Behavioral features in semantic dementia vs other forms of progressive aphasias

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Abstract—*Objective:* To compare the behavioral profiles in different variants of primary progressive aphasia (PPA). *Methods:* We classified 67 patients with PPA into three clinical variants: semantic dementia (SEMD), progressive nonfluent aphasia (PNFA), and logopenic progressive aphasia (LPA), and we compared the severity of behavioral dysfunction, as measured by the Neuropsychiatric Inventory, in these groups and patients with frontotemporal dementia (FTD) and Alzheimer disease (AD). *Results:* SEMD was associated with significantly more socioemotional behavioral dysfunction than the other two variants of PPA and than AD, specifically more disinhibition, aberrant motor behavior, and eating disorders—behaviors that are typical of FTD. In contrast, PNFA and LPA did not differ from each other or from AD in the type or severity of behavioral dysfunction. Behavioral abnormalities increased in severity with disease duration in SEMD, but this association was not detected in PNFA or LPA. *Conclusions:* Semantic dementia is associated with significantly more behavioral dysfunction than other variants of primary progressive aphasia, specifically behavioral features typical of frontotemporal dementia.

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Primary progressive aphasia (PPA) is a neurodegenerative syndrome in which deterioration in speech and language is the primary cause of functional impairment for at least the first 2 years of the illness.[1,2] PPA can present with various types of speech and language dysfunction, ranging from nonfluent speech and agrammatism to fluent but empty speech.[3] In a recent study,[4] we identified three clinical variants of PPA: 1) semantic dementia (SEMD) characterized by progressive loss of knowledge about words and objects, 2) progressive nonfluent aphasia (PNFA), characterized by hesitant, effortful speech and agrammatism, and 3) logopenic progressive aphasia (LPA), defined by progressive decrease in speech output with anomia and short term verbal memory difficulties.

Even though speech and language deficits are, by definition, the most prominent symptoms in all cases of PPA, these deficits are variably associated with less prominent impairments in non-language functions that may aid diagnosis.[3] Accordingly, the most commonly used diagnostic criteria for SEMD are based on core features of semantic memory impairment (manifested by language and object recognition deficits), but the supportive criteria include behavioral abnormalities including loss of sympathy and empathy, narrowed preoccupations, and parsimony.[5] Although these features are described, the criteria provide no guidance as to how these features can be used to support a diagnosis of SEMD. Rather, the diagnosis can be made based purely on the language and object recognition deficits outlined as core features. In addition, the criteria do not suggest metrics by which the behavioral features of SEMD can be measured. In fact, the supportive clinical criteria for PNFA also include "late" behavioral changes similar

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to FTD,[5] making the use of behavioral features as outlined in the criteria even more difficult for separation of these PPA syndromes. Our goal in this analysis was to better characterize the behavioral abnormalities that occur in SEMD vs other forms of PPA, so that in the future they might be more useful in determining a diagnosis of SEMD and in following disease progression in PPA.

Methods. *Patients.* Behavioral data were collected from 67 patients (32 men, 35 women, mean age 68.3 years, SD = 11.14 years) with PPA who had been evaluated at the UCSF Memory and Aging Center (MAC). Twenty-seven of these patients were included in a previous study of PPA,[4] and the diagnosis of PPA was made based on criteria outlined in that study. Specifically, all patients had speech and language dysfunction as the presenting symptom, which remained relatively isolated for at least 2 years. All patients included here were fluent speakers of English. All data presented here were collected at or near the time of first presentation to the UCSF Memory and Aging Center (within 3 months).

