Progressive Nonfluent Aphasia: Language, Cognitive, and PET Measures Contrasted with Probable Alzheimer’s Disease

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Abstract

The purpose of this study was to compare the language and cognitive profiles of four progressive nonfluent aphasia (PNFA) patients with 25 probable Alzheimer’s disease (pAD) patients, and to identify the distinct cortical defects associated with cognitive deficits in PNFA using positron emission tomography (PET). Longitudinal observations of PNFA patients revealed progressively telegraphic speech and writing and a gradual deterioration of sentence comprehension, but memory and visual functioning were relatively preserved. Direct contrast with pAD patients revealed that PNFA patients are significantly impaired on grammatical phrase structure aspects of sentence comprehension and expression, phonemic judgments, repetition, and digit span, but not on other cognitive measures. PET studies of PNFA revealed reduced cortical activity throughout the left hemisphere. In addition, there was a prominent defect in left superior and middle temporal and inferior frontal regions of PNFA patients that differed significantly from the distribution of regional cerebral dysfunction in pAD. We conclude that PNFA is associated with a distinct profile of language and cognitive difficulty, and that this pattern of impairment is related to cortical dysfunction in a specific distribution of the left hemisphere.

INTRODUCTION

Probable Alzheimer’s disease (pAD) is certainly the most common of progressive neurodegenerative conditions. More recently, an unusual neurodegenerative condition called primary progressive aphasia has been described (Chawluk et al., 1986; Gustafson, 1987; Heath, Kennedy, & Kapur, 1983; Jagust, Davies, Tiller-Borich, & Reed, 1990; Kirshner, Tanridag, Thurman, & Whetsell, 1987; Lippa, Cohen, Smith, & Drachman, 1991; Mehler, Horoupian, Davies, & Dickson, 1987; Mesulam, 1982, 1987; Neary, Snowden, Northen, & Goulding, 1988; Sapin, Anderson, & Pulaski, 1989). The hallmark of these cases is said to be progressive speech and language difficulty in the context of relatively preserved performance in memory and nonverbal domains. However, there is considerable controversy regarding the presence and nature of language and cognitive deficits in progressive aphasia. The purpose of this study was to contrast patterns of language, cognitive, and cerebral dysfunction in pAD with a distinct subset of progressive aphasic patients.

Cognitive and Language Impairments in Progressive Nonfluent Aphasia

Several recent reports have compared progressive aphasics with pAD patients. Green, Morris, Gandson, McKeel, and Miller (1990) and Karbe, Kertesz, and Polk (1993) did not note differences in the episodic memory or visual functioning of their two groups. Karbe and coworkers (1993) reported some distinctions between progressive aphasics and pAD patients on portions of the Western Aphasia Battery, including the spontaneous speech and naming subscales. Weintraub, Rubin, and Mesulam (1990) found differing patterns of confrontation naming difficulty in progressive aphasia and pAD. Several recent reports (Casselli & Jack, 1992; Casselli, Jack, Peterson, Wahner, & Yanagihiri, 1992; Snowden, Neary, Mann, Goulding, & Testa, 1992; Tyrrell, Warrington, Frackowiak, & Rossor, 1990) have emphasized the heterogeneous nature of progressive aphasia, and these comparisons with pAD are difficult to interpret since mixed groups of progressive aphasics were assessed. In the present study, we focus on a subgroup of patients thought to have progressive nonfluent aphasia (PNFA). Recent studies have provided brief clinical descriptions of some patients with PNFA (Casselli & Jack, 1992; Casselli et al., 1992; Snowden et al., 1992; Tyrrell et al., 1990). However, only one PNFA patient has been characterized in detail (Kartsonis, Crellin, Crewes, & Toone, 1991). This patient’s spontaneous speech and repetition were telegraphic in quality, and his confrontation naming was relatively preserved. The PNFA patient described by Kartsonis et al. (1991) was not contrasted directly with pAD, but demonstrated a normal IQ and good recall and
recognition memory. He performed adequately on the Token test of sentence comprehension, but had difficulty understanding longer texts. If PNFA and pAD are clinically distinct, detailed evaluations should reveal at least two types of differences: More widespread and severe nonlanguage difficulties among pAD patients, and a distinct profile of language impairments in PNFA patients.

Regional Cerebral Defects in Progressive Nonfluent Aphasia

Functional imaging techniques have been employed to identify regional cerebral dysfunction in progressive neurodegenerative conditions where structural imaging with MRI has not reliably identified a locus of cerebral defect. Positron emission tomography (PET) has frequently been used to characterize the pattern of cortical defects in pAD (Alavi, Jolles, Jamieson, Reivich, & Chawluk, 1989; Benson, Kuhl, Hawkins, Phelps, Cummings, & Tsai, 1983; Cutler et al., 1985; Duara et al., 1986; Foster et al., 1984; Frackowiak et al., 1981; Friedland, Budinger, Koss, & Ober, 1985; Hashby, Duara, Grady, Cutler, & Rapoport, 1985; McGurk et al., 1986). With few exceptions (Lowenstein et al., 1989), these investigations have reported diminished cerebral functioning that is most notable in parietal and posterior temporal cortices without preferential involvement of the left or right hemisphere. PET and single photon emission computed tomography (SPECT) studies of mixed groups of progressive aphasics have found reduced cortical functioning that is most evident in the left hemisphere (Caselli & Jack, 1992; Caselli et al., 1992; Chawluk et al., 1986; Foster & Chase, 1983; Graff-Radford, Damasio, & Hyman, 1990; Kempler et al., 1990; Miller et al., 1990; Tyrrell et al., 1990), and Caselli et al. (1992) and Kartsounis et al. (1991) observed that PNFA patients have predominantly left anterior defects on SPECT images. However, the SPECT images of PNFA patients reported by Snowden et al. (1992) did not demonstrate cortical defects restricted to left anterior cortices, and others have reported bifrontal defects (e.g., Tyrrell, Kartsounis, Frackowiak, Findley, & Rossor, 1991). SPECT images are not quantitative and have poorer spatial resolution than PET. There have been no PET studies of PNFA to resolve this discrepancy. We compared PET imaging in four PNFA patients with pAD to determine whether a specific pattern of cortical defect is associated with PNFA.

RESULTS

Case Studies

Case 1

This 78-year-old, high school-educated native English speaker presented in 1990 with a 3 year history of staccato speech. She had been in perfect health prior to the onset of her speech problems, and was not being followed for other medical conditions. Her family history was negative. General physical examination was normal. Neurologic examination when she first presented to the Cognitive Neurology clinic revealed the patient's mental status to be alert. Clinical evaluation of language functioning revealed nonfluent, hesitant, and dysarthric spontaneous speech compared to her more fluent and well-articulated automatic speech and singing. Her confrontation naming was quite compromised. Repetition and writing to dictation were telegraphic in quality due to the frequent omission of small grammatical words and bound grammatical morphemes such as "ed" that modify content words. Comprehension was intact for single content words and some simple sentences, but she encountered significant difficulty understanding grammatical aspects of sentences such as the passive voice. Oral reading was hesitant and contained many paraphasias and omissions, and her reading comprehension was compromised. Overall, the pattern of language impairment closely resembled that seen in nonfluent aphasia. By comparison, her recall of words and designs at 1 and 5 min following presentation was essentially intact. Her ability to match pairs of visuospatial designs was intact, and her ability to copy a complex geometric design was preserved. She exhibited some buccofacial apraxia, but was not compromised in limb apraxia. The remainder of her neurological examination revealed mildly spastic tone and a mild reduction in strength in the right upper extremity. Her deep tendon reflexes were also somewhat brisker on the right than the left, and her right great toe was extensor in response to plantar stimulation of the feet. The patient's MRI, obtained at the time of the PET scan in 1991 and about 4 years following the onset of her complaints, is shown in Figure 1. This revealed atrophy that was more pronounced in the left hemisphere.

