Neural basis for sentence comprehension deficits in frontotemporal dementia

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Abstract

Many patients with frontotemporal dementia (FTD) have impaired sentence comprehension. However, the pattern of comprehension difficulty appears to vary depending on the clinical subgroup. The purpose of this study was to elucidate the neural basis for these deficits in FTD. We studied patients with two different presentations: Three patients with Progressive Non-Fluent Aphasial (PNFA), and five non-aphasic patients with a dysexecutive and social impairment (EXEC). The FTD patient subgroups were compared to a cohort of 11 healthy seniors with intact sentence comprehension. We monitored regional cerebral activity with blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) while subjects read sentences featuring both a grammatically complex object-relative center-embedded clause and a long linkage between the head noun phrase (NP) and the gap where the NP is interpreted in the center-embedded clause. Subjects decided whether the agent of the action is a male or a female. Healthy seniors activated both ventral portions of inferior frontal cortex (vIFC) and dorsal portions of IFC (dIFC) in the left hemisphere, often associated with grammatical and working memory components of these sentences, respectively. PNFA patients differed from healthy controls since they have reduced activation of left vIFC, while EXEC patients have less recruitment of left dIFC. We conclude that FTD subgroups have distinct patterns of sentence comprehension difficulty in part because of selective interruptions of a large-scale neural network for sentence processing.

1. Introduction

Frontotemporal dementia (FTD) is a neurodegenerative condition with progressive language, cognitive, and behavioral impairments (Grossman, 2002; Snowden, Neary, & Mann, 1996). Some cases of FTD are linked to a mutation on chromosome 17 that codes for tau, a microtubule-associated protein, while others show a very similar pattern of abnormally decreased tau levels in post-mortem biochemical studies of FTD brains (Foster et al., 1997; Zhukareva et al., 2001). Clinical-pathological studies involving functional neuroimaging have related this pattern of clinical and biochemical impairment to neuronal dropout and vacuolar degeneration that affects frontal and anterior temporal brain regions (Turner, Kenyon, Trojanowski, Gonatas, & Grossman, 1996). FTD has been sorted into clinical subgroups (Davis, Price, Moore, Campea, & Grossman, 2001; Neary et al., 1998; Price, Davis, Moore, Campea, & Grossman, 2001). One subgroup of FTD patients presents with progressive aphasia. Progressive Non-Fluent Aphasial (PNFA) patients appear to have effortful agrammatic speech and grammatical comprehension difficulty. Other progressive aphasias have Semantic Dementia (SD), involving a naming deficit and empty speech with poor single word comprehension. By comparison, another subgroup of FTD patients without obvious aphasia has an executive disorder that includes poor working memory (WM), and/or a behavioral disorder with altered personality and impaired social
conduct (abbreviated here as EXEC to avoid confusion with acronyms similar to FTD). Researchers have begun to elucidate the neuroanatomic basis for these difficulties with structural (Chan et al., 2001; Chan, Fox, & Scanhill, 2001; DeVita, Lin, Gee, Moore, & Grossman, 2002; Mummery, Patterson, Price, & Hodges, 2000) and functional (Grossman et al., 1998; Mummery et al., 1999) neuroimaging techniques. In the present study, we report our initial evaluation of the functional neuroanatomy of FTD while patients are performing a sentence comprehension task.

Pick first noted speech difficulty in a patient with apparent FTD over a century ago (Pick, 1892). Sentence comprehension difficulty has been documented in FTD as well (Grossman et al., 1996a; Hodges & Patterson, 1996; Snowden et al., 1996). Our model of sentence comprehension includes at least two components—core grammatical processing, and executive resources such as working memory—and comprehension difficulty in FTD may be due to a deficit with one or both of these components. Some researchers have described grammatical impairments in FTD patients (Hodges & Patterson, 1996; Mesulam, 1982; Snowden & Neary, 1994; Snowden, Neary, Mann, Goulding, & Testa, 1992; Turner et al., 1996; Weintraub, Rubin, & Mesulam, 1990). For example, PNFA patients have greater difficulty understanding oral sentences containing subordinate clauses (“The eagle that chased the hawk was fast”) than grammatically simple sentences (e.g., “The fast eagle chased the large hawk”) (Grossman et al., 1996b). Their comprehension impairment was not related to sentence length. Based on observations such as these, we hypothesized that grammatically impaired PNFA patients would demonstrate limited recruitment of the neural substrate for grammatical processes in the large-scale neural network that supports sentence processing.

