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Progressive non-fluent aphasia is associated with hypometabolism centred on the left anterior insula

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Summary

Progressive non-fluent aphasia (PNFA) is a syndrome in which patients lose the ability to communicate fluently in the context of relative preservation of single word comprehension and non-linguistic cognitive abilities. Neuroimaging in case studies with PNFA has failed to identify a consistent neural substrate for the language disorder. In this study of a group of patients (*n* = 10) whose presenting complaint was progressive dysfluency, resting cerebral metabolism was measured using [^{18}F]fluorodeoxyglucose-PET and analysed with the technique of statistical parametric mapping (SPM). Regional atrophy was assessed with voxel-based morphometry (VBM). Seven patients had a 'pure' PNFA syndrome, while the remaining three had additional features of a more pervasive dementia. Compared with controls, the patients showed hypometabolism in several regions that, most notably, included the left anterior insula/frontal opercular region. The VBM analysis revealed only one small area of atrophy in the left peri-Sylvian region. Analysis of the pure PNFA cases (*n* = 7) relative to controls yielded qualitatively similar results to those of the whole group, suggesting that these cases were also at risk of a more generalized dementia, a finding borne out in subsequent follow-up of two cases to date. The PNFA group was then compared with a group with Alzheimer's disease (*n* = 10) whose clinical profile did not include non-fluent aphasic features. In this analysis, the only persisting hypometabolic region was that centred over the left anterior insula. VBM did not identify any regional differences in atrophy between PNFA and Alzheimer's disease. In the light of current theories of fluent language production, the findings offer anatomical evidence that the breakdown in fluency is due to a motor articulatory planning deficit (speech apraxia) combined with a variable degree of agrammatism.

Keywords: progressive non-fluent aphasia; PET; insula; voxel-based morphometry

Abbreviations: BA = Brodmann area; CMRglc = cerebral metabolic rate for glucose; FDG = [^{18}F]fluorodeoxyglucose; FTD = frontotemporal dementia; FWHM = full width at half-maximum; MMSE = Mini-Mental State Examination; MND = motor neuron disease; MNI: Montreal Neurological Institute; PNFA = progressive non-fluent aphasia; RCPM = Raven's coloured progressive matrices; SPECT = single photon emission computerized tomography; SPM = statistical parametric mapping; TROG = Test for the Reception of Grammar; VBM = voxel-based morphometry; VOSP = Visual Object and Space Perception Battery; WCST = Wisconsin card sorting test

Introduction

Primary progressive aphasias are neurodegenerative syndromes in which there is a progressive and relentless deterioration of normal language function, with relative preservation of non-linguistic cognitive abilities. The syndrome can be subdivided further into fluent and non-fluent forms, the former being synonymous with the syndrome of semantic dementia in which there is a progressive degradation of semantic knowledge [word meanings, knowledge of objects and facts (Snowden *et al*., 1989; Hodges *et al*., 1992; Neary *et al*., 1998)]. Slowly progressive aphasia was first reported in the modern era by Mesulam (1982) and over the subsequent two decades by numerous other authors with both fluent and non-fluent varieties. In a later review, Mesulam and Weintraub (1992) proposed that 'primary progressive aphasia' (fluent or non-fluent) be defined '…when a progressive dissolution of language (not just speech) is the only salient finding for at least two years and when this deficit becomes the only factor that compromises daily living activities…'.

Pathologically, progressive non-fluent aphasia (PNFA) has been considered one of the clinical syndromes subsumed under the rubric of fronto-temporal dementia (FTD) (Neary *et al*., 1998), although a review of the literature suggests that a heterogeneous group of pathologies can give rise to PNFA. Some post-mortem analyses of PNFA have yielded pathology consistent with FTD (Snowden *et al*., 1992; Kertesz *et al*., 1994; Turner *et al*., 1996; Engel and Fleming, 1997), including 'classic' Pick's disease (Case records of the Massachusetts General Hospital, 1986; Karbe *et al*., 1993; Sakurai *et al*., 1998), FTD associated with motor neuron disease (MND) (Caselli *et al*., 1993; Bak *et al*., 2001) and chromosome 17-linked FTD (Basun *et al*., 1997); others have reported pathological changes of corticobasal degeneration (Lippa *et al*., 1991; Lang, 1992; Sakurai *et al*., 1996; Mimura *et al*., 2001) and even Alzheimer's disease (Green *et al*., 1990; Karbe *et al*., 1993; Greene *et al*., 1996; Galton *et al*., 2000). Two particularly perplexing cases presented with a clinical syndrome consistent with MND and non-fluent aphasia, but at post-mortem one had Alzheimer's disease and the other Lewy body pathology (Doran *et al*., 1995).

Neuropsychologically, PNFA is characterized by a relentlessly progressive disruption of language fluency, ultimately leading to muteness. Patients typically present with distorted, hesitant speech characterized by reduced phrase length (Kartsounis *et al*., 1991; Thompson *et al*., 1997) and diminished use of grammatical elements (Kartsounis *et al*., 1991; Snowden *et al*., 1992; Grossman *et al*., 1996; Hodges and Patterson, 1996; Thompson *et al*., 1997; Sakurai *et al*., 1998; Tree *et al*., 2001). Speech is littered with phonological errors (Weintraub *et al*., 1990; Kartsounis *et al*., 1991; Snowden *et al*., 1992; Kertesz *et al*., 1994; Hodges and Patterson, 1996; Sakurai *et al*., 1998; Tree *et al*., 2001) and, consistent with this feature, errors on confrontation naming are typically phonological in nature (Weintraub *et al*., 1990; Harasty *et al*., 2001). Single word comprehension is relatively preserved (Karbe *et al*., 1993; Grossman *et al*., 1996; Hodges and Patterson, 1996), but comprehension of complex grammatical structures, such as passive or embedded sentences, is impaired (Grossman *et al*., 1996; Hodges and Patterson, 1996; Tree *et al*., 2001). When specifically investigated, deficits in processing of verbs, relative to nouns, have been reported (Bak *et al*., 2001), and impaired sentence comprehension has been found to correlate with impairments of verb processing (Rhee *et al*., 2001). Repetition has often been reported to be impaired (Grossman *et al*., 1996; Sakurai *et al*., 1998; Tree *et al*., 2001), but also occasionally spared (Mimura *et al*., 2001). There is relative preservation of non-language domains and activities of daily living, at least in the early years (Weintraub *et al*., 1990; Karbe *et al*., 1993; Grossman *et al*., 1996; Hodges and Patterson, 1996), though more widespread deficits have been reported after longitudinal follow-up (Green *et al*., 1990).