Patients at the MAC undergo neurologic and nursing evaluations and neuropsychological testing to evaluate memory, executive function, language, and mood using a previously described standard protocol.[6] In addition, patients with PPA participate in supplementary speech and language assessments to better define their deficits. This battery includes tests evaluating speech output (including motor speech abilities and syntax), lexical retrieval and semantic memory, syntactic comprehension, and single word reading skills.[4] Based on their clinical and neuropsychological evaluation, patients were classified into three variants of PPA: 1) SEMD (n = 33, 21 men, 12 women, mean age 65.6 years, SD = 8.66 years), 2) PNFA (n = 17, 2 men, 15 women, mean age 63.3, SD = 11.42 years), and 3) LPA (n = 17, 9 men, 8 women, mean age 69.1 years, SD = 8.36 years). Specifically, SEMD was diagnosed in patients with fluent, grammatically intact speech, severe anomia (with deficits in confrontation naming), semantic deficits for words (loss of comprehension for word meanings) and objects (loss of knowledge about object identity and use), and relatively spared comprehension of syntax. PNFA was diagnosed in patients with effortful, hesitant (non-fluent) speech, agrammatism (decreased use of grammatic function words), labored articulation (difficulties with enunciation characterized by repeated attempts to pronounce words with poor selection or improper ordering of syllables, sometimes referred to as "speech apraxia" and tested by asking patients to quickly repeat multisyllabic words such as "caterpillar" multiple times), impaired comprehension of syntactically complex sentences, and preserved comprehension of single words. LPA was diagnosed in patients with nonfluent speech that was grammatically simple but correct, and whose hesitancy was mostly due to word finding pauses and not to motor speech impairment. LPA patients also show deficits in sentence repetition and have relative sparing of semantics and single word comprehension.

Two additional cohorts recruited for comparison included 50 patients with FTD (33 men, 17 women, mean age 59.8 years, SD = 7.57 years), and 119 patients with AD (45 men, 74 women, mean age 73.2 years, SD = 10.71 years). Diagnoses of AD and FTD were made according to the most recently published consensus criteria.[5,7]

The terms SEMD, FTD, and progressive aphasia are used in several ways in the literature. FTD is often used to describe histologic/biochemical pathology,[8] but also to denotes a clinical-anatomic entity characterized by degeneration of the frontal and temporal cortex.[9] In the diagnostic scheme used here, the term FTD is used to refer only to the clinical syndrome defined by progressive socioemotional behavioral deficits, usually associated with primarily frontal degeneration. As such, FTD is one of three clinical variants associated with frontotemporal degeneration, the other two being SEMD and PNFA. All of these are grouped under the term frontotemporal lobar degeneration (FTLD).[5] By this diagnostic scheme, FTD is differentiated from SEMD and PNFA because the former presents primarily with behavioral difficulties while the latter two present with a predominant language symptom. As noted in the introduction, supportive criteria for SEMD include socioemotional behavioral abnormalities. However, because SEMD can be diagnosed solely on the basis of core criteria and PNFA is also said to show "late" behavioral changes similar to FTD,[5] behavioral features are not an important determinant for a diagnosis of SEMD vs other forms of PPA in our clinic.

Identification of behavioral abnormalities. Behavioral abnormalities were measured using the Neuropsychiatric Inventory (NPI[10]), a validated, caregiver-based behavioral rating system developed for the assessment of dementia. The NPI measures the frequency (rated 1 to 4, 4 being most frequent) and severity (rated 1 to 3, 3 being most severe) of 12 major behavioral disorders including delusions, hallucinations, aggression/agitation, depression, anxiety, elation/euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, sleep disturbances, and eating disorders. For this analysis, we created an index of severity for each behavioral variable by multiplying the frequency and severity scores (creating a frequency by severity product, FxSprod), as has been done in the past using the NPI.[11]

Data from the NPI were combined across domains in two ways. First, the individual FxSprod scores were summed across all domains to create an NPI total score (NPI_{Total}). Second, the FxSprod score for the five behaviors most typically associated with FTD (elation/euphoria, apathy, disinhibition, aberrant motor behavior, and eating disorders)[11,12] were summed to create an FTD-specific NPI total score (NPI_{FTD}).