Case 2

This 71-year-old native English speaker with 2 years of college education presented in 1989 with a 2-year history of garbled and hesitant speech. Her past medical history was otherwise noncontributory, and her family history was negative. Neurologic examination revealed the patient's mental status to be alert, and she was fully oriented to person, place, and time. Evaluation of speech and language revealed dysarthric speech that was mildly telegraphic in quality due to the occasional omission of small grammatical words and bound grammatical morphemes, in contrast to her fluent and relatively well-articulated singing. Repetition and oral reading were also telegraphic. Her comprehension of oral and written words and simple grammatical sentences was reasonably preserved, but she was inconsistent in her comprehension of sentences with grammatical features such as the passive voice. Spontaneous writing and writing to dictation were also telegraphic. Visual confrontational naming
Figure 1. MRI scans in patients with progressive nonfluent aphasia. These images were obtained at the time of the PET scans and are at the approximate levels of the PET image shown in Figure 3 (with the exception of case 3). Transverse and coronal images are oriented so that the left hemisphere is on the right of the image. A long TR (2600 msec), long TE (90 msec) technique was used for transverse images, and a short TR (600 msec), short TE (20 msec) technique was used for coronal images. (A) Case 1 is illustrated by a transaxial image of the mid-temporal lobe (on the left) and a coronal image of the anterior temporal lobe (on the right). Relative atrophy is seen in the left hemisphere. (B) Case 2 demonstrates a transaxial image of the mid-temporal lobe (on the left) and a coronal image of the anterior temporal lobe (on the right). Relative atrophy can be seen in the left hemisphere. (C) Case 3 is illustrated by transaxial images at the inferior temporal lobe level (on the left) and middle temporal lobe level (on the right) (coronal MRI images were not available). (D) Case 4 shows transaxial images at the mid-temporal lobe level (on the left) and inferior temporal lobe level (on the right).

was poor. She closely resembled a mild nonfluent aphasic. By comparison, her memory was intact for the recall of words and visual designs at 1 and 10 min following presentation. She encountered no difficulty matching pairs of visuospatial designs, and she was accurate in her ability to reproduce a complex geometric design. Buccofacial apraxia was evident, but limb praxis was normal. The remainder of her neurologic examination was within normal limits. This patient’s MRI, displayed in Figure 1 and obtained at the time of the PET scan in 1991 and 4 years after the onset of her complaints, revealed mild left hemisphere atrophy.

Case 3
This 59-year-old, college-educated native English speaker presented in 1989 with a 2-year history of difficulty repeating sequences of digits at her job. Her medical history was significant only for excessive alcohol consumption in the remote past. Her family history was negative. Neurological examination revealed the patient’s mental status to be alert, and she was fully oriented to person, place, and time. Evaluation of speech and language revealed hesitant speech with occasional word-finding pauses and circumlocutions but fluent singing. Repetition was telegraphic in quality due to the omission of small grammatical words, but oral reading was normal. Spontaneous written expression and writing to dictation were also preserved. Comprehension was within normal limits for most content words and simple sentences. She had occasional difficulty understanding grammatical aspects of sentences such as the passive voice. Visual confrontation naming was mildly compromised. She resembled a mild nonfluent aphasic. By comparison, this patient’s memory was perfectly intact for the recall of words and visual designs at 1 and 10 min following presentation. Her ability to match pairs of visuospatial designs was accurate and she was able to copy a complex geometric design without any difficulty. She exhibited minimal buccofacial apraxia, and had no difficulty on tests of limb praxis. The remainder of the neurological examination was within normal limits. This patient’s MRI, obtained at the time of the PET scan in 1991 and 4 years after her difficulty began, is illustrated in Figure 1.

Case 4
This 66-year-old, high school-educated, native English speaker presented in 1990 with a 2-year history of speech difficulty. Her past medical history was negative, and her family history was negative. Neurologic examination revealed the patient’s mental status to be alert, and she was fully oriented to person, place, and time. Evaluation of speech and language revealed mildly dysarthric speech that was telegraphic in quality due to the omission of small grammatical words. Her singing was more fluent and better articulated. Repetition and
oral reading were telegraphic, and her spontaneous writing and writing to dictation were also telegraphic. Visual confrontation naming was poor. She exhibited fair comprehension of single words and simple sentences, but she encountered considerable difficulty understanding grammatical aspects of sentences. Overall, she closely resembled a nonfluent aphasic. By comparison, she was able to recall words and designs at 1 and 5 min following presentation without any difficulty. She matched pairs of visuoperceptual designs accurately, and she was able to copy a complex geometric design without difficulty. She exhibited buccofacial apraxia, but limb praxis was normal. The remainder of the neurologica! examination was significant for deep tendon reflexes brisker on the right than the left. This patient’s MRI, obtained at the time of the PET scan and 3 years after the beginning of her complaints, is illustrated in Figure 1.

Natural History

Table 1 summarizes the natural history of the four PNFA cases. As can be seen, there was a significant deterioration in several domains of speech and language functioning in all four patients, particularly in spontaneous speech, repetition, and comprehension. Three of the four patients became mute. Performance on most measures of memory and visual functioning was relatively stable during the same period of time. These longitudinal observations indicate that the pattern of impairment in PNFA appeared to persist for several years following the onset of their complaints.

Cognitive Studies

Verbal Neuropsychological Assessment

A verbal neuropsychological assessment battery was administered to determine whether PNFA patients display features of a dementia such as in pAD. The tasks, summarized in Table 2, assessed nonlinguistic measures in the verbal modality such as memory, attention, and executive functioning. The battery was administered at the time of PET scanning in three PNFA patients at about 4 years after the onset of their complaints. The fourth PNFA patient (case 1) was too impaired to give a full spectrum of performance at the time of PET scanning, so her data were taken from an earlier point in her evaluation, about 4 years after the onset of her complaints. The data were converted to $z$-scores on the basis of the performance of 25 age- and education-matched controls, as described in the Methods section, where $z < -1.96$ differs from control performance at the $p < 0.025$ level and $z < -2.32$ differs from control performance at the $p < 0.01$ level. It can be seen that PNFA patients differed significantly from controls only on measures of category naming and digit span.

Figure 2 summarizes the direct contrasts between PNFA patients and 25 age- and education-matched pAD patients. It can be seen that the PNFA patients were significantly less impaired on all of the episodic and remote memory measures. The PNFA patients were also less impaired on category naming than pAD patients. However, the PNFA patients were more impaired than pAD patients on digit span. PNFA patients thus were not universally superior or inferior to pAD patients in their verbal neuropsychological performance, but displayed a qualitatively distinct profile of impairment.

Nonverbal Neuropsychological Assessment

Nonverbal neuropsychological assessments, summarized in Table 3, were administered to PNFA patients to determine whether their impairment is material-specific. PNFA patients regularly differed from controls only in their category drawing and buccofacial praxis.

Figure 3 summarizes the contrasts between PNFA and pAD patients in their nonverbal performance. The PNFA patients were superior to the pAD patients on the evaluations of visual memory and other visual measures. These findings identify additional differences between PNFA and pAD, and underline the material-specific nature of the neuropsychological deficits in PNFA.

Language Studies

Standard Language Assessment

Language assessments were administered to distinguish the pattern of language difficulty in PNFA from that seen in other progressive neurodegenerative conditions, and to characterize in more detail the nature of the language impairment in PNFA. Consider first the assessments of standard language performance in PNFA patients relative to control subjects, summarized in Table 4. In contrast to their verbal and visual neuropsychological performance, PNFA patients differed from controls on many language tasks. There were three exceptions. Reading comprehension was relatively preserved. Oral comprehension, where patients responded to simple requests such as "Point to the window," was also relatively intact. Our abbreviated assessment of confrontation naming was intact as well. Since this probed only high-frequency names, we also administered the Boston Naming Test (Kaplan et al., 1983) to three PNFA patients at the time of PET scanning. Their scores were 31/60 (Case 2), 48/60 (Case 3), and 47/60 (Case 4), indicating only a mild to moderate naming impairment in PNFA. Thus, PNFA patients are compromised on many language tasks.

A summary of the observations of PNFA patients in comparison to pAD patients is provided in Figure 4. It can be seen that the language profile in PNFA patients did not duplicate that seen in pAD. Repetition and phonemic discrimination were more impaired in PNFA than in pAD. However, reading comprehension and confrontation naming were less impaired in PNFA. Oral expression was also less compromised in PNFA, but
Table 1. Clinical Follow-up in Progressive Nonfluent Aphasia

<table>
<thead>
<tr>
<th>Date</th>
<th>Conf nam</th>
<th>Nam flu</th>
<th>Repet</th>
<th>Oral comp</th>
<th>Speech</th>
<th>Write</th>
<th>Vrb mem</th>
<th>Vis mem</th>
<th>LTM</th>
<th>Dig span</th>
<th>Pt span</th>
<th>Rey copy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sep-90</td>
<td>Reduced</td>
<td>Fair</td>
<td>Intact</td>
<td>Mild</td>
<td>Reduced</td>
<td>Reduced</td>
<td>100%</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Oct-90</td>
<td>60% (recog)</td>
<td>na</td>
<td>na</td>
<td>Mod/agram</td>
<td>Telegraphic</td>
<td>na</td>
<td>100% (recog)</td>
<td>70%</td>
<td>na</td>
<td>na</td>
<td>5</td>
<td>Poor</td>
</tr>
<tr>
<td>Feb-91</td>
<td>60% (recog)</td>
<td>na</td>
<td>na</td>
<td>Sev/agram</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>70%</td>
<td>na</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Apr-91</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>Severe</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Feb-92</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>Severe</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
</tbody>
</table>