Neurological examination often reveals the presence of buccofacial apraxia (Tyrrell *et al*., 1990, 1991; Caselli and Jack, 1992; Cappa *et al*., 1996; Grossman *et al*., 1996; Sakurai *et al*., 1998), and some authors report associated dysarthria (Tyrrell *et al*., 1991; Cappa *et al*., 1996; Grossman *et al*., 1996; Sakurai *et al*., 1998). MND-associated PNFA is associated additionally with the development of a progressive bulbar palsy, and a more rapid rate of decline (Caselli *et al*., 1993; Bak *et al*., 2001). Occasionally, right-sided motor signs have been reported (Turner *et al*., 1996; Engel and Fleming, 1997).

In contrast to progressive fluent aphasia (semantic dementia), imaging in PNFA has not been as precise in pinpointing the anatomical site of pathology, but instead has yielded considerable variability across studies. Reports of structural imaging in individual cases range from normal (Caselli and Jack, 1992; Cappa *et al*., 1996; Bak *et al*., 2001), to left hemispheric atrophy (Caselli and Jack, 1992; Snowden *et al*., 1992; Grossman *et al*., 1996; Galton *et al*., 2000), left fronto-temporal atrophy (Doran *et al*., 1995; Hodges and Patterson, 1996; Abe *et al*., 1997; Galton *et al*., 2000), bi-frontal atrophy (Mimura *et al*., 2001) and generalized atrophy (Caselli *et al*., 1992; Cappa *et al*., 1996; Bak *et al*., 2001; Harasty *et al*., 2001). Reports of functional imaging [PET or single photon emission computerized tomography (SPECT)], usually in single cases, appear slightly more specific, with several reports localizing pathology to the frontal lobes (Tyrrell *et al*., 1990, 1991; Kartsounis *et al*., 1991; Snowden *et al*., 1992; Cappa *et al*., 1996; Bak *et al*., 2001; Mimura *et al*., 2001) or the left fronto-temporal region (Delecluse *et al*., 1990; McDaniel *et al*., 1991; Caselli and Jack, 1992; Caselli *et al*., 1992; Doran *et al*., 1995; Cappa *et al*., 1996; Turner *et al*., 1996; Abe *et al*., 1997). Cases with more diffuse left hemisphere abnormalities (Snowden *et al*., 1992; Cappa *et al*., 1996; Graham *et al*., 2003) or, alternatively, normal scans (Galton *et al*., 2000) have also been reported. The most specific imaging finding was a single case with MRI and SPECT changes localized to the left frontal operculum (Caselli *et al*., 1992).

To date, group studies using functional imaging have employed the region of interest (ROI) method only. Using PET, Grossman *et al*. (1996) reported that a group of PNFA cases had general left hemisphere hypometabolism relative to controls, and more specific hypometabolism in the left inferior frontal, superior and middle temporal gyri relative to cases of probable Alzheimer's disease. Of two SPECT studies employing ROI analyses, one found hypoperfusion in bi-frontal and left temporo-parietal regions (Talbot *et al*., 1995), and the other in left dorso-lateral prefrontal cortex and left subcortical nuclei (Newberg *et al*., 2000). In summary, imaging studies suggest a bias of pathology towards the frontal or left fronto-temporal regions, but with considerable variability between reports. Given the relatively focal nature of the cognitive deficit, it is perhaps surprising that neuroimaging findings have been relatively non-specific/inconsistent.

In an attempt to localize more precisely a neural substrate underlying the language disorder in a group of PNFA cases, this study aimed to map the distribution of metabolic deficits

using [^{18}F]fluorodeoxyglucose-PET (FDG-PET) and statistical parametric mapping (SPM). In addition, the contribution of regional brain atrophy was assessed in a voxel-based morphometry (VBM) analysis of the MRI data. If one hypothesizes that there is a common factor underpinning non-fluency in this group, the critical region ought to be common to all subjects and, therefore, more statistically robust in a group design compared with non-critical defects which may vary between subjects. Advances in localizing the site of abnormality in non-fluent aphasia would not only enhance understanding of the clinical syndrome, but would also assist theoretical studies that use PNFA as a lesion model to study language production (e.g. Croot *et al*., 1998; Tree *et al*., 2001). As the primary aim of this study was to define the neural associations of non-fluency, we included some cases with additional cognitive deficits on neuropsychological testing who would not meet the Mesulam and Weintraub (1992) criteria for primary progressive aphasia. However, the 'pure' non-fluent cases were also analysed separately in order to characterize the PET profile of this syndrome.

Methods

Subjects

Patients were recruited from the memory clinic at Addenbrooke's Hospital, Cambridge, UK. Written, informed consent was obtained from all patients and, where necessary, their carers, and control volunteers after detailed explanation of the procedures involved. The study had the approval of the Local Regional Ethics Committee and the Administration of Radioactive Substances Advisory Committee, UK.

All 10 PNFA cases presented with non-fluent language output as their predominant complaint (clinical features at the time of scanning are summarized in Table 1). Non-fluency was defined as reduced speech output with distortion of articulatory planning. None of the cases of non-fluency could be attributed solely to either prolonged word-finding pauses (so-called logopenic aphasia) or to dynamic aphasia. In addition to a decrease in speech fluency, cases had to show at least minimal evidence of agrammatism on formal testing as assessed by comprehension of grammatical structures – =1.5 SDs below control mean on the Test for the Reception of Grammar (TROG) (Bishop, 1989). Reduced fluency in conversation ranged from hesitant, stuttering-like output to virtual mutism. Phonological errors were common (Table 2) and speech quality was sometimes distorted. Buccofacial apraxia was common, though not formally assessed in all cases [of seven subjects administered a 10-item buccofacial apraxia battery (Croot, 2000), three had impairments]. No case, at the time of scanning, had other focal neurological signs. All 10 were native English speakers; nine were right-handers and one was left-handed (the left-handed case, M.R., also had left hemisphere predominant hypometabolism on visual inspection and SPM analysis of the PET scan; re-analysing the data with this case excluded did not qualitatively change the results). Although language dysfunction was the most prominent deficit in all cases, the presence of additional cognitive deficits was, as already mentioned, not considered an exclusion criterion. Three subjects had significant deficits in other cognitive domains and needed assistance with activities of daily living, while the seven remaining cases fulfilled Mesulam and Weintraub's (1992) criteria for primary progressive aphasia.

As comparison groups, 10 healthy controls and 10 dementia controls (probable Alzheimer's disease, by National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria, without non-fluent aphasia) were matched for age and education (Table 3). The PNFA group, on average, had a shorter reported symptom duration compared with the Alzheimer's disease group, but this was not statistically significant ($P = 0.15$). PNFA and Alzheimer's disease groups did not differ significantly on either Mini-Mental State Examination (MMSE) (Folstein *et al*., 1975) or Addenbrooke's Cognitive Examination (Mathuranath *et al*., 2000), a 100 point bedside test instrument that incorporates the MMSE but probes memory and language in more detail (for instance, category and letter fluency and a 10-item picture naming task are included).