Establishment of disease duration. Individual patients can present to subspecialty clinics at different times in the course of their disease, depending on a variety of psychological and social factors, and this may affect their likelihood of showing particular symptoms. In order to assess the effect of disease duration on behavior, chart reviewers (K.R. or S.C.A.) made a retrospective assessment of disease duration up until presentation to the MAC based on the information available in the chart regarding the earliest symptoms recalled by the caregiver or the patient. The reliability of the duration assessment was rated on a 0 to 2 scale (0 = unreliable; 1 = moderately reliable, but there were inconsistencies or the caregiver or patient did not appear to be certain; 2 = reliable). Features that made the duration estimate less reliable included the caregiver's inability to give a specific estimate of the time of earliest symptoms, or the physician's indication that the year of onset is uncertain. If patient and caregiver estimates disagreed, and the patient was well known to the caregiver (e.g., a close family member) the caregiver's estimate was used. Duration estimates with a reliability of 1 or 2 were kept for analysis.

Statistical analysis. Demographic variables and the NPI_{Total} and NPI_{FTD} summary scores were in most cases normally distributed, and thus they were compared across groups using one-way analyses of variance. In cases where the data were homoscedastic, post hoc pairwise comparisons were performed using Tukey's HSD, and in cases where they were heteroscedastic, we used the Games-Howell test for post hoc comparisons. To account for potential confounds affecting group differences in NPI summary scores, correlations between demographic variables and NPI summary scores were assessed using Pearson's r statistic, and analyses of covariance were performed using variables significantly correlated with NPI_{Total} and NPI_{FTD} as covariates to ensure that group differences for NPI_{Total} and NPI_{FTD} were still significant. Because NPI scores for individual domains are heteroscedastic and are typically not normally distributed (with certain values being impossible because of the scoring system), differences across groups for individual behaviors were examined using the Kruskal-Wallis test. For those tests showing a significant effect across groups, the Mann-Whitney *U* test was then used with Bonferroni correction to conduct eight non-orthogonal pairwise comparisons: FTD, SEMD, PNFA, and LPA were each compared to each other and PNFA and LPA were both compared to AD.

In addition, we wished to examine whether patients with PPA have an increasing tendency to develop FTD-like behavioral abnormalities and to evaluate this tendency in different variants of PPA and the other dementia syndromes. To accomplish this, we entered the NPI_{Total} and NPI_{FTD} scores as dependent variables into regression models that included terms for disease duration, diagnostic group, and group-duration interaction, weighting each group equally to identify those with significant effects of duration on NPI scores. All statistical analyses were carried out using SPSS (version 10.1.0 for Windows; SPSS, Chicago, IL).

Table 1 *Demographic characteristics for the study groups, including sex, age, years of education, MMSE score, total CDR and box score, and disease duration*

	Sex, % male	Age, y	Education, y	MMSE	CDR total	CDR box score	Duration, y
FTD	66	59.8 (7.57)	16.06 (2.43)	22.8 (7.16)	1.2 (0.68)	7.1 (3.36)	5.8 (4.01)
SEMD	64	65.6 (8.66)	15.9 (3.67)	17.3 (8.89)	0.9 (0.66)	4.4 (3.21)	5.9 (4.31)
PNFA	12	63.3 (11.42)	15.1 (2.09)	23.1 (8.26)	0.6 (0.57)	2.8 (2.48)	3.7 (1.65)
LPA	53	69.1 (8.36)	16.1 (3.24)	18.1 (6.53)	0.9 (0.61)	5.0 (3.42)	4.7 (2.24)
AD	38	73.2 (10.71)	14.4 (3.81)	19.2 (6.61)	1.0 (0.59)	6.1 (3.54)	4.9 (2.90)
Overall	47	68.3 (11.14)	15.2 (3.46)	20.0 (7.40)	1.0 (0.63)	5.8 (3.55)	5.2
Test statistic	$\chi^2[4] = 23.67$*	$F[4,231] = 19.03$*	$F[4,223] = 2.98$†	$F[4,197] = 4.03$‡	$F[4,197] = 3.47$‡	$F[4,197] = 5.51$*	$F[4,209] = 2.98$ (NS)

Values are mean (SD).

* $p < 0.001$.
‡ $p < 0.01$.
† $p < 0.05$.