**CASE 2**

| Sep-89 | 100% | Fair | Severe | Mild | Paraph/telegraphic | Paragra | intact | ?      | ?   | ?        | ?       | ?        |
| Dec-89 | 80%  | 15/min | Severe | Mild | Paraph/telegraphic | Paragra  | 100%   | 90%   | Intact | 4  | 5       | 35      |
| Nov-90 | 50%  | 8/min (written) | Severe | Mild | Paraph/telegraphic | Paragra  | 100%   | 100%  | Intact | 3  | 4       | 32      |
| Jan-91 | 70% (written) | 9/min (written) | Severe | Mod/agram | Paraph/telegraphic | Paragra  | 100%   | 100%  | Intact | 3  | 4       | 32      |
| Apr-91 | 50% (written) | 7/min (written) | Severe | Mod/agram | Paraph/telegraphic | Paragra  | na     | 100%  | Intact | na | 5       | 32      |
| Sep-91 | 60% (written) | 4/min (written) | na      | Sev/agram | na     | Agram  | na     | 100%  | na   | 5       | na      | 5       |
| Dec-91 | 60% (written) | 3/min (written) | na      | Sev/agram | na     | Agram  | na     | 100%  | na   | 5       | na      | 5       |
| Apr-92 | na     | na     | na    | Severe    | na     | na    | na     | na     | na   | na       | na      | na       |
| Feb-93 | na     | na     | na    | Severe    | na     | na    | na     | na     | na   | na       | na      | na       |
| June-93 | na    | na     | na    | Severe    | na     | na    | na     | na     | na   | na       | na      | na       |

**CASE 3**

| Oct-89 | 100% | Fair | Intact | Intact | Paraphasic | Intact | 100%   | ?      | ?   | ?        | ?       | ?        |
| Feb-90 | 90%  | 15/min | Mild   | Intact | Paraph/telegraphic | Intact | 100%   | 100%  | Intact | 4  | 5       | 32      |
| May-90 | 100% | 10/min | Mild   | Intact | Paraph/telegraphic | Intact | 100%   | 100%  | Intact | 4  | 5       | 32      |
| Oct-91 | 80%  | 13/min | Moderate | Mild | Paraph/telegraphic | Intact | 100%   | 100%  | Intact | 4  | 5       | 36      |
| Feb-92 | 80%  | 10/min | Moderate | Mild | Paraph/telegraphic | Intact | 100%   | 100%  | Intact | 4  | 5       | 36      |
| Sep-92 | 80%  | 8/min  | Moderate | Mild | Paraph/telegraphic | Intact | 100%   | 100%  | Intact | 5  | 5       | 34      |
| Feb-93 | 60%  | 8/min  | Moderate | Mild | Paraph/telegraphic | Intact | 100%   | 100%  | Intact | 4  | 5       | 34      |
| Oct-93 | 60%  | 8/min  | Moderate | Mild | Paraph/telegram | Intact   | 100%   | 100%  | Intact | 5  | 5       | 32      |

**CASE 4**

| May-90 | 100% | Fair | Moderate | Mild | Paraph/telegraphic | Paragra | intact | ?      | ?   | ?        | ?       | ?        |
| Jul-90 | 50%  | 9/min | Mod/agram | Mild | Paraph/telegraphic | Paragra  | 90%    | 100%  | Intact | 4  | 6       | 34      |
| Nov-90 | 60%  | 7/min | Mod/agram | Mod/agram | Paraph/telegraphic | Paragra  | 100%   | 100%  | Mild   | 4  | 5       | 34      |
| May-91 | 60%  | 7/min | Severe   | Mod/agram | Telegraphic | Paragra  | 100%   | 100%  | Intact | 4  | 5       | 35      |
| Sep-91 | 60%  | 4/min | Severe   | Mod/agram | Telegraphic | Paragra  | 100%   | 100%  | Intact | 4  | 5       | 35      |
| Jan-92 | 40%  | 3/min | Severe   | Severe | Paraph/telegraphic | Telegraphic | Agram  | na     | na   | 5       | 5       |
| Jun-92 | 60% (written) | na      | na      | Severe | Severe | Paragra | na     | na     | na   | 5       | 5       |
| Nov-92 | 60% (written) | na      | na      | Severe | na     | Agram  | na     | na     | na   | 5       | 5       |
| Jun-93 | na     | na     | na      | Severe | na     | na     | na     | na     | na   | na       | na      | na       |

"Percentages refer to proportion correct. Scores for digit span and pointing span refer to the number of items reproduced in the correct order, and score for the Rey copy refers to the 36-point scoring system described in Lezak (1983). The missing data in the first contact are due to the referring physician describing the characteristic qualitatively or not performing the task. "na" refers to the patient’s inability to perform the task—usually due to muteness on a task requiring verbal production. Recog, recognition; writ, written; parap, paraphasic; parag, paragragmatic; telelg, telegraphic; agram, agrammatic; mod, moderate; sev, severe. The clinical evaluation was as follows: Conf nam, visual confrontation naming of 10 familiar objects; Nam flu, semantic category naming fluency for a familiar superordinate target for 1 min; Repet, repetition of 2 sentences and 2 multisyllabic words; Oral comp, responding to simple statements and to questions about grammatically complex sentences; Speech, an analysis of conversational speech; Write, an analysis of a writing sample; Vrb mem, recall of 4 words in the correct order at 1 and 5 min following presentation; Vis mem, recall of 3 objects in the room in the correct order at 1 and 5 min following presentation; LTM, recall of political events and personalities; Dig span, accurate repetition of a sequence of digits; Pt span, accurate repetition of a sequence of circles indicated by pointing; Rey copy, copy of the Rey figure.

Qualitatively distinct patterns were seen in the two groups. The oral expression of PDA patients was characterized by word-finding pauses and circumlocutory speech, while PNFA patients expressed a clear message in a telegraphic manner. These findings suggest that the language deficit in PNFA is not merely an attenuated or exaggerated form of the deficit seen in PDA, but instead suggest unique patterns of language impairment.

Kartsonis et al. (1991) reported that a PNFA patient performed reasonably well on the Token test of sentence comprehension, but was impaired in his understanding of longer texts. We performed several additional studies of sentence comprehension to examine grammatical features of sentences more directly. These tasks are described in the Methods section. We report the results of only three PNFA patients in most of these studies since...
Table 2. z-scores of Individual Progressive Nonfluent Aphasics on Verbal Neuropsychological Measures

<table>
<thead>
<tr>
<th>Group</th>
<th>ID</th>
<th>Orientation</th>
<th>Letter fluency</th>
<th>Category Naming</th>
<th>Digit span</th>
<th>Supraspan 15-min delay</th>
<th>Supraspan recog memory</th>
<th>Remote memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNFA</td>
<td>Case 1</td>
<td>0.00</td>
<td>-1.18</td>
<td>-3.66</td>
<td>-3.37</td>
<td>-1.74</td>
<td>-1.08</td>
<td>-1.05</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>0.00</td>
<td>-0.89</td>
<td>-3.10</td>
<td>-1.05</td>
<td>-0.78</td>
<td>0.60</td>
<td>-0.09</td>
</tr>
<tr>
<td></td>
<td>Case 3</td>
<td>0.00</td>
<td>-0.53</td>
<td>-0.30</td>
<td>-2.44</td>
<td>-0.78</td>
<td>0.60</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>Case 4</td>
<td>0.00</td>
<td>-1.08</td>
<td>-2.26</td>
<td>-1.98</td>
<td>0.18</td>
<td>0.60</td>
<td>0.88</td>
</tr>
</tbody>
</table>

The verbal neuropsychological tasks were Orientation, orientation assessed the patient's appreciation of self, place, and time on a 10-point scale adapted from the Mini Mental State Exam (Folstein et al., 1975); Letter fluency, letter fluency (Benton et al., 1983) evaluated the patient's ability to name words beginning with a target letter in 1 min; Category naming, category naming (Grossman, 1981) assessed the patient's ability to name exemplars of a target superordinate category in 1 min; Digit span, digit span (Wechsler, 1987) required the patient to repeat progressively longer lists of digits until 2 lists of the same lengths were not repeated accurately; Supraspan 15 min delay, and Supraspan recog memory, memory was assessed with the Rey Auditory Verbal Learning Test (Lezak, 1983), a supraspan measure involving the immediate recall of 15 words on 5 successive trials (we compared patients' performance using the difference between recall on the fifth presentation and recall on the first presentation), a delayed recall trial 15 min after the last presentation of the list, and a recognition trial where half of the words were not from the presented list; Remote memory, remote verbal memory was assessed by asking the patient to name the previous 8 presidents.

