Patients with primary progressive aphasia have sentence comprehension difficulty. Clinical observations describe changing speech patterns over time, but longitudinal studies of declining sentence comprehension are found only in informal descriptions of case reports. The non-fluent form of progressive aphasia, known as primary progressive non-fluent aphasia (PNFA), presents with effortful speech that may be agrammatic or dysarthric. Clinical descriptions of non-fluent aphasia (PNFA), presents with effortful speech fluently. In the present study, we examined the contributions finding pauses and circumlocutions, and difficulty understanding a sentence is complex. In brief, information represented in the individual content words of a sentence must be determined. This includes both single word meaning and the thematic relationships specified by content words such as who can do what to whom. The long distance, grammatically mediated relationships between words in the sentence also must be established. Sentences emerge over time, so executive resources like working memory are needed to retain words and phrases of a sentence transiently until they can be incorporated into the sentence. Sentence comprehension impairment in PNFA has been documented on measures of sentence-picture matching and by responses to simple probes of sentences such as who performed the sentence's action. These reports have emphasised the role of a grammatical deficit in PNFA patients' sentence comprehension difficulty by showing reduced comprehension accuracy for sentences that feature more complex grammatical structures. On-line studies of sentence comprehension also have been reported that minimise the confounding role of task related resources. In this work, subjects are asked to detect a word in a sentence. Unbeknownst to subjects, the word occasionally follows a grammatical agreement violation. Control subjects demonstrate their sensitivity to grammatical agreements by showing a slight but reliable delay in word detection during the temporal window for processing a grammatical agreement immediately following a grammatical violation relative to their latency to detect a word immediately following a correct grammatical agreement. PNFA patients, by comparison, do not show this kind of delay. One study interpreted this as evidence for their insensitivity to grammatical agreements. Another study showed that PNFA patients are delayed in word detection following a grammatical agreement violation only when the target word occurs well after the normal processing window. This pattern of on-line performance correlated with a measure of working memory. The authors suggested that slowed information processing speed allows information to degrade in working memory during the course of grammatical processing. These observations implicate...
grammatical and working memory components of sentence processing in the comprehension deficits of PNFA patients.

Studies of SD have documented relatively preserved grammatical processing,20 21 and one on-line assessment of grammatical agreement sensitivity in a small number of SD patients showed a reasonably normal pattern of performance.22 Impaired sentence comprehension nevertheless may be seen in these patients, possibly due to the degraded neural representation of the individual content words constituting a sentence. This can interfere with single word meaning and with thematic roles specifying who can do what to whom in a sentence.

While this work suggests a role for single word, grammatical, and working memory limitations in the sentence comprehension difficulties of PNFA and SD, it is unclear how these components conspire to worsen sentence comprehension over time in these patients. The present study was designed to investigate declining sentence comprehension longitudinally in PNFA and SD, and to examine the relative contributions of single word, grammatical, and working memory components to the progressive sentence comprehension deficits observed in these patients.

METHODS

Subjects

We studied 24 patients with progressive aphasia who met published clinical criteria for frontotemporal dementia.22 23 Initial clinical diagnosis was established by an experienced neurologist (MG). This diagnosis was consistent with the results of serum studies, structural imaging studies such as MRI or CT, and a range of functional neuroimaging studies such as SPECT or PET. Subsequently, at least two trained reviewers of a consensus committee confirmed the presence of specific diagnostic criteria based on independent reviews of a semi-structured history, detailed mental status exam, and complete neuropsychological exam (imaging and laboratory studies were not available to the consensus committee). If the reviewers disagreed in their diagnosis (18% of the entire series of 220 cases, including patients with other neurodegenerative diseases), consensus was established through open discussion by the full committee. These patients and their legal representatives participated in an informed consent protocol approved by the Institutional Review Board at the University of Pennsylvania.

Fourteen of these patients had PNFA. PNFA is marked by slow, effortful speech with phonemic paraphasic errors that may be associated with agenesis or dysarthria. We also examined 10 patients with SD. These patients characteristically have fluent and circumlocutory spontaneous speech with word finding pauses and possibly semantic errors. Subgroup criteria were based on published diagnostic features modified to improve reliability.24 25 We used the consensus mechanism described above to establish subgroup diagnosis. Table 1 summarises the demographic and clinical features of these patients when first enrolled in this study. PNFA and SD patient groups were matched in age (F_{1,22} = 0.24; NS), education (F_{1,22} = 1.86; NS), duration of disease (F_{1,22} = 1.98; NS), and Mini Mental State Exam (MMSE) score (F_{1,22} = 0.23; NS). The speech characteristics of these patients at first contact are summarised in table 2, and their neuropsychological performance at the initial evaluation is summarised in table 3.

