and partially unique to these neurodegenerative diseases. An area of left lateral temporal cortical atrophy is shared across these neurodegenerative diseases and thus appears to contribute to the lexical retrieval component of naming that is impaired in AD, FTD and CBD. The left lateral temporal cortex may play a role in selecting an abstract representation of a name that corresponds to a concept in semantic memory. Lexical retrieval is a complex process, moreover, and other brain regions may contribute to different components of retrieval and associated downstream processes. For example, ventrolateral portions of the left frontal cortex may contribute to selection during the retrieval process (possibly mediating inhibitory control or phonological assembly), while dorsolateral portions of the left frontal cortex may support verbal working memory and mental search strategies during the lexical retrieval process. The right lateral temporal cortex may help limit the scope of the mental search for a target name. Other components of the naming process are also selectively compromised in these patients. Interpretation of the visual perceptual–spatial properties of a stimulus appears to be associated with the right inferolateral temporal and right dorsolateral frontal cortices, and semantic memory may be related in part to specific aspects of the temporal cortex. Some of these features can be detected clinically, yielding distinct patterns of naming difficulty that may be helpful in clinical situations such as differential diagnosis. The patterns of correlation between naming difficulty and cortical atrophy

suggest several additional ways in which the large-scale neural network for naming may be interrupted without obvious behavioural manifestations.

Acknowledgements

Portions of this work were presented at the meeting of the Academy of Aphasia, New York, in October 2002 and at the Fourth International Conference on Frontotemporal Dementia held in Lund, Sweden, in April 2003. This work was supported in part by the US Public Health Service (AG15116 and AG17586).

References

Alsop DC, Detre JA, Grossman M. Assessment of cerebral blood flow in Alzheimer's disease by spin-labeled magnetic resonance imaging. Ann Neurol 2000; 47: 93–100.

Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings H, Zilles K. Broca's region revisited: cytoarchitecture and intersubject variability. J Comp Neurol 1999; 412: 319–41.

Arnold SE, Hyman BT, Flory J, Damasio AR, van Hoesen GW. The topographic and neuroanatomicalal distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1991; 1: 103–16.

Ashburner J, Friston KJ. Voxel-based morphometry: the methods. Neuroimage 2000; 11: 805–21.

Bak TH, O'Donovan DG, Xuereb JH, Boniface S, Hodges JR. Selective impairment of verb processing associated with pathological changes in Brodmann areas 44 and 45 in the motor neurone disease-dementia-aphasia syndrome. Brain 2001; 124: 103–20.

Baron J-C, Chételat G, Desgranges B, Perchey G, Laudeau B, de la Sayette V, et al. In vivo mapping of grey matter loss with voxel-based morphometry in mild Alzheimer's disease. Neuroimage 2001; 14: 298–309.

Beeman M, Friedman R, Grafman J, Perez E, Diamond S, Lindsay MB. Summation priming and coarse semantic coding in the right hemisphere. J Cogn Neurosci 1994; 6: 26–45.

Benson DF. Neurologic correlates of anomia. In: Whitaker H, Whitaker HA, editors. Studies in neurolinguistics, Vol. 4. New York: Academic Press; 1979. p. 1–15.

Bergeron CB, Pollanen MS, Weyer L, Black SE, Lang AE. Unusual clinical presentations of cortico-basal ganglionic degeneration. Ann Neurol 1996; 40: 893–900.

Black SE. Aphasia in corticobasal degeneration. In: Litvan I, Goetz CG, Lang AE, editors. Corticobasal degeneration and related disorders. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 123–33.

Boeve BF, Maraganore DM, Parisi JE, Ahlskog JE, Graff-Radford N, Caselli RJ, et al. Pathologic heterogeneity in clinically diagnosed corticobasal degeneration. Neurology 1999; 53: 795–800.

Boxer AL, Rankin KP, Miller BL, Schuff N, Weiner M, Gorno-Tempini ML, et al. Cinguloparietal atrophy distinguishes Alzheimer's disease from semantic dementia. Arch Neurol 2003; 60: 949–56.

