American Journal of Alzheimer's Disease & Other Dementias®
Volume 23 Number 2
April/May 2008 184-191

10.1177/1533317507312621
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Correlative Studies of Structural and Functional Imaging in Primary Progressive Aphasia

P. K. Panegyres, PhD, M. McCarthy, MBBS, A. Campbell, PhD, N. Lenzo, MBBS, M. Fallon, MBBS, and J. Thompson, BSc

Rationale: To compare and contrast structural and functional imaging in primary progressive aphasia (PPA). *Methods:* A cohort of 8 patients diagnosed with PPA presenting with nonfluency were prospectively evaluated. All patients had structural imaging in the form of MRI and in 1 patient CAT scanning on account of a cardiac pacemaker. All patients had single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging. *Results:* SPECT and PET imaging had 100% correlation. Anatomical imaging was abnormal in only 6 of the 8 patients. Wernicke's area showed greater peak Z score reduction and extent of area affected than Broca's area (McNemar paired test: $P = .008$ for Z score reduction; $P = .0003$ for extent). PET scanning revealed significant involvement of the anterior cingulum. *Conclusion:* Functional imaging in PPA: (*a*) identified more patients correctly than anatomic imaging highlighting the importance of SPECT and PET in the diagnosis; and (*b*) demonstrated the heterogeneous involvement of disordered linguistic networks in PPA suggesting its syndromic nature.

Keywords: primary progressive aphasia; imaging

Introduction

Mesulam[1] was responsible for the first definition of primary progressive aphasia (PPA). The term describes patients who have linguistic disorders with lobar atrophy in which the language difficulty predominates for at least 2 years. These patients tend not to be demented, are younger, and in general are a distinct clinicopathologic group. A number of types of linguistic disorder and lobar atrophy have been characterized such as PPA, semantic dementia, and other forms. Primary progressive aphasia is a subgroup of frontotemporal lobar degeneration (FTLD).[2,3] Controversy rages in their differentiation. The study of linguistic disorders and lobar atrophy provides fascinating insights into the mechanisms of speech and language.

The studies of Mesulam et al,[4] Chawluk et al,[5] and Tyrrell et al[6] highlight the value of functional imaging including single-photon emission computed tomography (SPECT) and positron emission tomography (PET) scanning in the diagnosis of PPA. Tyrrell et al[6] suggested heterogeneity in the metabolic defect using PET imaging in PPA.

To our knowledge there are no studies which compare structural and functional imaging along with neurostatistical analysis, in a group of patients with PPA characterized by non fluency. Here we describe this experience.

Methods

A total of 8 patients were studied from 2002 to 2004. All patients were diagnosed with PPA using the criteria

From the Neurosciences Unit, Health Department of Western Australia, Mt Claremont (PKP), Department of Nuclear Medicine, Royal Perth Hospital, Perth (MM, AC, NL, JT), WA PET/Cyclotron Service, Sir Charles Gairdner Hospital, Shenton Park (MM, NL), Nuclear Medicine Service, Perth Radiological Clinic, Subiaco (MM, MF), and Neurodegenerative Disorders Research, Subiaco (PKP), Western Australia, Australia.

Address correspondence to: Peter K. Panegyres, PhD, FRACP, Neurosciences Unit, Department of Health, Cnr Mooro Drive and John XXII Avenue, Mt Claremont, Western Australia 6010, Australia; e-mail: macfarlane4@optusnet.co.au.