Exclusion criteria included the presence of other neurologic conditions such as stroke or hydrocephalus, primary psychiatric disorders such as depression or psychosis, or a systemic illness that can interfere with cognitive functioning. Most of these patients were taking a fixed dosage of an acetylcholinesterase inhibitor (for example, donepezil, rivastigmine, or galantamine). Some of these patients may have been medicated with a low dosage of a non-sedating anti-depressant (for example, serotonin specific re-uptake inhibitors such as sertraline) or an atypical neuroleptic agent (for example, quetiapine), as indicated clinically, but none of the patients demonstrated any evidence of sedation suggesting over-medication.

Materials and procedure

We assessed performance on measures of sentence comprehension, single word meaning, and verbal working memory. Tasks were administered amongst other measures during a 45 min session in a quiet room by a trained technician, and were presented in a fixed order (sentence comprehension before working memory and word meaning). This protocol was typically administered on an annual basis, and was repeated for as many sessions as the patient was able to participate. PNFA patients were tested over an average (standard deviation) of 3 (1.3) sessions separated on average by 11 (6.2) months. SD patients were tested over an average of 3 (1.2) sessions separated on average by 11 (2.8) months. Rates of longitudinal observation did not differ between groups. In the context of a longitudinal course of 4–5 years following diagnosis,26 this represents reasonable coverage of the patient's testable lifespan. The cognitive measures included sentence comprehension, verbal working memory, and single word meaning.

Sentence comprehension

Patients responded to a simple question about the agent or the patient delivered in a brief, aurally presented sentence composed of familiar content words. The sentences had a simple subject-verb-object structure (for example, “The fat old chicken chased the young duck: which bird was chased?”) (“simple” sentences; n = 4) or a subordinate clause structure featuring a subject-relative clause (for example, “The eagle that chased the hawk is fast: which bird was chased?”) or an object-relative clause (for example, “The car that the truck hit was green: which vehicle was hit?”) (“complex” sentences; n = 8). Simple and complex sentences were created for word length and changed grammatical complexity by manipulating the number of filler sentences.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic features of PNFA and SD patients at first contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNFA (n = 14)</td>
<td>SD (n = 10)</td>
</tr>
<tr>
<td>Age, years</td>
<td>64.1 (10.3)</td>
</tr>
<tr>
<td>Education, years</td>
<td>14.4 (2.8)</td>
</tr>
<tr>
<td>Duration, months</td>
<td>29.1 (17.9)</td>
</tr>
<tr>
<td>MMSE, max = 30</td>
<td>23.3 (6.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Percent of PNFA and SD patients with impaired speech characteristics at first contact*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNFA</td>
<td>SD</td>
</tr>
<tr>
<td>Dysarthria (%)</td>
<td>7.1</td>
</tr>
<tr>
<td>Reduced speech rate (%)</td>
<td>78.6</td>
</tr>
<tr>
<td>Word finding pauses (%)</td>
<td>92.9</td>
</tr>
<tr>
<td>Circumlocutions (%)</td>
<td>42.9</td>
</tr>
<tr>
<td>Grammatical errors (%)</td>
<td>35.7</td>
</tr>
<tr>
<td>Phonemic paraphasic errors (%)</td>
<td>57.1</td>
</tr>
<tr>
<td>Semantic paraphasic errors (%)</td>
<td>28.6</td>
</tr>
<tr>
<td>Impaired repetition (%)</td>
<td>71.4</td>
</tr>
</tbody>
</table>

*The clinical chart of one SD patient was unavailable due to technical reasons.
adjectives. All sentences were semantically unbiased so that neither noun of a sentence was more likely to be the agent of the named action. Content words were matched for frequency across grammatically simple and complex sentences. Patients heard the sentences twice, presented at a natural cadence with a normal stress pattern. A sentence was repeated at a patient’s request.