MMSE = Mini-Mental State Examination; FTD = frontotemporal dementia; SEMD = semantic dementia; PNFA = progressive nonfluent aphasia; LPA = logopenic progressive aphasia; AD = Alzheimer disease; NS = not significant.

Results. *Group characteristics.* Table 1 shows the demographic characteristics for the study groups. Sex distribution was tested with the $\chi 2$ statistic, and the effects of group, age, years of education, Mini-Mental State Examination (MMSE), CDR and CDR Box Score, and duration were tested with analysis of variance (ANOVA) (F statistic). Age, sex, years of education, MMSE, CDR and CDR box score varied significantly across groups. Duration did not vary significantly across groups. Table 2 (first row) shows the frequency of behavioral problems of any type or severity across groups. At least some behavioral difficulty was very common (80% or more of patients) in all groups.

Correlation analysis revealed that age, duration, and CDR scores were correlated with NPI_{Total} and NPI_{FTD}.

NPI summary scores across groups. The figure shows the mean NPI_{Total} and NPI_{FTD} FxSprod scores across all diagnostic groups. As would be expected, FTD was associated with the most severe behavioral problems. Among the three variants of PPA, SEMD clearly showed the most behavioral dysfunction. PNFA and LPA showed lower levels of behavioral dysfunction and were more similar to AD.

ANOVA and ANCOVA across groups revealed significant differences with respect to both NPI_{Total} ($F_{[4,192]} = 33.00$) and NPI_{FTD} ($F_{[4,206]} = 53.10$), which were still significant after including age, sex, duration, and CDR box score as covariates. Results for post hoc pairwise comparisons (Games-Howell) were the same for both NPI_{Total} and NPI_{FTD}. FTD and SEMD differed significantly from each

Table 2 *Frequency of behaviors and mean frequency by severity product score for individual Neuropsychiatric Inventory (NPI) behaviors across groups*

	FTD	SEMD	PNFA	LPA	AD
Percent with any behavior on NPI	100	90	81	100	80
Frequency by severity product scores					
Delusions	0.95	0.08	0	0	0.59
Hallucinations	0.25	0.21	0	0	0.03
Agitation*	2.95	1.42	1.00	0.40	0.86
Depression	1.10	1.29	0.56	1.33	1.30
Anxiety	2.48	1.58	0.56	1.20	1.16
Elation/euphoria†	1.65	1.38	0.38	0.07	0.01
Apathy*‡§	7.78	3.63	1.75	2.60	2.13
Disinhibition*†§‖¶	4.10	2.96	0.38	0.33	0.20
Irritability	2.05	0.96	1.12	0.47	1.22
Ab motor beh*†§¶	4.53	3.00	1.19	0.07	0.56
Sleep beh	1.43	1.67	0.19	1.07	0.75
Eating D/O*†‡§	6.10	3.04	0.44	0.67	0.93

Correlation analysis revealed that age, duration, and CDR scores were correlated with NPI_{Total} and NPI_{FTD}.

* $p < 0.05$ FTD vs LPA (Mann-Whitney, after Bonferroni correction).
† $p < 0.05$ SEMD vs AD (Mann-Whitney, after Bonferroni correction).
‡ $p < 0.05$ FTD vs SEMD (Mann-Whitney, after Bonferroni correction).
§ $p < 0.05$ FTD vs PNFA (Mann-Whitney, after Bonferroni correction).
‖ $p < 0.05$ SEMD vs PNFA (Mann-Whitney, after Bonferroni correction).
¶ $p < 0.05$ SEMD vs LPA (Mann-Whitney, after Bonferroni correction).

FTD = frontotemporal dementia; SEMD = semantic dementia; PNFA = progressive nonfluent aphasia; LPA = logopenic progressive aphasia; AD = Alzheimer disease.

