

Primary Progressive Aphasia: A Review of 112 Cases

Chris Westbury

*Department of Neuropsychology, Montreal Neurological Institute, 3801 University Street,
Montreal, Quebec H3A 2B4, Canada*

and

Dan Bub

*Department of Psychology, University of Victoria, P.O. Box 3050, Victoria,
British Columbia V8W 3P5, Canada*

Primary progressive aphasia (PPA) was first recognized by Mesulam in 1982. Although dozens of cases have since been described, it has been difficult to place these cases into a coherent framework due to the wide variation in measures which have been reported. We review 170 contacts with 112 patients to provide a clinical, neuroanatomical, and neuropsychological profile of patients with the disorder. The progression of the disease is analyzed over a 10-year reporting period starting from symptom onset to show how progression affects five general linguistic skills: oral and written naming, reading, repetition, and general comprehension. The pattern of functional and neurological deficits in PPA is heterogeneous. Differences in the distribution of neurological anomalies between patients with bilateral and unilateral changes suggest that there may be two separate disease processes involved. © 1997

Academic Press

In 1982, Mesulam published a report describing six patients having as a symptom a slowly progressive aphasia without any accompanying signs of dementia. Although such cases had been previously reported in the literature (Poeck & Luzzatti, 1988), it was the publication of Mesulam's case which led to the recognition of the syndrome characterized in its early stages by pure aphasia without dementia, now known as either Mesulam's syndrome or (more commonly) primary progressive aphasia (PPA). The existence of PPA has been widely documented in the years since Mesulam's initial publication. Unfortunately, the published literature is unsystematic, consisting largely of single case reports which have relied upon a wide variety of different neuropsychological instruments, many of which were developed for other purposes (Caplan, 1992). These limitations have made it difficult to place the published results into a coherent theoretical structure. This paper is an attempt to remedy this deficit by documenting the general clinical, biographi-

cal, neuroanatomical, and neuropsychological profiles of patients with the disorder and by making a rough attempt to chart its progression as it affects the five most frequently examined general linguistic skills: oral and written naming, reading, repetition, and general comprehension. The review suggests that these five skills are differentially affected by the progression of the disorder.

METHOD

We reviewed French and English papers which were specifically concerned with describing subjects who had been diagnosed with primary progressive aphasia. We excluded papers which referred to patients who were seen before Mesulam defined the syndrome. We included papers on semantic dementia, a subtype of progressive aphasia which spares syntactic abilities while affecting naming, word comprehension, and reading (see Hodges, Patterson, Oxbury, & Funnell, 1992), because very few progressive aphasics have had the semantic testing necessary to differentiate them from patients with semantic dementia. Papers describing patients who were later shown to have a known progressive disorder other than PPA were not excluded, since we are interested in progressive aphasia as a syndrome and since the known rate of misdiagnosis (as documented below) suggests that many PPA patients who have not yet been shown to have a known progressive disorder do in fact have one.

In order to allow for the progressive nature of the disorder to be examined, the neuropsychological data were encoded in the following way. First, each test result reported was mapped to a single-digit code ranging from 0 to -3. A code of 0 was given if the test result was reported to be within the normal range or if the test result was not more than one standard deviation below the average when standard deviations were reported. A code of -1 was given if the patient was described as "mildly impaired," or if the reported test scores fell below one but above two standard deviations below normal scores. A code of -2 was assigned if the patient attained a score described as "moderately impaired," or if his score fell below two but above three standard deviations from the norm. A code of -3 was assigned if the patient's performance on a test was described as "severely impaired," or if his scores were more than three standard deviations below normal scores.

In cases in which the patient's performance was reported to be impaired but no scores were provided, a code of -1 was conservatively assigned. Codes drawn from numerical data took precedence over codes assigned from textual descriptions: that is, if numerical data were available for coding a result, then any textual descriptions of that same result were ignored. Data were coded by patient, since there are several patients who have been reported in the literature more than once.

It proved impossible to code data from many papers using the above criteria, since papers have occasionally been published by authors who neglected to report standard scores or even assign textual severity labels to patient performance. In cases where no code could be assigned using the above criteria, an assumption was made that the test used had a normal mean of 90% and a standard deviation of 10%. The results were then coded accordingly, as described above. Although this assumption about normal performance is clearly ad hoc, it has some heuristic value. The assumed mean and standard deviation are extremely conservative for the kinds of tests reported, since normal performance on these tests is usually near ceiling. Any error introduced by the assumption can thus be reasonably supposed to fall on the side of underestimating symptom severity.

Although the raw encoded data and the raw average coded scores are reported in this paper, a second set of results for each test is also reported, in which a rule of "retroactive normality" was applied. This rule had the assumption that if a patient scored in the normal range on a test during a given reporting period, then that same patient would also have scored in the

normal range if he or she had been given the same test at an earlier period. In applying this rule, every coded score of zero which was found 1 or more years after symptom onset was "carried back" to every previous year since that patient's symptom onset. The application of the rule simply helps to clarify the real pattern of degeneration within the entire population, compensating somewhat for the skew toward pathology which is due to the fact that only results documenting deficits are publishable.

The data were encoded into 11 reporting periods, 1 for each year since symptom onset from 0 to 9, and 1 for all test results obtained more than 10 years after onset. When more than 1 result was reported within a single test period, the most severe result was used. A 12th category was used to code all results which could not be related to the time since symptom onset.

Results for all reported tests were coded in five broad classes: tests of oral naming, written naming, reading, repetition, and comprehension. Results from tests of comprehension are particularly difficult to compare, as opinions about what constitutes a test of comprehension vary more widely than opinions about testing the other abilities. For the purposes of this paper, any result of a test claimed as a test of comprehension in either the written or spoken modality was encoded as a test of comprehension.

RESULTS

Demographic Data

Data were reported for 112 patients: 73 (66%) males and 39 (34%) females. Of the 70 (62%) for whom handedness was specified, 68 (97%) were right-handed and 2 (3%) were left-handed. Eighty (71%) patients had only a single contact reported, with the remainder (29%) ranging up to six contacts over an average of 3.3 years from the initial contact. The average time since symptom onset for those patients for whom only a single contact was reported was 4.3 years.