Executive impairments such as diminished WM resources also contribute to sentence processing difficulty (Caplan & Waters, 1999; Just & Carpenter, 1992). Dual task paradigms in healthy seniors, in which syntactic processing becomes impaired during concurrent performance of a secondary task (Blackwell & Bates, 1995), emphasize the role of limited cognitive resources in sentence comprehension. Another way to assess the contribution of WM to sentence processing is with a cross-modal lexical priming paradigm administered to healthy seniors who have age-related WM limitations (Zurif, Swinney, Prather, Wingfield, & Brownell, 1995). In a sentence such as “[The boy], with black hair who the girl chased e, was bored,” for example, the displaced noun phrase (NP) “the boy” is retained in WM until its reactivation at the site of the gap (the gap is indicated by “e”), and the linkage between the antecedent NP and the gap from which it is moved is indicated by the subscript “i”). Healthy seniors demonstrated reactivation of the antecedent noun phrase during object-relative sentences only when the distance between the antecedent noun phrase and the gap was decreased to less than seven words, suggesting an age-related WM limitation during sentence processing.

A relationship between sentence comprehension difficulty and limited executive functioning has also been observed in some FTD patients without progressive aphasia. For example, EXEC patients who were insensitive to grammatical agreement information in an “online” word detection procedure had impaired “off-line” sentence comprehension on a task that required answering a probe question about an orally presented sentence (Grossman, 2002). Moreover, performance in the “off-line” comprehension task correlated with a reverse digit span task that requires WM and with a trail-making task that requires planning. Based on these observations, we hypothesized that EXEC patients with a WM impairment but little clinically apparent progressive aphasia would have difficulty recruiting portions of a sentence processing network that are important for WM-related features of a sentence.

A neural substrate for some aspects of sentence processing has begun to emerge in neuroimaging activation studies of healthy adults during studies of sentence comprehension. A necessary component of this large-scale neural network appears to include inferior frontal cortex (IFC) and postero-lateral temporal cortex (PLTC) of the left hemisphere (Caplan, Alpert, & Waters, 1998; Just, Carpenter, Keller, Eddy, & Thulborn, 1996; Michael, Keller, Carpenter, & Just, 2001; Ni et al., 2000). The distribution of activation within this sentence comprehension network appears to depend at least in part on the grammatical and WM properties of the sentence material (Cooke et al., 2002; Grossman et al., 2002a). Left ventral IFC (vIFC) was recruited for object-relative sentences containing a long linkage between the antecedent NP and the gap where it is interpreted. In addition, we observed activation in dorsal IFC (dIFC) and premotor cortex of the left hemisphere. This region has been associated with WM for letters, possibly a frontal rehearsal component that helps maintain verbal information in WM (Awh et al., 1996; Jonides et al., 1997; Paulesu, Frith, & Frackowiak, 1993; Smith & Jonides, 1999). This left dIFC region was up-regulated during an fMRI study of sentence comprehension in healthy seniors with age-related WM limitations, implying a role for this brain region in WM (Grossman et al., 2002a).

Neuroimaging studies have demonstrated the vulnerability of some of these brain structures in FTD, suggesting a neural basis for FTD patients’ sentence comprehension impairments. Limited left hemisphere glucose metabolic activity was seen in PET studies of progressive aphasia patients (Chawluk et al., 1986; Tyrrell, Warrington, Frackowiak, & Rossor, 1990). A SPECT correlation study of FTD patients associated...
difficulty understanding sentences containing a grammatically subordinate clause with reduced perfusion of the lateral superior and inferior portions of the left frontal lobe and left anterior superior temporal lobe (Grossman et al., 1998). A perfusion fMRI study correlated sentence comprehension difficulty with reduced activity in left frontal cortex of FTD patients (Grossman, Alsop, & Detre, 2001). Difficulty with resource-related aspects of cognitive processing has been associated with frontal brain regions as well. Limited cerebral blood flow activity thus was seen in dorsolateral prefrontal cortex in FTD patients during a resource-demanding word production task (Warkentin & Passant, 1997).

In this report, we present BOLD fMRI data from a study designed to assess the neural basis for sentence comprehension difficulty in PNFA and EXEC subgroups of FTD. To address comprehension deficits associated with each subgroup, we used sentences featuring both an object-relative center-embedded clause and a long linkage between the antecedent NP and the gap from which the NP has been displaced. These sentences have reliably produced vIFC and dIFC activation in the left hemisphere of healthy adults, and these regions of activation within IFC appear to be related in part to the grammatical and WM components of this sentence material, respectively. Based on the findings discussed above, we predicted that PNFA patients would have less activation of left vIFC than healthy seniors during processing of the grammatical features of sentences. We also expected that EXEC patients would exhibit relatively decreased recruitment compared to healthy seniors in the left dIFC-premotor area associated with verbal WM.