**Verbal working memory**

A sequence of random single digits was presented at a rate of 1/s, and patients repeated the digits in an order reversing the order of presentation. The stimulus sequence began at a length of two digits, and sequence length increased by one digit until a patient failed to repeat two trials of a reversed sequence at a specific length.

**Single word meaning**

Patients were shown 48 familiar stimuli one at a time and asked to judge whether each was a member of a known target category. One target category was natural (vegetables) and another was manufactured (tools). Half of the stimuli were category exemplars and half were foils. For each category and each stimulus type, half of the items were individual words printed on a 3×5 inch index card and half were colour photos. Stimuli were matched across categories for frequency and familiarity; the picture stimuli were also matched for visual complexity. The category exemplars and foils were presented in a fixed random order and were otherwise blocked by category and material.

**Statistical considerations**

The relative contribution of grammatical, single word meaning, and working memory to sentence comprehension was assessed at first presentation with t tests and Pearson correlations. We used a Cox regression procedure to evaluate the longitudinal sentence comprehension performance of patients. To place the patients’ performance in the context of their progressive disease, we used each primary caregiver’s determination of the historical point of disease onset, and then divided the patient’s clinical history into 6 month segments. Disease onset was then aligned across individual patients, and we placed cognitive probes on this time line prior to analyzing performance with a Cox survival analysis. To evaluate the grammatical component of sentence comprehension, we assessed comprehension of grammatically simple sentences separately from grammatically complex sentences. We set a performance end point at 50% correct (that is, random response to a dichotomous probe). We investigated the role of verbal working memory and individual word meaning in sentence comprehension by dividing the cohorts of patients depending on their verbal working memory performance and their single word meaning performance at the first assessment. The cut off for impaired verbal working memory or impaired word meaning was a z score less than −1.96 (significant at the p<0.05 level, two tailed), relative to a group of 25 age and education matched healthy elderly subjects.

**RESULTS**

**Cross sectional characteristics of sentence comprehension difficulty**

Sentence comprehension accuracy in PNFA and SD patients when first seen is summarised in table 4. It can be seen that comprehension at first contact was more impaired for the complex sentences than the simple sentences in PNFA, while the simple sentences were more difficult than the complex sentences for the SD patients. Inspection of individual patient performance profiles showed a pattern of worse performance for grammatically complex sentences compared to grammatically simple sentences in eight (57%) of the 14 PNFA patients, while two additional patients were equally impaired in their comprehension of grammatically simple and grammatically complex sentences. The pattern of worse performance for grammatically complex sentences compared to grammatically simple sentences was seen only in two (20%) of the SD patients (χ² = 4.56; p<0.05). There was little correlation between comprehension accuracy for simple sentences and complex sentences (PNFA: r = −0.13; SD: r = −0.18) at first contact.

Correlations between sentence comprehension, verbal working memory, and single word meaning when first seen are provided in table 5. We found a significant correlation between comprehension of grammatically complex sentences and verbal working memory performance in PNFA near the onset of the disease process. This correlation was specific for grammatically complex sentences in PNFA, since there were no significant correlations with grammatically simple sentences. None of these correlations were significant in SD when first seen. These findings suggest a deficit in grammatical comprehension early in the course of PNFA that is related in part to the limited working memory of PNFA patients.

Table 4 shows that sentence comprehension accuracy declined in PNFA and SD. We performed paired sample t tests for each type of sentence in each group. We found a significant difference between performance at presentation and at the final assessment only in SD and only for grammatically complex sentences (PNFA: χ² = 4.56; p<0.05). Performance on measures of verbal working memory and single word meaning is also summarised in table 4. Declines in working memory and single word meaning were present but relatively modest. We used paired sample t tests to evaluate the longitudinal performance of each group on each task by comparing performance at presentation and at the final assessment. We found significant longitudinal decline only in SD and only for single word meaning (t(9) = 2.58; p<0.05).

**Longitudinal studies of sentence comprehension**

Cox regression analyses were used to examine declining sentence comprehension in PNFA and SD. The decline in overall sentence comprehension did not differ between PNFA and SD (χ² = 0.99; NS). Half of the PNFA patients and half of the SD patients reached their end points of random (50% accurate) performance at 3.5 years after disease onset. However, inspection of the slopes of decline suggested a difference between PNFA and SD. Thus, 20% of PNFA patients attained their end point at 2 years after onset, and 80% attained their end point at 6 years after disease onset. By
The association between limited working memory and impaired grammatical comprehension at the onset of PNFA does not apparently lead to additional comprehension difficulty in these patients over time.