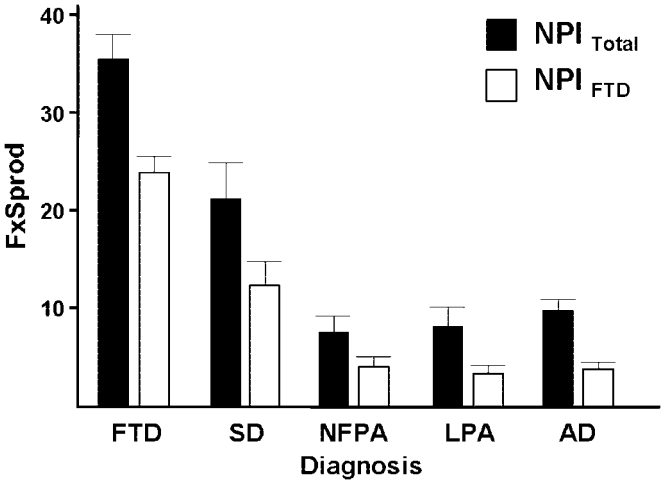

Figure. Mean frequency by severity product scores summed across all Neuropsychiatric Inventory domains (NPI_{Total}) and across domains usually associated with frontotemporal dementia (NPI_{FTD}) for the three primary progressive aphasia variants and for FTD and Alzheimer disease.

of the other groups, and PNFA, LPA, and AD did not differ significantly from each other.

NPI domains across groups. Data for individual NPI domain subscores are summarized in table 2. Of the 12 behaviors, 9 showed significant differences across groups (Kruskal-Wallis test): delusions, agitation, anxiety, euphoria, apathy, disinhibition, aberrant motor behavior, sleep disorders, and eating disorders. Pairwise comparisons for these nine variables revealed that when SEMD was compared with FTD, the two disorders differed in two domains: apathy and eating disorders were more severe in FTD. When compared with FTD, PNFA showed significantly lower NPI scores in several domains, including apathy, disinhibition, aberrant motor behavior, and eating disorders. LPA showed lower NPI scores than FTD in agitation, apathy, disinhibition, aberrant motor behaviors, and eating disorders.

When compared with SEMD, PNFA showed significantly less disinhibition (differences for sleep disturbances and eating disorders were at $p < 0.10$ after Bonferroni correction). LPA showed significantly less disinhibition and aberrant motor behavior than SEMD. When compared with SEMD, AD showed significantly lower scores on elation/euphoria, disinhibition, aberrant motor behavior, and eating disorders, as has been demonstrated previously.[12,13]

When PNFA and LPA were directly compared with each other, no significant differences were seen in any domain. Because previous findings indicated that PNFA is associated with frontal atrophy, while LPA is associated with predominantly parietal atrophy,[4] identifying a difference between these two groups was of particular a priori interest. Thus, we also inspected this contrast without Bonferroni correction. Without Bonferroni correction, there was a trend toward lower values for depression and sleep disturbances in PNFA than LPA ($p < 0.10$ uncorrected).

PNFA and LPA showed significantly less euphoria when compared with AD. There were trends toward decreased scores for delusions in both PNFA and LPA compared with AD and for sleep disturbances in PNFA compared with AD ($p < 0.10$ corrected).

Effects of disease duration on NPI scores. Although the patient groups did not differ significantly in terms of disease duration, the severity of behavioral abnormalities was correlated with duration in the group as a whole, and we anticipated that this effect may be detectable in some groups but not others. Thus, we performed regression analyses to examine interactions between group and the effect of duration on behavioral dysfunction. NPI_{Total} was not significantly related to duration in any group, although in SEMD increasing duration appeared to be associated with higher NPI_{Total} scores (B = 0.098, SE = 0.059, $p < 0.10$). Increasing duration was correlated with higher NPI_{FTD} scores in SEMD ($\beta = 0.132$, SE = 0.051, $p < 0.05$). In FTD, increasing duration appeared to be associated with higher NPI_{FTD} scores ($\beta = 0.073$, SE = 0.052, $p < 0.20$). Duration did not appear to show a relationship with NPI_{FTD} in any other group.