The three subjects who, at the time of scanning, had evidence of a more extensive dementia have continued to deteriorate. Of the remaining seven 'pure' cases, two cases declined follow-up (K.R. and R.P.) and one has died but post-mortem was refused (S.A.). Of the remaining four cases, one is independent and continues to have a relatively pure non-fluent aphasic syndrome, with symptoms of 2–3 years duration (M.R.). One case went on to develop a global dementia, suggestive of Alzheimer's disease, 8 years after the onset of aphasic symptoms (W.K.). One case developed signs of corticobasal degeneration (including alien limb and limb apraxia) 6 years after symptom onset (H.K.). The final case developed aggressive behaviour and memory symptoms also 6 years after symptom onset (D.H.). Of the nine cases who are still alive, six have consented to post-mortem tissue donation.

Neuropsychological assessments

Neuropsychological assessments included tests of attention/working memory (forward and backward digit span), executive and problem-solving [Wisconsin card sorting test (WSCT) (Heaton, 1981) and Raven's Coloured Progressive Matrices (RCPM) (Raven, 1962)], visuospatial function [Visual Object and Space Perception Battery (VOSP) (Warrington and James, 1991) and copy of the Rey figure (Osterreith, 1944)], episodic memory [Recognition Memory Test (Warrington, 1984) and delayed recall of the Rey figure (Osterreith, 1944)] and language and semantics [category fluency, letter fluency (F, A and S), Pyramids and Palm Trees test (Howard and Patterson, 1992) and picture naming and

Table 1 *Summary of clinical description recorded for each PNFA case*

Subject	Sex	Age (years)	Years since onset*	MMSE /30	TROG /80	CT	Description of language	Significant non-language deficits
K.R.	M	58	4	28	76	NT	Distorted, single word utterances; frequent phonemic errors; comprehension of conversation intact	Nil
R.P.	M	75	4	28	76	18	Slow, laboured speech; omission of phonemes; errors selecting pronouns and conjugating verbs; some dysprosody; comprehension of conversation intact.	Nil
M.R.	M	66	2	28	69	74.2	Hesitant, stuttering speech; some phonemic and grammatic errors; comprehension of conversation intact	Nil
D.H.	M	79	4	27	69	16.6	Slow, distorted, dysarthric speech; grammatical errors and omission of suffixes; comprehension of conversation intact	Nil
S.A.	M	76	1	25	73	60	Slow speech; phonemic errors; comprehension of conversation intact	Nil
W.K.	M	69	6	24	64	33.3	Slow, hesitant speech; phonemic errors; comprehension of conversation intact	Nil
H.K.	F	74	4	24	61	3.2	Virtually mute; comprehension 'appeared' to be preserved	Nil
R.S.	M	55	3	14	62	9.5	Hesitant with long pauses; phonemic and semantic errors; single word comprehension intact	Memory deficit
A.S.	M	68	2	12	28	1.1	Slow, laboured, distorted speech; phonemic errors; single word comprehension intact	'Reasoning' problems
B.R.	M	62	4	11	44	9.4	Sparse, laboured, single word utterances; comprehension of simple conversation intact	Memory and orientation deficits

*Symptom duration at time of PET, all cases had subsequent follow-up >2 years; MMSE = Mini-Mental State Examination; TROG = Test for the Reception of Grammar (elderly controls scored 78.8 ± 1.9); CT = Cookie Theft Picture description (elderly controls spoke at 92.5 ± 20.3 words/min); NT = not tested.

Table 2 *Examples of phonological errors made by PNFA subjects in conversation and *picture naming*

Target	Response
Behind	be'hond
Words	wads
Constructed	con'stracted
Spoonerism	spoozerism
Trumpet*	trambet
Cucumber*	cufedent
Volcano*	vol'kako
Skeleton*	skelekon
Pagoda*	pa'golo
Sextant*	santinet
Snail*	eskarto

' indicates that the following syllable was stressed in the patient's response.

spoken word–picture matching from the Hodges and Patterson semantic battery (Bozeat *et al*., 2000)].

In addition, comprehension of complex syntactic structures was assessed using the TROG (Bishop, 1989), in which subjects are asked to match each of 80 target sentences of increasing syntactic complexity to one of four line drawings. Initial blocks test simple structures such as single adjectives or negatives, whereas later sections require the comprehension of more complex structures such as embedded or relative clauses. Verbal fluency in propositional speech was measured by words/minute generated in a description of the Boston Cookie Theft picture. Single word repetition was assessed with a list of 11 four-syllable words.

Imaging

Image acquisition

All subjects were studied, using an identical protocol, on scanners in the Wolfson Brain Imaging Centre, University of Cambridge, UK. Each subject underwent a T_1-weighted 3D spoiled gradient echo sequence volumetric MRI (echo time 5 ms, recovery time 19.1 ms) on a 3 T Bruker system for co-registration to PET. The field of view was 25.6 × 22.0 × 18.0 cm with a matrix size of 256 × 256 × 256. PET scans were performed on a General Electric Advance system in 3D mode, voxel size 2.35 × 2.35 × 4.25 mm with a field of view of 30 × 30 × 15.3 cm. Prior to the PET scan, subjects fasted for a minimum of 8 h; 30 min before isotope injection, a

Table 3 *Demographics of the three groups in the imaging experiments*

	PNFA n = 10 (1F)	AD n = 10 (4F)	Controls n = 10 (4F)
Age (years)	68.8 ± 7.8 (71.5 ± 7.1)	68.1 ± 7.4	65.9 ± 6.1
MMSE (/30)	22.1 ± 7.0* (26.3 ± 1.9*)	22.8 ± 1.8*	29.8 ± 0.4
Addenbrooke's Cognitive Examination (/100)	61.6 ± 23.4* (74.4 ± 13.0*)	73.7 ± 9.2*	96.9 ± 2.5
Education (years)	11.2 ± 1.9 (11.6 ± 2.0)	10.7 ± 1.4	11.9 ± 1.5
Symptom duration (years)	3.4 ± 1.4 (3.6 ± 1.6)	4.8 ± 2.6	

PNFA (n = 7 'pure' cases' data in parentheses), Alzheimer's disease and controls (*Mann–Whitney U tests $P < 0.001$ compared with controls, all other contrasts not significant).

radial arterial cannula was inserted for glucose and radioactivity measurements, and a venous cannula for FDG injection. The subjects were then positioned in a plastic head cradle; ear plugs and blindfolds were not used but all subjects were scanned under the same conditions in a dimly lit, quiet room. A 10 min transmission scan was performed for attenuation correction using rotating $^{68}Ge/^{68}Ga$ sources, after which the subjects were injected with 74 MBq (2 mCi) of FDG over 30–60 s. PET images were then acquired from t + 35–55 min post-injection, whilst 14 arterial blood samples were taken over the 55 min post-injection to define the FDG input function. Images were reconstructed using the PROMIS algorithm (Kinahan and Rogers, 1989) with corrections applied for attenuation, dead time, scatter and random coincidences. Cerebral metabolic rate for glucose (CMRglc) was calculated from the image and blood data using the autoradiographic technique (Phelps *et al*., 1979).