Braver TS, Cohen JD, Nystrom LE, Jonides J, Smith EE, Noll DC. A parametric study of prefrontal cortex involvement in human working memory. Neuroimage 1997; 5: 49–62.

Burgund ED, Lugar HM, Miezin FM, Petersen SE. Sustained and transient activity during an object-naming task: a mixed blocked and event-related fMRI study. Neuroimage 2003; 19: 29–41.

Busatto GF, Garrido GEJ, Almeida OP, Castra CC, Camargo CH, Cid CG, et al. A voxel-based morphometry study of temporal lobe grey matter reductions in Alzheimer's disease. Neurobiol Aging 2003; 24: 221–31.

Butters N, Samuels I, Goodglass H, Brody BA. Short-term visual and auditory memory disorders after parietal and frontal lobe damage. Cortex 1970; 6: 440–59.

Cappa SF, Binetti G, Pezzini A, Padovani A, Rozzini L, Trabucchi M. Object and action naming in Alzheimer's disease and fronto-temporal dementia. Neurology 1998; 50: 351–5.

Caselli RJ, Jack CR Jr, Petersen RC, Wahner HW, Yanagihara T. Asymmetric cortical degenerative syndromes: clinical and radiologic correlations. Neurology 1992; 42: 1462–8.

Chan D, Fox NC, Scahill RI, Crom WR, Whitwell JL, Leschziner G, et al. Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. Ann Neurol 2001; 49: 433–42.

Chertkow H, Bub DN, Caplan D. Constraining theories of semantic memory processing: evidence from dementia. Cogn Neuropsychol 1992; 9: 327–65.

Chételat G, Desgranges B, de la Sayette V, Viader F, Berkouk K, Laudeau B, et al. Dissociating atrophy and hypometabolism impact on episodic memory in mild cognitive impairment. Brain 2003; 126: 1955–67.

Corbetta M, Miezin FM, Shulman GL, Petersen SE. A PET study of visuospatial attention. J Neurosci 1993; 13: 1202–26.

Coull JT, Frith CD, Frackowiak RSJ, Grasby PM. A frontal-parietal network for rapid visual information processing: a PET study of sustained attention and working memory. Neuropsychologia 1996; 34: 1085–95.

Courtney SM, Ungerleider LG, Keil K, Haxby JV. Object and spatial visual working memory activate separate neural systems in human cortex. Cereb Cortex 1996; 6: 39–49.

Crone NE, Hao L, Hart J Jr, Boatman D, Lesser RP, Irizarry R, et al. Electrocorticographic gamma activity during word production in spoken and sign language. Neurology 2001; 57: 2045–53.

Cronin-Golomb A, Keane MM, Kokodis A, Corkin S, Growdon JH. Category knowledge in Alzheimer's disease: normal organization and a general retrieval deficit. Psychol Aging 1992; 7: 359–66.

Croot K, Patterson K, Hodges JR. Single word production in non-fluent progressive aphasia. Brain Lang 1998; 61: 226–73.

Damasio H, Grabowski TJ, Tranel D, Hichwa RD, Damasio AR. A neural basis for lexical retrieval. Nature 1996; 380: 499–505.

Davis KL, Price CC, Moore P, Campea S, Grossman M. Evaluating the clinical diagnosis of frontotemporal lobar degeneration: a re-examination of Neary et al. 1998 [abstract]. Neurology 2001; 56 (8 Suppl 3): A144–5.

Demb JB, Desmond JE, Wagner AD, Vaidya CJ, Glover GH, Gabrieli JDE. Semantic encoding and retrieval in the left inferior prefrontal cortex: a functional MRI study of task difficulty and process specificity. J Neurosci 1995; 15: 5870–8.

Evans AC, Collins DL, Mills SR, Brown ED, Kelly RL, Peters TM. 3D statistical neuroanatomicalal models from 305 MRI volumes. In: Klaisner LA, editor. Nuclear Science Symposium and Medical Imaging Conference, Vol. 1–3, IEEE Conference Record. San Francisco, 31 October – 6 November 1993. Piscataway (NJ): IEEE Service-Center; 1993. p. 1813–7.

