Cognitive Deficits and Reduced Insight in Primary Progressive Aphasia

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Primary progressive aphasia (PPA) is a form of dementia caused by frontotemporal lobar degeneration. Unlike aphasia due to stroke, in which the association between particular aphasia profiles and insight has been well characterized, this relationship has not been investigated in PPA. Reduced insight is seen in other neurological conditions, but tends to involve right hemisphere damage, whereas PPA is predominantly a left hemisphere disorder. The aim of the current study was to examine whether fluent aphasia with less meaningful speech output, associated with diminished insight in stroke, is also characteristic of PPA patients with reduced insight. Fourteen PPA patients were studied. Results indicated that reduced information content in speech and poor performance on a nonlanguage test, the Pyramids and Palm Trees test, predicted reduced insight. This study has implications for the anatomical network involved in insight and clinical implications in terms of selecting interventions appropriate for individual patients with PPA.

Keywords: dementia; primary progressive aphasia; insight; awareness; frontotemporal dementia

P rimary progressive aphasia (PPA) is caused by neurodegenerative disease that leads to an initially isolated breakdown of language abilities.[1-3] PPA is part of a wider spectrum of neurodegenerative disorders caused by frontotemporal lobar degeneration (FTLD),[3,4] which also includes another clinical condition, behavioral variant frontotemporal dementia (bvFTD). BvFTD is characterized by initial changes in behavior and loss of insight into these changes, with relative preservation of other cognitive functions. In PPA, the few studies completed on this topic thus far indicate that insight is not entirely intact and that it tends to diminish with progression of the disease. As the disease progresses neuroanatomically from initial

isolated dysfunction in the perisylvian language regions to involve other cortical and subcortical regions, insight appears to concurrently diminish.[5] Additionally, PPA is a fairly heterogeneous condition, with various language profiles represented among affected individuals who may also display differing levels of insight. As such, PPA provides a compelling model with which to investigate the relationship between language symptoms, other cognitive symptoms, and reduced insight. As numerous definitions of insight exist,[6] in this article we will take the broad definition "awareness of symptoms or characteristics of a disease process."

The specific characteristics of the language disorder in PPA differ among patients. Numerous attempts have been made to subgroup PPA patients based on prominent linguistic characteristics such as speech fluency.[4,7] In patients with aphasia from stroke, those with fluent, grammatically correct but empty speech and poor naming appear to be less aware of their impairments,[8] although they rarely lose insight entirely.[9] Those with nonfluent, grammatically impaired but informative speech and relatively preserved naming appear to be aware of and, as a result, depressed by their deficits. In PPA, the fluent–nonfluent distinction is difficult due to the fact that the disease is progressive and most patients

progress to a point where they have significantly reduced output and even mutism, regardless of their initial presentation. However, patients differ in terms of the flow and informational content of their speech. Thus, it might be possible to assess insight with respect to the level of fluency, meaningfulness of speech content, and other language characteristics in patients with PPA.

There have been some studies on insight within the group of dementias caused by FTLD. The most prevalent clinical presentation in this group is bvFTD,[10,11] a core diagnostic criterion of which is reduced insight.[4] Eslinger et al[12] assessed various aspects of awareness in patients with either bvFTD or the language variant (divided into semantic dementia and progressive nonfluent aphasia subgroups). They found the aphasic patients to be capable of accurately assessing their performance on various cognitive tasks (self-monitoring) but to be unaware of the behavioral symptoms, such as apathy and lack of empathic concern, of which their caregivers complained.

The initial aphasia profile and the other deficits that emerge over time (ie, nonlanguage deficits) in PPA patients are governed by the location and extent of the neurodegenerative changes and vary from patient to patient. In the early stages, damage tends to be restricted to the dominant hemisphere perisylvian language areas,[13] although Gorno-Tempini et al[7] noted that patients with semantic dementia also exhibited some right anterior temporal lobe atrophy in addition to atrophy in a similar distribution, although more prominent, in the left hemisphere.