Figure 2. Mean (SD) z-score performance on verbal neuropsychological measures in 4 progressive nonfluent aphasics and 25 probable Alzheimer's disease patients with reference to age- and education-matched controls. Tasks are described in Table 2. The bold horizontal line indicates the level of performance differing from age- and education-matched controls at the \( p < 0.01 \) level. Significant differences were found between PNFA and pAD patients on measures of cat nam (semantic category naming fluency) \( \kappa(27) = 2.20, p < 0.03 \), dig span (digit span) \( \kappa(27) = 2.62, p < 0.01 \), STM 5-1 (supraspan verbal learning on trial 5 minus trial 1) \( \kappa(27) = 6.05, p < 0.0001 \), STM del (supraspan verbal learning free recall after a 15 min delay) \( \kappa(27) = 11.54, p < 0.0001 \), STM rec (supraspan verbal learning recognition after a 15 min delay) \( \kappa(27) = 10.69, p < 0.0001 \), and remote (remote memory) \( \kappa(27) = 3.66, p < 0.001 \). Differences were not found on orient (orientation) or let flu (category letter fluency).

the fourth patient was too impaired to participate at the time of PET scanning when these tests were administered.

As can be seen in Table 5, the PNFA patients were better than the pAD patients and differed from random in their ability to point to one of four pictures on the basis of an orally presented, grammatically simple, subject-verb-object (SVO) sentence. However, PNFA patients were worse than pAD patients and did not differ from random when asked to point to a picture on the basis of an orally presented sentence containing a terminal subordinate phrase or a center-embedded subordinate phrase. On probes of oral sentences, PNFA patients were worse during their attempts to understand sen-
Table 3. z-scores of Individual Progressive Nonfluent Aphasics on Nonverbal Neuropsychological Measures*

<table>
<thead>
<tr>
<th>Group</th>
<th>ID</th>
<th>Point span</th>
<th>Scanning attention</th>
<th>Design fluency</th>
<th>Category drawing</th>
<th>Rey copy</th>
<th>Rey recall</th>
<th>Remote memory</th>
<th>Perceptual matching</th>
<th>Praxis</th>
<th>Calcs</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNFA</td>
<td>Case 1</td>
<td>-2.21</td>
<td>-4.57</td>
<td>-1.21</td>
<td>-2.84</td>
<td>0.56</td>
<td>1.28</td>
<td>-1.02</td>
<td>0.30</td>
<td>-4.50</td>
<td>-0.14</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>-1.22</td>
<td>0.18</td>
<td>-0.83</td>
<td>-2.46</td>
<td>0.56</td>
<td>1.60</td>
<td>-0.25</td>
<td>0.30</td>
<td>-4.50</td>
<td>-0.14</td>
</tr>
<tr>
<td></td>
<td>Case 3</td>
<td>-1.22</td>
<td>0.18</td>
<td>1.47</td>
<td>-0.23</td>
<td>0.56</td>
<td>1.14</td>
<td>0.53</td>
<td>-3.25</td>
<td>0.41</td>
<td>-1.04</td>
</tr>
<tr>
<td></td>
<td>Case 4</td>
<td>-0.23</td>
<td>0.43</td>
<td>-1.40</td>
<td>-0.90</td>
<td>0.56</td>
<td>0.55</td>
<td>0.53</td>
<td>0.30</td>
<td>-1.55</td>
<td>-2.82</td>
</tr>
</tbody>
</table>

*Nonverbal neuropsychological tasks were Point span, pointing span (Wechsler, 1987) required the patient to reproduce a sequence of pointing to circles arrayed randomly on a sheet paper until 2 sequences of the same length were not reproduced accurately; Scanning attention, visual scanning (Weintraub & Mesulam, 1985) assessed the patient’s ability to identify 40 triangles from among 300 geometric figures arrayed randomly on a sheet of paper; Design fluency, for design fluency (Jones-Gotman & Milner, 1977), the patient produced different nonnamable designs composed only of curvy lines for 5 min; Category drawing, category drawing (Grossman, 1988) evaluated the patient’s ability to draw exemplars of a familiar superordinate category with 8 colored felt pens for 3 min; Rey copy, patients were asked to copy the Rey–Osterreith figure, scored according to a 36-point scale (Lezak, 1983); Rey recall, visual memory was assessed by asking patients to reproduce the Rey figure 5 min after presentation; Remote memory, remote memory was assessed by evaluating the patient’s ability to name 4 familiar faces from the 1960s; Perceptual matching, the patients were asked to judge whether 6 pairs of graded geometric designs (Beery & Buktenica, 1967) matched, where half of the pairs differed by one feature; Praxis, patients were asked to mime familiar representational and oral gestures (Goodglass & Kaplan, 1983); Calcs, calculations were adopted from the Wechsler Adult Intelligence Scale (Wechsler, 1981).

Figure 3. Mean (SD) z-score performance on nonverbal neuropsychological measures in 4 progressive nonfluent aphasics and 25 probable Alzheimer's disease patients with reference to age- and education-matched controls. Tasks are described in Table 3. The bold horizontal line indicates the level of performance differing from age- and education-matched controls at the $p < 0.01$ level. Significant differences were found between PNFA and pAD patients on measures of Rey copy (copy of the Rey–Osterreith figure) ($t(27) = 3.17, p = 0.005$, and Rey rec (recall of the Rey–Osterreith figure at 5 min following presentation) $t(27) = 17.39, p < 0.0001$. Differences approached significance on remote (remote memory) and percep (perceptual matching). Differences were not seen on measures of point span (pointing span), attention (scanning visual attention), design fluency, category drawing (with a meaningful target), praxis (oral and limb representational praxis), and calcs (calculations).

tences containing subordinate or center-embedded phrases in comparison to their own performance on simple sentences. PNFA patients also were worse than pAD patients on probes of oral sentences containing subordinate or center-embedded phrases. It may be noted as well that performance in PNFA was worst for object-relative center-embedded sentences compared to subject-relative sentences on both sentence-picture matching and responses to probes of oral sentences. Table 5 demonstrates, by comparison, that the impairment in their performance on probes of written sentences containing subordinate or center-embedded phrases was milder than their oral sentence comprehension difficulty, and did not consistently differ from their performance on written simple sentences.

As far as sentence expression is concerned, Figure 5 illustrates representative spontaneous writing samples from two PNFA patients. In each case, the patient was
Table 4. z-Scores of Individual Progressive Nonfluential Aphasics on Language Measuresa

| Group | ID  | Oral express | Written express | Repetition | Written dictation | Confront naming | Oral compreben | Grammatical compreben | Reading compreben | Phonemic discrim |
|-------|-----|--------------|----------------|------------|------------------|----------------|----------------|------------------------|------------------|----------------|-----|
| PNFA  | Case 1 | -1.00        | -7.25          | -12.35     | -6.29            | 0.23           | -2.42         | -6.66                  | -1.00            | -11.13         |
|       | Case 2 | 0.00         | -7.25          | -12.35     | -6.29            | 0.23           | 0.36          | -1.88                  | -0.10            | -9.23           |
|       | Case 3 | -5.00        | 0.40           | -6.01      | -1.24            | 0.23           | 0.36          | -1.88                  | 0.81             | 0.38            |
|       | Case 4 | -1.50        | -11.84         | -6.01      | -6.29            | 0.23           | -0.99         | 0.50                   | 0.81             | -5.37           |

aThe language tasks were Oral express and Written express, spontaneous oral expression and written expression about familiar topics (a description of the patient's house/apartment or the patient's most recent job) were scored for semantic content, grammatical form, and mechanical attributes such as dysartria; Repetition and Written dictation, repetition and written dictation each involved the reproduction of 4 sentences of graded length (range=4 to 15 words) that were scored for the accurate replication of the model; Confront naming, confrontation naming assessed the patient's ability to name 8 high frequency objects and line drawings; this was supplemented by the Boston Naming Test (Kaplan et al, 1985), as described in the test; Oral compreben, oral comprehension required the patient to respond to 8 grammatically simple target sentences (Goodglass & Kaplan, 1985) (e.g., "Point to the window," "Is it summer outside?" "Do you put your shoes on before your socks?"); Grammatical compreben, grammatical comprehension assessed the patient's ability to answer simple questions about sentences in the passive voice or sentences containing subordinate phrases (e.g., "Jane kicked Dick. Who was kicked?" "The eagle that chased the hawk was last. Which bird was chased?"") (Grossman et al, 1991); Reading compreben, reading comprehension required the patient to answer 8 grammatically simple questions about a Grade 6 level paragraph composed of 8 sentences (MacGinitie et al., 1978); Phonemic discrim, phonemic discrimination measured the patient's ability to discriminate between 8 pairs of one syllable words that differed by 1 feature of 1 phoneme (Kertesz, 1979).