Folstein MF, Folstein SF, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975; 12: 189–98.

Forman SD, Cohen JD, Fitzgerald M, Eddy WF, Mintun MA, Noll DC. Improved assessment of significant activation in functional magnetic resonance imaging (fMRI): use of a cluster-size threshold. Magn Reson Med 1995; 33: 636–47.

Forman MS, Zhukareva V, Bergeron CB, Chin SS, Grossman M, Clark C, et al. Signature tau neuropathology in grey and white matter of corticobasal degeneration. Am J Pathol 2002; 160: 2045–53.

Frackowiak RSJ, Friston KJ, Frith CD, Dolan RJ, Mazziotta JC. Human brain function. San Diego: Academic Press; 1997.

Freedman M, Black S, Ebert P, Binns M. Orbitofrontal function, object alternation and perseveration. Cereb Cortex 1998; 8: 18–27.

Galton CJ, Patterson K, Graham KS, Lambon Ralph MA, Williams G, Antoun N, et al. Differing patterns of temporal atrophy in Alzheimer's disease and semantic dementia. Neurology 2001; 57: 216–25.

Garrard P, Patterson K, Watson PC, Hodges JR. Category specific semantic

loss in dementia of Alzheimer's type: functional-anatomical correlations from cross-sectional analyses. Brain 1998; 121: 633–46.

Garrard P, Lambon Ralph MA, Watson PC, Powis J, Patterson K, Hodges JR. Longitudinal profiles of semantic impairment for living and nonliving concepts in dementia of the Alzheimer's type. J Cogn Neurosci 2001; 13: 892–909.

Garrett M. Disorders of lexical selection. Cognition 1992; 42: 143–80.

Gee JC, Haynor DR. Numerical methods for high dimensional warps. In: Toga AW, editor. Brain warping. San Diego: Academic Press; 1999. p. 101–14.

Good CD, Johnsrude IS, Ashburner J, Henson RNA, Friston K, Frackowiak RSJ. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001; 14: 21–36.

Good CD, Scahill RI, Fox NC, Ashburner J, Friston KJ, Chan D, et al. Automated differentiation of anatomical patterns in the human brain: validation with studies of degenerative dementias. Neuroimage 2002; 17: 29–46.

Goodglass H. Understanding aphasia. San Diego: Academic Press; 1993.

Grady CL, Haxby JV, Horwitz B, Sundaram M, Berg G, Schapiro M, et al. Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. J Clin Exp Neuropsychol 1988; 10: 576–96.

Grady CL, Haxby JV, Horwitz B, Ungerleider LG, Schapiro, MB, Carson PE, et al. Dissociation of object and spatial vision in human extrastriate cortex: age-related changes in activation of regional cerebral blood flow measured with 15O-water and positron emission tomography. J Cogn Neurosci 1992; 4: 23–34.

Grady CL, McIntosh AR, Bookstein F, Horwitz B, Rapoport S, Haxby JV. Age-related changes in regional cerebral blood flow during working memory for faces. Neuroimage 1998; 8: 409–425.

Grimes DA, Lang AE, Bergeron CB. Dementia as the most common presentation of cortical-basal ganglionic degeneration. Neurology 1999; 53: 1969–74.

Grisoli M, Fetoni V, Savoiardo M, Girotti F, Bruzzone MG. MRI in corticobasal degeneration. Eur J Neurol 1995; 2: 547–52.

Grossman M. Frontotemporal dementia: a review. J Int Neuropsychol Soc 2002; 8: 564–583.

Grossman M, D'Esposito M, Hughes E, Onishi K, Biassou N, White-Devine T, et al. Language comprehension profiles in Alzheimer's disease, multi-infarct dementia and frontotemporal degeneration. Neurology 1996a; 47: 183–9.

Grossman M, Mickanin J, Onishi K, Hughes E, D'Esposito M, Ding XB, et al. Progressive non-fluent aphasia: Language, cognitive and PET measures contrasted with probable Alzheimer's disease. J Cogn Neurosci 1996b; 8: 135–54.

