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## Primary Progressive Aphasia: Relationship Between Gender and Severity of Language Impairment

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### Abstract

**Background/Aims**—Factors influencing the course and severity of symptoms in primary progressive aphasia (PPA), a language-based dementia, have not been fully elucidated. The current study examined the influence of gender on performance on tests of naming and verbal fluency in patients with PPA. Comparisons were also made within a group of probable Alzheimer disease (AD) patients to determine whether gender differences were present in the most common form of neurodegenerative dementia.

**Methods**—Performance was compared by gender within each diagnostic group on 3 language measures: the Boston Naming Test, category fluency (animals), and lexical fluency (FAS). Scores were compared at baseline (Visit 1) and in a subset of participants 6 to 15 months later (Visit 2).

**Results**—Compared to men, women with PPA demonstrated significantly greater impairment on word fluency tests at both visits and also had a more aggressive rate of decline between visits. AD patients showed no differences by gender on any measure.

**Conclusions**—The results suggest gender-based vulnerability in PPA where women express more severe language impairments than men given a similar duration of illness.

### Keywords

dementia; frontotemporal dementia; sex differences; Alzheimer disease

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Primary progressive aphasia (PPA) is a neuropsychologically and neuroanatomically focal dementia syndrome, characterized by a primary dissolution of language, with relative sparing of other mental faculties for at least the first 2 years of illness.<sup>1,2</sup> PPA is recognized as the *language variant* in the frontotemporal dementia spectrum of disorders.<sup>3–5</sup> Although PPA can present with any form of aphasia, the most common finding among patients in the early stages of PPA is anomia (difficulty thinking of words in conversation and/or deficiencies in object naming).<sup>2</sup> Neuroanatomically, the pathologic changes in PPA are selective and most severe in the region of the perisylvian language network.<sup>6–9</sup>

The epidemiology and risk factors of PPA are largely unknown. However, an initial review of the literature by Mesulam and Weintraub<sup>6</sup> and a subsequent review by Westbury and Bub,<sup>10</sup> indicate that symptom onset was generally in the presenium (<65 y old) and approximately twice as many men as women were reported as having PPA. There is some evidence that gender

prevalence may differ by PPA subtype with male predominance in the semantic subtype and female prevalence in the nonfluent subtype.<sup>11–13</sup> However, group estimates suggest that the demographic profile of PPA, in general, differs from that of Alzheimer disease (AD), an amnesic dementia with a demographic profile in which the majority of patients are over 65 and female.<sup>14,15</sup> Studies assessing genetic risk factors found an association between PPA and the prion protein PRNP-129MV genotype<sup>16</sup> and overrepresentation of the (H1) haplotype of the *tau* gene.<sup>17</sup> Most recently, identification of mutations in the progranulin gene on chromosome 17 have been associated with ubiquitin-positive frontotemporal degeneration on postmortem neuropathology.<sup>18,19</sup> The presence of the epsilon 4 allele of apolipoprotein E, a risk factor for AD, does not seem to be a factor for PPA.<sup>20</sup>

Clinical observations of patients examined at the Northwestern Neurobehavior and Memory Health Clinic suggest that women with PPA demonstrate more severe language deficits than men. Based on this observation the present study sought to identify differences in severity by gender in PPA using 3 objective tests of language that measure different aspects of anomia, namely, the Boston Naming Test (BNT),<sup>21</sup> the FAS Test of lexical fluency,<sup>22</sup> and a test of category fluency (animals).<sup>23</sup> Given the common early presentation of anomia and the progressive nature of PPA, these tests are useful as markers to gauge both disease progression and severity. Scores from these tests were compared by gender at baseline and then 6 to 15 months later in a subset of patients who completed a follow-up visit. A similar comparison was made in a sample of patients with probable AD to determine whether gender-related differences on tests of language were present in other neurodegenerative dementias.

## METHODS

### Participants

Archival data were obtained from the Clinical Core registry of consecutively enrolled subjects at the Northwestern Alzheimer's Disease Center (NADC). Creation of the NADC registry was approved by Northwestern University's Institutional Review Board. Upon enrollment into the NADC registry, all subjects and their study partners gave written informed consent. To maximize accuracy of the patient's medical history and symptoms, both patients and their study partners (usually caregivers) were interviewed. Information about the onset of symptoms [approximate date and description of presenting symptom(s)], current symptoms, and their impact on daily living activities was collected. Subjects also underwent detailed neuropsychologic and language assessments as part of their participation in the research.