Figure 4. Mean (SD) z-score performance on language measures of 4 progressive nonfluential aphasics and 25 probable Alzheimer's disease patients with reference to age- and education-matched controls. Tasks are described in Table 4. The bold horizontal line indicates the level of performance differing from age- and education-matched controls at the p < 0.01 level. Significant differences were found between PNFA and pAD patients on measures of oral exp (oral expression) t(27) = 5.04, p < 0.005, repet (repetition) t(27) = 6.21, p < 0.0001, naming (visual confrontation naming) t(27) = 6.00, p < 0.01, read comp (reading comprehension) t(27) = 2.92, p < 0.01, and phon disc (phonemic discrimination) t(27) = 3.09, p < 0.005. Differences were not found on measures of writ exp (written expression), writ dic (written dictation), oral comp (oral comprehension), or gram comp (grammatical comprehension).

asked to provide a complete and full sentence describing the weather. It can be seen that writing samples were progressively telegraphic in nature, and contained grammatical agreement errors. Nevertheless, the patients were able to provide an accurate sense of the weather. Performance on the sentence completion task is summarized in Table 6. All PNFA patients were able to participate in the written sentence completion task, but Case 1 and Case 2 were unable to perform the sentence completion task in the oral modality. We do not have
Table 5. Proportion of Correct Responses on Sentence Comprehension Tasks That Vary Grammatical Structure in Progressive Nonfluent Aphasia and Probable Alzheimer’s Disease$^a$

<table>
<thead>
<tr>
<th></th>
<th>Oral sentence-picture match</th>
<th>Oral sentence probe comprehension</th>
<th>Written sentence probe comprehension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Simple</td>
<td>Subordin</td>
<td>Cent-emb</td>
</tr>
<tr>
<td>PNFA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>100</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>Case 3</td>
<td>85</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>Case 4</td>
<td>100</td>
<td>44</td>
<td>31</td>
</tr>
<tr>
<td>Controls</td>
<td>94</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>pAD</td>
<td>69</td>
<td>65</td>
<td>75</td>
</tr>
</tbody>
</table>

$^a$See Methods section for a description of the tasks. subordin, terminal subordinate; cent-emb, center-embedded subordinate.

comparison data from the pAD patients on this task. It can be seen that PNFA patients generally provided more grammatically incorrect responses in their sentence expression than semantic errors. More detailed analyses of expression errors revealed that the PNFA patients frequently omitted material, particularly grammatical morphemes, but added or substituted material less often. These findings emphasize the nonfluent and telegraphic nature of the language expression impairments seen in PNFA.

Lexical semantic assessment was performed by evaluating their performance on picture and word category membership judgment tasks. PNFA patients correctly judged the category membership of 90.41% pictures [range = 86.30 to 94.52% correct], and judged the category membership of 95.67% words accurately [range = 93.50 to 100% correct]. pAD patients were 70.66% [SD = 7.63] correct in their category membership judgments of pictures, and 86.97% [SD = 6.54] correct in their judgments of words. In contrast to their performance with sentences, PNFA patients were reasonably accurate in their comprehension of single words.

PET Studies

Figure 6 illustrates PET images from each of the PNFA patients. Inspection of these images reveals a relative reduction of cortical functioning throughout the left hemisphere in comparison to homologous regions of the right hemisphere.

We used region-to-whole brain ratios to compare PNFA and pAD patients because of the different etiologies underlying these progressive disorders. These are summarized for the group of PNFA patients in Figure 7. The normalized left:right ratio for each brain region in PNFA patients, pAD patients, and controls is provided in Table 7. An analysis of variance using a group (control, PNFA, pAD) × hemisphere (2) × cerebral region (11) design revealed significant interaction effects for group × hemisphere [F(2.19) = 4.32, p < 0.02] and group × region [F(20,190) = 2.38, p < 0.002]. As suggested by Figures 6 and 7, cortical activity was reduced throughout the left hemisphere in PNFA. This was found in 36 (81.8%) of the 44 comparisons of region:whole brain activity in homologous regions of the left hemisphere and the right hemisphere in Table 7 [p < 0.05, according to the sign test]. Right hemisphere functioning did not differ between PNFA and controls.

Table 7 provides direct comparisons of regional cerebral activity in PNFA and pAD. As can be seen, there were several cortical regions where asymmetries were significantly greater in PNFA than pAD. Reductions in left hemisphere activity were most evident in PNFA, when contrasted with pAD, in left inferior frontal and left superior and middle temporal gyri. Differences were also evident in medial frontal and primary occipital regions, cerebral areas that are relatively preserved in PET studies of pAD patients.

DISCUSSION

We sought to learn more about the cerebral basis for language functioning in this study by contrasting the cognitive, language, and cerebral function profiles of two patient groups with distinct neurodegenerative conditions. In the first part of the discussion below, we evaluate evidence suggesting that PNFA is distinct from pAD on the basis of nonlanguage measures of neuropsychological functioning. We conclude that PNFA patients have some specific impairments that may contribute to their cognitive difficulties, but differ from pAD patients since they are not demented. In the second part of the discussion, we review the particular pattern of cognitive impairment associated with the distinct nonfluent language profile seen in PNFA. We hypothesize that deficits in several specific aspects of language processing con-
Figure 5. Spontaneous writing samples describing the weather in progressive nonfluent aphasia: Case 2 (A) and Case 4 (B).

A

The summer hot and humid, I
have relief and rest,
you well, and thanks everyone.
December, 1989

The weather cold
November, 1990

The weather warm, anyone know;

The weather to pleasant
January, 1991

the temperature 91°
April, 1991

Cold & Wind
December, 1991

B

The day is sun day,
July, 1990

The weather in sunshine & bright.
November, 1990

weather are cold
September, 1991

The weather Cold.
January, 1992
Table 6. Proportion of Correct Grammatical and Semantic Responses on Written Sentence Completion and Proportions of Specific Expression Errors in Progressive Nonfluent Aphasia

<table>
<thead>
<tr>
<th></th>
<th>Error type&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Grammatical</th>
<th>Semantic</th>
<th>Omissions</th>
<th>Additions</th>
<th>Substitutions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Phrase</td>
<td>Open</td>
<td>Close</td>
<td>Morph</td>
<td>Phrase</td>
</tr>
<tr>
<td>PNFA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td></td>
<td>0</td>
<td>92</td>
<td>19</td>
<td>33</td>
<td>15</td>
</tr>
<tr>
<td>Case 2</td>
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<td>19</td>
<td>85</td>
<td>15</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Case 3</td>
<td></td>
<td>92</td>
<td>96</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Case 4</td>
<td></td>
<td>4</td>
<td>59</td>
<td>8</td>
<td>11</td>
<td>15</td>
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<td>Controls</td>
<td></td>
<td>96</td>
<td>98</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup>In oral sentence completion, Case 3 was grammatically correct on 92% of her responses and semantically correct on 92% of her responses; Case 4 was grammatically correct on 44% of her responses and semantically correct on 70% of her responses.

<sup>b</sup>The proportions of errors do not add up to 100% because of miscellaneous errors that involved multiple violations and could not be incorporated into the scoring schema.