VBM analysis

The volumetric MRI data were used to perform a VBM analysis of regional grey matter volume loss. A method identical to that described by Good *et al*. (2001) was employed using their optimized segmentation procedure, volume correction and a bespoke template [our template was created from n = 17 age-matched controls, smoothed with an 8 mm full width at half-maximum (FWHM) Gaussian filter]. The resulting grey matter segments for each subject were smoothed (12 mm FWHM) and two-population comparisons made between 'pure' PNFA versus controls, all PNFA versus controls and all PNFA versus Alzheimer's disease (statistical thresholds used are described in the relevant Results sections).

PET analysis

In order to minimize normal inter-subject variability in resting brain metabolism, PET scans were first normalized to the CMRglc of the cerebellar vermis (nCMRglc) using AnalyzeAVW software (Biomedical Imaging Resource, Mayo Foundation, Rochester, MN). This region is thought primarily to reflect inter-subject differences in brain metabolism (Ichimiya *et al*., 1994) and has been used in similar PET studies of Alzheimer's disease (Desgranges *et al*., 1998). The remaining stages of image processing and statistical analysis were performed with SPM99 (Wellcome Department of Cognitive Neurology, London, UK) and Matlab5.2 software (Mathworks Inc., Natick, MA). The PET scans were co-registered to each individual's volumetric MRI and then spatially normalized to the T_1-MRI template in SPM99 [based on the Montreal Neurological Institute (MNI) brain]. Finally, to minimize effects of inter-individual variation in sulcal pattern and to render the data more normal for statistical analysis, the PET data were smoothed with a 16 mm FWHM Gaussian filter.

The first analysis compared the 'pure' PNFA group with controls to assess the metabolic landscape of PNFA (as defined by Mesulam and Weintraub's criteria). The second analysis compared the expanded group (n = 10) with controls both to examine the effect of adding advanced cases to the analysis and to increase the power for the third analysis. Statistical analyses were performed at P(corrected) = 0.05 for the first and second analyses. The third compared the PNFA group with Alzheimer's disease as a dementia control group to investigate specifically the neural basis of non-fluency: for this analysis, the statistical threshold was lowered until abnormalities were identified and then PNFA was subtracted from Alzheimer's disease, and vice versa. The threshold for analysis of voxels was set at >40% of whole brain mean. The accuracy of localization of abnormalities in the peri-Sylvian region was checked by application of a non-linear transformation as described by M. Brett (see http://www.mrc-cbu.cam.ac.uk/Imaging/).

Results

Neuropsychological results

Performance on the various neuropsychological assessments for the three groups of participants is summarized in Table 4. The PNFA group had markedly reduced forwards and backwards digit span. This almost certainly reflects disruption of phonological working memory, although impaired executive function, as evidenced by poor performance on the WCST, may also have contributed. In contrast, the RCPM, a test of problem solving that does not tax set-shifting and/or working memory ability, did not reveal any deficit in the PNFA group. Visuospatial performance was preserved in all cases. The PNFA patients' episodic recognition memory for

Table 4 *Summary of neuropsychological performance of PNFA and Alzheimer's disease groups*

Group	PNFA	AD	Aged controls: mean ± SD
Attention/working memory			
Forward digit span	3.7 ± 1.1† (4.1 ± 0.9†)	6.7 ± 1	7.1 ± 0.9
Backward digit span	2.7 ± 1.3* (3.0 ± 0.8)	4.3 ± 1.7	5.4 ± 1.4
Executive/problem solving			
Wisconsin card sort test (/6)	2.7 ± 2.2 (3.1 ± 2.2)	3.4 ± 1.9	5.9 ± 0.4
Raven's Coloured Progressive Matrices (/36)	29.0 ± 4.0 (30.0 ± 3.5)	NT	27 = 75th centile; 30 = 90th centile
Visuospatial			
Copy of Rey figure (/36)	32.8 ± 2.1 (33.3 ± 2.0)	31.7 ± 3.8	34.2 ± 1.6
Visual Object and Space Perception battery (VOSP)			
Incomplete letters (/20)	18.5 ± 1.6 (18.4 ± 1.8)	18.6 ± 1.1	19.2 ± 0.8
Cube analysis (/10)	8.0 ± 2.3 (9.1 ± 0.9)	8.1 ± 1.6	9.3 ± 1.5
Episodic memory			
Rey complex figure (delayed recall)	12.3 ± 5.4* (12.6 ± 5.6†)	2.8 ± 2.5	18.3 ± 5.2
Recognition Memory Test			
Faces (/25)	20.3 ± 6.5 (24.0 ± 1.4*)	20.6 ± 2.6	24.4 ± 0.6
Words (/25)	19.4 ± 4.6 (21.9 ± 2.6*)	17.0 ± 3.7	24.5 ± 1.0
Language and semantics			
Picture naming (/64)	43.3 ± 18.0* (53.8 ± 8.0)	59.8 ± 4.1	62.9 ± 1.6
Spoken word–picture matching (/64)	60.9 ± 7.2 (63.7±0.5)	62.9 ± 1.7	63.8 ± 0.4
Pyramids and Palm Trees test (words) (/52)	46.8 ± 6.6 (49.8 ± 1.9)	50.1 ± 1.9	51.1 ± 1.1
Pyramids and Palm Trees test (pictures) (/52)	47.6 ± 6.2 (50.3 ± 1.5)	49.0 ± 2.4	51.6 ± 1.0
Category fluency (four categories)	19.8 ± 12.2* (26 ± 9.2)	37.3 ± 12.7	60.3 ± 12.6
Letter fluency (F, A and S)	13.5 ± 11.5* (18.0 ± 10.6*)	38.4 ± 14.9	41.1 ± 11.6
Cookie Theft Picture description (words spoken/min)	25.0 ± 25.9 (34.2 ± 27.6)	NT	92.5 ± 20.3
Test for the Reception of Grammar (/80)	62.2 ± 15.3 (69.7 ± 5.8)	NT	78.8 ± 1.9
Four-syllable word repetition (/11)	5.8 ± 3.8 (6.7 ± 3.6‡)	NT	NT

Results in parentheses are for the subgroup with 'pure' PNFA; NT = not tested; Mann–Whitney U tests: *$P < 0.05$, †$P < 0.005$ PNFA versus Alzheimer's disease; ‡in two cases, repetition was preserved, i.e. scored 11/11; age-matched controls from the MRC-Cognition and Brain Sciences Unit panel, $n = 31$, age 68.5 ± 7.2.

both words and faces was somewhat low compared with controls and similar to the Alzheimer's disease group, but delayed recall of the Rey figure in the PNFA group was relatively preserved and much superior to that of the Alzheimer's disease participants.