Inclusion criteria for the present study required: (1) a clinical diagnosis of PPA (contingent upon adherence to the clinical diagnostic criteria outlined by Mesulam<sup>2</sup>; Table 1) or a clinical diagnosis of probable AD<sup>24</sup>; (2) neuropsychologic test scores from at least 1 of 3 language measures (BNT, category or lexical fluency) administered as part of their research participation; and (3) native speaker of English.

Eighty-five PPA subjects met these criteria for at least 1 visit. Forty-five subjects also had data from a second visit 6 to 15 months later. In this sample, the attrition rate between Visits 1 and 2 was a result of either the patient living too far away to return or the patient's disinterest in longitudinal follow-up, and was not a consequence of being too severely impaired to participate. With the exception of 2 female patients who were too impaired to be given fluency tests, missing data for these measures were a reflection of either (1) practical constraints on time in the clinical evaluation or (2) a change in the standard battery administered in our center over time and does not relate to the patient's condition.

Ninety probable AD patients met criteria at both Visit 1 and Visit 2 (6 to 15 mo later).

At the initial evaluation patients were screened for other neurologic disorders, and serious medical disease. Diagnosis was achieved by consensus of neurologists and neuropsychologists based on their examinations. As a part of the diagnostic evaluation, clinical neuroimaging information was used to further assist in the differential diagnosis and to highlight features that are consistent with a diagnosis of either PPA<sup>6,7,9</sup> or rule out possible causes other than probable AD.

### Language Measures

The present study analyzed data from 3 neuropsychologic tests: (1) The BNT,<sup>21</sup> (2) a controlled oral word association test using the letters F, A, and S,<sup>25</sup> and (3) a category fluency test (animals).<sup>23</sup> The standard administration of the BNT had been altered to begin with the first item rather than item 30, and the test was discontinued after 6 consecutive failures. All other standard administration and scoring procedures were followed (ie, provision of semantic and/phonemic cues). For the letter fluency test, subjects were given 60 seconds to state as many different words as possible that begin with the letter F. This procedure was repeated for the letters A and S and the score was the total number of words produced for all 3. For the category fluency test subjects were asked to state as many animal names as possible in 60 seconds. Standard scoring (a sum of the total unique words generated in the allotted time) and administration procedures were followed for both fluency measures.

### Data Analysis

No direct comparisons were made between the PPA and AD patient groups as these patient populations differed substantially in age (average age: PPA = 62.9, AD = 71.5;  $P < 0.001$ ) and education (average years of education: PPA = 15.4, AD = 14.1;  $P = 0.002$ ).

Demographic variables for each subjects included age at symptom onset, education (years), and symptom duration (number of months since symptom onset as determined by a detailed interview with an informant) and these were analyzed using  $t$  tests. As socioeconomic factors could influence the level of premorbid language abilities, each subjects was assigned to 1 of 6 classes of primary occupation used by Barona et al<sup>26</sup> to create an algorithm for calculating estimates of premorbid IQ. The Mini Mental State Examination (MMSE)<sup>27</sup> was administered to patients and the Clinical Dementia Rating (CDR)<sup>28</sup> scale was completed to rate general dementia severity and level of functional impairment, respectively. A Mann-Whitney  $U$  test was used to compare the distribution of primary occupation categories and CDR scores between men and women. MMSE scores for each visit were compared using separate analyses of covariance, covarying for symptom duration.

Separate analyses of covariances were conducted for each test measure at each visit, covarying for symptom duration, to investigate gender differences (Bonferroni correction  $P = 0.025$ ).

The *rate of decline*, in those tested on 2 occasions, was computed using the following equation:

$$\text{Rate of decline} = \frac{(\text{Visit 2 score} - \text{Visit 1 score})}{(\text{Visit 1 Score})(\text{Symptom duration 2} - \text{Symptom duration 1})}$$

This equation takes into account initial performance (Visit 1) and adjusts for the amount of time between visits (symptom duration difference). Separate  $t$  tests were then used to analyze differences in rate of decline between women and men for each neuropsychologic measure. The program SPSS 11.0 for Windows was used for statistical analyses.