In the 1987 description of his original six patients, Mesulam wrote that in the terminal stages of PPA, cognitive impairments and other signs of dementia might be present, but "not before eight to twelve years after onset" (Mesulam, 1987, p. 553), implying that a necessary component of the syndrome is an initial period of at least 8 years during which language-related deterioration is the only cognitive deficit. Mesulam's suggestion does not appear to be widely accepted. Only 17 (15%) of the 112 patients for whom time since symptom onset is reported were ever seen 8 or more years after symptom onset. Weintraub, Rubin, and Mesulam (1990) and Kertesz (1994) have both suggested that a period of 2 years of purely language-related deterioration is sufficient for making the diagnosis. Seventy-six (68%) of the patients whose span since symptom onset is reported met this criteria.

The average age of symptom onset for all patients is 59.1 years (SD = 9.6 years). The modal value is 64 years. The average age of symptom onset did not differ significantly for males and females ($p(1, 80) = 0.884$). The great majority of the patients (98, or 87%) reported were native English speakers. The rest comprised 8 (7%) French speakers, 3 (3%) German speakers, and 1 Japanese, 1 Dutch, and 1 Italian speaker. The demographic data are presented in more detail in Table 1.

TABLE 1
Demographic Data of All Patients

	Average	SD	HI	LO	N
Male	—	—	—	—	73
Female	—	—	—	—	39
Right-handed	—	—	—	—	68
Left-handed	—	—	—	—	2
Handedness unspecified	—	—	—	—	43
Number of contacts ^a	1.5	1	6	1	170
Total symptom span ^b	5	2.9	15	1	81
Span medically followed ^c	3.3	2.6	11	1	33
Single-contact span ^d	4.3	2.8	14	1	80
Age when seen	63.4	9.4	80	17	97
Time since onset when seen	3.3	2.8	14	0	112
Age at onset	59.1	9.6	80	17	82
Male	59.3	7.7	77	40	50
Female	58.9	12	78	17	32

^a Number of data collection contacts reported.

^b Years from symptom onset to last reported contact.

^c Years from first contact to last contact (if seen more than once).

^d Years since onset for patients with only one contact reported.

Presenting Problem

The most commonly reported presenting problem was word-finding difficulty, which was reported by 42 patients (59% of the patients for whom the presenting problem was mentioned and 37% of the total population). The next most common problem was a comprehension deficit, which was mentioned 22 times, accounting for 32% of the patients for whom the presenting problem is known and 20% of the total population. Naming deficits, mentioned 16 times, were a problem at presentation for 14% of the total population and thus for 23% of the reporting population. Other problems mentioned at presentation included speech hesitancy, phonemic paraphasias, dysarthria, slowed speech, and stuttering. These presenting problem data are summarized in Table 2.

Neuroanatomical Data

Data related to the site and nature of the brain degeneration were compiled from three sources: reports of MRI scans, reports of PET and SPECT scans, and reports from autopsy studies.

MRI. Of the total 104 MRI scans reported, 87 (84%) revealed a structural anomaly. These anomalies were classified by site for each of the 12 time measurement periods. The scans are summarized by hemisphere and time period in Table 3. Forty-nine (56%) of the 87 positive studies reported anom-

TABLE 2
Presenting Problems

Presenting problem	<i>N</i>	% ^a	R% ^b
Unspecified	42	37	0
Word-finding	31	27	44
Comprehension	22	20	32
Naming	16	14	23
People	6	5.3	8.5
Objects	4	3.5	5.6
Places	2	1.8	2.8
Unspecified speech	12	12	18
Writing	6	5.3	8.5
Hesitancy	4	3.5	5.6
Articulation	4	3.5	5.6
Phonemic paraphasia	3	2.7	4.2
Reading	3	2.7	4.2
Pronunciation	2	1.8	2.8
Nonfluency	2	1.8	2.8
Slow effortful speech	2	1.8	2.8
Stuttering	1	0.9	1.4
Semantic paraphasia	1	0.9	1.4

^a Percentage of total population.

^b Percentage of patients for whom the presenting problem was reported.

alies in the left hemisphere only. The remaining 38 studies (43%) reported bilateral anomalies.

Comparisons between studies are made difficult by the lack of a common vocabulary for reporting results. Thus, for example, one study might report "a widening of the Sylvian fissure" where another might have reported the identical anomaly as "a temporo-parietal anomaly" or "evidence of degeneration in the superior temporal lobe." We did not make an attempt to unify the vocabulary, and we report the results here in the terminology of the original descriptions.

The 50 scans which revealed exclusively left hemisphere anomalies are summarized in Table 4. The total number of measurements in this table does not sum to the total number of scans, since a single scan often uncovers anomalies at more than one site.

The most commonly reported sites of anomaly among the MRI scans which revealed evidence of exclusively left hemisphere degeneration were the Sylvian fissure ($N = 31$) and the temporal lobe ($N = 20$). Evidence of anomaly in the frontal lobes was reported less than half as often ($N = 9$), while evidence of a parietal lobe anomaly was mentioned only once.