Grossman M, Payer F, Onishi K, White-Devine T, Morrison D, D'Esposito M, et al. Constraints on the cerebral basis for semantic processing from neuroimaging studies of Alzheimer's disease. J Neurol Neurosurg Psychiatry 1997; 63: 152–8.

Grossman M, Payer F, Onishi K, D'Esposito M, Morrison D, Sadek A, et al. Language comprehension and regional cerebral defects in frontotemporal degeneration and Alzheimer's disease. Neurology 1998; 50: 157–63.

Grossman M, Smith EE, Koenig P, Glosser G, Rhee J, Dennis K. Categorization of object descriptions in Alzheimer's disease and frontotemporal dementia: limitation in rule-based processing. Cogn Affect Behav Neurosci 2003; 3: 120–32.

Grossman M, Rhee J, Antiquena P. Sentence processing in frontotemporal dementia. Cortex. In press.

Haxby JV, Grady CL, Koss E, Horwitz B, Heston L, Schapiro M, et al. Longitudinal study of cerebral metabolic asymmetries and associated neuropsychological patterns in early dementia of the Alzheimer type. Arch Neurol 1990; 47: 753–60.

Haxby JV, Grady CL, Horwitz B, Ungerleider LG, Mishkin M, Carson RE, et al. Dissociation of object and spatial visual processing pathways in human extrastriate cortex. Proc Natl Acad Sci USA 1991; 88: 1621–5.

Hillis AE, Wityk RJ, Tuffiash E, Beauchamp NJ, Jacobs MA, Barker PB, et al. Hypoperfusion of Wernicke's area predicts severity of semantic deficit in acute stroke. Ann Neurol 2001; 50: 561–6.

Hodges JR, Patterson K. Nonfluent progressive aphasia and semantic dementia: A comparative neuropsychological study. J Int Neuropsychol Soc 1996; 2: 511–24.

Hodges JR, Salmon DP, Butters N. The nature of the naming deficit in Alzheimer's and Huntington's disease. Brain 1991; 114: 1547–58.

Hodges JR, Patterson K, Oxbury S, Funnell E. Semantic dementia: progressive fluent aphasia with temporal lobe atrophy. Brain 1992a; 115: 1783–806.

Hodges JR, Salmon DP, Butters N. Semantic memory impairment in Alzheimer's disease: failure of access or degraded knowledge? Neuropsychologia 1992b; 30: 301–14.

Hodges JR, Graham N, Patterson K. Charting the progression of semantic dementia: implications for the organization of semantic memory. Memory 1995; 3: 363–95.

Hodges JR, Patterson K, Graham N, Dawson K. Naming and knowing in dementia of Alzheimer's type. Brain Lang 1996; 54: 302–25.

Horwitz B, Grady C, Haxby J, Ungerleider LG, Schapiro MB, Mishkin M, et al. Functional associations among human posterior extrastriate brain regions during object and spatial vision. J Cogn Neurosci 1992; 4: 311–22.

Howard D, Patterson K, Wise R, Brown WD, Friston K, Weiller C, et al. The cortical localization of the lexicons. Brain 1992; 115: 1769–82.

Huff FJ, Corkin S, Growdon JH. Semantic impairment and anomia in Alzheimer's disease. Brain Lang 1986; 28: 235–49.

Indefrey P, Levelt WJM. The neural correlates of language production. In: Gazzaniga MS, editor. The New Cognitive Neurosciences. Cambridge (MA): MIT Press; 2000. p. 845–66

Jagust WJ, Reed BR, Seab JP, Kramer JH, Budinger TF. Clinical-physiologic correlates of Alzheimer's disease and frontal lobe dementia. Am J Physiol Imaging 1989; 4: 89–96.

Johnson KA, Kijewski MF, Becker JA, Garada B, Satlin A, Holman BL. Quantitative brain SPECT in Alzheimer's disease and normal aging. J Nucl Med 1993; 34: 2044–8.

Jonides J, Smith E, Koeppe R, Awh E, Minoshima S, Mintun M. Spatial working memory in humans as revealed by PET. Nature 1993; 363: 623–5.