Discussion. The goal of the current analysis was to examine the behavioral abnormalities in three variants of PPA: SEMD, PNFA, and LPA. In all groups, patients presented with a clinical history indicating predominantly language dysfunction within the first 2 years, consistent with a diagnosis of PPA. However, by the time of presentation to our clinic the majority of patients in all three groups were beyond 2 years of symptoms, increasing the likelihood of additional non-language symptoms. Of the three groups, only SEMD was associated with behavioral abnormalities that were similar to those seen in FTD, including disinhibition, aberrant motor behavior, and eating disorders. Neither PNFA nor LPA was associated with any more FTD-like behavioral disturbances than AD. These results support previous descriptions suggesting that SEMD is associated with more severe behavioral disturbances than other variants of PPA, and furthermore that these behavioral disturbances are similar to those seen in FTD.

The current data are consistent with several prior analyses indicating that SEMD is associated with behavioral disturbances that are similar in quality to those seen in FTD.[12-14] However, this is the first analysis to formally show that other variants of PPA are not associated with these types of deficits, at least in the first few years of illness. These findings have important clinical implications. Early in the course of any of the PPA syndromes, patients may present with prominent anomia, but no frank semantic memory loss. In these situations, emerging behavioral symptoms may be an important clue supporting a diagnosis of SEMD, and the NPI is a useful tool for assessing this. Furthermore, our retrospective data correlating disease duration with NPI suggest that, if they are not apparent at first, such behavioral abnormalities emerge over time in SEMD. If this result is confirmed by other prospective studies, it could be useful both for clinical assessment and in treatment studies.

Our findings may have implications regarding pathologic diagnosis as well. Autopsy studies suggest that SEMD is often associated with ubiquitin-positive, tau-negative inclusions and no amyloid plaques, and rarely associated with tau-positive Pick-like inclusions.[3,15-17] Both these patterns are part of the pathologic spectrum of FTLD. However, SEMD is also associated with AD pathology in about one-third of cases.[17] In one recent study where 16 of 18 cases of SEMD had non-AD pathology,[16] eight had early behavioral problems, whereas these were not present in the two patients with AD pathology. The possibility that continued absence of FTD-like behavioral dysfunction over time in the setting of SEMD is predictive of AD pathology should be evaluated in the future.

The tendency for SEMD to show behavioral abnormalities similar to those of FTD may reflect the specific sites of anatomic involvement in SEMD. In prior neuroimaging analyses, SEMD has been associated with left greater than right temporal atrophy, consistent with the language impairments that characterize the disorder, but also with tissue loss in orbitofrontal, medial frontal, and insular regions that are important for emotional processing.[4,12,18,19] Furthermore, recent analyses show that FTD-like

behavioral abnormalities, including disinhibition, apathy, aberrant motor behavior, and eating disorders, are associated with tissue loss in the right orbitofrontal, medial frontal, and insular regions.[20,21] Many of the patients in the current analysis were included in the prior brain-behavior analyses from our group.[4,21] The fact that SEMD likely begins with left temporal degeneration and only later involves right sided frontal structures[18,22,23] may account for the fact that behavioral dysfunction was less severe in SEMD than FTD. In contrast to SEMD, prior studies have shown that PNFA and LPA are primarily associated with left perisylvian atrophy, with frontal predominance in PNFA and parietal predominance in LPA.[4] This tendency for PNFA and LPA not to involve medial and orbital frontal structures, particularly on the right, may explain the relative absence of FTD-like behaviors.

As noted in the Introduction and Methods, the consensus criteria for SEMD include behavioral abnormalities as supportive features.[5] It could be argued that, to the extent these behavioral features were used for diagnosis, our results were a foregone conclusion. Unfortunately, the Neary criteria do not provide guidance on how these behavioral features can be measured, or how severe they must be to support the diagnosis. In addition, these behavioral features are neither necessary nor sufficient for a diagnosis of SEMD, and cannot substitute for any of the core features. Thus, despite their inclusion, they provide little added diagnostic value in their current form, and to date we have based our diagnoses of SEMD on purely language and semantic features. Rather than being determined by the diagnostic criteria, our findings support the importance of behavioral features in the diagnosis. Future diagnostic schema might incorporate these features and some measure of their severity more systematically.

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