Table 1. Clinical Features of Patients With Primary Progressive Aphasia

No.	Sex	Date of Birth	Age of Onset	Age at Imaging	Mode of Onset
1	F	April 22, 1941	58	63	Nonfluency
2	M	April 17, 1943	54	61	Nonfluency and ↓ comprehension
3	M	May 6, 1939	63	65	Nonfluency
4	F	March 31, 1932	68	72	Nonfluency + ↓ memory
5	M	September 22, 1942	59	62	Nonfluency
6	F	April 1, 1934	67	70	Nonfluency
7	M	February 28, 1930	73	75	Nonfluency + Δ behavior
8	F	March 15, 1945	54	59	Nonfluency

of Mesulam.[7] The clinical details of the patients are summarized in Table 1. All patients presented with nonfluency. There were 4 men and 4 women. The mean age of onset was 62.0 years (range 54.0 to 73.0 years). The mean age at the time of the study was 66.49 years (range 59.82 to 75.1 years). All patients were right handed and had achieved an educational level beyond high school. Detailed clinical histories of these patients are available on request from the authors (e-mail: macfarlane4@optusnet.com.au).

All patients underwent both ^{99m}Tc-HMPAO (hexamethyl propylene amine oxime) brain SPECT and ^{18}FDG (fluorine-18 deoxyglucose) brain PET functional imaging together with anatomical imaging as part of their assessment.

The SPECT, PET, and the magnetic resonance imaging/computed tomography (MRI/CT) imaging of the 8 cases with PPA, were mixed with imaging from a random group of 10 PET, SPECT, and a mix of MRI and CT patients who had been referred for assessment of impaired cognitive function. In our experience, PET has 100% specificity in the diagnosis of PPA (Table 2). All cases were visually assessed by 2 experienced nuclear medicine specialists, using simultaneous consensus reporting and a single neuroradiologist. Frontal, parietal, and temporal lobes, along with Wernicke's and Broca's areas were scored as to their degree of reduction (0 = normal, 1 = subtle reduction, 2 = moderate reduction, 3 = severe reduction) by comparison of each area with a normal region. Interrater reliability was almost 100% for the regional scoring system, blood flow, metabolism, and the diagnosis of PPA. All scoring was performed blinded to the result from each modality and from the clinical diagnosis. Comparisons between the SPECT and PET scores were made using the Wilcoxon matched-pairs signed ranks test[8] with *P* values of .05 or less being taken as significant. The PET/SPECT and MRI/CT images were also rated as being consistent or not with PPA, based on the presence or absence left temporal hypoperfusion on SPECT, hypometabolism with PET, and involution on MRI, which are the typical changes seen with PPA. Scores in our test were assigned without knowledge of scores of the other tests to help in the validity of the analysis.

Table 2. Diagnostic Accuracy of PET in the Diagnosis of Dementia

Condition	N	Sensitivity[a] (%)	Specificity[a] (%)
Alzheimer's disease	49	78 (63-83)	81 (68-86)
Frontotemporal dementia	17	53 (28-66)	95 (88-97)
Dementia with Lewy bodies	6	83 (36-97)	99 (94-99.9)
Primary progressive aphasia	6	50 (12-76)	100 (96-99.9)
Depression	11	18 (2-36)	100 (96-99.9)

[a]Values in parentheses indicate 95% confidence intervals

Brain SPECT images were acquired after intravenous injection of 750 MBq of ^{99m}Tc-HMPAO. Transaxial images were reconstructed using a Butterworth filter (software zoom 2) and applying Chang attenuation correction. ^{18}F-FDG brain PET imaging for assessment of neuronal metabolism was performed following intravenous injection of 5 to 7 MBq/kg of ^{18}F-FDG. Positron emission tomography images were acquired on a Philips Allegro GSO PET scanner. Transaxial images were reconstructed using iterative reconstruction (3D-RAMLA) and measured transmission attenuation correction. Magnetic resonance imaging was performed using a standardized brain protocol with a 1.5-Tesla coil magnet and in the single patient with CT a 16-slice study was performed with 5-mm slice thickness.