Descriptions of the 38 MRI scans which revealed bilateral degeneration (Table 5) also mentioned the temporal lobe ($N = 6$) and the Sylvian fissure ($N = 4$) as the most common sites of degeneration. The frontal lobes were

TABLE 3
MRI Anomalies: Overall Summary

	Years postonset											Totals	
	0	1	2	3	4	5	6	7	8	9	9+		?
Total	4	7	15	11	18	13	5	2	4	2	4	20	105
Left Only	2	6	7	5	7	4	3	0	2	1	1	11	49
Left and Right	1	1	6	5	8	6	2	2	1	1	2	3	38
Negative	1	0	2	1	2	3	0	0	1	0	1	6	17
Positive	3	7	13	10	15	10	5	2	3	2	3	14	87

TABLE 5
MRI Anomalies: Bilateral, by Site, by Years from Symptom Onset

	Years postonset											Totals	
	0	1	2	3	4	5	6	7	8	9	9+		?
Unspecified	1	0	2	4	1	3	1	1	1	1	2	1	18
Temporal lobe	0	1	0	0	1	2	0	1	0	0	0	1	6
Pole	0	0	0	0	1	0	0	0	0	0	0	1	1
Anterior	0	1	0	0	0	1	0	0	0	0	0	0	2
Inferior	0	0	0	0	0	0	0	0	0	0	0	0	0
Sylvian fissure	0	0	0	2	2	0	0	0	0	0	0	0	4
Cerebellum	0	0	0	1	0	0	0	0	0	0	0	0	1
Ventricles	0	0	0	0	1	0	0	0	0	0	0	0	1
Subcortical	0	0	1	0	0	0	0	0	0	0	0	0	1
Frontal lobe	0	0	2	1	2	0	1	0	0	0	0	0	6

mentioned just as often ($N = 6$). However, 18 scans mentioned bilateral degeneration without specifying the location.

PET and SPECT. Data from 59 PET and SPECT scan studies of PPA patients were reported. Fifty-seven (97%) of these studies reported finding anomalies in blood flow. These anomalies were classified by site for each of the 12 time measurement periods. The 59 studies are summarized by hemisphere and time period in Table 6.

Forty (69%) of the 58 scans which revealed abnormal results showed evidence of anomalies in the left hemisphere only. The remaining 18 studies (31%) showed evidence of bilateral anomalies. Note that the total number of measurements in each of these tables does not necessarily sum to the total number of scans, since a single scan can uncover anomalous findings at more than one site.

Twenty-three (58%) of the 40 studies reporting unilaterally left results (Table 7) found anomalies in the left temporal lobe. In addition, another 12 (30%) reported anomalies in one of the fronto-temporal regions, the temporo-parietal regions, or the temporo-occipital regions, and 2 (5%) specified perisylvian region involvement. Eighteen (45%) of the studies reported frontal lobe involvement, with an additional 7 (18%) reporting either fronto-temporal involvement or fronto-parietal involvement. Only 8 (20%) of the studies reported evidence of parietal lobe anomalies, though an additional 8 (20%) reported evidence of either fronto-parietal or temporo-parietal involvement. A single study (3%) reported evidence of anomalies in the left occipital lobe.

In Table 8, the 33 scans which revealed unilaterally left-sided anomalies are presented by patient, in order to allow better understanding of the pattern of distribution of the anomalous findings.

No study reported finding exclusively parietal or occipital involvement. In every case in which involvement of either the parietal or the occipital lobe was reported, there was also temporal or frontal involvement. Two cases were reported (6%) in which both temporal and parietal lobe anomalies were found without any frontal lobe anomalies, and two cases (6%) in which both frontal and parietal involvement were found without temporal involvement. Nine studies (27%) reported frontal and temporal involvement without parietal involvement. Nine other studies (27%) uncovered evidence of involvement of the frontal, temporal, and parietal lobes.

The breakdown of information from the 18 scans with bilateral anomalies (Table 9) shows a different pattern. The most commonly reported site of bilateral anomaly was the frontal lobe, which was reported in 13 (72%) of the studies. Bilateral anomalies of the temporal lobe were reported in only 4 (22%) of the studies, and bilateral parietal lobe anomalies were reported in only 3 (17%) of the studies.

Autopsy data. Autopsy data were available for 16 patients. The average time since symptom onset at death was 5.5 years ($SD = 2.2$). Three (19%) of the patients were deemed on the basis of autopsy results to have suffered

TABLE 6
 PET- and SPECT-Verified Anomalies: Overall Summary

	Years postonset											Totals	
	0	1	2	3	4	5	6	7	8	9	9+		?
Total	1	6	6	8	12	6	3	3	1	1	2	10	59
Left Only	1	4	3	6	9	3	3	0	1	0	1	8	39
Left and Right	0	2	3	1	3	3	0	3	0	1	1	1	18
Negative	0	0	0	1	0	0	0	0	0	0	0	1	2
Positive	1	6	6	7	12	6	3	3	1	1	2	9	57

TABLE 8
 PET- and SPECT-Verified Anomalies: Left Hemisphere Only, by Scan, by Years from Symptom Onset

	Years postonset											Totals	
	0	1	2	3	4	5	6	7	8	9	9+		
Frontal and temporal	0	2	2	1	3	1	0	0	0	0	0	0	9
All three	0	1	0	3	1	1	1	0	1	0	1	1	9
Temporal only	0	1	1	1	4	0	0	0	0	0	0	0	7
Frontal only	0	0	0	1	1	1	0	1	0	0	0	0	4
Frontal and parietal	1	0	0	0	0	0	1	0	0	0	0	0	2
Temporal and parietal	0	0	0	0	1	0	1	0	0	0	0	0	2
Total	1	4	3	6	10	3	3	1	1	0	1	1	33

from dementia of Alzheimer's type; 2 (13%) patients were judged to have had Pick's disease, and 1 (6%) was diagnosed as having had Creutzfeldt–Jakob disease. Of the remaining 10 patients, 6 (38% of all autopsied patients, and 60% of all autopsied patients not given another diagnosis) showed “spongiform changes” in layers II and III. Four of these patients also had neuronal loss, limited mainly to the frontal and temporal lobes and the frontoparietal area. The remaining 4 patients (25% of all autopsied patients, and 40% of all autopsied patients not given another diagnosis) did not have spongiform changes. Relatively little information is available for these patients. The autopsy data for the 10 patients who did not receive a diagnosis other than PPA are summarized in Table 10.

Neuropsychological Testing

Encoding all neuropsychological tests results yielded a sparse matrix. Of the 6720 cells (112 patients by 12 reporting periods by 5 test categories) only 356 (5.2%) had values. The application of the “retroactive normality” heuristic added inferred zero values to a further 250 cells, leaving 7.6% filled. Because the data matrix is so sparse, it is not reproduced here. Instead, the average raw and normality-adjusted results for each of the five test categories are summarized graphically in Figs. 1 through 5. The number of observations per reporting period and in total is reported above each of the five graphs.