Jonides J, Schumacher EH, Smith EE, Lauber EJ, Awh E, Minoshima S, et al. Verbal working memory load affects regional brain activation as measured by PET. J Cogn Neurosci 1997; 9: 462–75.

Jonides J, Smith EE, Marshuetz C, Koeppe RA, Reuter-Lorenz PA. Inhibition in verbal working memory revealed by brain activation. Proc Natl Acad Sci USA 1998; 95: 8410–3.

Kaplan E, Goodglass H, Weintraub S. The Boston naming test. Philadelphia: Lea and Febiger; 1983.

Kapur S, Rose R, Liddle PF, Zipursky RB, Brown GM, Stuss D, et al. The role of the left prefrontal cortex in verbal processing: semantic processing or willed action? Neuroreport 1994; 5: 2193–6.

Karas GB, Burton EJ, Rombouts SARB, van Schijndel RA, O'Brien JT, Scheltens P, et al. A comprehensive study of grey matter loss in patients with Alzheimer's disease using optimized voxel-based morphometry. Neuroimage 2003; 18: 895–07.

Karbe H, Kertesz A, Davis J, Kemp BJ, Prato FS, Nicholson RL. Quantification of functional deficit in Alzheimer's disease using a computer-assisted mapping program for 99mTc-HMPAO SPECT. Neuroradiology 1994; 36: 1–6.

Kertesz A, Martinez-Lage P, Davidson W, Munoz DG. The corticobasal degeneration syndrome overlaps progressive aphasia and frontotemporal dementia. Neurology 2000; 55: 1368–75.

Kohn SE, Goodglass H. Picture naming in aphasia. Brain Lang 1985; 24: 266–83.

Kompoliti K, Goetz CG, Boeve BF, Maraganore DM, Ahlskog JE, Marsden CD, et al. Clinical presentation and pharmacological therapy in corticobasal degeneration. Arch Neurol 1998; 55: 957–61.

Laakso M, Frisoni GB, Kononen M, Mikkonen M, Beltramello A, Geroldi C, et al. Hippocampus and entorhinal cortex in frontotemporal dementia and

Alzheimer's disease: a morphometric MRI study. Biol. Psychiatry 2000; 47: 1056–63.

Lambon Ralph MA, Patterson K, Hodges JR. The relationship between naming and semantic knowledge for different categories in dementia of Alzheimer's type. Neuropsychologia 1997; 35: 1251–60.

Lambon Ralph MA, Graham KS, Ellis AW, Hodges JR. Naming in semantic dementia—what matters? Neuropsychologia 1998; 36: 775–84.

Lambon Ralph MA, McClelland JL, Patterson K, Galton CJ, Hodges JR. No right to speak? The relationship between object naming and semantic impairment: neuropsychological evidence and a computational model. J Cogn Neurosci 2001; 13: 341–56.

Levelt WJM. Lexical access in speech production. Amsterdam: Elsevier; 1992.

Litvan I, Agid Y, Goetz CG, Jankovic J, Wenning GK, Brandel JP et al. Accuracy of the clinical diagnosis of corticobasal degeneration: a clinicopathologic study. Neurology 1997; 48: 119–25.

Lund and Manchester Groups. Clinical and neuropathological criteria for frontotemporal dementia. J Neurol Neurosurg Psychiatry 1994; 57: 416–8.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34: 939–44.

McKhann GM, Albert MS, Grossman M, Miller BL, Dickson D, Trojanowski JQ. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. Arch Neurol 2001; 58: 1803–9.

Mickanin J, Grossman M, Onishi K, Auriacombe S, Clark C. Verbal and non-verbal fluency in patients with probable Alzheimer's disease. Neuropsychology 1994; 8: 385–94.

Miller BL, Chang L, Mena I, Boone K, Lesser IM. Clinical and imaging features of right focal frontal lobe degenerations. Dementia 1993; 4: 204–13.

Miller BL, Ikonte C, Ponton M, Levy M, Boone K, Darby A, et al. A study of the Lund–Manchester research criteria for frontotemporal dementia: clinical and single-photon emission CT correlations. Neurology 1997; 48: 937–42.

