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Grammatical and resource components of sentence processing in Parkinson’s disease
An fMRI study

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Abstract—Background: Sentence comprehension requires linguistic processing as well as cognitive resources such as working memory (WM) and information-processing speed (IPS). The authors hypothesize that sentence comprehension difficulty in patients with mild PD is due to degradation of the large-scale neural network that supports cognitive resources during sentence processing. Objective: To understand the neural basis for sentence comprehension difficulty in PD. Method: Regional brain activity with blood oxygenation level–dependent fMRI was monitored while seven PD patients and nine healthy seniors answered a simple probe about written sentences that vary in their grammatical and cognitive resource properties. Results: Healthy seniors recruited posterolateral temporal and ventral inferior frontal regions of the left hemisphere, brain regions associated with grammatical processing that were also activated by PD patients. Healthy seniors also recruited left dorsal inferior frontal, right posterolateral temporal, and striatal regions that are associated with cognitive resources during sentence processing. Direct contrasts showed that striatal, anteromedial prefrontal, and right temporal regions are recruited to a significantly lesser degree in PD, but these patients have increased activation of right inferior frontal and left posterolateral temporal–parietal areas during sentence comprehension. Conclusions: These findings associate impaired sentence comprehension in PD with interruption of a large-scale network important for cognitive resources during sentence processing. These results also imply compensatory up-regulation of cortical activity that allows patients with mild PD to maintain sentence comprehension accuracy.

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Nondemented PD patients are impaired at understanding grammatically complex sentences. Additional material related to this article can be found on the Neurology Web site. Go to www.neurology.org and scroll down the Table of Contents for the March 11 issue to find the title link for this article.

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demented, based on extensive neuropsychological testing and Mini-Mental State Examination scores (mean ± SD score = 28.3 ± 1.4), and they were not depressed, based on clinical interview and the Beck Depression Inventory (mean ± SD score = 8.1 ± 5.5). There was no evidence for visual–spatial difficulty that could have compromised performance on a reading task. Other causes of parkinsonism were ruled out on the basis of clinical and laboratory exams. These patients were compared with nine healthy, right-handed seniors who were age matched (means ± SD: PD = 71.0 ± 10.2 years; controls = 65.7 ± 10.2 years; t[12] = 0.91, NS) and education matched (means ± SD: PD = 15.6 ± 1.1 years; controls = 15.8 ± 2.1 years; t[12] = 0.27, NS) with the PD patients. All subjects had normal structural MRI scans. These seniors were selected from among 13 healthy older control subjects so that they matched the mean sentence comprehension accuracy of PD patients during imaging, as summarized in table 1. Because of a technical malfunction, sentence comprehension accuracy had to be reaccessed in two of the PD patients and one healthy senior outside of the magnet bore.

**Materials** Table 1 summarizes the four types of sentences presented to the subjects. In brief, we assessed grammatical features of comprehension by administering sentences with a center-embedded clause that is subject-relative or object-relative. WM was evaluated in each of these sentences by including a short, three-word series of words between the head noun phrase and the gap where the displaced noun phrase is interpreted in the center-embedded clause or a longer, seven-word series between the head noun phrase and the gap. Each written sentence was presented in a word-by-word fashion, and the types of sentences were matched in word frequency, word length, and syllable length. Subjects responded to each sentence with a button press as soon as they felt they knew the answer to the single probe provided at the beginning of each run: "Did a male or female perform the action described in the sentence?" All sentences contained a male and a female equally distributed in each noun position in each type of sentence, so that the male was the correct response in 50% of each type of sentence. The button press initiated the presentation of the next sentence following a 1,000-millisecond break. We presented two 40-second blocks of each type of sentence in a pseudo-random order in each run, together with two 40-second blocks of a pseudo-font control task requiring similar sensory–motor processes. The pseudo-font stimuli consisted of brief (two to eight units in length) strings of simple, letter-like geometric shapes presented in a string-by-string manner, parallelizing the word-by-word presentation of sentences. Subjects responded with a button press as soon as they saw one of two target geometric designs that were presented at the beginning of the run. The blocks of stimuli were presented continuously, and subjects were not informed that blocks of different types of sentences were being administered. Healthy subjects performed four runs alternating at presentation rates of 750 or 500 ms/word, and we grouped data across levels of this factor in the analyses presented below. PD patients performed the task only at the 750-ms/word presentation rate as they were less reliable at performing the task at the faster rate. Forcing PD patients to perform the task at the faster rate would have introduced resource-related interpretive confounds due to relative task difficulty and would have prevented equating performance accuracy across groups because of increased errors in PD. Subjects were familiarized with the word-by-word presentation technique and the gender probe prior to entering the magnet bore, and the task was practiced by each subject.