DISCUSSION

Demographic Data

The reported data reveal a number of interesting findings. The demographic data are surprisingly skewed toward males (by a ratio of nearly 2:1), despite the fact that females outnumber males among the elderly group from which the patients were drawn. This may reflect either a sampling bias or a true sex difference. Although the average age at symptom onset, 59.1 years is surprisingly low, the standard deviation (9.6 yr) is quite high, reflecting the fact that PPA symptoms have been reported (Mesulam, 1982) in patients as young as 17 years.

Presenting Problem

The most commonly reported presenting symptom, a word-finding deficit, is also the most commonly documented aphasic symptom associated with dementia of Alzheimer's type (Sim & Sussman, 1962; Irigaray, 1967; Barker & Lawson, 1968; Appell, Kertesz, & Fisman, 1982; Bayles & Tomoeda, 1983; Rosen, 1983; Cummings, Benson, Hill, & Read, 1985; Hier, Hagenlocker, & Shindler, 1985; Flicker, Ferris, Crook, & Bartus, 1987; Murdoch, Chenery, Wilks, & Boyle, 1987). The fact that word-finding deficits are experienced subjectively and are often reported by patients as memory

deficits may account in part for the fact that PPA went undetected until it was first defined by Mesulam in 1982. Diagnosticians must carefully distinguish between naming errors and memory deficits.

Neuroanatomical Data

The fact that 43% of the MRI scans showed evidence of anomalies in both hemispheres suggests that many cases of PPA are probably not pure, but could reasonably be expected to have deficits that are not confined exclusively to language skills.

For almost half (18 of 38, or 47%) of the scans purported to show bilateral changes, the locations of these anomalies were not specified. The lack of detail suggests that the bilateral scans may have shown diffuse global degeneration, lending support to the idea (discussed below in the context of autopsy data) that many patients who have been diagnosed with PPA may have been patients whose brains were generally deteriorating due to some known dementing process.

Although the PET and SPECT scans showed a lower rate of bilateral involvement, they still suggest bilateral involvement in 31% of the cases diagnosed as PPA. The frontal lobe was strongly implicated, mentioned alone or in conjunction with other sites, in 72% of the bilateral scans and 63% of the left-sided scans. This accords with our own clinical experience that frontal lobe signs are often seen as part of PPA.

The temporal lobe was mentioned as a site of anomaly in 90% of the 40 scans reporting left-sided anomalies only, but in only 22% of the 18 scans reporting bilateral involvement, a disparity whose magnitude raises the possibility that there are two distinct processes responsible for the degenerative processes which are predominantly left and for those which are bilateral.

The autopsy results summarized in Table 10 suggest that PPA is often misdiagnosed. Six (38%) of the 16 patients who came to autopsy were shown on the basis of that autopsy to have suffered from another dementing disorder.

Neuropsychological Testing

Although comprehension deficits are reported quite commonly, this finding is somewhat misleading and difficult to interpret, since for the purposes of this paper all tests of comprehension in any modality and at any level of receptive complexity have been lumped together. The other tests give a clearer picture. It is quite clear that the initial symptoms of PPA are extremely likely to involve verbal production. Seventy-one percent of the specified presenting symptoms involved verbal production in one way or another. In contrast, only 5% of the specified presenting symptoms involved written production, and only 3% specifically involved reading.

Perhaps it is because written production difficulties are so rarely encoun-

TABLE 10
Autopsy Summaries of the 10 Patients Who Did Not Receive a Diagnosis Other Than PPA

	Duration				
	8	5	8	10	
	8	5	8	3	
Atrophy	Lateral and third ventricle dilated bilaterally	Slight atrophy of frontal lobes	Mild diffuse cortical atrophy, especially right and left frontal and sup. temporal gyri; spared pre- and postcentral gyri	2 focal areas in left inferior frontal and superior temporal gyri	Symmetric cerebral and cerebellar atrophy
Neuronal loss		Mild		Limited mainly to layer II	
Plaques	Yes	No	None		No
Tangles	Yes	No	Rare		No
Spongiosis	In nucleus basalis of Meynert, left amygdala, left superior temporal lobe	Spongiform change in layer II			Left frontal lobe, with changes both intracellular and extracellular
Pick bodies		No			
Astrocytosis/gliosis	Hypertrophic astrocytes in nucleus basalis of Meynert and left amygdala	Especially in Broca's and rest of frontal lobe		Limited mainly to layer II	
Other		Depigmented substantia nigra	Depigmented substantia nigra; microvacuolation in frontal, temporal, and parietal lobes		

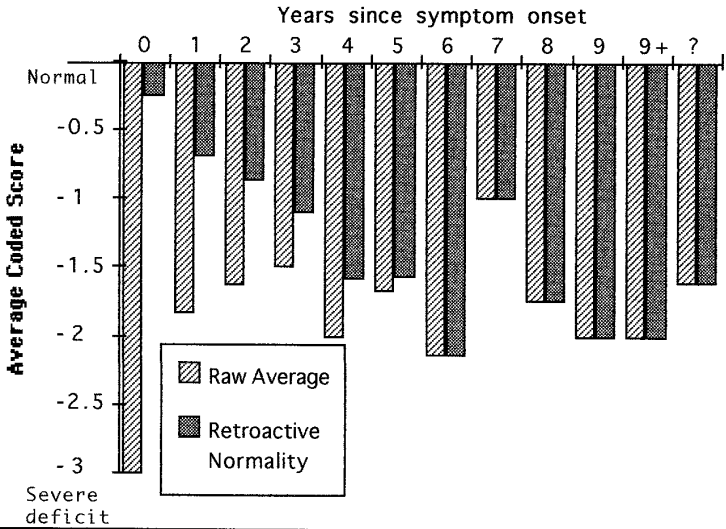


FIG. 1. Tests of oral naming: Coded results by reporting period.