As for assessments of language and semantic memory, the PNFA cases were moderately anomic, particularly in the full group, though less dramatically so in the pure subset. Apart from omissions, naming errors in the PNFA group were almost exclusively phonological in nature, whereas Alzheimer's disease patients' naming errors were typically semantic (the mild Alzheimer's disease patients tested here made few errors in picture naming). Comprehension of single concrete concepts, as assessed either by word–picture matching or by associative judgements to words and pictures (Pyramids and Palm Trees test), was slightly reduced in the full PNFA cohort but not for the pure subgroup. Verbal fluency for letters and semantic categories was severely impoverished in the PNFA patients and even in the pure subgroup, relative to Alzheimer's disease and to normal participants. All PNFA patients were at the lower end of, or considerably below, the control range of fluency in propositional speech as measured by words/minute produced in the Cookie Theft picture description, although there was considerable variability across the cases, ranging from 1.1 (i.e. virtually mute) to 74.2 (i.e. essentially normal) words/minute (data available on $n = 9$ cases). The PNFA cases were all impaired, again to varying degrees, on the TROG. The Alzheimer's disease group were not given this test, but previous studies have established that patients with mild Alzheimer's disease, lacking signs of non-fluent aphasia, find this a relatively easy task. For instance, seven typical Alzheimer's disease cases with a mean MMSE of 22.3 ± 2.6, previously tested in our research group, scored 78.1 ± 1.3/80 on the TROG. In the PNFA group, TROG scores did not correlate significantly with fluency in picture description (Pearson's $r = 0.54$, $P > 0.1$), a point that will be taken up in the General discussion. The PNFA patients, as a group, were also impaired at repeating long, four-syllable words (e.g. 'asparagus'), a task that both normal controls and mild Alzheimer's disease subjects perform flawlessly.

Imaging results

'Pure' PNFA compared with controls

In the VBM comparison of the 'pure' PNFA group ($n = 7$) with controls at P(corrected) = 0.05, no areas of regional grey matter loss survived threshold. Reducing the threshold to

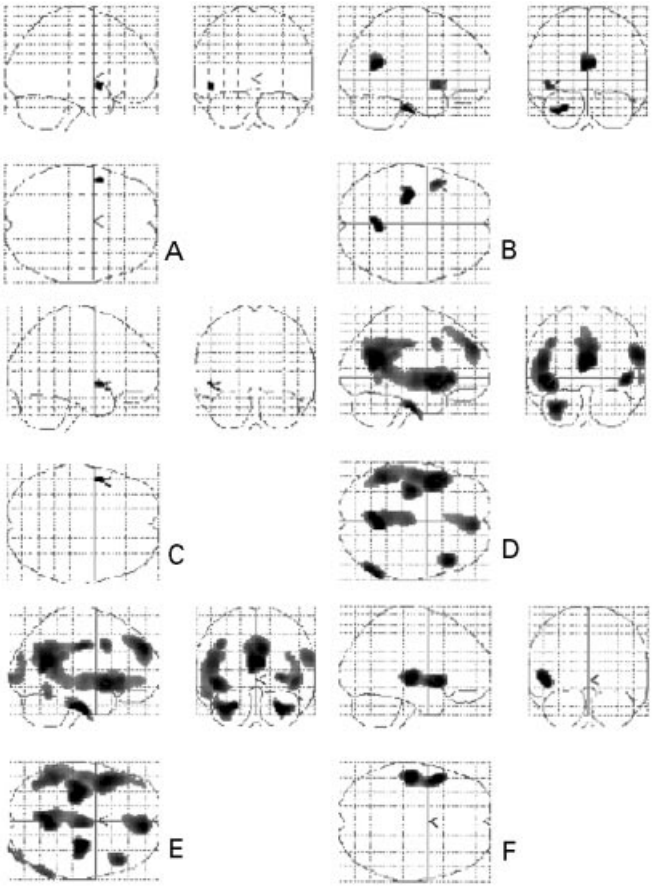

Fig. 1 Glass brain images. (**A**) VBM analysis of regional atrophy in the pure PNFA group (n = 7) compared with controls at P(uncorrected) = 0.001. (**B**) PET hypometabolism in the pure PNFA group compared with controls at P(corrected) = 0.05. (**C**) VBM analysis of regional atrophy in the whole PNFA group (n = 10) compared with controls at P(uncorrected) = 0.001. (**D**) PET hypometabolism in the whole PNFA group compared with controls at P(corrected) = 0.05. (**E**) PET hypometabolism in the pure PNFA group compared with controls at P(uncorrected) = 0.0001. (**F**) PET hypometabolism in the whole PNFA group compared with Alzheimer's disease at P(uncorrected) = 0.01.

P(uncorrected) = 0.001 revealed a single small cluster in the left peri-Sylvian region (x = –50, y = 8, z = –6; T = 4.39) (Fig. 1A). The PET comparison of the 'pure' PNFA group with controls, at P(corrected) = 0.05, is illustrated in Fig. 1B. Three clusters were identified: in the left anterior insula (x = –44, y = 10, z = –6; T = 6.41); the posterior cingulate, Brodmann area (BA) 23/30/31 (x = 6, y = –52, z = 18; T = 6.76); and subjacent to the left parahippocampal and fusiform gyri, BA 36/20 (x = –28, y = –24, z = –34; T = 6.92).

Discussion of the results of the pure PNFA versus controls

This analysis mapped the structural and metabolic defects in the group of cases with a 'pure' non-fluent aphasic syndrome. VBM analysis of regional grey matter volume loss revealed a single small cluster in the left peri-Sylvian region at the reduced statistical threshold of P(uncorrected) = 0.001. Owing to the small size of this cluster, it is not possible to comment more precisely on its localization. In contrast to the VBM results, PET hypometabolism was considerably more significant, showing an abnormality in the left insular region. Despite an apparent focal clinical syndrome, however, two further abnormal regions were identified in posterior cingulate and parahippocampal/fusiform region. Indeed, the posterior cingulate defect was slightly more statistically significant than that measured in the left insula (T = 6.76 and T = 6.41, respectively). Posterior cingulate hypometabolism is a significant feature of mild Alzheimer's disease (Minoshima *et al*., 1997) where the key deficit is mnemonic, rather than linguistic; this region was therefore deemed unlikely to be relevant to the aphasic syndrome and not analysed further. The posterior cingulate finding may imply that Alzheimer's disease pathology is present in some of these cases; however, as the specificity of posterior cingulate hypometabolism in Alzheimer's disease, as opposed to non-Alzheimer's disease, dementias is uncertain, we feel it is prudent to avoid speculation until pathological data are available.