Functional data were analyzed semiquantitatively using the Neurostat brain analysis software package. Each study was transformed using linear scaling and nonlinear warping to match the Neurostat standard

Table 3. Image Ratings for Consistency With Primary Progressive Aphasia

	Imaging Changes—Suggestive of PPA			
Patient No.	SPECT	PET	MRI/CT	Findings
1.	Yes	Yes	No	Mild symmetric parietal atrophy
2.	Yes	Yes	Yes	Severe left temporal atrophy
3.	Yes	Yes	Yes	Mild to mod left temporal involution
4.	Yes	Yes	Yes	Moderate left temporal atrophy
5.	Yes	Yes	No	No significant atrophy
6.	No	No	Yes	Frontotemporal-parietal atrophy worse left
7.	Yes	Yes	Yes	Atrophy anterior temporal especially left
8.	Yes	Yes	Yes	Disproportionate left temporal atrophy

Abbreviations: PPA, primary progressive aphasia; SPECT, single-photon emission computed tomography; PET, positron emission tomography; MRI, magnetic resonance imaging; CT, computed tomography.

Talairach anatomical atlas. Maximum cortical activity was extracted using the three-dimensional stereotactic surface projection (3D-SSP) method described by Minoshima et al[9] and the data sets were normalized to the average cerebral count for each patient. The 3D-SSP images for SPECT and PET were compared individually and as a group with age-appropriate and modality-appropriate normal databases using pixel-by-pixel Z score analysis. A statistically significant threshold, controlling for multiple pixel comparisons and the shape of the stochastic process on the 3D-SSP format, of $Z = 4.53$ ($P < .05$) was used. The severity of reductions in each of the lobes, including Wernicke's and Broca's areas, was evaluated using volume of interest analysis of the 3D-SSP group analysis. The extent of reductions was also assessed and the percentage of surface pixels within an area having a Z score reduction of greater than 2.

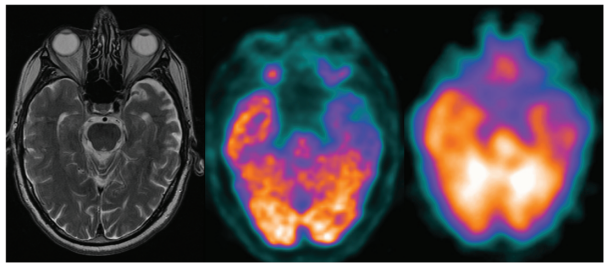

Figure 1. Imaging in patient 3 with primary progressive aphasia. (a) Magnetic resonance image showing left temporal lobe atrophy with corresponding abnormalities clearly visible on the (b) PET and (c) SPECT images.

Results

There was 100% agreement between the functional imaging when rated as being consistent or not with PPA (see Table 3). Seven of 8 patients had HMPAO and FDG abnormalities consistent with PPA. In the one case not consistent with PPA on both SPECT and PET, there were isolated bilateral posterior frontal changes (Table 3, patient 6). On review of the anatomical imaging this case was consistent with PPA, with widespread atrophy worse on the left, rather than the more localized left-sided changes usually seen. Two of the 8 patients showed minimal changes on anatomic imaging but had definite predominantly temporal reduction on functional imaging (patients 1 and 5). This contrasts with the other patients in whom temporal lobar atrophy on structural imaging correlated well with functional changes on both SPECT and PET imaging (Figures 1 and 2).

The median severity scores for the right temporal and parietal lobes were 0 to 1 (Table 4). Patient 1 had right a parietal score of 3 on PET and 0 on SPECT. This was the only patient showing this degree of discordance between the functional imaging modalities and this was the only lobe where it was present. The left-sided changes were significantly more marked for PET than SPECT for the left parietal lobe in comparison to anatomic imaging than those on the right (Wilcoxon matched-pairs signed ranks test: parietal lobe: SPECT $P = .008$; PET $P = .016$; temporal lobe: SPECT $P = 0.016$; PET $P = .008$).