In other neurological disorders there is often a robust anatomic association between damage to the right hemisphere, most often the parietal lobes, and anosognosia.[14,15] In addition, involvement of the right frontal lobe appears to be associated with loss of insight for hemiplegia following stroke[16] and for reduced insight into deficits following traumatic brain injury.[17] However, reduced insight is not limited to patients with damage in the parietal or frontal lobes, but is also seen in Anton's syndrome; cortical blindness caused by occipital damage, where patients adamantly insist that they can see[18,19]; and in patients with hemiplegia following damage to the thalamus or lenticular nucleus.[20] These studies indicate that a large distributed network is involved in insight regarding disease state.[21]

Prigatano,[22] using Mesulam's[23] model of cortical function, proposed a model of insight, suggesting that the heteromodal association areas, responsible for consolidation of multimodal information from internal and external sources, underlie higher-order functions including insight. In fact, atrophy in these areas, not only in the right frontal region but also in the temporoparietal region, is associated with reduced insight in dementia.[24-26] Prigatano[22] also argued that the paralimbic areas, important for meshing emotional and cognitive data, are important in insight. The voxel-based morphometry study of PPA patients by Gorno-Tempini et al[7] suggested that various areas mostly within the left hemisphere are implicated in PPA. However, the semantic dementia subgroup they describe had some right hemisphere damage to the temporal pole, a paralimbic region. Unlike the other PPA patients, this group also did particularly poorly on an object associations test, the Pyramids and Palm Trees (PPT) test. Performance of tests similar to PPT are associated with bilateral anterior temporal lobe (ie, paralimbic areas) activation.[27] This combination of findings, that some patients with PPA have right hemisphere paralimbic atrophy, provides a potential explanation for reduced insight in such patients. It could therefore be expected that the PPA patients who score poorly on PPT might also have reduced insight.

As yet, no studies have assessed the relationship between linguistic and cognitive features of aphasia and reduced insight into illness in PPA. The current study aimed to identify whether there is a relationship in PPA between reduced language comprehension and fluent, empty speech and insight, similar to that seen in stroke-related aphasia. In addition to these language symptoms, poor performance at nonlanguage cognitive tasks, which imply the spread of disease beyond the language areas, especially when a degree of right hemisphere involvement is implicated, were expected to be predictive of reduced insight in PPA.

Methods

Participants

Fourteen right-handed patients (7 males; mean age = 66.9, standard deviation = 7.43; mean years of education = 16.29 years, standard deviation = 2.56) with current diagnoses of PPA were recruited from the Clinical Core registry of the Northwestern Alzheimer's

Disease Center. The research measures were conducted during the participants' annual research visits, with their written consent, and were approved by the Northwestern University Institutional Review Board. During these visits, participants undergo a neurological examination and neuropsychological tests. Study partners, usually the patient's primary caregiver, complete questionnaires regarding neuropsychiatric symptoms and activities of daily living. Only patients with comprehension levels sufficient for the completion of the measures were included in this study. Any patient scoring 50/60 or below on the Western Aphasia Battery (WAB) Auditory Verbal Comprehension Yes/No Questions subtest was excluded from the study as he or she may not have been able to understand the Frontal Behavioral Inventory (FBI) questions. Participants' clinical neuroimaging findings and a subset of their test scores are listed in Table 1.

One patient (number 9) carried a clinical diagnosis of semantic dementia without visual agnosia according to the Uniform Data Set diagnostic criteria.[28] No other patient carried clinical diagnoses of semantic dementia, and patients were not subgrouped for the purposes of the current study.

Procedures

Two insight measures were used. The neurologist who examined the patient during the annual research visit completed the modified Clinician's Insight Rating (mCIR) scale. This scale was modified from the original CIR,[29] which was developed to assess awareness in Alzheimer's disease. The only adaptation consisted of replacing the item querying awareness of memory impairment with one querying changes in cognition or behavior. The mCIR consists of a brief 4-item checklist rating the patient's insight on each item (awareness of situation, ie, reasons and circumstance for the office visit, specific awareness of cognitive impairment or behavioral change, awareness of impairment in activities of daily living, awareness of progression of deficit). Ratings are made on a 3-point scale—full awareness (0), partial awareness (1), or no awareness (2)—providing a total score in the range of 0 to 8.

The FBI[30] is a tool used to assess severity of 24 symptoms associated with FTLD, mostly related to behavioral symptoms but with some items focusing on cognitive deficits. Responses to FBI questions are usually elicited from the caregiver; however, for the purposes of the current study, the FBI also was completed with the patient via interview with the examiner. The patient score minus the caregiver score on this measure, the "FBI discrepancy score," served as an index of the patients' insight into their symptoms, with scores at or above 0 indicating that patients complain of their symptoms to a similar or more severe degree than their caregivers, reflecting intact insight, and negative scores suggesting reduced insight.