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Figure 6. PET images of patients with progressive nonfluent aphasia. All images were obtained at rest with eyes open and ears unplugged. The images are oriented so that the left hemisphere is on the right of each image. (A) Case 1 is illustrated with a transverse image of a [18F]fluorodeoxyglucose (FDG) scan at the middle temporal lobe level and a coronal image at the level of the anterior temporal lobe. There is relative left hemisphere glucose hypometabolism that is most prominent anteriorly in the left temporal lobe (arrow). (B) Case 2 is illustrated with a transverse image of a FDG scan at the middle temporal lobe level and a coronal image at the level of the anterior temporal lobe. There is relative left hemisphere glucose hypometabolism that is most prominent in the left temporal lobe (arrow). (C) Case 3 is illustrated with a transverse image of a [15O]H2O cerebral blood flow (CBF) scan at the middle temporal lobe level and a coronal image at the level of the anterior temporal lobe. There is relative left hemisphere hypoperfusion that is most prominent in the left temporal lobe (arrow). (D) Case 4 is illustrated with transverse images of a FDG scan at the superior and the middle temporal lobe levels. There is relative left hemisphere glucose hypometabolism that is most prominent in left temporal cortex (arrow).
Table 7. Normalized Ratios of Left:Right Regional Cortical Functioning in Progressive Nonfluent Aphasics, Control Subjects, and Probable Alzheimer's Disease Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>ID</th>
<th>Medial Superior</th>
<th>Middle</th>
<th>Inferior</th>
<th>Superior</th>
<th>Middle</th>
<th>Inferior</th>
<th>Supramarginal</th>
<th>Angular</th>
<th>Cuneus</th>
<th>Lingual</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNFA</td>
<td>Case 1</td>
<td>0.95</td>
<td>0.97</td>
<td>0.97</td>
<td>0.98</td>
<td>0.88</td>
<td>0.78</td>
<td>0.70</td>
<td>0.89</td>
<td>0.85</td>
<td>0.91</td>
</tr>
<tr>
<td></td>
<td>Case 2</td>
<td>0.97</td>
<td>0.94</td>
<td>0.91</td>
<td>1.00</td>
<td>0.91</td>
<td>0.85</td>
<td>0.88</td>
<td>0.91</td>
<td>0.89</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td>Case 3</td>
<td>1.01</td>
<td>1.01</td>
<td>1.00</td>
<td>1.00</td>
<td>0.88</td>
<td>0.75</td>
<td>0.74</td>
<td>0.96</td>
<td>1.00</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td>Case 4</td>
<td>0.92</td>
<td>0.89</td>
<td>0.88</td>
<td>0.85</td>
<td>0.83</td>
<td>0.88</td>
<td>0.89</td>
<td>0.90</td>
<td>0.87</td>
<td>1.05</td>
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<tr>
<td>PNFA</td>
<td>Mean</td>
<td>0.96</td>
<td>0.96</td>
<td>0.94</td>
<td>0.95</td>
<td>0.87</td>
<td>0.81</td>
<td>0.81</td>
<td>0.92</td>
<td>0.96</td>
<td>0.94</td>
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<tr>
<td></td>
<td>SD</td>
<td>0.04</td>
<td>0.05</td>
<td>0.06</td>
<td>0.09</td>
<td>0.03</td>
<td>0.06</td>
<td>0.10</td>
<td>0.03</td>
<td>0.02</td>
<td>0.09</td>
</tr>
<tr>
<td>pAD</td>
<td>Mean</td>
<td>1.10</td>
<td>1.03</td>
<td>1.06</td>
<td>1.12</td>
<td>0.99</td>
<td>0.93</td>
<td>0.93</td>
<td>0.98</td>
<td>0.98</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.12</td>
<td>0.13</td>
<td>0.14</td>
<td>0.15</td>
<td>0.15</td>
<td>0.15</td>
<td>0.17</td>
<td>0.15</td>
<td>0.12</td>
<td>0.11</td>
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<tr>
<td>PNFA ×</td>
<td>t test</td>
<td>2.23</td>
<td>1.10</td>
<td>1.62</td>
<td>2.72</td>
<td>2.85</td>
<td>2.01</td>
<td>1.54</td>
<td>0.82</td>
<td>0.18</td>
<td>2.41</td>
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<tr>
<td>pAD</td>
<td>level</td>
<td>&lt;0.05</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
<td>&lt;0.05</td>
<td>&lt;0.02</td>
<td>&lt;0.06</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
<td>&gt;0.10</td>
<td>&lt;0.04</td>
</tr>
<tr>
<td>Control</td>
<td>Mean</td>
<td>1.11</td>
<td>1.06</td>
<td>1.10</td>
<td>1.11</td>
<td>0.99</td>
<td>0.96</td>
<td>1.02</td>
<td>0.94</td>
<td>0.99</td>
<td>1.09</td>
</tr>
<tr>
<td></td>
<td>SD</td>
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<td>0.05</td>
<td>0.07</td>
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<td>0.06</td>
<td>0.09</td>
<td>0.08</td>
<td>0.06</td>
<td>0.06</td>
</tr>
</tbody>
</table>

These data were normalized by forming ratios of regional CMRgl or regional CBF to whole brain CMRgl or whole brain CBF, respectively. Whole brain CMRgl in Case 1 was 3.0 mg/100 g/min, in Case 2 was 2.8 mg/100 g/min, and in Case 4 was 5.4 mg/100 g/min. Whole brain CBF in Case 3 was 28.44 ml/100 g/min, in pAD patients was 21.10 ml/100 g/min, and in control subjects was 37.72 ml/100 g/min.

tribute to their difficulties. In the third section of the discussion, we review the distinct pattern of cortical dysfunction evident in PNFA. We hypothesize that their profile of cognitive impairment is related to cerebral defects in inferior frontal and superior and middle temporal portions of the left hemisphere.

Progressive Nonfluent Aphasia Is Distinct from Probable Alzheimer's Disease

Verbal and nonverbal neuropsychological evaluations indicated that PNFA patients are not completely free of intellectual impairment, but that their pattern of difficulty is distinct from that seen in pAD. PNFA patients are superior to pAD patients with respect to verbal episodic memory. The clinical hallmark of pAD is a memory disorder (Cummings & Benson, 1992; Sjogren, Sjogren, & Lindgren, 1952), so we would expect this difference if the progressive aphasics are not demented. By comparison, we found that PNFA patients are more impaired than pAD patients in their digit span performance. This double dissociation emphasizes that PNFA patients are not simply more or less impaired than pAD patients in some nonspecific fashion, but that PNFA is distinct clinically from pAD.

Previous reports directly comparing progressive aphasics and pAD patients have not found distinct neuropsychological differences between these groups. Green et al. (1990) found that memory and other neuropsychological measures were equally compromised in the progressive aphasics and pAD patients that they described. The discrepancy between Green's observations and ours may be due in part to differences in the patients that were examined. The pAD patients in the present report exhibited a wider range of dementia, including both mild and moderate degrees of overall impairment, while Green et al. (1990) assessed only mildly demented patients. It is difficult to attribute all discrepancies to the more severe dementia in some of the pAD patients in this study, however, since the pAD patients were more impaired on some tasks (e.g., episodic memory) but less impaired on other tasks (e.g., digit span) compared to the progressive aphasics. Green et al. (1990) also indicated that the presenting complaint in many of their progressive aphasics was "dysnomia," differing from the PNFA patients in the present study whose initial complaints often referred to their halting speech.

Krarbe and co-workers (1993) also directly compared a series of 10 patients exhibiting apparently progressive language difficulty with 10 pAD patients. Karbe et al. found that their progressive aphasics had memory difficulties and scored well within the "demented" range on the Dementia Rating Scale. This was attributed to the patients' language deficits on the verbal portions of the Dementia Rating Scale, although direct comparisons with pAD patients were not provided. Only three of Karbe's patients appeared to have met the criterion of
persistent difficulty restricted to language on follow-up. Without additional characterizations of their patients, it is difficult to determine whether some of their progressive aphasics were in fact Alzheimer’s disease patients who happened to present with predominantly left hemisphere involvement (Kirshner, Webb, Kelly, & Wells, 1984; Martin, 1990; Pogacar & Williams, 1984; Wechsler, 1977).

PNFA patients in the present study were also significantly less impaired than pAD patients on most nonverbal measures, emphasizing the material-dependent nature of the impairment in PNFA. Visual memory, perceptual, and construction difficulties might be expected in pAD but not progressive aphasia because of the symmetric distribution of histopathologic and neurochemical abnormalities involving left and right hemispheres that typically occurs in AD (Moossy, Zubenko, Martinez, & Rao, 1988; Zubenko, Martinez, Zhao, Kopp, & Hanin, 1989; Zubenko, Moossy, Martinez, Zhao, Kopp, & Hanin, 1989). Similar deficits would not be expected in PNFA since progressive aphasia preferentially compromises left hemisphere functioning (Chawluk et al., 1986; Kempler et al., 1990; Tyrrell et al., 1990). Our findings of relatively preserved visual functioning differ from the results of Karbe et al. (1993). On the drawing and block design subtests of the Western Aphasia Battery, Karbe et al. apparently found that their progressive aphasics were as impaired as pAD patients. These discrepancies with the present study again raise the possibility that a heterogeneous group of progressive aphasics may account in part for some of the nonverbal neuropsychological deficits seen in Karbe’s patients.

The PNFA patients assessed in the present study exhibited several subtle neuropsychological impairments only when compared to controls but not to pAD patients. In particular, they differed from control subjects on category fluency naming and drawing tasks. A similar deficit has been described in other progressive aphasics (Snowden et al., 1992). It is less likely that they encountered difficulty appreciating the mental representation of the target material in semantic memory since their category membership judgments of words and pictures were accurate and they did not produce category violations on semantically guided fluency tasks. The relatively accurate performance of PNFA patients on visual perceptual and constructional tasks suggests that their category drawing deficit may have been due to difficulty with an aspect of the task that was not particularly visual. Verbal and visual fluency deficits such as these may be seen following left or right hemisphere insult (De Renzi, Scotti, & Spinnler, 1969; Grossman, 1993; McCarthy & Warrington, 1990), and have been associated with frontal and anterior temporal disease (Grossman, 1981, 1988; Jones-Gotman & Milner, 1977). A more parsimonious explanation may be that they experienced difficulty organizing and planning their category-based production.

The PNFA patients also differed from control subjects on an assessment of praxis. Buccofacial apraxia has been reported previously in progressive aphasia (Caselli et al., 1992; Green et al., 1990; Mesulam, 1982; Tyrrell et al., 1990, 1991). Kartsounis et al. (1991) argued that the buccofacial apraxia accounted for the verbal planning difficulties in PNFA. However, pAD patients with quite different language patterns were also apractic in the present study. Moreover, such a motor planning deficit
could not account for the particular sentence comprehension and expression profiles that we observed in PNFA.