Morris JC, Heyman A, Mohs RC, Hughes JP, van Belle G, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989; 39: 1159–65.

Mummery CJ, Patterson K, Hodges JR, Price CJ. Functional neuroanatomy of the semantic system: divisible by what? J Cogn Neurosci 1998; 10: 766–77.

Mummery CJ, Patterson K, Wise RJS, Vandenbergh R, Price CJ, Hodges JR. Disrupted temporal lobe connections in semantic dementia. Brain 1999; 122: 61–73.

Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Ann Neurol 2000; 47: 36–45.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 1998; 51: 1546–54.

Nestor PJ, Graham NL, Fryer TD, Williams GB, Patterson K, Hodges JR. Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula. Brain 2003; 126: 2406–18.

Nobre AC, Coull JT, Frith CD, Mesulam M-M. Orbitofrontal cortex is activated during breaches of expectation in tasks of visual attention. Nat Neurosci 1999; 2: 11–12.

Ojemann GA, Schoenfield-McNeill J. Activity of neurons in human temporal cortex during identification and memory for names and words. J Neurosci 1999; 19: 5674–82.

Perry RJ, Hodges JR. Attention and executive deficits in Alzheimer's disease: a critical review. Brain 1999; 122: 383–404.

Perry RJ, Hodges JR. Differentiating frontal and temporal variant frontotemporal dementia from Alzheimer's disease. Neurology 2000; 54: 2277–84.

Pillon B, Dubois B. Memory and executive processes in corticobasal degeneration. In: Litvan I, Goetz CG, Lang AE, editors. Corticobasal degeneration and related disorders. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 91–101.

Pillon B, Blin J, Vidailhet M, Deweer B, Sirigu A, Dubois B, et al. The neuropsychological pattern of corticobasal degeneration: comparison with progressive supranuclear palsy and Alzheimer's disease. Neurology 1995; 45: 1477–83.

Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JDE. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. Neuroimage 1999; 10: 15–35.

Poldrack RA, Temple E, Protopapas A, Nagarajan S, Tallal P, Merzenich M, et al. Relations between the neural bases for dynamic auditory processing and phonological processing: evidence from fMRI. J Cogn Neurosci 2001; 13: 687–97.

Price CC, Davis KL, Moore PN, Campea S, Grossman M. Clinical diagnosis of frontotemporal dementia (FTD) [abstract]. Neurology 2001; 56 (8 Suppl 3): A176.

Rahman S, Sahakian BJ, Hodges JR, Rogers RD, Robbins TW. Specific cognitive deficits in mild frontal variant frontotemporal dementia. Brain 1999; 122: 1469–93.

Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marschuetz C, et al. Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET. J Cogn Neurosci 2000; 12: 174–87.

Rhee J, Antiquena P, Grossman M. Verb comprehension in frontotemporal degeneration: the role of grammatical, semantic and executive components. Neurocase 2001; 7: 173–84.

Riley DE, Lang AE. Clinical diagnostic criteria. In: Litvan I, Goetz CG, Lang AE, editors. Corticobasal degeneration and related disorders. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 29–34.

Rinne JO, Lee MS, Thompson PD, Marsden CD. Corticobasal degeneration: a clinical study of 36 cases. Brain 1994; 117: 1183–96.

Rogers RD, Owen AM, Middleton HC, Williams EJ, Pickard JD, Sahakian BJ, et al. Choosing between small, likely rewards and large, unlikely rewards activates inferior and orbital prefrontal cortex. J Neurosci 1999; 19: 9029–38.

Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. Neurology 2002a; 58: 198–208.

Rosen HJ, Kramer JH, Gorno-Tempini M, Schuff N, Weiner M, Miller BL. Patterns of cerebral atrophy in primary progressive aphasia. Am J Geriatr Psychiatry 2002b; 10: 89–97.

Savoiardo M, Grisoli M, Girotti F. Magnetic resonance immaging in CBD, related atypical parkinsonian disorders and dementias. In: Litvan I, Goetz CG, Lang AE, editors. Corticobasal degeneration and related disorders. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 197–208.