A battery of neuropsychological tests was also administered to each patient. This included the WAB[31] and the PPT.[32] The WAB is a comprehensive set of tests used to assess all aspects of aphasia. Notable for the current study, it provides a test of Spontaneous Speech, which consists of a series of questions relevant to functioning in everyday life (eg, "How are you today?" "What is you address?"). This test also involves description of a complex scene. The Spontaneous Speech test yields 2 subscores. The first is Information Content, which represents the meaningfulness of responses, without regard for grammar or syntax. The second is Fluency, the scoring of which mostly emphasizes rhythm, speech flow, and syntax. Fluent speech featuring poor information content is characteristic of Wernicke's aphasia (usually caused by stroke), which is frequently associated with reduced insight.[9] The WAB also includes various tests of comprehension, including a single Auditory Word Recognition test, where patients are instructed to point to an item (either a line drawing or a real object) when its name is spoken by the examiner. The PPT is a test of semantic associations consisting of both picture and word subtests. For this study, only the pictures subtest was used to probe subjects' knowledge of objects in the absence of words. PPA patients' language deficits could affect performance on the word condition of the PPT in the absence of a loss of semantic knowledge about the objects themselves. There are 52 items, each comprising a page with 3 line drawings, 1 at the top and 2 at the bottom. One of the pictures on the bottom is associated with the picture at the top (eg, a pyramid with a palm tree), while the second picture on the bottom is a semantically related foil (eg, a pine tree). These tests were given among a battery of other language and nonlanguage neuropsychological tests, including the Boston Naming Test (BNT),[33] a 60-item confrontation naming task.

Table 1. Participants' Test Results and Reported Results of Clinical Neuroimaging

Number	Duration of Illness (Years)	Neuroimaging Findings	BNT	WAB Info Content (/10)	WAB Commands (/80)	WAB Repetition (/100)	WAB Fluency (/10)	WAB Aphasia Quotient (/100)	Pyramids and Palm Trees (/52)	Total CIR	FBI Discrepancy Score
1	7	MRI: Normal	35	9	73	94	6	85.2	ND	0	3
2	4	MRI: Normal EEG: Nonspecific slowing in *left* hemisphere	60	9	70	78	6	90.0	52	0	4
3	3	MRS: Focal reduction in NAA concentration *left* frontal and anterior temporal cortices	60	10	68	96	9	95.5	52	1	−1
4	3	MRI: Atrophy and widening of the left perisylvian fissure	39	8	62	70	5	93.7	ND	1	−2
5	2	MRI: Mild age-related atrophy SPECT: diminished perfusion in the left temporal lobe and posterior parietal lobe	44	8	67	66	5	74.8	ND	0	1
6	4	MRI: Mild to moderate cerebral volume loss, prominent in the medial temporal lobes bilaterally EEG: intermittent left hemisphere slowing, especially in temporal region	52	9	80	70	5	79.2	49	0	−13
7	3	MRI: Small vessel ischemic disease, mild hippocampal atrophy	41	10	80	78	9	91.6	50	0	−6
8	3	MRI: Increase in size of the *left* perisylvian cistern PET: Mild decrease in parietal and temporal metabolism, more so on the *left*	60	10	80	100	9	97.4	52	0	−2
9[a]	4	MRI: Mild cortical atrophy EEG: Normal	6	9	58	100	8	75.4	40	3	−19
10	6	MRI: Normal other than cerebral atrophy	NA	NA	78	NA	NA	NA	49	4	−5

(*continued*)

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Number	Duration of Illness (Years)	Neuroimaging Findings	BNT	WAB Info Content (/10)	WAB Commands (/80)	WAB Repetition (/100)	WAB Fluency (/10)	WAB Aphasia Quotient (/100)	Pyramids and Palm Trees (/52)	Total CIR	FBI Discrepancy Score
11	4	MRI: Mild cerebral atrophy EEG: Dysrhythmia and left temporal slowing	58	10	68	10	6	70.7	50	0	0
12	4	MRI: Some symmetric atrophy FDG PET: diminished activity at the level of the left temporal lobe and left frontal lobe	9	5	44	32	5	4.5	49	4	−1
13	5	MRI: Atrophy in *left* parietal and inferior temporal regions EEG: Normal	55	9	41	84	9	84.6	49	4	−5
14	9	MRI: Unremarkable	3	6	26	38	5	45.4	40	6	−8