**Procedures.** An LCD projector (Epson 5000, Long Beach, CA) compatible with high magnetic fields was used to back-project visual stimuli onto a screen at the magnet bore. The subject viewed the screen through a system of mirrors available on the GE head coil (Milwaukee, WI). A portable computer (Macintosh 1400C, Cupertino, CA) outside the magnet room used PsyScope presentation software to present stimuli and record response accuracy. This experiment was carried out at 1.5 T on a GE Echospeed scanner. We used the standard clinical quadrature radiofrequency head coil. Foam padding was used to restrict head motion. Each imaging protocol began with a 10- to 15-minute acquisition of 5-mm-thick adjacent slices for determining regional anatomy, including sagittal localizer images (repetition time [TR] = 500 ms, echo time [TE] = 10 ms, 192 × 256 matrix), T2-weighted axial images (fast spin echo, TR = 2,000 ms, TEeff = 85 ms), and T1-weighted axial images of slices used for fMRI anatomic localization (TR = 600 ms, TE = 14 ms, 192 × 256 matrix). Gradient echo-planar images were acquired for detection of alterations.

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**Table 1 Examples of sentence materials and accuracy during sentence comprehension challenges in healthy seniors and PD patients**

<table>
<thead>
<tr>
<th>Sentence type</th>
<th>Stimulus example†</th>
<th>Healthy elderly, n = 9</th>
<th>Mean (SD) % correct</th>
<th>PD, n = 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject-relative: short linkage</td>
<td>[The strange man], in black who t, adored Sue was rather sinister in appearance.</td>
<td>94.6 (4.9)</td>
<td>97.8 (3.2)</td>
<td></td>
</tr>
<tr>
<td>Subject-relative: long linkage</td>
<td>[The cowboy], with the bright gold front tooth who t, rescued Julia was adventurous.</td>
<td>91.1 (6.3)</td>
<td>86.1 (15.9)</td>
<td></td>
</tr>
<tr>
<td>Object-relative: short linkage</td>
<td>[The flower girl], who Andy punched t, in the arm was five years old.</td>
<td>88.5 (7.7)</td>
<td>75.4 (21.1)</td>
<td></td>
</tr>
<tr>
<td>Object-relative: long linkage</td>
<td>[The messy boy], who Janet the very popular hairdresser grabbed t, was extremely hairy.</td>
<td>90.7 (5.1)</td>
<td>84.1 (9.9)</td>
<td></td>
</tr>
</tbody>
</table>

† An analysis of variance comparing sentence comprehension accuracy in healthy seniors and PD patients revealed a significant main effect for clausal grammatical structure (F[1,16] = 9.84, p < 0.01) and a significant interaction effect for clausal structure × antecedent noun-trace distance (F[1,16] = 9.24, p < 0.01). However, there was no main effect for group (F[1,16] = 3.68, NS), and group did not interact significantly with any sentence comprehension factors.
of blood oxygenation accompanying increased mental activity. All images were acquired with fat saturation, a rectangular field of view of 20 × 15 cm, flip angle of 90°, 5 mm slice thickness, an effective TE of 50 milliseconds, and a 64 × 40 matrix, resulting in a voxel size of 3.75 × 3.75 × 5 mm. The echo-planar acquisitions consisted of 24 contiguous axial slices covering the entire brain every 2 seconds. A separate acquisition lasting 1 to 2 minutes was needed for phase maps to correct for distortion in echo-planar images. Raw data were stored by the MRLI computer on DAT tape and then processed off-line.

Initial image processing was carried out with Interactive Data Language (Research Systems, Inc. Sun Ultrix 60 workstation). Raw image data were reconstructed using a two-dimensional fast Fourier transform with a distortion correction to reduce artifact due to magnetic field inhomogeneities. Individual subject data were then prepared and analyzed statistically using statistical parametric mapping (SPM99), operating on a MatLab platform, developed by the Wellcome Department of Cognitive Neurology. In brief, the images in each subject’s time series were registered to the initial image in the series. The images were then aligned to a standard coordinate system.21 The data were scaled to equate global blood oxygenation level–dependent signal across groups and spatially smoothed with a 12-mm Gaussian kernel to account for small variations in the location of activation and gyral anatomy across subjects, and low-pass temporal filtering was implemented to control auto-correlation with a first-order auto-regressive method.