Silveri MC, Leggio MG. Influence of disorders of visual perception in word-to-picture matching tasks in patients with Alzheimer's disease. Brain Lang 1996; 54: 326–34.

Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. Topographical layout of hand, eye, calculation and language-related areas in the human parietal lobe. Neuron 2002; 33: 475–87.

Smith EE, Jonides J, Koeppe RA. Dissociating verbal and spatial working memory using PET. Cereb Cortex 1996; 6: 11–20.

Smith CD anderson AH, Kryscio RJ, Schmitt FA, Kindy MS, Blonder LX, et al. Differences in functional magnetic resonance imaging activation by category in a visual confrontation naming task. J Neuroimag 2001; 11: 165–70.

Snowden JS, Goulding PJ, Neary D. Semantic dementia: a form of circumscribed cerebral atrophy. Behav Neurol 1989; 2: 167–82.

Steinmetz H, Seitz RJ. Functional anatomy of language processing: neuroimaging and the problem of individual variability. Neuropsychologia 1991; 29: 1149–61.

Sylvester C-YC, Wager TD, Lacey SC, Hernandez L, Nichols TE, Smith EE, et al. Switching attention and resolving interference: fMRI measures of executive functions. Neuropsychologia 2003; 41: 357–70.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart: Thieme; 1988.

Taylor SF, Kornblum S, Lauber E, Minoshima S, Koeppe R. Isolation of specific interference processing in the Stroop task: PET activation studies. Neuroimage 1997; 6: 81–92.

Thompson CK, Ballard KJ, Tait ME, Weintraub S, Mesulam M. Patterns of language decline in non-fluent primary progressive aphasia. Aphasiology 1997; 11: 297–331.

Thompson-Schill SL, D'Esposito M, Aguirre G, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: a re-evaluation. Proc Natl Acad Sci USA 1997; 94: 14792–7.

Thompson-Schill SL, Jonides J, Marshuetz C, Smith EE, D'Esposito M, Kan IP, et al. Impairments in the executive control of working memory following prefrontal damage: a case study [abstract]. Soc Neurosci Abstr 1999; 25: 1143.

Tippett LJ, Farah MJ. A computational model of naming in Alzheimer's disease: unitary or multiple impairments? Neuropsychology 1994; 8: 3–13.

Tulving E, Kapur S, Craik FIM, Moscovitch M, Houle S. Hemispheric encoding/retrieval asymmetry in episodic memory: positron emission tomography findings. Proc Natl Acad Sci USA 1994; 91: 2016–20.

Turner RS, Kenyon LC, Trojanowski JQ, Gonatas N, Grossman M. Clinical, neuroimaging and pathologic features of progressive non-fluent aphasia. Ann Neurol 1996; 39: 166–73.

Ungerleider LG, Mishkin M. Two cortical visual systems. In: Ingle DJ, Goodale MA, Mansfield RJW, editors. Analysis of visual behavior. Cambridge (MA): MIT Press; 1982. p. 549–80.

van Turennout M, Ellmore T, Martin A. Long-lasting cortical plasticity in the object naming system. Nat Neurosci 2000; 3: 1329–34.

Wagner AD, Pare-Blagoev EJ, Clark J, Poldrack RA. Recovering meaning: Left prefrontal cortex guides controlled semantic retrieval. Neuron 2001; 31: 329–36.

Weintraub S, Rubin NP, Mesulam M-M. Primary progressive aphasia: longitudinal course, neuropsychological profile and language features. Arch Neurol 1990; 47: 1329–35.

Whatmough C, Chertkow H, Murtha S, Hanratty K. Dissociable brain regions process object meaning and object structure during picture naming. Neuropsychologia 2002; 40: 174–86.

Wood JN, Grafman J. Human prefrontal cortex: processing and representational perspectives. Nat Rev Neurosci 2003; 4: 139–47.

Zatorre RJ, Meyer E, Gjedde A, Evans AC. PET studies of phonetic processing of speech: review, replication and reanalysis. Cereb Cortex 1996; 6: 21–30.