**DISCUSSION**

Our observations provide the first empirical evidence that sentence comprehension declines over time in patients with primary progressive aphasia.\(^7^,8\) We found that patients with PNFA are quite impaired in their sentence comprehension when first seen, particularly their comprehension of grammatically complex sentences. A correlation analysis associated their grammatical comprehension deficit at presentation with limited working memory. PNFA patients’ sentence comprehension declined modestly over time, probably because the patients were so impaired when first seen that they did not differ from random performance. SD patients’ sentence comprehension did change over time. SD patients with impaired single word meaning declined more significantly in their comprehension of grammatically complex sentences than SD patients with relatively preserved single word meaning. We argue below that degraded single word representations and impaired working memory contribute to distinct patterns of declining sentence comprehension in PNFA and SD.

### Table 4  
Mean sentence comprehension, working memory, and single word meaning in PNFA and SD patients at first contact and last contact\(^*\)

<table>
<thead>
<tr>
<th></th>
<th>Sent comp—simple</th>
<th>Sent comp—complex</th>
<th>Working memory</th>
<th>Single word meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>First contact</td>
<td>Last contact</td>
<td>First contact</td>
<td>Last contact</td>
</tr>
<tr>
<td>PNFA</td>
<td>66.1 (27.0)</td>
<td>60.7 (21.3)</td>
<td>60.7 (18.9)</td>
<td>54.5 (24.8)</td>
</tr>
<tr>
<td>SD</td>
<td>77.5 (23.7)</td>
<td>50.0 (26.4)</td>
<td>71.3 (25.0)</td>
<td>54.3 (23.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD SEM impaired</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PNFA SEM impaired</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Sentence comprehension (Sent comp) and single word meaning measures are % correct, and working memory measure is the number of digits repeated correctly in the reverse order; \(\chi^2\) significant differences (p<0.05, according to \(t\) tests) between first contact and last contact were found in SD for comprehension of grammatically complex sentences and single word meaning. Values in parentheses are standard deviations.

### Table 5  
Correlations between sentence comprehension accuracy and performance on measures of working memory and single word meaning in PNFA and SD

<table>
<thead>
<tr>
<th></th>
<th>Sentence comprehension</th>
<th>Verbal working memory</th>
<th>Semantic memory</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNFA</td>
<td>Simple</td>
<td>0.09</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Complex</td>
<td>0.53(^*)</td>
<td>0.50</td>
</tr>
<tr>
<td>SD</td>
<td>Simple</td>
<td>0.04</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td>Complex</td>
<td>0.31</td>
<td>0.30</td>
</tr>
</tbody>
</table>

\(^*\)This correlation is significant at the p<0.05 level.
Early in the course of progressive aphasia, patients with PNFA have greater difficulty understanding grammatically complex sentences compared to grammatically simple sentences. This effect for grammatical complexity has been observed in other assessments of sentence comprehension in PNFA.36,39,40 One factor contributing to the deficit with grammatically complex sentences early in the course of PNFA appears to be verbal working memory. Previous work suggested that verbal working memory contributes to comprehension of grammatical features such as interpreting subordinate clauses in sentences,41 characteristic of the grammatically complex sentences used in the present study. For example, working memory may be necessary to retain a noun phrase mentally when encountered early in a sentence until it can be linked to a subordinate clause that occurs later in the sentence.41 We have shown that this working memory deficit is related to the comprehension of sentences rather than task related resources in a study of on-line sentence processing in PNFA.42

We did not observe a significant decline in comprehension accuracy over time in PNFA. These patients may not have been able to decline much further statistically since their performance with grammatically complex sentences did not differ from random at presentation. This may be related in part to the neuroanatomic distribution of disease in PNFA. Studies examining cortical atrophy and limited cortical metabolism have associated PNFA with disease in the left inferior frontal region,7,33,35 and a correlation study associated difficulty understanding grammatically complex sentences with a voxel based morphometric analysis of left inferior frontal cortical volume in PNFA.16 A BOLD fMRI study of sentence comprehension in healthy elderly subjects showed left inferior frontal activation during the comprehension of grammatically complex sentences,6, but PNFA patients with grammatical comprehension difficulty showed only limited left inferior frontal recruitment during their performance with the same sentences.7 A portion of the verbal working memory network is represented in a frontal region adjacent to this grammatical area,6, and recent work has demonstrated the contribution of this area to the processing of grammatically complex sentences.6,39 Cortical atrophy in this area appears to be related to impaired working memory in PNFA. These observations are consistent with the hypothesis that the neuroanatomic distribution of disease early in the course of PNFA compromises brain regions crucial to grammatical aspects of sentence comprehension and the working memory support contributing to the processing of these sentences.