Based on focal lesion studies, the peri-Sylvian region is, in contrast, likely to be highly relevant. The statistical peak of this cluster was at x = –44, y = 10, z = –6 which, in the stereotaxic atlas of Talairach (Talairach and Tournoux, 1988), localizes to the left Sylvian fissure adjacent to the anterior insular cortex. The dimensions of this cluster extended rostrally from x = –48, y = 20, z = –6 (inferior frontal gyrus, BA 47) to posterior x = –42, y = 4, z = –6 (insula). This is an anatomically complex region. A small error in localization has the potential to alter the conclusions by moving the location of the cluster maximum between the anterior insula, inferior frontal lobe or even superior temporal lobe. To minimize the possibility that differences between the MNI and Talairach brains could have contributed to a false localization, the coordinates of this cluster peak were transformed using the non-linear transform of MNI to Talairach described by M. Brett (http://www.mrc-cbu.cam.ac.uk/Imaging/). As this peak was close to the origin in y and z planes (i.e. y = 0, z = 0), this procedure had no significant impact (MNI coordinates: x = –44 mm, y = 10 mm, z = –6 mm; Talairach coordinates: x' = –43.56 mm, y' = 9.44 mm, z' = –5.52 mm).

The statistical peak, however, only defines a single point within a cluster, which, in turn, may be positioned eccentrically in relation to the peak. The cluster was, therefore, projected back onto the spatially normalized coronal MRI of each of the PNFA individuals (example shown in Fig. 2); in other words, the anatomical data in the form of the MRI and the hypometabolic cluster are both in the same standardized space. As shown in Fig. 2, this procedure revealed that the hypometabolic cluster involved the left frontal opercular region and extended along the insular cortex. The images presented in Fig. 2 were then compared directly with the

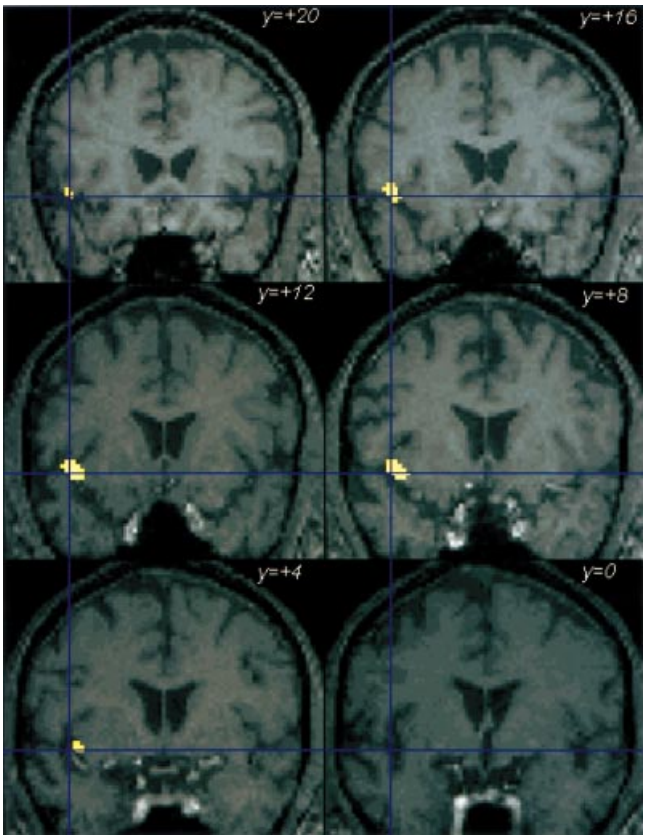

Fig. 2 Comparison of the $n = 7$ 'pure' PNFA cases with controls projected onto the spatially normalized brain of a PNFA subject at P(corrected) = 0.05.

corresponding coronal brain slices in the Duvernoy atlas (Duvernoy, 1999). From this atlas, the cluster peak involved the short insular gyri of the anterior insula.

The third cluster identified, in the left parahippocampal/fusiform gyrus region, should be considered with caution. While it may offer evidence of more diffuse cerebral involvement, possibly anticipating the onset of a more generalized dementia, certain features suggest that this cluster may be artefactual. The location of the coordinates in the z-plane is ~10 mm inferior to the temporal lobe. Applying the non-linear transform of MNI to Talairach brought them closer (e.g. $x = -28$, $y = -24$, $z = -34$; $x' = -27.7$, $y' = -24.6$, $z' = -27.3$), but the peak was still located outside the brain. Furthermore, when this comparison was performed without analysis threshold masking, the cluster appeared even more likely to be originating from outside the brain. Examining the cases as individuals, it appeared that this effect may have been generated by an inordinately high value at this point in one control.

The whole PNFA group compared with controls

In spite of adding three further cases, the VBM analysis at P(corrected) = 0.05 identified no areas of significant regional atrophy. Reducing the statistical threshold to P(uncorrected) = 0.001 again revealed one small cluster of grey matter volume loss in the left peri-Sylvian region ($x = -50$, $y = 6$, $z = -6$, $T = 4.21$, Fig. 1C). In contrast to VBM, the PET comparison of the PNFA group with controls at P(corrected) = 0.05 revealed far more extensive abnormalities than those seen in the $n = 7$ pure cases. Overall there was a greater burden of hypometabolic voxels in the left, compared with the right, hemisphere (Fig. 1D). The most extensive region of hypometabolism was in the left peri-Sylvian region extending from ventro-lateral frontal lobe, through the frontal opercular region, along the insula to the superior temporal lobe. The anterior part of this region was mirrored by an abnormal cluster in the, homologous, right ventro-lateral frontal region. Abnormal clusters were also found in the posterior cingulate, right posterior temporal region, mesial prefrontal lobes, left fusiform gyrus and a small area in the left dorso-lateral prefrontal cortex.

Discussion of the results of the whole PNFA group versus controls

Compared with the pure ($n = 7$) PNFA group, this analysis yielded significantly more extensive PET hypometabolism, although without significantly greater atrophy as measured by VBM. The aim of this analysis was 2-fold; first, to increase power for the comparison with fluent Alzheimer's disease subjects (next section), and secondly to address the clinical issue of the relationship of PNFA to generalized dementias. Thus three cases whose initial deficit was non-fluent aphasia but who, at the time of PET scanning, had developed more pervasive cognitive decline were included. Ongoing follow-up of the 'pure' group has, to date, found that two of these cases have developed significant additional deficits. This data set therefore contains subjects on a continuum from isolated PNFA, to those that subsequently converted to dementia through to those that had already made this conversion. Predictably, the inclusion of the advanced cases was associated with more extensive hypometabolism. It appears, however, that the difference in results compared with the 'pure' PNFA is quantitative rather than qualitative; if the pure group's results (Fig. 1B) are re-analysed at the less rigorous statistical threshold of P(uncorrected) = 0.0001, the parametric map (Fig. 1E) looks almost identical to that of the whole group (Fig. 1D). The combined evidence from the imaging findings for the pure and expanded groups with the clinical follow-up data suggests that cases presenting with PNFA are, in general, at significant risk of ultimately developing dementia. The lack of qualitative differences between the narrow and expanded groups suggests that the present stipulation that aphasia be an isolated finding for 2 years in order to diagnose primary progressive aphasia is, at least in the case of PNFA, arbitrary and possibly not useful.