## RESULTS

### Patient Characteristics

**PPA Demographics**—Eighty-five individuals (40 women, 45 men) had a baseline visit and met the outlined inclusion criteria for a diagnosis of PPA. Of these 85 subjects at Visit 1 there were 81 with BNT scores, 80 with semantic fluency scores, and 44 with lexical fluency scores. A subset of the 85 patients ( $n = 45$ ) also had a follow-up visit 6 to 12 months later. Of these 45 subjects there were 43 with BNT scores, 40 with category fluency scores, and 30 with lexical fluency scores. For both the fluency tasks slightly more women than men were lost to follow-up (category fluency: 18 women, 12 men; FAS: 8 women, 4 men). Each gender group lost an equal number of patients ( $n = 19$ ) at Visit 2 for the BNT. Given the different numbers of subjects with relevant data for each test measure and each time interval, separate demographic analyses were run for each visit and each language test. Results indicated no significant differences for age at onset, education, or symptom duration for any of the comparisons. As the demographic characteristics for PPA patients remained similar for each test measure, they were summarized and presented as a group in Table 2. There were no significant gender differences in the proportion of subjects within primary occupation categories ( $U = 691.5$ ,  $P = 0.178$ ).

For the 45 PPA subjects (20 women, 25 men) with 2 visits, the average time between visits was 7.85 months for women and 8.65 months for men and this difference was not statistically significant ( $P = 0.33$ ).

**PPA Dementia Severity**—MMSE scores were reported for 75 of the 85 subjects (35 women, 40 men) at Visit 1 and 39 of the 45 subjects (18 women, 21 men) at Visit 2. After controlling for symptom duration, there were no significant differences in MMSE scores by gender (Visit 1: mean scores  $22.4 \pm 5.4$  women,  $22.9 \pm 5.7$  men,  $F = 0.499$ ,  $P = 0.482$ ; Visit 2: mean scores =  $16.3 \pm 7.6$  women,  $18.2 \pm 8.9$  men,  $F = 2.088$ ,  $P = 0.157$ ). CDR level was reported for all 85 subjects (40 women, 45 men) at Visit 1 and 39 subjects (18 women, 21 men) at Visit 2. Results revealed no significant differences in CDR scores by gender (Visit 1:  $U = 867.5$ ,  $P = 0.740$ ; Visit 2:  $U = 138.5$ ,  $P = 0.111$ ). At Visit 1 a majority of the patients had a CDR score of 0.5 (60% women, 62% men). At Visit 2 a majority of the women had a CDR of 1.0 (61%) whereas the men were more evenly distributed between a CDR of 0.5 (52%) and 1 (43%).

**Language Measures in Women Versus Men With PPA**—At Visit 1, the mean scores for women were worse than for men on all 3 language measures and reached significance for both fluency measures ( $P \leq 0.006$ ; Table 3) but not the BNT ( $P = 0.135$ ). At Visit 2 women had significantly greater impairments than men on 2 of the 3 language measures (Bonferroni correction,  $P \leq 0.025$ ; Table 3). A comparison of the rate of decline by gender over the 6 to 12 month interval of follow up only revealed significant results for the FAS and category fluency tests ( $P < 0.05$ ; Table 4).

**AD Demographics**—Ninety AD patients (57 women, 33 men) met the required criteria for participation. Male and female AD patients did not differ in their demographic characteristics (Table 2) and their MMSE scores were similar (mean score Visit 1:  $21.7 \pm 4.9$  women,  $20.3 \pm 4.8$  men,  $F = 1.002$ ,  $P = 0.32$ ; Visit 2:  $20.1 \pm 5.6$  women,  $18.7 \pm 5.9$  men,  $F = 0.892$ ,  $P = 0.347$ ). The average time between visits was 10.67 months for women and 10.89 months for men and this difference was not statistically significant ( $P = 0.74$ ).

**AD Dementia Severity**—After controlling for symptom duration, there were no significant differences in MMSE scores by gender (Visit 1: mean scores  $21.7 \pm 4.9$  women,  $20.3 \pm 4.8$  men,  $F = 1.002$ ,  $P = 0.32$ ; Visit 2: mean scores =  $20.1 \pm 5.6$  women,  $18.7 \pm 5.9$  men,  $F = 0.892$ ,  $P = 0.35$ ). There was no significant relationship between gender and level of functional

impairment as measured by CDR scores (Visit 1:  $U = 848.5$ ,  $P = 0.389$ ; Visit 2:  $U = 736.5$ ,  $P = 0.204$ ). At Visit 1 a majority of the patients had a CDR score of 1 (56% women, 55% men). At Visit 2 scores were more evenly distributed between a CDR of 0.5 (52% women, 45% men) and a CDR of 1.0 (32% women, 36% men).

**Language Measures in Women Versus Men With AD**—There were no differences in language tests scores by gender at Visit 1 or Visit 2 after controlling for symptom duration ( $P > 0.40$ ; Table 3). In addition, there were no significant differences in the rates of change on any of the language measures by gender. Overall, the results of these analyses indicate no gender-related differences in fluency or naming test scores in patients with AD.