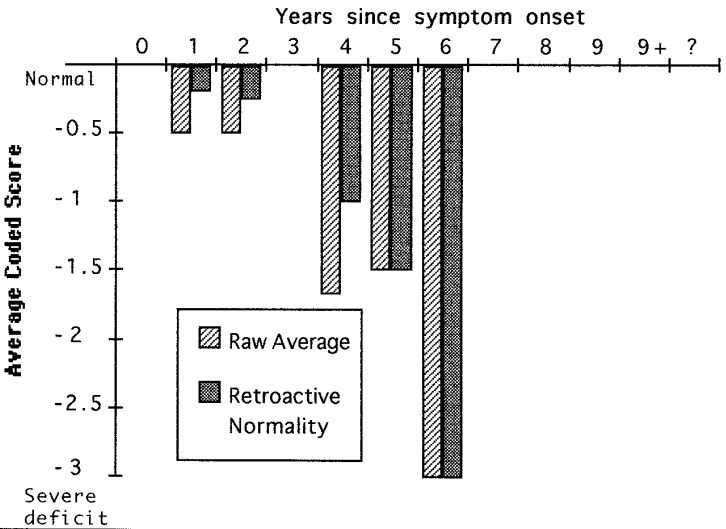
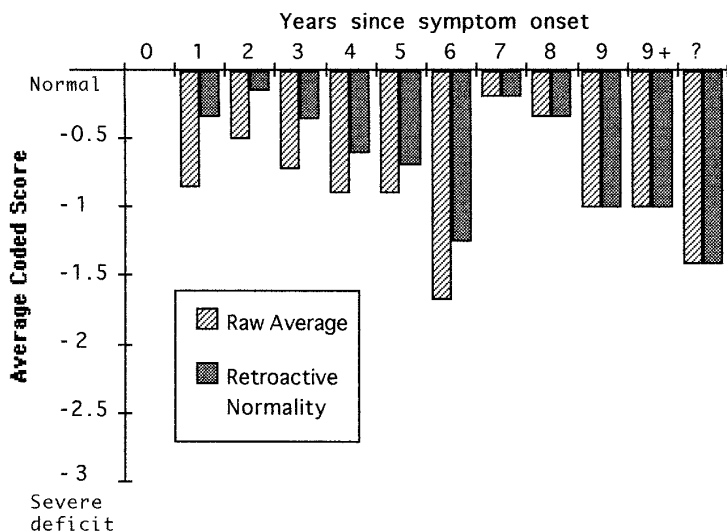
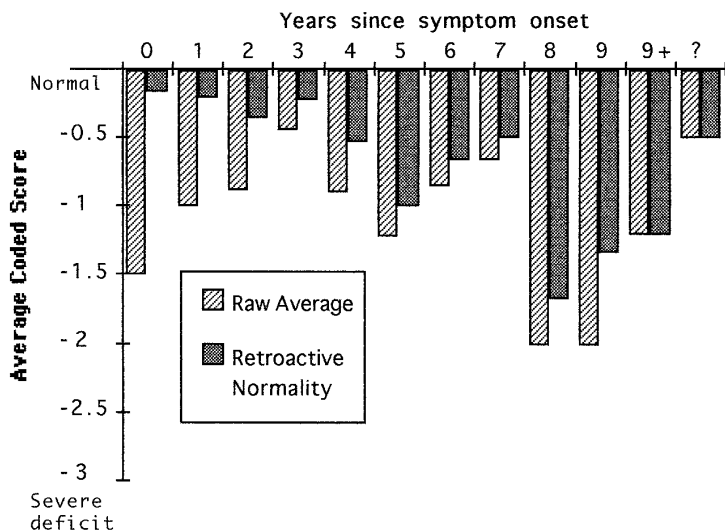


FIG. 2. Tests of written naming: Coded results by reporting period.



YEARS	0	1	2	3	4	5	6	7	8	9	9+	?	TOTAL
RAW N	0	7	4	7	10	10	6	5	3	2	1	5	60
RETRO N	13	18	13	14	15	13	8	5	3	2	1	5	110

FIG. 3. Tests of reading: Coded results by reporting period.



YEARS	0	1	2	3	4	5	6	7	8	9	9+	?	TOTAL
RAW N	2	4	8	9	9	14	7	6	5	2	5	12	83
RETRO N	19	19	20	18	15	17	9	8	6	3	5	12	151

FIG. 4. Tests of repetition: Coded results by reporting period.

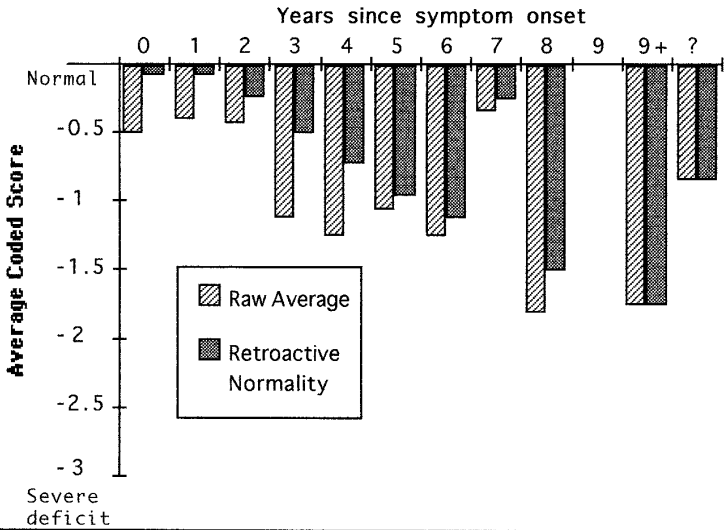


FIG. 5. Tests of comprehension: Coded results by reporting period.

tered as a presenting problem that written production skills have been tested so rarely in PPA patients. Only 12 of the cases reviewed reported results from tests of written naming, just over a tenth (112) as reported results from tests of oral naming. The lack of such results, and the total absence in the literature of written naming test results gathered more than 5 years after symptom onset, makes it impossible to be sure that written production is not differentially affected in PPA.