The data were pooled across subjects within groups prior to parametric analysis with a fixed effects model using t-test comparisons converted to z-scores for each compared voxel. As we are testing specific hypotheses, we provide contrasts that are stringent at the p < 0.001 level uncorrected for multiple comparisons that are in a cluster of at least 20 voxels. For convenience and readability, we refer to activated regions provided in the tables and figure with shorthand anatomical terms such as PLTC and dlFC, and these terms do not refer to fixed regions of interest with independent anatomical boundaries.

Results. The regional anatomic distribution of activation in healthy seniors during comprehension of the four types of sentences is shown in a pseudo-color figure, see figure 1A. The coordinates and magnitude of peaks associated with these activations are also summarized (additional material can be found on the Neurology Web site; go to www.neurology.org). Brain regions recruited significantly for all types of sentences in healthy seniors included left PLTC (Brodmann area [BA] 21/22), left vIFC extending into dIFC/premotor cortex (BA 6/44), and bilateral occipital cortex. Healthy seniors also recruited right PLTC (BA 21/22) for all types of sentences and adjacent portions of right parietal cortex (BA 40/7) for WM-demanding sentences with a long noun-gap linkage. Direct contrasts of activation patterns in sentences with long and short noun-gap linkages indicated subjects with a longer link recruited right PLTC and right parietal cortex to a significantly greater extent than sentences with a short linkage (additional material can be found on the Neurology Web site). This emphasizes the role of right temporal–parietal cortex in WM demands during sentence processing. We also found striatal activation for sentences with a long noun-gap linkage compared with sentences with a short linkage (additional material can be found on the Neurology Web site). Left vIFC (BA 47/45) was significantly activated for the object-relative sentences with a long noun-gap linkage. Direct contrasts of the different types of sentences emphasized the role of the left vIFC region in sentences with combined grammatical and WM demands (additional material can be found on the Neurology Web site).

Regional brain activation patterns during sentence comprehension in PD, compared with a pseudo-font baseline, are illustrated in figure 1B. The coordinates and magnitude of peaks associated with these activations are also summarized (additional material can be found on the Neurology Web site). For healthy seniors, we found significant activation in left PLTC, left dIPFC/premotor, right PLTC, and bilateral occipital cortices for all sentence conditions and in right parietal cortices for WM-demanding sentences with a long noun-gap linkage. Direct contrasts of sentences with long and short noun-gap linkages again indicated that sentences with a long linkage recruited right temporal–parietal cortex to a significantly greater extent than sentences with a short linkage (additional material can be found on the Neurology Web site). We also found activation of left IFC in PD. Direct contrasts of the different types of sentences emphasized the role of this brain region in grammatically demanding sentences in PD (additional material can be found on the Neurology Web site). We did not see activation of the striatum in PD as we did in healthy seniors.

Discussion. In the current study, we sought to determine whether linguistic or cognitive resource components of a large-scale neural network for sentence processing are interrupted in patients with mild PD by examining regional brain activation during the comprehension of several types of sentences. Our findings suggest that neural activation in PD during sentence comprehension differs in subtle but important ways from the pattern seen in healthy seniors. For example, there appear to be changes in the recruitment of components of a frontal–striatal–thalamic loop that may be one source of cognitive difficulty in PD.24 We found that PD patients have significantly reduced striatal recruitment during sentence processing compared with age-matched control subjects. The striatum appears to contribute to cognitive resources such as WM and IPS. In the current study, for example, healthy seniors recruited the striatum during comprehension of long-linkage sentences. Other fMRI work with nonlinguistic material in healthy young subjects has associated striatal recruitment with cognitive resources such as WM22,23 and IPS,24,25 and an fMRI assessment of sentence processing in young adults showed that the striatum contributes to IPS during comprehension.21 Studies of PD patients using nonlinguistic materials have reported limited WM26,27 and slowed IPS,28,29 and functional neuroimaging studies in PD have shown reduced striatal recruitment during similar nonlinguistic tasks.15,16 Ischemic insult to the caudate did not interfere with an early left anterior negativity shift in electrocortical activity, according to one evoked potential study of sentence processing,34 and follow-up work has related striatal disease instead to late electrocortical changes associated with an effort-related integrative component of sentence interpretation. In the context of PD patients’ cognitive resource limitations during sentence processing,5,6,31 our observations are consistent with the claim that the sentence comprehension pattern seen in PD is due in part to their restricted striatal recruitment.
Figure 1. Regional activation patterns associated with contrasts of each type of sentence minus the pseudo-font baseline in healthy seniors (A) and PD patients (B). Left hemisphere and right hemisphere lateral views of each type of sentence in each group of subjects: 1 = subject-relative short-linkage sentences; 2 = subject-relative long-linkage sentences; 3 = object-relative short-linkage sentences; 4 = object-relative long-linkage sentences.
We also found reduced activation of left anteromedial prefrontal cortex in PD, another component of a frontal–striatal–thalamic loop.\textsuperscript{14} Several studies have shown reduced resting brain activity in this distribution in PD.\textsuperscript{32,33} Much work has related medial frontal activation in a superior distribution to cognitive resources such as selective attention and performance monitoring in fMRI activation studies of healthy adults.\textsuperscript{34,35} and frontal activation also has been associated with IPS.\textsuperscript{36} Although we are not aware that anteromedial prefrontal cortex has been related previously to sentence comprehension, fMRI studies have associated activation of this brain region with a form of WM important for processing the structure of complex configurations of verbal information\textsuperscript{17,38} and the processing of subgoals during complex problem solving.\textsuperscript{39} Additional work is needed to specify the relationship between this anterior prefrontal distribution of changed activation and sentence processing.