Several investigators have called for the existence of progressive aphasia on the basis of the presence of visual neuropsychological impairments, suggesting that these deficits indicate an unusual presentation of a common entity such as pAD (Cole, Wright, & Banker, 1979; Graff-Radford et al., 1990; Green et al., 1990; Gordon & Selnes, 1984; Holland, McBurney, Moosy, & Reimuth, 1985; Kempler et al., 1990; Mandell, Alexander, & Carpenter, 1989; Morris, Cole, Banker, & Wright, 1984; Neary et al., 1988; Pocek & Luzzatti, 1988; Scheltens, Hazenberg, Lindeboom, & Wolters, 1990; Wechsler, Verity, Rosenschein, Fried, & Scheibel, 1982). Indeed, a subgroup of patients with pAD may present with an aphasia (Kirshner et al., 1984; Martin, 1990; Pogacar & Williams, 1984; Wechsler, 1977). Direct comparisons of PNFA and pAD patients, however, appear to support the claim that PNFA is a distinct clinical entity that can be differentiated from other progressive neurodegenerative conditions such as pAD. It must be emphasized that the patients described in the present report are representative of a distinct subgroup of progressive aphasics, so our findings cannot be generalized to all patients with progressive language disturbances. Moreover, we emphasize that the distinction between PNFA and pAD may be ascertained only relatively in the natural history of these disease processes, and that PNFA patients may be difficult to distinguish from demented patients during late stages of the disease. Against this background, we discuss below the distinct patterns of language deficit and regional cerebral dysfunction in PNFA.

Patterns of Language Dysfunction in Progressive Nonfluent Aphasia

The PNFA patients studied in the present report frequently exhibited nonfluent, telegraphic, oral and written language expression that was often characterized by the omission of grammatical morphemes or by grammatical agreement violations. Significant difficulty with repetition was seen as well. Single word comprehension was relatively preserved in PNFA. In addition, PNFA patients were able to point to pictures and answer questions about grammatically simple oral and written sentences. However, they were compromised in their comprehension of sentences that required the interpretation of more demanding grammatical structures such as subordinate phrases. The observations of agrammatic speech and poor repetition with relatively preserved single word comprehension replicate the findings of Kartsounis et al. (1991). These data emphasize that the language characteristics of PNFA differ in important ways from the typical language features of pAD. Language expression in pAD has been notable for its fluent and empty characteristics; repetition and sentence comprehension are said to be relatively preserved, and impairments in confrontation naming and single word comprehension are frequent (Appel, Kertesz, & Fisman, 1982; Cummings, Benson, Hil, & Read, 1985; Huff, 1991; Kertesz, Appel, & Fisman, 1986; Nebes, Brady, & Jackson, 1989).

A small number of studies has directly compared progressive aphasics with pAD patients on some language measures (Karbe et al., 1993; Weintraub et al., 1990). Both Karbe et al. and Weintraub et al. observed naming difficulty in progressive aphasia and pAD, as we did, although confrontation naming may not be as compromised in the subgroup of PNFA patients. Karbe and co-workers observed differences between progressive aphasics and pAD patients on the spontaneous speech subtest of the Western Aphasia Battery. Qualitative characteristics of the speech of progressive aphasics were not described, but it was asserted that progressive aphasics were nonfluent on the basis of their reduced output on a category naming test. Karbe et al. did not find differences between progressive aphasia and pAD on the comprehension subtests that were administered, although they did not specifically assess the ability to appreciate grammatical aspects of sentences.

It is important to emphasize the nature of the sentence comprehension impairments in PNFA. In particular, sentences with subordinate phrases were generally difficult for PNFA patients to understand in both sentence-picture matching and sentence probe paradigms when compared with grammatically simpler, SVO sentences. A similar pattern was observed in sentence completion. Given the increased length of subordinate-phrase sentences compared to the better understood SVO sentences, one possible interpretation is that PNFA patients have a deficit in the ability to use auditory-verbal short-term memory on sentence comprehension tasks such as these (Caramazza et al., 1981; McCarthy & Warrington, 1987; Saffran & Martin, 1990; Schwartz, Liebarger, Saffran, & Pate, 1987). Additional support for this view may be derived from their repetition difficulty as well as their limited digit span. Moreover, comprehension improved somewhat under conditions where the retention of auditory-verbal material was less critical. Their understanding of a written paragraph and written sentences thus was relatively spared. However, there are several reasons for believing that difficulty at the level of auditory-verbal short-term memory is not the complete explanation for the language deficit in PNFA. For example, written expression, oral reading, and spontaneous speech were all telegraphic in nature, performance patterns that are difficult to attribute to a short-term memory deficit. Phonemic judgment difficulties also cannot be explained easily by a short-term memory deficit. Our observations thus are consistent with the hypothesis that sentence processing deficits in PNFA are multifactorial and are also due in part to difficulty appreciating certain grammatical attributes of sentences. An excer-
bating factor for oral speech comprehension may be their phonemic discrimination difficulty. Clearly additional work is needed to help specify the cognitive and language processing limitations of narrowly defined subgroups of patients with progressive aphasia.

Caution must be urged in generalizing the patterns of language difficulty that we observed to all progressive aphasias. For example, the language characteristics of PNFA patients appear to differ from those of progressive fluent aphasias. Basso, Capitani, and Laiaccona (1988) reported a progressive aphasic with a category-specific semantic memory impairment. Hodges, Patterson, Oxbury, and Funnell (1992) described a semantic memory impairment in several patients with apparent progressive fluent aphasia. Parkin (1993) reported a progressive fluent aphasic with an amnesia for living items more than nonliving items, a surface dyslexia, and a surface dysgraphia. Indeed, the PNFA patients we studied were not necessarily homogeneous in their performance patterns. Case 3 reported above exhibited a performance profile that differed at times from the remaining three patients but resembled more closely the patients described by Kartsounis et al. (1991) and Tyrrell et al. (1991). For example, her oral expression was more compromised than her written expression, and her phonemic discrimination judgments were performed reasonably well. It is difficult to determine on the basis of such a small sampling of PNFA whether Case 3 and the Kartsounis and Tyrrell patients with deficits predominantly involving nonfluent oral expression represent a systematic distinction from the three PNFA patients reported above with oral and written comprehension and expression difficulty. Regardless of the validity of these distinctions within the population of progressive nonfluent aphasics, our findings support the hypothesis that the language profile of PNFA systematically differs from that of pAD. PNFA patients are specifically compromised in the appreciation of certain grammatical features of sentences such as phrase structure, and their sentence processing may be further hampered by their short-term memory and phonemic perception difficulties.

Regional Cerebral Dysfunction in Progressive Nonfluent Aphasia

Observations of regional brain functioning suggest that the nonfluent sentence comprehension and expression difficulties of PNFA patients are associated with a distinct pattern of cerebral dysfunction. All four PNFA patients exhibited reduced cortical activity throughout the left hemisphere, and the most prominent functional defect in each PNFA patient was in left superior and middle temporal and left inferior frontal regions. Other PET scan studies of progressive aphasics (Chawhuk et al., 1986; Kempler et al., 1990; Tyrrell et al., 1990) often have revealed predominantly left hemisphere dysfunction. Parkin (1993) described a progressive fluent aphasic reported by Tyrrell et al. (1990) who had left peri-Sylvian hypometabolism. Kartsounis et al. (1991) observed a left frontal cortical defect on the SPECT scan of the PNFA patient he studied, and Caselli et al. (1992) found left anterior defects on SPECT in some PNFA patients. However, Tyrrell et al (1991) reported progressive mutism in association with bilateral frontal hypometabolism on PET, and lateralized defects were not necessarily seen in the PNFA patients described by Snowden et al. (1992) and Tyrrell et al. (1990). These inconsistent findings are difficult to interpret given the limited clinical descriptions and the nonquantitative nature of SPECT in many of these patients. We compared regional cerebral functioning in PNFA and pAD directly, and confirmed reduced left hemisphere activity in several brain regions of PNFA patients that was not evident in pAD. Left hemisphere defects were most notable in superior and middle temporal and inferior frontal regions. We also observed medial frontal and primary occipital asymmetries in PNFA when compared to pAD. Activity in these latter brain areas is invariably preserved and symmetric in pAD, and the relative asymmetries in these areas in PNFA probably reflect the general reduction of cortical activity throughout the left hemisphere rather than a particular focus of cortical dysfunction.

It should be emphasized that we do not aim to refute the finding that PET studies of some pAD patients reveal an asymmetric pattern of regional cerebral dysfunction, and that these patients have associated language deficits. Predominant left hemisphere hypometabolism has been noted in one study of pAD (Lowenstein et al., 1989), and other investigators have observed relatively reduced left hemisphere activity in some pAD patients (Foster et al., 1984; Friedland et al., 1985; Haxby et al., 1985). It is important to note, however, that this regional cerebral dysfunction in pAD, even when involving predominantly the left hemisphere, is in a different anatomic distribution from that seen in PNFA. Thus, compromised unilaterial cerebral activity is typically seen in parietal rather than in the inferior frontal and superior and middle temporal distribution seen in the PNFA patients.