We found a different longitudinal pattern of sentence comprehension decline in SD. This difference cannot be explained by non-specific factors such as overall disease severity or disease duration since PNFA and SD patients were matched in these regards. Progressive sentence comprehension decline in SD instead appears to be influenced by a lexical semantic deficit that contributes to sentence processing. Specifically, SD patients with impaired single word comprehension have a steeper decline in their performance with grammatically complex sentences than SD patients with relatively preserved single word comprehension. Yet, single word meaning did not correlate directly with sentence comprehension difficulty. These findings suggest that another facet of a word’s representation contributes to the sentence comprehension deficit in SD. Thematic role information is also represented in single words. This helps constrain sentence interpretation by specifying who can do what to whom, and this may be particularly valuable in the comprehension of sentences featuring grammatically complex long distance dependencies.43 Single word meaning correlates with left posterolateral and ventral temporal atrophy in SD.44,45 We are aware of only one report examining the neural correlate of sentence comprehension difficulty in SD.46 This study showed a correlation between sentence comprehension accuracy and cortical volume in the posterolateral portion of left temporal cortex. Additional work is needed to determine more directly whether thematic role knowledge correlates with left temporal atrophy in SD.

We cannot rule out that working memory also contributes to sentence comprehension difficulty in SD. Considerable decline was observed in SD patients with impaired working memory, although our sample was too small to examine this empirically. Working memory itself is a multi-component process that is thought to include a limited capacity, limited duration storage device for verbal material, and processes for maintaining this information in short term memory such as a phonological rehearsal loop.44 Functional neuroimaging studies associate a storage component of verbal working memory with left inferior parietal cortex.45 While this region may not be compromised in SD, other patients with a fluent form of progressive aphasia may have disease in this distribution that contributes to their sentence comprehension difficulty.44

Regardless of the basis for sentence comprehension difficulty in these patients, the different patterns of impaired sentence processing in PNFA and SD suggest that there are at least two distinct subgroups of patients with progressive aphasia.1 In contrast to clinical descriptions suggesting that progressive aphasia is a single, undifferentiated syndrome,47 our findings are more consistent with comparative empirical observations48,49 and quantitative structural imaging studies44 suggesting that PNFA and SD represent distinct subgroups of progressive aphasia.

Several caveats should be kept in mind when interpreting our findings. It would be important to determine whether other grammatical features of sentence structure are equally difficult for PNFA patients. The relatively modest number of follow up studies for each individual, and the small number of patients contributing to each subgroup, suggest caution in the interpretation of the Cox regression analyses. Our
findings, nevertheless, suggest that sentence comprehension declines over time in primary progressive aphasia. The precise longitudinal course of this difficulty appears to vary depending on several interacting factors. Among these are the states of grammatical processing, the integrity of the single word representations, and the condition of working memory in each subgroup of progressive aphasia. PNFA patients appear to have a grammatical comprehension deficit near the beginning of their disease, related in part to their early working memory impairment. Grammatical comprehension declines over time in SD, by comparison, apparently related to progressive difficulty with single word representation.

-------------

**Authors’ affiliations**

M Grossman, P Moore, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA

Portions of this work were supported by the US Public Health Service (AG17586, AG15116, and NS44266)

Competing interests: none declared

**REFERENCES**


A longitudinal study of sentence comprehension difficulty in primary progressive aphasia
M Grossman and P Moore

J Neurol Neurosurg Psychiatry 2005 76: 644-649
doi: 10.1136/jnnp.2004.039966

Updated information and services can be found at:
http://jnnp.bmj.com/content/76/5/644

These include:

References
This article cites 34 articles, 12 of which you can access for free at:
http://jnnp.bmj.com/content/76/5/644#BIBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections
Dementia (1020)
Memory disorders (psychiatry) (1390)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/