Although differences in the severity scores were not significant in the left temporal and parietal lobes, they do suggest a trend, with more severe scores in the PET images as compared to SPECT (Table 4:

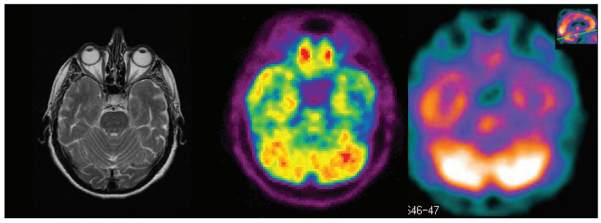

Figure 2. Imaging in patient 5 with primary progressive atrophy. (a) Magnetic resonance image showing no aphasia. Temporal hypoperfusion and hypometabolism revealed on (b) PET and (c) SPECT.

Wilcoxon signed rank test $P = .1875$, NS PET vs SPECT left temporal; $P = .1563$, NS, left parietal). Scoring of Wernicke's area also revealed a trend suggesting more severe changes in functional imaging compared with anatomic imaging with median scores for SPECT and PET of 2 and 1 for anatomic imaging (Wilcoxon signed rank test $P = .3125$, NS, PET vs anatomic; $P = .375$, NS, SPECT vs anatomic).

Figure 3 shows 3D-SSP Z score SPECT and PET images for each patient and for the patients grouped by modality. Volume of interest analysis of the grouped modality data, reveals the severity and extent of reductions in each of the frontal, temporal, parietal, and occipital lobes along with Wernicke's and Broca's areas are shown in Table 5. The data demonstrate marked left-sided temporal defects, in agreement with visual assessment. Statistically significant Z-score reductions ($Z > 4.53$, $P < .05$) are seen in the left parietal, frontal, and temporal lobes. Right-sided temporal and parietal changes are much less. The right frontal lobe Z score almost achieves statistical significance on SPECT. Wernicke's area is reduced to levels of significance for both SPECT and PET images with Broca's being below the threshold. The anterior cingulate reaches to levels of significance bilaterally on PET imaging but is normal on SPECT. No significant changes are seen in the posterior cingulate or in the occipital lobes.

The extent of assessment is also shown in Table 5. Temporal lobe extent was the same on PET and SPECT at 87%. The extent was greater on SPECT than on PET in the frontal, parietal and Wernicke's area. The anterior cingulate had a greater area peak Z-score reduction and extent of involvement on PET imaging in comparison to SPECT. Wernicke's area had significantly greater peak Z-score reduction (McNemar paired test $P = .0088$) and extent (McNemar paired test $P = .0034$) in comparison with Broca's area for both PET and SPECT.

Discussion

Functional imaging detected more cases of PPA than anatomic imaging in our population of patients who presented with nonfluency. This confirms the findings of Clark et al,[10] San Pedro et al,[11] and Sinnatamby et al,[12] who found that functional imaging was useful in the diagnosis. The main limitation of our study being the relatively small numbers of patients; however, PPA is not a common condition.

Fukui and Kertesz[13] showed that brain atrophy can vary in primary progressive aphasia and frontotemporal dementia with focal brain atrophy associated with language impairments. It is well accepted that focal brain atrophy correlates with language impairments in frontotemporal dementia.[13] In younger adults, frontotemporal lobar degeneration (FTLD) represents one of the most common causes of dementia. Approximately 20% of patients with FTLD have linguistic disorders and lobar atrophy.[14]

Studies have also shown that Alzheimer's disease has a wide presentation and there can be an overlap with primary progressive aphasia.[15,16] Our patients were thought not to represent Alzheimer's disease as they shared a predominant language defect, which persisted for 2 years prior to development of cognitive deficits.