A fairly clear pattern emerges from the oral naming data (Fig. 1). Oral naming is increasingly affected for up to 5 years after symptom onset, after which only a single result (of 39 results coded during or after the fifth year postonset) showed no deficit at all. This suggests that the oral naming deficit in PPA peaks will certainly be manifest after 5 years. At that time the average deficit is not profound, with an average coded score for an oral naming deficit in each year after the fifth year above -2 , within or above the moderately impaired range.

Figure 6 breaks down the results by years from onset and by the proportional representation of each code in order to make the pattern of the deficit clearer. Representing the data in this proportional manner masks the progressive nature of the disorder and renders data from the first few years unreliable, since the number of measures obtained from those years is small. Despite these limitations, the graph clearly shows that by the third year the

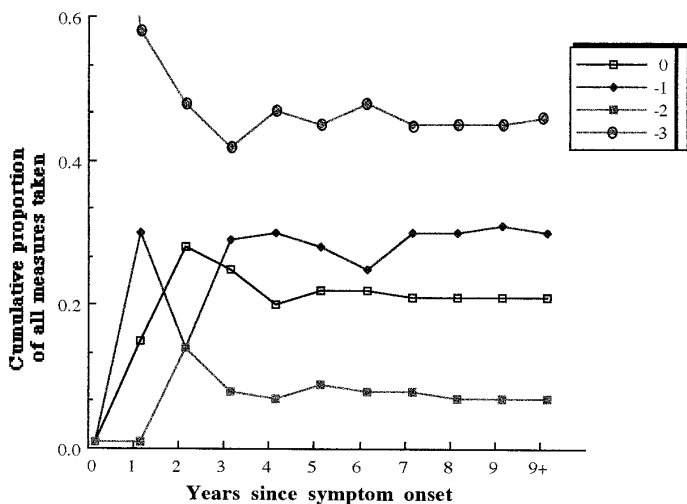


FIG. 6. Oral naming: Cumulative proportion of scores by code and years since symptom onsets. Codes run from 0 (Normal) to -3 (Severely Impaired). (Data from the first few years are unreliable, since the number of measures on those years is small.)

distribution of deficits is relatively constant. From that time on, a large proportion (roughly 45%) of the test results indicate the presence of a severe naming deficit. About half that many results indicate no deficit at all—although the application of the retroactive normality rule would raise that proportion. A slightly larger number of tests results (about 30%) show a mild deficit. Relatively few patients score a deficit in the moderately impaired range. Moreover, the proportion of patients who do show such a deficit does not increase with time. This may indicate that the degeneration is quite rapid once it begins, so that a random probe (i.e., the administration of a naming test) will be unlikely to catch the process in progress.

Figure 3 shows a relatively low average reading deficit throughout the reporting period. The breakdown of the results of the reading test (Fig. 7) confirms that reading is relatively intact in many PPA patients. Although a majority (ranging from just over half in the second and third years postonset to just under half by the seventh and eighth years) of tests uncover a mild deficit, a relatively large and constant proportion (roughly 35–40%) of test results show no deficit at all. The proportion of results indicating a severe deficit rises quite rapidly from the third to the sixth year postonset (at approximately the same rate as the proportion indicating a moderate deficit decreases), but never rises above a peak of about 20% in the sixth year. Severe reading deficits in PPA rarely appear before the first 4 or 5 years after symptom onset.

The repetition results (Figs. 4 and 8) are somewhat similar to the reading

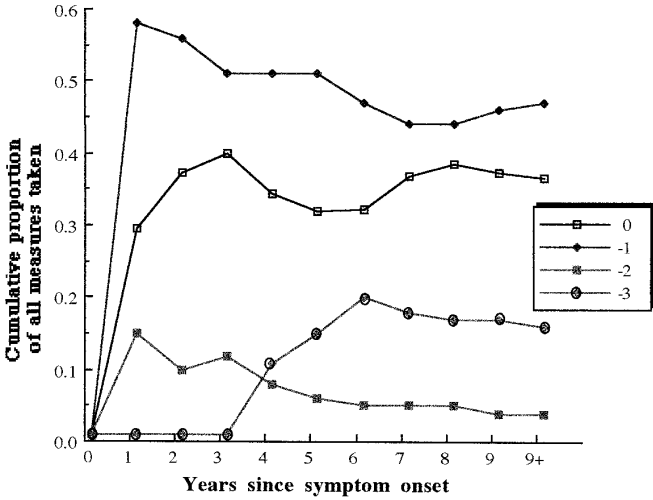


FIG. 7. Reading: Cumulative proportion of scores by code and years since symptom onset. Codes run from 0 (Normal) to -3 (Severely Impaired). (Data from the first few years are unreliable, since the number of measures in those years is small.)

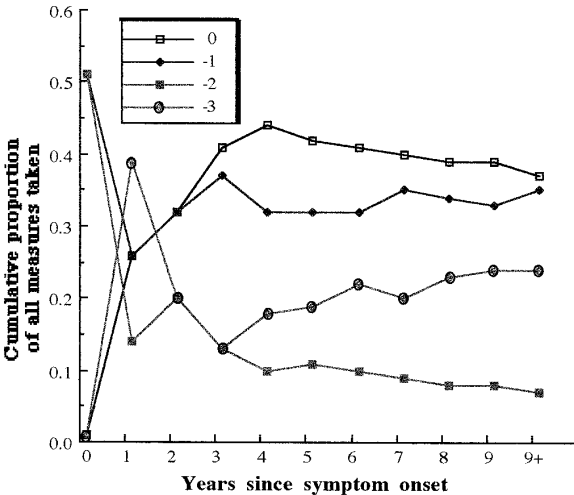


FIG. 8. Repetition: Cumulative proportion of scores by code and years since symptom onset. Codes run from 0 (Normal) to -3 (Severely Impaired). (Data from the first few years are unreliable, since the number of measures in those years is small.)