## DISCUSSION

The present study compared severity of language impairment in men and women with a clinical diagnosis of PPA using scores from neuropsychologic measures of naming and verbal fluency. Baseline measures were obtained an average of three and a half years after purported symptom onset in women and 4 years after onset in men. Scores, adjusted for symptom duration, were compared at baseline and at a subsequent visit 6 to 12 months after the first assessment. Results revealed that verbal fluency performance at individual visits and the rates of decline between visits were significantly worse for women than men. Although woman also had lower naming test scores than men, the difference was not significant at either visit time. The present results suggest that the performance disparity between genders on tests of verbal fluency seems to be special to PPA and not a more general finding in other forms of dementia, because a similar comparison in AD patients did not reveal any significant differences in language test scores by gender at any time point.

The reasons why women might have more severe symptoms, with potentially more rapid decline than men with PPA are not immediately apparent. However, there are other examples of neurologic disease with gender-specific effects. One of these, autism, is also marked by abnormal communication and language skills. Although male gender is more prevalent in autism, females with this disorder tend to have more profound deficits in language and communication than males.<sup>29,30</sup>

One factor that could influence our findings is the potential difference in premorbid level of verbal ability of the men and women in our sample. We do not believe this to be the case as educational levels were similar in both groups and, furthermore, we demonstrated that the groups did not differ in their levels of occupational attainment, an indirect reflection of achievement.

Fluency tests require intact language and executive function abilities for successful performance. Although performance on executive functions tests was not examined in this cohort, the majority of patients were not hampered by significant executive function deficits as implied by their relatively mild CDR scores (0.5 to 1.0). Thus, the potential impact of executive function deficits on word list generation was not considered a significant factor in performance. However, future studies of this nature should also determine the level of executive function impairment with the use of nonlinguistic measures.

The difference in performance by gender in PPA patients on the BNT did not reach statistical significance. It is possible that the duration between visits was too short to capture a significant decline. The nature of the fluency test, spontaneous generation of lexical items, may be harder than a naming test which provides distinct perceptual cues. As a result, fluency tests may be more susceptible to decline in PPA.

The men and women with AD did not differ in severity of impairment on language measures. This finding is complementary to some studies<sup>31,32</sup> and contradictory to others.<sup>31–35</sup> Results reported by both McPherson et al<sup>31</sup> and Ripich et al<sup>32</sup> were similar to those of the present study in that there were no gender differences on verbal fluency tasks in male and female AD patients. However, these studies observed significant gender differences on the BNT.<sup>31,32</sup> Another study found that females with AD performed worse than males on *semantic memory tasks*, including the BNT, verbal fluency, extended range vocabulary, and the National Adult Reading Test.<sup>33</sup> However, there were methodologic and participant sample differences between these studies and the present results that may account for the discrepancies in results. For example, severity and duration of symptoms were not consistently controlled for in the analyses. Barnes et al<sup>33</sup> used combined scores from several neuropsychologic tests, reporting summary measures of cognitive function rather than individual test scores, which made it hard to directly compare their results to those of the current study.

There are several limitations of the present study that may influence the extent to which results can be generalized. First, PPA is a rather heterogeneous syndrome in that the nature of the language deficit and the course and timing of the disease are variable from person to person.<sup>2</sup> Second, participants in this study were not characterized by aphasia subtype (eg, semantic, agrammatic, logopenic), which might play an independent role in symptom progression. Third, reliance on patient and caregiver interviews to determine time of symptom onset may lead to inaccurate estimates of time course. However, the practice of judging symptom duration by this method is widely used in dementia research and short of objective longitudinal data from a time before symptom onset, it is the best estimate available. Finally, the data used were archival and the analyses retrospective in nature, which limited the study design and affected participant numbers. Nevertheless, these results suggest that gender differences in PPA deserve further exploration.

Overall, the findings suggest that gender may be an important predictor in determining the severity of aphasic symptoms in PPA patients, that is, PPA may be more virulent in women than men. This difference cannot be accounted for by differences in socioeconomic status (eg, education, primary occupation), symptom duration, or age, as all of these variables were similar between the men and women with PPA. Prospective studies, that are longer in duration and include very mild PPA patients, will be needed to further characterize gender differences and other epidemiologic features of PPA.