Abbreviations: BNT, Boston Naming Test; WAB, Western Aphasia Battery; CIR, Clinician's Insight Rating; FBI, Frontal Behavioral Inventory; MRI, magnetic resonance imaging; EEG, electroencephalogram; MRS, magnetic resonance spectroscopy; SPECT, single photon emission computed tomography; ND, not determined; PET, positron emission tomography; NA, not applicable.

a Patient 9 had a clinical subdiagnosis of semantic dementia without agnosia. Other patients were not subgrouped or were considered PNFA.

Data Analysis

Spearman's ρ was used to assess correlation between the 2 awareness measures, the mCIR and the FBI discrepancy score, due to the ordinal nature of scores on the former measure.

Initially, univariate Pearson's correlations were performed to investigate associations between potential predictors (raw scores on the BNT and PPT and from the WAB Information Content, Spontaneous Fluency, and Word Recognition Comprehension) and each of the outcome variables, mCIR and FBI discrepancy score.

Second, predictors that emerged as significant from the correlation analyses were entered into 2 forward-selection, linear-regression models, one using the FBI discrepancy score as an outcome variable and the other using the mCIR. Required probability of F to enter the model was $P < .05$.

Results

The FBI discrepancy score and the total mCIR score were not significantly correlated with one another. Univariate analyses indicated that lower scores on the PPT ($r = -.663$; $P = .026$), Information Content ($r = -.692$; $P = .009$), and BNT ($r = -.706$; $P = .007$) all correlated significantly with the lower levels of insight as measured by the mCIR, whereas lower scores on the PPT ($r = .708$; $p = .015$) and Word Recognition ($r = .625$; $p = 017$) both correlated significantly with reduced insight as measured by the FBI discrepancy score.

Regression analyses revealed that a worse score on Information Content was the best predictor of a high mCIR score indicating poor insight (Table 2) and worse performance on the PPT was the best predictor of a more negative FBI discrepancy score, also indicating poor insight (Table 3).

Discussion

This study aimed to detect language and other cognitive correlates of reduced disease-related insight in patients with PPA. Insight was assessed both by the clinician and with a technique comparing the difference between the patients' opinion and their caregivers' on a questionnaire regarding cognitive and behavioral symptoms of their disorder. Results indicated that the 2 measures were not correlated with one another, but both insight measures generally implied that the PPA patients in this study had relatively intact insight, as expected. However, some scores did suggest a reduction in insight. The regression models demonstrated that reduced information content in conversation and poor ability on a semantic associates test predicted reduced insight in PPA. Other linguistic features, namely, confrontation naming, single word comprehension, and fluency of speech, were not significant predictors of insight.

The lack of significant correlation between the clinician's insight rating and the FBI discrepancy score may have important implications for how insight should be measured in this population. It is possible that the caregivers and clinicians differ in opinion regarding the patients' condition, and both measures are quite subjective. Alternatively, the 2 methods could be assessing quite different constructs: the mCIR assesses factors such as awareness of progression of deficit and reduction in independence that are not featured in the FBI, which is more specific to the actual symptoms of the disease. For clinical purposes, a measure with strong psychometric properties such as predictive validity would be very useful; future research is required to ascertain such properties in these instruments.

Although the aspects of PPA patients' aphasia that predicted reduced insight in our study are associated with particular neuroanatomical regions, conclusions that can be made regarding anatomical associations are limited. Poor performance on the PPT is generally associated with the subtype of PPA known as semantic dementia,[7] a group in whom speech has little information content in the context of fluent, syntactically correct output, and poor language comprehension. Of note, the patients in our study with worse PPT scores, who also produced speech with less meaningful content, had the lowest levels of insight. These patients are more similar to Gorno-Tempini's semantic dementia and, to a lesser extent, logopenic subgroup, in comparison with their nonfluent progressive aphasia subgroup (who exhibit more dysfluent, but meaningful speech and generally intact PPT performance). In their voxel-based morphometry study, Gorno-Tempini et al[7] demonstrated that semantic dementia patients exhibited the most atrophy in the medial and lateral aspects of the anterior temporal lobes bilaterally, and logopenic patients' atrophy was located in the temporoparietal regions of the angular gyrus. Collectively, these are paralimbic and heteromodal

Table 2.   Forward Selection Regression Analyses of Predictors of Total mCIR Score
(Model R^2 =.594; df = 1, 8; P = .009)

Predictor	β (in)	t	P	$r_{partial}$
Boston Naming Test	−0.453	−2.165	.067	−.663
Information Content	−0.982	−3.425	.009	−.771
Pyramids and Palm Trees	−4.070	−1.208	.067	−.415

Abbreviation: df, degree of freedom; mCIR, modified Clinician's Insight Rating.