The other main finding from our study is the strong positive correlation between SPECT and PET imaging and dysfunction in the left hemisphere. This is clearly shown in the lateral surface projection views in the grouped Neurostat analysis and is confirmed with the most significant reductions in the grouped Z-score analysis in this lobe. This concurs with the findings of others. The study of Soriani-Lefevre et al[17] showed that with SPECT imaging there is reduced perfusion in temporal cortices. Clark et al[10] performed a comparison of clinical and functional neuroimaging in patients with fluent versus nonfluent primary progressive aphasia where patients underwent either PET or SPECT imaging. The authors found left hemispheric changes with functional modalities. San Pedro et al,[11] in a correlative study with SPECT and structural imaging, showed that SPECT scanning was associated with reduced perfusion of both frontotemporal lobes. They also noted the extent

Table 4. The Severity Scores[a] for SPECT and PET in Primary Progressive Aphasia

	Parietal Right			Parietal Left			Temporal Right			Temporal Left			Wernicke's			Broca's		
Patient No.	SPECT	PET	Anatomic	SPECT	PET	Anatomic	SPECT	PET	Anatomic	SPECT	PET	Anatomic	SPECT	PET	Anatomic	SPECT	PET	Anatomic
1.	0	3	1	3	3	1	1	1	1	3	2	1	2	3	1	2	1	1
2.	0	0	1	2	1	1	0	0	1	3	3	3	3	0	2	3	0	2
3.	0	0	1	1	3	1	0	0	1	2	3	2	1	3	1	1	3	1
4.	0	0	1	1	2	1	0	0	2	3	3	3	2	3	2	3	3	2
5.	1	0	1	2	3	1	0	0	1	1	3	1	2	2	1	0	1	1
6.	1	0	2	2	3	2	0	0	1	0	1	1	1	1	1	1	0	2
7.	0	1	1	2	2	1	0	1	1	2	2	2	0	2	1	1	1	1
8.	0	1	1	2	3	1	0	1	1	2	3	2	2	2	2	2	2	1
Median	0	0	1	2	3	1	0	0	1	2	3	2	2	2	1	1.5	1	1

Abbreviations: SPECT, single-photon emission computed tomography; PET, positron emission tomography.

[a] Four-point severity scale: 0 = normal; 1 = subtle reduction; 2 = moderate reduction; 3 = severe reduction.

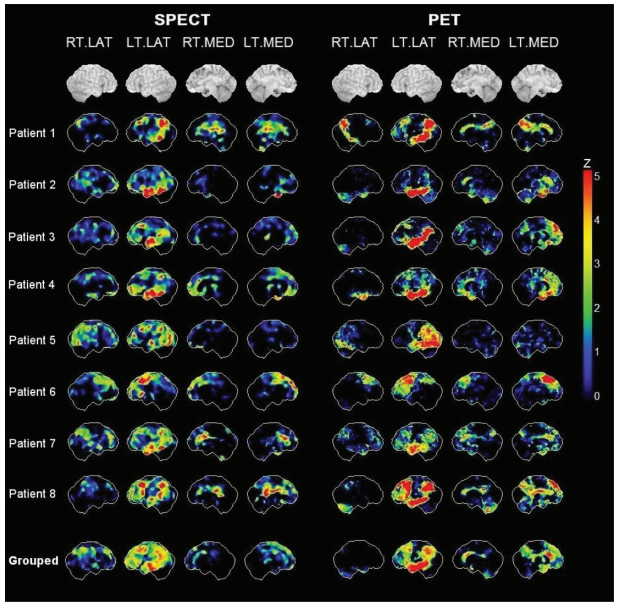

Figure 3. Three-dimensional stereotactic surface projection Z score SPECT and PET images for each patient and grouped by modality.

of deficit was greater on SPECT imaging than on structural imaging, in agreement with our study.

Our patients presented with nonfluency, associated with greater functional abnormalities in Wernike's area as opposed to Broca's area. Gorno-Tempine et al,[18] Serrano et al,[19] and Ferrer et al[20] point to the heterogeneity of linguistic disorders associated with lobar atrophy. The studies of Nestor et al,[21] which investigated progressive nonfluent aphasia in a group of 10 patients, observed hypometabolic defects in the left anterior insula region. Our study is divergent from this observation, by revealing a consistent and measurable deficit on 2 functional modalities predominantly involving Wernicke's area, that is, posterior to the Sylvian fissure and at contrast with the dogma that anterior Sylvian lesions affect fluency whereas posterior Sylvian lesions affect comprehension.[4,22] To our knowledge, ours observations are the first in the study of PPA which reveals a very extensive defect in Wernicke's area in patients with the nonfluent form of PPA.