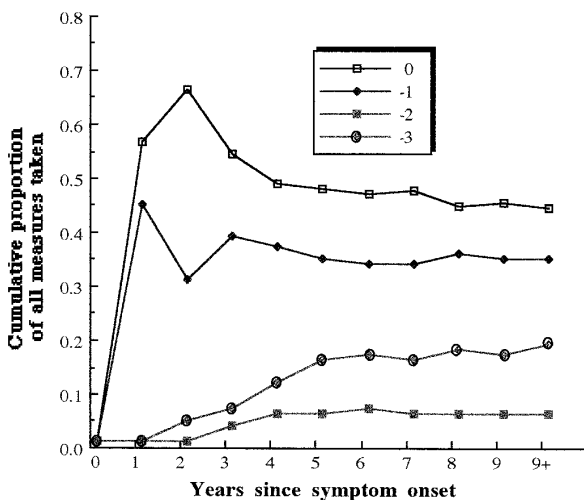


FIG. 9. Comprehension: Cumulative proportion of scores by code and years since symptom onsets. Codes run from 0 (Normal) to -3 (Severely Impaired). (Data from the first few years are unreliable, since the number of measures in those years is small.)

results. Again, the group averages (Fig. 4) suggest that there is a minimal deficit in repetition in the early years, although by the eighth and ninth years, the average effect seems to be that of a moderate deficit. The breakdown in Fig. 8 reveals that the large majority of tests show either no deficit (roughly 40%) or a mild deficit only (roughly 35%) throughout the entire reporting period. The rising average deficit in Fig. 4 reflects the steady rise of severe repetition deficits beginning in the third year and continuing throughout the reporting period. Such severe deficits account for just over 10% of all results in the third year and about 20% by the ninth year. In the same time span, there is concomitant decrease in the number of moderate deficits and in the number of tests which uncover no repetition deficit at all.

Although the comprehension data are particularly difficult to interpret because the term is used so loosely in the literature, the averages graphed in Fig. 5 do suggest that there is a general increase in comprehension difficulties which rises quite rapidly from the first year postonset. The breakdown by severity and time in Fig. 9 reveals a slow but steady decline in the proportion of measures which uncover no deficit or a mild deficit only and a slow but steady increase in the proportion of measures which uncover a severe deficit. By the ninth year almost 20% of all measures reveal a severe comprehension deficit (up from less than 5% at year 2), while about 50% find no deficit (down from about 70% at year 2). Mild deficits are found about 40% of the time throughout the measuring period, although the proportion declines very slowly during that time.

There are many difficulties in the interpretation of these data. Severe symptoms often degenerate into untestable symptoms, so that severe pathology will be underrepresented in later years. Mild pathology or lack of pathology may be underreported, for different reasons, in early years. Moreover, our results are by test result, not patient, so there is a mixture of within-patient and between-patient data in these graphs.

CONCLUSION

Although this review makes clear the great heterogeneity in the symptoms of patients diagnosed with PPA, some tentative general conclusions may be drawn.

The variability in the pattern of neuropsychological deficits reflects the variability in the underlying pathology of PPA. However, it is clear that naming is the most common and earliest deficit. By the third year about 45% of all tests of PPA patients have a severe naming deficit, while about 30% have a mild deficit. The majority of the remainder show no deficit at all. Reading deficits, if they appear at all, are likely to appear later, with severe deficits rarely seen before about the fourth or fifth years after symptom onset, and are never seen in about 80% of cases. Most PPA patients never show more than a mild reading deficit. Repetition is affected at about the same rate, and in approximately the same manner, as reading, with severe deficits likely to be seen in only about 20% of cases by the ninth year. Many patients show no comprehension deficits, especially in the first 2 years, but the numbers showing a severe deficit rise from the first year after onset, to a peak of about 20% by the ninth year.

Forty-three percent of MRI scans and 31% of PET scans showed evidence of bilateral cerebral anomalies. Differences in the distribution of anomalies between the groups with bilateral and unilateral changes suggest that there may be two separate processes involved.

REFERENCES

- Appell, J., Kertesz, A., & Fisman, M. 1982. A study of language functioning in alzheimer patients. *Brain and Language*, **17**, 73–91.
- Barker, M., & Lawson, J. 1968. Nominal aphasia in dementia. *British Journal of Psychiatry*, **114**, 1351–1356.
- Bayles, K., & Tomoeda, C. 1983. Confrontation naming impairment in dementia. *Brain and Language*, **19**, 98–114.
- Béland, R., & Ska, B. 1992. Interaction between verbal and gestural language in progressive aphasia: A longitudinal case study. *Brain and Language*, **43**, 355–385.
- Benson, D., & Zaias, B. 1991. Progressive aphasia: A case with postmortem correlation. *Neuropsychiatry Neuropsychology and Behavioral Neurology*, **4**, 215–223.
- Caplan, D. 1992. *Language: Structure, processing, and disorders*. Cambridge, MA: MIT Press.
- Chawluk, J., Mesulam, M-M., Hurtig, H., et al. 1986. Slowly progressive aphasia without generalized dementia: Studies with positron emission tomography. *Annals of Neurology*, **19**, 68–74.