Table 3.   Forward Selection Regression Analyses of Correlates of FBI Discrepancy
Score (Model R^2 = .402; df = 1, 8; P = .015)

Predictor	β (in)	t	P	$r_{partial}$
Word Recognition Comprehension	0.377	1.053	.323	.349
Pyramids and Palm Trees	1.307	3.005	.015	.708

Abbreviation: df, degree of freedom; FBI, Frontal Behavioral Inventory.

areas according to Mesulam's model.[23] Prigatano's[22] theory stipulated that these areas appear to be involved in reduced awareness.

Studies in stroke aphasia suggest that insight in fluent, Wernicke's aphasia is not always diminished. The few studies that have been completed suggest that patients who exhibit fluent, jargon-filled speech are more likely to have suffered bilateral damage.[34,35] The current study found a prominent symptom of Wernicke's aphasia (reduced information content in spontaneous speech) to be a predictor of reduced insight and the PPT, a test associated with bilateral damage, to be another strong predictor. This topic warrants further investigation, but it may be that patients with isolated left hemisphere damage are aware of their symptoms, whereas those with some degree of bilateral damage have reduced insight. This is exemplified by the 1 patient in our study who had bilateral medial temporal lobe atrophy, although electroencephalogram continued to indicate more prominent left temporal dysfunction. This patient had a negative FBI discrepancy score (suggesting poor insight), although the examining physician felt that he demonstrated good insight. An additional, or alternative, explanation could be that damage to more anterior aspects of the temporal lobe is required for PPA patients to show reduced insight. The paralimbic nature of this region, and its apparent function in binding emotional reactions to cognitive processes, could provide a potential mechanism for reduced insight. However, clinical neuroimaging for the most part was relatively nonspecific in this group of patients, in keeping with other reports of early structural imaging in PPA. Future studies involving both structural and functional imaging, with a larger group of patients who could potentially be subtyped according to the Gorno-Tempini criteria, may further elucidate the neuroanatomic underpinnings of reduced insight in PPA.

Previous studies in patients with stroke aphasia associated with reduced insight have suggested that the anosognosia is not complete, that is, they have specific "blind spots" in awareness, being aware of some aspects of their deficits but not others.[36] Despite some intact insight, such patients show only minimal benefits from interventions using delayed auditory feedback.[34] This finding combined with results from the current study has implications in terms of which PPA patients may benefit the most from particular interventions by speech language pathologists, whose treatment has been shown to be beneficial in PPA.[37] Adding insight measures to the battery of tests administered to patients with PPA in clinic may thus provide important information regarding treatment options.

The current study is preliminary and assessed insight in a small group of heterogeneous PPA patients. Several limitations of this study and areas for future research should be discussed. The small number of patients involved becomes an issue especially given the use of multiple regression.[38] Studies of other neurodegenerative diseases point to disease

duration and presence of behavioral disturbance or executive dysfunction as correlates of reduced insight; however, the relatively small group in the present study prevented investigation of these other potential correlates. Another limitation is the lack of a quantitative measure of rate of speech and speech errors. Adding a measure such as mean length of utterance, or words per minute, would permit testing of the hypothesis that more fluent patients with more paraphasias are likely to have less awareness into their aphasia than nonfluent patients with more meaningful speech. Although the current study took a more general approach to insight, further research on this area may also assess whether these same language characteristics relate to insight into specific language, other cognitive or behavioral deficits. It may be that poor insight in PPA predicts development of future behavioral problems, which occurs in some PPA patients.[39] This would be relevant clinically in terms of preparing families for the future.

In conclusion, results suggest that most patients with PPA have good levels of insight, but some have reduced awareness of their deficits. Reduced awareness was associated with speech that lacked meaningful content and a loss of the ability to appreciate semantic associates among groups of pictures that may imply more bilateral involvement.

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