We also found reduced activation of right PLTC in PD patients relative to healthy seniors. In the current study, direct contrasts of sentences with long linkages compared with those with short linkages suggested that healthy seniors recruit right PLTC to support comprehension of sentences with greater WM demands. We have associated right PLTC activation with sentence WM in young adults as well.\textsuperscript{12} Other labs also have related right PLTC activation to WM demands during sentence processing.\textsuperscript{40,41} Many reports have described sentence-processing impairments following right hemisphere stroke,\textsuperscript{42,43} and some of this work (e.g., syllogistic reasoning) seems to involve considerable resource demands that have been associated with right hemisphere activation.\textsuperscript{44,45} These findings are consistent with the claim that brain regions supporting cognitive resources during comprehension have limited activation in PD. Reduced right PLTC activation in PD may be related indirectly to the visual–spatial impairments that are seen in mildly impaired PD patients.\textsuperscript{46} Although obvious visual–spatial difficulty was not evident in this group of PD patients, we cannot rule out that visual sentence presentation made the task more difficult for PD patients. Subtle differences in the anatomic distribution of left perisylvian activation have been reported in the one study directly comparing visual and auditory modalities of sentence presentation, although this work did not find any evidence that the modality of presentation interacted with resource-related process-

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Brain region (Brodman area; coordinates)\textsuperscript{†} & Coordinates & Subject-relative & Object-relative \\
& & X & Y & Z & Short & Long \\
\hline
Recruitment less in PD than healthy seniors\textsuperscript{‡} & & & & & & \\
Left posterolateral temporal (BA 21/22) & $-56$ & $-40$ & $-4$ & 3.83 & 3.10 & 3.33 & 4.32 \\
Right posterolateral temporal (BA 21/22/39) & 36 & $-52$ & 12 & 4.19 & 2.87\textsuperscript{§} & 3.68 & 3.68 \\
Bilateral striatum & 20 & 12 & 20 & $-$ & 3.82 & $-$ & 3.79 \\
Bilateral anteromedial prefrontal (BA 32/10) & $-16$ & 52 & 28 & 3.46 & 3.48 & 3.08 & 3.66 \\
Left ventral inferior frontal (BA 47) & $-48$ & 24 & $-4$ & $-$ & $-$ & $-$ & 3.14 \\
Bilateral occipital (BA 17/18) & $-4$ & $-72$ & 20 & 5.71 & 3.79 & 4.98 & 4.36 \\
\hline
Recruitment greater in PD than healthy seniors & & & & & & \\
Left posterolateral temporal parietal (BA 22/40) & $-44$ & $-56$ & 32 & 4.65 & 4.00 & 4.57 & 4.32 \\
Right inferior frontal (BA 45/47) & 24 & 44 & 28 & 5.05 & 3.34 & 3.50 & 3.46 \\
Right parietal occipital (BA 19/39) & 20 & $-72$ & 44 & 4.65 & 4.28 & 3.57 & 3.96 \\
\hline
\end{tabular}
\caption{Magnitude of peak brain changes in direct contrasts of PD patients and healthy seniors during sentence comprehension\textsuperscript{*}}
\end{table}

\textsuperscript{*} Data refer to $z$-scores indicating height of peak activation in a cluster. All values are significant at least at the $p < 0.001$ level uncorrected for multiple comparisons, except where $\textsuperscript{§}$ indicates a peak approaching significance. Dashes indicate a region that did not show activation for the indicated type of sentence.

\textsuperscript{†} Representative coordinates refer to X-, Y-, and Z-axes in Talairach space,\textsuperscript{21} taken from object-relative sentences with a long linkage.