- Chiacchio, L., Grossi, D., Stanzone, M., & Trojano, L. 1993. Slowly progressive aphasia associated with surface dyslexia. *Cortex*, **29**(1), 145–152.
- Cohen, L., Benoit, N., Van Eeckhout, P., Ducarne, B., & Brunet, P. 1993. Pure progressive aphemia. *Journal of Neurology, Neurosurgery, and Psychiatry*, **56**, 923–924.
- Craenhals, A., Raison-Van Ruymbeke, A., Rectem, D., Seron, X., & Laterre, E. 1990. Is slowly progressive aphasia actually a new clinical entity? *Aphasiology*, **4**(5), 485–509.
- Cummings, J., Benson, F., Hill, M., & Read, S. 1985. Aphasia in dementia of the Alzheimer type. *Neurology*, **35**, 394–397.
- Delecluse, F., Andersen, A., Waldemar, G., et al. 1990. Cerebral blood flow in progressive aphasia without dementia. *Brain*, **113**, 1395–1404.
- Flicker, C., Ferris, S., Crook, T., & Bartus, R. 1987. Implications of memory and language dysfunction in the naming deficit of senile dementia. *Brain and Language*, **31**, 187–200.
- Goulding, P., Northen, B., Snowden, J., Macdermott, N., & Neary, D. 1989. Progressive aphasia with right-sided extrapyramidal signs: Another manifestation of localised cerebral atrophy. *Journal of Neurology, Neurosurgery, and Psychiatry*, **52**(1), 128–130 [Letter].
- Graff-Radford, N., Damasio, A., Hyman, B., et al. 1990. Progressive aphasia in a patient with Pick's disease: A neuropsychological, radiologic, and anatomic study. *Neurology*, **40**, 620–626.
- Graham, K., Hodges, J., & Patterson, K. 1994. The relationship between comprehension and oral reading in progressive fluent aphasia. *Neuropsychologia*, **32**(3), 299–316.
- Green, J., Morris, J., Sandson, J., McKeel, D., & Miller, J. 1990. Progressive aphasia: A precursor of global dementia? *Neurology*, **40**, 423–429.
- Habib, M., Pelletier, J., & Khalil, R. 1993. Aphasie primaire (Syndrome de Mesulam). *La Presse Medicale*, **22**, 757–764.
- Hier, D., Hagenlocker, K., & Shindler, A. 1985. Language disintegration in dementia: Effects of etiology and severity. *Brain and Language*, **25**, 117–135.
- Hodges, J., Patterson, P., Oxbury, S., & Funnell, E. 1992. Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain*, **115**, 1783–1806.
- Irigaray, L. 1967. Approche psycholinguistique du langage des dements. *Neuropsychologia*, **5**, 25–52.
- Karbe, H., Kertesz, A., & Polk, M. 1993. Profiles of language impairment in primary progressive aphasia. *Archives of Neurology*, **32**, 193–201.
- Kempler, D., Metter, E., Riege, W., Jackson, C., Benson, D., & Hanson, W. 1990. Slowly progressive aphasia: Three cases with language, memory, CT, and PET data. *Journal of Neurology, Neurosurgery, and Psychiatry*, **53**, 987–993.
- Kertesz, A. 1994. In A. Kertesz (Chair), *Primary Progressive Aphasia*. Symposium conducted at the meeting of the World Federation of Neurology, Budapest, Hungary, June 1994.
- Kirshner, H., Tanridag, O., Thurman, L., & Whetsell, W. 1987. Progressive aphasia without dementia: Two cases with focal spongiform degeneration. *Annals of Neurology*, **22**, 527–532.
- Lippa, C., Cohen, R., Smith, T., & Drachman, D. 1991. Primary progressive aphasia with focal neuronal achromasia. *Neurology*, **41**, 882–886.
- Mandell, A., Alexander, M., & Carpenter, S. 1989. Creutzfeldt–Jakob disease presenting as isolated aphasia. *Neurology*, **39**(1), 55–58.
- McDaniel, K., Wagner, M., & Greenspan, B. 1991. The role of brain single photon emission computed tomography in the diagnosis of primary progressive aphasia. *Archives of Neurology*, **48**, 1257–1260.
- Mendez, M., & Zander, B. 1991. Dementia presenting with aphasia: Clinical characteristics. *Journal of Neurology, Neurosurgery, and Psychiatry*, **54**(6), 542–554.
- Mesulam, M-M. 1982. Slowly progressive aphasia without any generalized dementia. *Annals of Neurology*, **11**, 592–598.
- Mesulam, M-M. 1987. Primary progressive aphasia—Differentiation from Alzheimer's disease. *Annals of Neurology*, **22**, 533–534.

- Mesulam, M-M., & Weintraub, S. 1992. Reply to diffuse involvement in progressive aphasia. *Annals of Neurology*, **13**, 225.
- Murdoch, B., Chenery, H., Wilks, V., & Boyle, R. 1987. Language disorders in dementia of the Alzheimer type. *Brain and Language*, **31**, 122–137.
- Patterson, K., & Hodges, J. 1992. Deterioration of word meaning: Implications for reading. *Neuropsychologia*, **30**(12), 1025–1040.
- Poeck, K., & Luzzati, C. 1988. Slowly progressive aphasia in three patients: The problem of accompanying neuropsychological deficit. *Brain*, **111**, 151–168.
- Rosen, W. 1983. Neuropsychological investigation of memory, visuoconstructional, visuo-perceptual, and language abilities in senile dementia of the Alzheimer type. In R. Mayeux & W. G. Rosen (Eds.), *The dementias*. New York: Raven Press.
- Sapin, L., Anderson, F., & Pulaski, P. 1989. Progressive aphasia without dementia: Further documentation. *Annals of Neurology*, **25**(4), 411–413.
- Scheltens, Ph., Hazenberg, G., Lindeboom, J., Valk, J., & Wolters, E. 1990. A case of progressive aphasia without dementia: “Temporal” Pick’s disease? *Journal of Neurology, Neurosurgery, and Psychiatry*, **53**, 79–80.
- Schwartz, M., & Chawluk, J. 1990. Deterioration of language in progressive aphasia: A case study. In M. Schwartz (Ed.), *Modular deficits in Alzheimer type dementia*. Boston, MA: MIT Press.
- Sim, A., & Sussman, I. 1962. Alzheimer’s disease: Its natural history and differential diagnosis. *Journal of Nervous and Mental Disorders*, **135**, 489–499.
- Snowden, J. S., Neary, D., Mann, D. M., Goulding, P. J., & Testa, H. J. 1992. Progressive language disorder due to lobar atrophy. *Annals of Neurology*, **31**, 174–183.
- Tyrrel, P., Warrington, E., Frackowiak, R., & Rossor, M. 1990. Heterogeneity in progressive aphasia due to focal cortical atrophy: A clinical and PET study. *Brain*, **113**, 1321–1336.
- Weintraub, S., Rubin, N., & Mesulam, M-M. 1990. Primary progressive aphasia: Longitudinal course, neuropsychological profile, and language features. *Archives of Neurology*, **47**, 1329–1335.
- Yamamoto, H., Tanabe, H., & Kashiwagi, A., et al. 1990. *Acta Neurol Scand*, **83**, 102–105.