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**TABLE 1****Diagnostic Criteria for Primary Progressive Aphasia<sup>2</sup>**

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- (1) There is an insidious onset and gradual but progressive impairment of word finding, object naming, syntax, or word comprehension manifested during conversation or assessed with the use of standard neuropsychologic tests of language.
  - (2) All major limitations in activities of daily living can be attributed to the language impairment for at least the first 2 years.
  - (3) Premorbid language function (except for developmental dyslexia) is known to be intact.
  - (4) Prominent apathy, disinhibition, loss of memory of recent events, visuospatial impairment, visual recognition deficits, and sensory-motor dysfunction are absent during the initial 2 years of illness, as indicated by the history, evaluation of activities of daily living, or neuropsychologic testing, so that the patient would not fulfill diagnostic criteria for any other dementia syndrome.
  - (5) Acalculia (inability to perform simple mathematical calculations) and ideomotor apraxia (inability to pantomime movement as instructed by an examiner) can be present even in the first 2 years of illness, and deficits in copying simple drawings and preservation may also be noted, but neither visuospatial deficits nor behavioral disinhibition substantially limits activities of daily living.
  - (6) Other cognitive functions may be affected after the first 2 years of illness, but language remains the most impaired function throughout the course of the illness and deteriorates faster than other affected functions.
  - (7) Specific causes of aphasia, such as stroke or tumor, as ascertained by neuroimaging, are absent.
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**TABLE 2**

## Demographic Data

	Female Mean (SD)	Male Mean (SD)	<i>P</i>
PPA patients			
n	40	45	
Age of onset	63.9 (6.8)	62.0 (7.9)	0.25
Education (y)	14.9 (2.3)	15.8 (2.7)	0.12
Visit 1 symptom duration (mo)	41.2 (24.7)	50.3 (30.2)	0.14
AD patients			
n	57	33	
Age of onset	71.8 (7.5)	71.1 (9.1)	0.82
Education (y)	13.9 (2.7)	14.4 (3.1)	0.38
Visit 1 symptom duration (mo)	46.9 (27.2)	52.8 (32.6)	0.36

Comparisons were made within patient groups by gender.

**TABLE 3**

Comparison of Language Test Scores by Gender\*

	F/M	Female Mean (SD)	Male Mean (SD)	P
PPA patients				
Category fluency Visit 1	37/33	8.9 (5.5)	12.7 (5.3)	0.001 <sup>†</sup>
Category fluency Visit 2	19/21	4.4 (4.9)	8.9 (5.2)	0.002 <sup>†</sup>
Letter fluency Visit 1	22/20	12.4 (7.9)	19.6 (9.3)	0.006 <sup>†</sup>
Letter fluency Visit 2	14/16	6.9 (7.3)	17.1 (9.4)	< 0.001 <sup>†</sup>
Boston Naming Test Visit 1	37/44	29.8 (19.9)	33.9 (20.4)	0.135
Boston Naming Test Visit 2	18/25	21.44 (17.1)	29.8 (22.5)	0.050
AD patients				
Category fluency Visit 1	46/26	10.2 (5.5)	10.8 (3.8)	0.629
Category fluency Visit 2		8.9 (3.8)	9.4 (4.8)	0.597
Letter fluency Visit 1	43/25	30.4 (15.2)	30.1 (13.8)	0.927
Letter fluency Visit 2		28.2 (14.1)	26.8 (14.1)	0.715
Boston Naming Test Visit 1	55/31	38.2 (13.7)	39 (14.3)	0.822
Boston Naming Test Visit 2		34.4 (14.5)	36.8 (15.8)	0.471

Data were analyzed using analysis of covariance, controlling for symptom duration. Note. Category fluency: Subjects are given 60 s to list as many animals as possible. Letter fluency: Subjects are given 60 s to list as many words as they can beginning with each letter F, A, and S. Boston Naming Test: Subjects are asked to name 60 line drawings.

\* Comparisons are made within diagnosis by gender.

<sup>†</sup> Denotes statistical significance  $P \leq 0.025$ .

**TABLE 4**

## Rate of Decline on Language Tests in Women and Men With PPA

	F/M	Female Mean (SD)	Male Mean (SD)	P
Category fluency	19:21	-0.07 (0.05)	-0.04 (0.05)	0.02*
Letter fluency	14:16	-0.07 (0.05)	-0.01 (0.07)	0.03*
Boston Naming Test	18:25	-0.04 (0.05)	-0.03 (0.04)	0.62

Rate of decline = (Visit 2 Score – Visit 1 Score)/[(Visit 1 Score) (Symptom Duration 2 – Symptom Duration 1)].

\* Denotes statistical significance  $P < 0.05$ .