\textsuperscript{‡} Reduced activations in PD patients relative to healthy seniors for object-relative sentences with a long linkage are illustrated in axial slices in figure 2A with the following distribution: 1-bilateral anteromedial prefrontal; 2-left ventral inferior frontal; 3- bilateral striatum; 4-left posterolateral temporal; 5-right posterolateral temporal; 6- bilateral occipital.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{Regional activation patterns in direct contrasts of PD patients and healthy seniors. (A) Areas of reduced activation in PD patients relative to healthy seniors for object-relative long-linkage sentences, including lateral views and representative transaxial views (left hemisphere on the left) at $z = 0$ mm (a), $z = +8$ mm (b), and $z = +16$ mm (c). 1 = Bilateral anteromedial prefrontal; 2 = left ventral inferior frontal; 3 = bilateral striatum; 4 = left posterolateral temporal; 5 = right posterolateral temporal; 6 = bilateral occipital. (B) Areas of increased activation in PD patients relative to healthy seniors for object-relative long-linkage sentences.}
\end{figure}
ing demands during sentence comprehension in healthy subjects. Additional work is needed to evaluate the role of presentation modality and resource demands during sentence processing in PD.

We also observed reduced activation in PD relative to healthy seniors in another region that is not part of a frontal–striatal loop: occipital cortex. We presented sentences at two rates in healthy seniors but only at the slower of these two rates in PD patients to minimize potential resource-related confounds associated with task performance rather than sentence interpretation. Reduced occipital activation in PD may have been due to the smaller number of words that these patients read during this blocked design paradigm. Additional work is needed to establish the precise basis for activation changes in this region in PD.

Our observations also showed that patients with mild PD with good comprehension appear to increase recruitment of several brain regions when directly compared with healthy seniors. For example, unlike the unilateral dIFC/premotor activation seen in healthy seniors with good sentence comprehension, we found bilateral IFC recruitment during sentence comprehension in PD. Up-regulation of the IFC verbal WM network has been seen in other nonlinguistic and linguistic fMRI studies of healthy seniors with age-related WM limitations. PD patients also showed increased activation in a portion of frontal brain systems during resource-demanding nonlinguistic tasks. These findings are consistent with the hypothesis that activation of relatively preserved WM-related brain regions compensates in part for cognitive resource limitations in PD. In the current study, this may have allowed patients with mild PD to achieve comprehension accuracy that is equivalent to healthy seniors.

Left posterolateral temporal–parietal cortex was upregulated in PD compared with healthy seniors in the current study as well. This appears to be a portion of the large-scale network that is central to linguistic aspects of sentence processing, implying that the neural substrate essential to sentence processing is relatively preserved in PD. Like healthy seniors, PD patients also recruit left vIFC and bilateral occipital cortices. The patterns of relative activation across specific types of sentences are remarkably similar in PD and healthy seniors, and the nonspecific decrease in activation levels in some of these regions in PD does not appear to have any clinical consequences.

Several caveats must be kept in mind when considering our results. We examined a small number of mildly impaired patients with PD, and we used a fixed-effects model to assess brain activation profiles, so our findings cannot be generalized beyond the group of patients studied for this report. These issues emphasize the caution that must be adopted when interpreting our observations, and additional work is needed to confirm the results of this report. We used a blocked design because of the relatively robust data acquired with this technique, and this appears to compensate for the reduced activation that may be associated with repeated presentation of the same type of sentence in a block. Functional neuroimaging techniques for groups of subjects have adopted several statistical conventions to compensate for the limited spatial resolution of the imaging techniques, the minor interindividual differences in regional sulcal anatomy, and the relatively weak clinical magnet we used to collect data. For reasons such as these, the data we report represent an approximation of the anatomic distribution of cerebral activation associated with sentence processing, and future work using techniques with better spatial resolution will be necessary.

With these caveats in mind, the observations described in the current report appear to be consistent with our neural model of sentence processing. We hypothesize two dynamically interactive, large-scale processing networks during sentence comprehension. One component appears to be concerned with written comprehension and becomes modified depending on the linguistic features of the sentence being processed. The anatomic distribution of these activated regions appears to overlap considerably in young adults, healthy seniors, and PD patients. Anatomic elements include left PLTC and ventral portions of left IFC. A second component is concerned with cognitive resources such as WM and IPS. As a sentence emerges over time, this network temporarily retains its constituents while processing these complex materials. This component includes dorsal portions of left IFC, left parietal cortex, striatum, anteromedial prefrontal cortex, and right PLTC. Portions of this component appear to be interrupted in PD, consistent with the pattern of sentence comprehension difficulty in these patients, but other brain regions appear to be up-regulated so that PD patients can achieve reasonably accurate sentence comprehension early in the course of their disease.

References

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