Several cases of progressive language deterioration have been shown to have Pick's disease (Cole et al., 1979; Holland et al., 1985; Pick, 1892; Scheltens et al., 1990; Wechsler et al., 1982). PET scanning in a case of Pick's disease (Kamo et al., 1987) demonstrated a pattern of cerebral dysfunction that resembles PNFA, although variability in the topographic distribution of the histopathologic abnormality in Pick's disease must be kept in mind (Corsellis, 1976; Jervis, 1971). It is important to emphasize in this context that PNFA is a clinical syndrome associated with several pathological diagnoses, including nonspecific spongiform degeneration (Kirshner et al., 1987), focal Alzheimer's disease (Jagust et al., 1990; Pogacar & Williams, 1984), focal neuronal achromasia (Lippa, Cohen, Smith, & Drachman, 1991), and combinations of these disorders (Morris et al., 1984).
We cannot establish the basis for PNFA in the patients described in the present report without histopathological analysis.

Regardless of the specific etiology underlying PNFA, it is interesting to speculate on the reason why such a prominent language impairment is seen in this disorder. One possible explanation may be the functional defect that is apparent throughout the left hemisphere. This would not account for the islands of relatively preserved language and verbal functioning in PNFA. Another hypothesis is related to the focus of the cerebral defect seen in PNFA. One area of dysfunction common to PNFA patients is the multimodal association region in the superior temporal sulcus that has reciprocal projections with auditory association cortex and the inferior frontal lobe (Cavada & Goldman-Rakic, 1989; Mesulam, van Heeschen, Pandya, & Geschwind, 1977). Additional work is needed to determine whether the defect in this region or some other peri-Sylvian locus is critical to the pattern of language and cognitive deficits seen in PNFA.

METHODS

Clinical and Cognitive Evaluation

Clinical Mental Status for Longitudinal Assessment of PNFA

The clinical assessment of the PNFA patients' mental status was documented with a standard clinical protocol administered during each office visit. This evaluation sampled comprehension and expression aspects of language, assessed memory and attention in verbal and visual modalities, and evaluated visuoconstructional performance. This assessment was quantified whenever possible. The evaluation is described in Table 1.

Verbal Neuropsychological Evaluation

Nonlinguistic neuropsychological measures were administered in the verbal modality to assess memory, attention, and executive functioning in more detail. These tasks are described briefly in Table 2.

Nonverbal Neuropsychological Evaluation

Nonverbal neuropsychological measures were also administered, usually in the visual modality, to assess attention, memory, visuo-perceptual functioning, and other aspects of cognition in more detail. The tasks are described briefly in Table 3.

Performance measures from these clinical and cognitive evaluations are presented as z-scores in relation to the performance of 25 age-matched (mean = 68.00 years; SD = 7.61; t(27) = 0.58, ns) and education-matched (mean = 14.44 years; SD = 2.10; t(27) = 0.42, ns) control subjects. Thus, a z-score of ~1.65 differs from the mean performance of control subjects at the p < 0.05 level, a z-score of ~1.96 differs from control subjects at the p < 0.025 level, and a z-score of ~2.32 differs from control subjects at the p < 0.01 level. The performance of 25 mildly and moderately impaired patients with pAD, diagnosed according to NINCDS-ADRDA criteria (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984), are provided as a contrast to the performance of the PNFA patients. These patients were age-matched (mean age = 70.56, SD = 8.41) to control subjects (t(48) = 0.98, ns) and PNFA patients (t(48) = 0.97, ns) and education-matched (mean education = 13.76, SD = 2.27) to control subjects (t(27) = 1.26, ns) and PNFA patients (t(27) = 0.17, ns). Mean disease duration did not differ in PNFA and pAD. The pAD patients were seen in the Cognitive Neurology Clinic at the Hospital of the University of Pennsylvania. The mean MMSE (Folstein, Folstein, & McHugh, 1975) score of the pAD patients was 18.85 (SD = 4.96). Although somewhat less than the MMSE score of PNFA patients (mean = 23.00; SD = 2.58), these did not differ statistically (t(27) = 1.62, ns).

Language Evaluation

Standard Language Assessment

This consisted of a standard evaluation involving measures of oral and written language expression, repetition, and comprehension. An a priori scoring procedure was developed to quantify performance on these measures. The tasks are described in Table 4.

Supplementary language tests to define sentence comprehension and sentence expression in greater detail in PNFA included the following:

An abbreviated, 48-item version of the sentence probe technique described in greater detail elsewhere (Grossman, Carvell, Stern, Gollomp, & Hurtig, 1991) was used to assess oral sentence comprehension. Briefly, equal numbers of sentences that were simple (e.g., "The eagle chased the hawk"), contained a terminal subordinate phrase (e.g., "The eagle chased the hawk that was fast"), or contained a center-embedded subordinate phrase (e.g., "The eagle that chased the hawk was fast") were administered to patients. Comprehension was assessed by asking patients to respond to a simple oral probe of the target sentence. Written sentence comprehension was assessed by administering a test in writing that contained identically structured sentences. Sentence-picture matching was assessed by asking patients to match 40 sentences such as these with one of four pictures. The pictured foils illustrated a reversed agent-theme relationship compared to the target sentence, the appropriate agent and theme participating in an activity different from the picture, and a different agent or theme compared to the target sentence.

Lexical semantic comprehension was assessed by asking patients to judge the category membership judgment of 76 colored pictures (Grossman & Mickanin, 1994).
About 40% of these depicted an instance of the target category "vegetable," and 60% depicted an item that could not properly be called a vegetable. A similarly structured set of single words was also presented for category membership judgments.

Sentence expression was assessed in a sentence-completion fashion described in greater detail elsewhere (Grossman et al., 1996). Briefly, the patients were presented with two pictures and told a two-sentence story about each set of pictures. The end of the second sentence was omitted, and the patients were required to complete each item. For example, to elicit the passive voice, the patients viewed pictures of children camping and a bear chasing the children. They heard: "The children were scared when they went camping. The children..." There were 27 items.

PET Scanning

In three of the four PNFA patients, [18F]fluoro-2-deoxy-o-glucose (FDG) was used to study regional cerebral glucose metabolism (rCMRgl). We used a standard technique that has been described in detail elsewhere (Reivich et al., 1979). Briefly, after catheterization of the radial artery at the right wrist and the left antecubital vein, 5 to 10 mCi of FDG was administered in bolus fashion. The patient rested with eyes open and ears unplugged in a quiet but darkened area while hearing white noise for 30 min prior to the commencement of scanning. A foam head restraint was used to position the patient's head during the scan, and head position was continuously monitored with a laser alignment system. The PET images were obtained by a scanner (UGM, Philadelphia, PA) that acquires 64 transverse slices simultaneously as a volume with a voxel size of 2 mm³. The spatial resolution of the device is 5.5 mm in X, Y, and Z axes (Karp et al., 1990). The attenuation correction method assumed an average attenuation coefficient for each image (Bergstrom, Litton, & Eriksson, 1982). Glucose metabolism was quantified on the basis of a three compartment model using arterial samples obtained every 15 sec for the first minute and then at progressively longer intervals, using a lumped constant and rate constants measured in our laboratory (Reivich et al., 1985). The images were analyzed using a region of interest (ROI) template system based on Talairach and Tournois (1988). The PET images, resliced in the anterior commissure-posterior commissure plane according to a standardized procedure, were 6 mm thick. The template was applied to each PET image in a user-independent fashion after a single global adjustment to the brain perimeter.

The fourth PNFA patient and representative subsets of 11 pAD patients and 7 control subjects were studied with an equilibrium cerebral blood flow (CBF) technique (Jones et al., 1985). Under the "resting baseline" condition of a multiscan activation procedure described in greater detail elsewhere (Grossman, Crino, Stern, Reivich, & Hurtig, 1992), CBF was assessed while the patient was resting quietly with eyes open and ears unplugged in the PET scanner. The room had subdued lighting and a white noise background was heard. CBF was thus measured under behavioral conditions that were identical to those used in the FDG-PET studies described above. Briefly, the equilibrium CBF technique involves the infusion of [15O]H₂O. This was administered to the antecubital vein while arterial samples were obtained every 3 min from the opposite radial artery at the wrist. [15O]H₂O was administered for 8 min to attain a steady state. PET data were then collected for 10 min while the [15O]H₂O administration was continued. rCBF was calculated from the equation (Subramanyan, Alpert, & Hoop, 1978)

\[ r\text{CBF} = \frac{\lambda}{C_a/C_T - 1/p} \]

where \( \lambda \) is the decay constant of [15O] (0.335/min), \( C_a \) is the arterial concentration of [15O]H₂O obtained from arterial blood samples drawn during the equilibrium phase, \( C_T \) is the tissue concentration of [15O] obtained from the PET scan, and \( p \) is the brain-blood partition coefficient for water (0.98 ml/g in gray matter). Image analysis was otherwise identical to the method described above. To relate CBF data to the results obtained using FDG, we report region-to-whole brain ratios for both data sets.

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