Turning to the specific hypometabolic regions found in this analysis, the left insular defect was considerably larger than

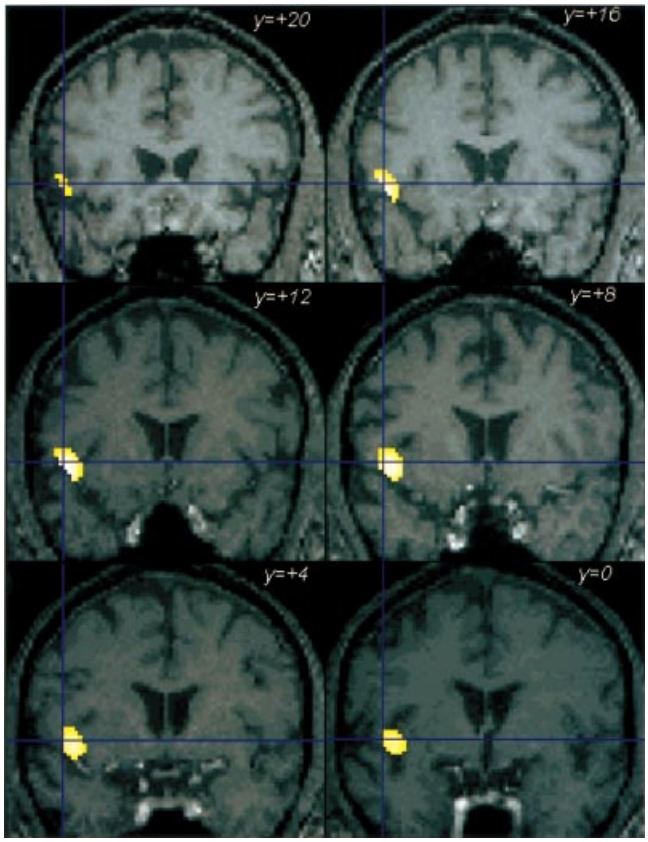

Fig. 3 Comparison of PNFA with Alzheimer's disease projected onto the spatially normalized brain of a PNFA subject at *P*(uncorrected) = 0.01.

that seen in the 'pure' group, extending rostrally to include Broca's area and caudally to the superior temporal gyrus. This is not surprising in that with advancing pathology, one would expect local spread of the neurodegenerative process. Two additional areas of frontal lobe hypometabolism were identified. First, hypometabolism in right BA 45/47 indicates that with clinical progression, pathological involvement of the inferior frontal gyrus, though asymmetric, is not unilateral. The second was in the dorso-medial frontal region. Medial frontal lobe lesions may affect language either as part of akinetic mutism or as seen in the syndrome of dynamic aphasia. The former is unlikely to be a factor in the present group as the lesion of akinetic mutism characteristically involves the anterior cingulate and the lack of verbal output has (unlike the PNFA group) a major avolitional element (Devinsky *et al*., 1995). Furthermore, the subjects in this PNFA series all had evidence of agrammatism and thus do not fit the profile of dynamic aphasia. Nevertheless, it may be that with advancing clinical status, a degree of adynamism further exacerbates the impoverished verbal output.

Finally, additional areas of hypometabolism were found in temporo-parietal regions broadly in keeping with the inclusion of cases with a more global dementia. As mentioned in the previous section, without pathological confirmation, we prefer to reserve judgement on the implications of such changes pending the ultimate histological diagnoses.

The PNFA group compared with Alzheimer's disease

The VBM comparison of PNFA versus Alzheimer's disease yielded no significant differences in regional grey matter loss even when the statistical threshold was lowered to *P*(uncorrected) = 0.05. In the PET comparison, however, significant differences between the two patient groups were identified at *P*(uncorrected) = 0.01 (Fig. 1F). Although this threshold is less rigorous, the first analysis had identified the left peri-Sylvian cluster as the most plausible 'candidate' region to underpin non-fluency in the PNFA group, and this analysis thus had an *a priori* hypothesis regarding the region of abnormality. At this threshold, the PNFA group relative to Alzheimer's disease showed a single hypometabolic cluster in the left frontal operculum, BA 44/47 region ($x = -48$, $y = 12$, $z = -4$). This extended along the entire length of the insular cortex (Fig. 3) to the attachment of the superior temporal gyrus ($x = -50$, $y = -18$, $z = 0$). Comparing Figs 2 and 3, the left insular/frontal opercular cluster is very similar in distribution. The reverse comparison of Alzheimer's disease with PNFA yielded a single cluster in the right precuneus/cuneus (BA 7/31/18) and lingual gyrus (BA18) (data not shown).

Discussion of the results of the PFNA group versus Alzheimer's disease

The rationale for this analysis was that if two groups of patients each have a degenerative brain disease but only one group displays non-fluent language, then differences in the topography of hypometabolism may help to identify the pathological locus specifically underpinning the language disorder (NB, the only cognitive tasks on which the PNFA group were worse than the Alzheimer's disease group were language related). As resting CMRglc was declining in both groups (relative to controls), it is not surprising that at conventional statistical thresholds of *P*(corrected) = 0.05, no significant differences were seen between the two patient groups. At *P*(uncorrected) = 0.01, the single area surviving threshold was in the left insula which is highly concordant with the anterior part of the hypometabolic distribution seen in the previous analysis. Although the statistical threshold required to identify this defect was not as stringent, we propose that it is more likely to be a significant finding than a false positive, given that the abnormality occurred (i) in the most likely candidate region for non-fluent aphasia as identified from the first analysis; and (ii) in the absence of abnormal clusters elsewhere.

General discussion

To our knowledge, this is the first study to examine the topography of metabolic deficits in a group of PNFA subjects. Unlike imaging results of previous single case studies which yielded patterns generally biased towards left anterior hemisphere involvement but with great variability, the approach adopted here of a group design with SPM produced a much more focal abnormality of the left insular region and frontal operculum extending onto the inferior frontal gyrus (BA 44/47). The epicentre of this hypometabolic cluster was in the anterior insula. The data were analysed in three ways: first in a group of subjects with a pure non-fluent aphasic syndrome; secondly in an expanded group that included more advanced cases who exhibited additional cognitive deficits; and finally by comparing this latter group with an Alzheimer's disease group, whose language output was fluent, in order to examine the metabolic deficits specific to PNFA. The comparison of the whole PNFA group with controls yielded several loci of hypometabolism of which only the cluster centred on the left anterior insula remained when the PNFA group was compared with Alzheimer's disease. The similarity of patterns of hypometabolism of the whole and more restricted 'pure' PNFA groups may suggest that a significant number of the 'pure' PNFA cases were also in the prodrome of a more global dementia, a hypothesis supported by longitudinal follow-up in two cases to date.