Westbury and Bub[23] [23] assessed 112 cases of PPA and confirmed the heterogeneity in functional deficits. These authors also found abnormalities unilaterally and bilaterally pointing to heterogeneity of the disorder. This is supported by the studies of Anderson et al.[24] The studies of Black[25] point to left perisylvian dysfunction as the basis of primary progressive aphasia. Our findings support that left hemisphere dysfunction especially posterior to the perisylvian region and involving Wernicke's area may be one of the functional substrates of patients presenting with linguistic disorders and lobar atrophy.

Hachisuka et al[26] studied patients with PET scans who had primary progressive aphasia and found reduced metabolism in the left supramarginal gyrus and surrounding areas, further pointing to the heterogeneity and supported by the findings of Nagy et al.[27]

Heterogeneity in language systems is further supported by the study of Vandenberghe,[28] who postulated that cognitive brain systems might show fluctuation as a result of plasticity in response to a pathogenic process. This suggests that the findings in our study might be a consequence of neuronal plasticity in the context of a neurodegenerative disorder, leading to more apparent involvement of Wernicke's area. The studies of McMillan et al[29] also highlight variations in the neuronal networks in disorders of speech, as do the studies of Whitewell et al.[30]

Our PET data indicate significant involvement of the anterior cingulum. The cingulum is the principal association bundle of the medial aspect of the cerebral hemispheres and lies within the white matter of the cingulate gyrus. The cingulum contains fibers of variable length that connect regions of the frontal and parietal lobes, the parahippocampal gyrus, and adjacent temporal cortical region. Our study suggests the importance of the anterior cingulum in speech functions and its derangements in patients presenting with nonfluency and PPA.

In the future, diffusion tensor imaging, which enables definition of white matter tracts, might help in differentiating linguistic networks with more precision in patients with linguistic disorders and lobar atrophy.

In conclusion, functional imaging in the form of PET and SPECT scanning complements structural imaging such as CT and MRI, in the diagnosis of linguistic disorders with lobar atrophy and points to the complexity of involvement of linguistic networks.

Ethics Committee approval was obtained in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants gave their informed consent to participate in this study.

Table 5. Severity and Extent of Defects[a] in Primary Progressive Aphasia

	PET				SPECT			
	Peak Z Score Reduction		Extent		Peak Z Score Reduction		Extent	
	Right	Left	Right	Left	Right	Left	Right	Left
Parietal	1.76	5.31[a]	0%	69%	3.53	4.99[a]	37%	79%
Temporal	3.40	6.60[a]	6%	87%	2.66	6.17[a]	3%	87%
Frontal	1.51	5.20[a]	0%	52%	4.45	5.11[a]	16%	74%
Occipital	0.80	4.37	0%	10%	3.30	4.16	3%	28%
Posterior cingulate	3.61	3.82	11%	32%	1.63	2.09	0%	1%
Anterior cingulate	4.68[a]	5.68[a]	33%	46%	3.35	3.25	8%	10%
Broca		4.17		47%		4.15		35%
Wernicke		4.95[a,b]		74%[c]		4.94[a,b]		77%[c]

Abbreviations: SPECT, single-photon emission computed tomography; PET, positron emission tomography.

[a]Areas where peak Z scores exceed the statistically significant threshold of Z = 4.53 ($P < .05$). Extent was taken as the percentage of the region with a Z score exceeding 2.0.

[b]McNemar paired test $P = .0088$, very significant, peak Z score reduction, Wernicke's versus Broca's for PET and SPECT.

[c]McNemar paired test $P = .0034$, extremely significant; extent Wernicke's versus Broca's for PET and SPECT.

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