Although it is tempting to speculate on the pathological diagnosis of these cases, we consider it more prudent to wait for pathological confirmation. Nevertheless, the findings of metabolic deficits in posterior brain regions, combined with follow-up suggesting clinical features of Alzheimer's disease and cortico-basal degeneration in two of the originally 'pure' cases, at least raise concerns about the current nosological claim that PNFA is exclusively a variant of FTD (Neary *et al*., 1998; Neary, 1999; Tolnay and Probst, 2001). It will clearly be of considerable interest to revisit these data when pathological diagnoses are finally established.

There was a considerable difference in results from the MRI/VBM and the PET/SPM analyses, with the former identifying far fewer significant voxels. Equally as striking was the finding of less extensive atrophy in the insular region as assessed by VBM in our PNFA group than in a group of typical Alzheimer's disease reported by Baron *et al*. (2001). Differences in the degree of regional brain atrophy are dependent on many factors including disease severity, patient numbers (n = 19 patients and n = 16 controls in the study of Baron *et al*., 2001), scanner characteristics (this study was done with 3 T acquired data whereas most VBM studies have used 1.5 T data) and VBM methodology (e.g. optimized versus conventional segmentation, etc.). More relevant in the present study is the direct comparison of VBM with PET derived from the same data set: highly significant hypometabolism was found in spite of only minor grey matter volume loss, illustrating the greater sensitivity of physiological as compared with anatomical measures in degenerative disease. These data also help to explain the highly variable reports of structural imaging in case studies of PNFA.

The insula has received scant attention in pathological studies of PNFA. Some authors have noted significant pathology in BA 44 and 45 (Sakurai *et al*., 1998; Bak *et al*., 2001), but there is virtually no specific mention of the insula, though some describe 'peri-Sylvian' pathology, without further qualification. The one notable exception (Harasty *et al*., 2001) is, however, instructive in this regard: unlike most pathological reports that describe the distribution of histopathological features, this study quantified the extent of neuronal, grey and white matter volume loss. The case (PNFA related to Alzheimer's disease histopathology) had severe neuronal loss in anterior and posterior insula with underlying white matter volume loss, when compared with controls and with a case of Alzheimer's disease-related progressive fluent aphasia. The non-fluent case also showed significant neuronal loss in BA 45, though, in keeping with the present results, this was less severe than the insular abnormality. The case of Harasty *et al*. (2001) also accords with the discrepancy in the present study between the marked metabolic changes with PET, but only minor atrophy with VBM. In spite of severe neuronal loss, the grey matter volume in the insular region was relatively preserved in their study.

With regard to the mechanism by which the region of abnormality identified in this study gives rise to non-fluent speech production, it is germane to consider the present neuropsychological and PET data in light of studies of motor articulation of speech and of syntactic processing, the two components of language production most likely to govern fluency.

Dysfunction of the motor articulation of speech gives rise to speech apraxia, defined by Dronkers as a pure motor speech disorder in which subjects make inconsistent approximations of target words, lack prosody and are non-fluent (Dronkers, 1996). Dronkers' lesion analysis study compared cases of left hemispheric stroke-associated speech apraxia with patients with similarly sized left hemispheric strokes but without speech apraxia; an area within the left insular cortex was consistently damaged in the former and spared in the latter (Dronkers, 1996). Fitting the notion that this area may represent a final common pathway in the articulation of language, a functional activation study of noun articulation, without a syntactic component, activated this region (Wise *et al*., 1999). Similarly, a study that included conditions of both propositional and non-propositional speech (the latter exemplified by counting and overlearned nursery rhyme recitation) found that activation of left anterior insula and adjacent frontal operculum was common to both conditions (Blank *et al*., 2002).

The cases in the present series could not be described as having a pure apraxia of speech in that their symptom profile included a degree of impairment in the comprehension of complex syntax. Functional imaging studies of syntactic processing have reported focal activation in the caudal part of Broca's area/frontal operculum (Stromswold *et al*., 1996;

Indefrey *et al*., 2001), corresponding to the rostral part of the hypometabolic region in the PNFA group. A further study that attempted to isolate syntactic processing from the possible confound of subvocal rehearsal (by having subjects repeat the word 'double' during the syntactic comprehension task) yielded activation of the rostral part of Broca's area (Caplan *et al*., 2000). This activation was >25 mm rostral to the peaks found in the studies that did not control for this confound. Considering the proposed role for the insula in motor articulatory planning (independent of the syntactic characteristics of the language output), this rostral shift in activation could suggest that there is a graded transition in the left frontal/insular network from more rostral involvement in syntactic processing to a more caudal role for motor articulation.

Considering the evidence from focal lesion and functional activation studies, we propose that the non-fluency of cases in the present study represents a combination of varying degrees of speech apraxia and syntactic processing deficits (or agrammatism). This formulation would help explain the heterogeneity between individual cases and would be consistent with the finding of lack of correlation between performance on syntactic comprehension and fluency of picture description in the PNFA group. For instance, two cases in the present study (M.R. and D.H. in Table 1) each scored 69/80 on the TROG; when asked to describe the Cookie Theft picture, however, M.R. generated 74.2 words/min while D.H. generated only 16.6 words/min. While the variability in fluency, in spite of equivalent scores on grammatical comprehension, could still be explained by grammatical difficulties affecting expressive speech more severely than receptive language, it seems more plausible to propose a greater degree of speech apraxia in the case of D.H. Further, this would explain the observation that some cases exhibited a severe loss of speech fluency in spite of only modest impairments in grammatical comprehension and is, in turn, in keeping with the finding that hypometabolism was maximal in the insula. At a pathological level, this would suggest that, in general, the maximal locus of neurodegeneration is in the insula with varying degrees of retrograde extension to Broca's area, the latter representing an earlier part of the language production network.

In summary, PNFA in 10 cases was associated with a focal reduction in glucose metabolism in the left insular cortex, maximal in its anterior region, which appears to correspond to the short insular gyri. The caudal parts of Broca's area (BA 44,47) were also involved, though to a less significant extent. In view of these findings—plus hypotheses regarding the roles of the insula and Broca's area in verbal output—test batteries designed to tease apart the relative contributions of syntactic processing and motor articulatory planning would be of considerable interest. The current imaging results would predict impairment of both processes, though with a greater contribution to loss of fluency from the articulatory deficit.

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