2. Methods

2.1. Subjects

We assessed eight patients with mild FTD diagnosed according to published criteria (McKhann et al., 2001; The Lund & Manchester Groups, 1994). Patients were subgrouped based upon clinical presentation using a revision (Davis et al., 2001; Price et al., 2001) of Neary et al.’s clinical diagnostic criteria (Neary et al., 1998). After conducting a chart review that included a semi-structured medical history and a comprehensive clinical neurological and neurocognitive examination, at least two independent raters arrived at a consensus subgroup diagnosis for each patient. Three PNFA patients were classified based on the insidious onset of nonfluent spontaneous speech with agrammatism, phonemic paraphasias, and anomia. Five EXEC patients were classified based on the insidious onset of executive limitations (e.g., poor planning, organization, and working memory) accompanied by a decline in social-interpersonal conduct (impairment in regulation of personal conduct, emotional blunting and loss of insight). Of the five EXEC patients, two did not have alterations of comportment or interpersonal conduct. Exclusionary criteria included other causes of dementia (e.g., metabolic, endocrine, vascular, structural, nutritional, infectious, and psychiatric disorders). Mean (± SD) age and education of PNFA and EXEC patients and 11 healthy seniors are given in Table 1. EXEC patients [t(14) = .138, ns] and PNFA patients [t(12) = 2.09, ns] were age-matched to healthy seniors. EXEC and PNFA patients were also age-matched to each other [t(6) = 1.61, ns]. EXEC patients and healthy seniors were education-matched [t(14) = 1.15, ns], but PNFA patients were not as well educated as either group. All subjects were paid for their participation and completed an informed consent procedure approved by the Institutional Review Board at the University of Pennsylvania.

Table 2 contains representative neuropsychological measures for FTD patients obtained independently of subgroup classification, compared to a group of eight age-matched healthy seniors. The Mini Mental Status Exam (MMSE) is a brief dementia index scored on a 30-point scale (Folstein, Folstein, & McHugh, 1975). The patients scanned in this experiment were mildly impaired. “Stroop” is a test of inhibitory control (Stroop, 1935). Subjects are given a list of 80 color names arrayed in five columns on a sheet of paper. Each name is printed in an ink color that does not correspond to the named color (e.g., the word “red” printed in a green color). Subjects are asked to name the color of ink of as many printed words as possible in 300 s. To perform this task, subjects must inhibit reading the name of the color while they report the color of ink. “Trails B” is a test of task switching and strategic planning (Reitan, 1958). Subjects are given a paper with 26 letters and numbers distributed randomly throughout the page. They are asked to draw a line connecting as many stimuli as

![Table 1 Mean (SD) age and education of healthy seniors (SENIOR), Progressive Non-Fluent Aphasic (PNFA) patients and dysexecutive/social (EXEC) patients](image-url)
possible in 300s, with the stipulation that the sequence alternate between a number and a letter in an ascending order. EXEC patients were impaired on these measures relative to PNFA patients. "Tokens" is a test of auditory sentence comprehension (De Renzi & Vignolo, 1962). We used a validated version of this task involving 12 items. Subjects are asked to move colored geometric shapes arrayed in front of them. To perform this task, subjects must successfully comprehend the structure of the oral instructions given by the examiner. PNFA patients performed more poorly than EXEC patients on this sentence comprehension task.

2.2. Materials

Sentences contained both a grammatically complex feature (object-relative center-embedded clause) and a heavy WM load (seven-word long antecedent-gap linkage). These sentences were embedded in the context of other sentences containing subject-relative constructions and shorter antecedent-gap linkages. To test our hypotheses, we could not analyze the sentences with object-relative constructions and a short linkage, or sentences with subject-relative constructions and a long linkage, because these materials do not fully dissociate grammatical and WM processes during aging in a uniform manner (Grossman et al., 2002a, 2002b). Using the same set of sentences to assess both processes also provided a useful control for other, unanticipated sources of processing demand, such as the interaction between these resource-demanding elements of a sentence. Half of each type of sentence had a female as the agent, the remainder a male. The task for all sentences was to decide whether a female or male is the agent of the action in the sentence. Subjects indicated their response by pressing one of two buttons with the thumb of the left hand or the right hand.

These sentences were presented in a written word-by-word manner, allowing us to fully control presentation rate. This also allowed us to avoid degradation of aural stimuli due to the loud (~80 dB) noise level associated with MRI magnet operation. Moreover, we avoided the interpretive confound of recruiting primary and secondary auditory cortices for the stimulus modality versus language-sensitive cortices in a left peri-Sylvian distribution. To equate for duty cycle and the amount of time needed to process sentences of unequal difficulty, subjects responded to a sentence as soon as they felt that they had the correct response, and the next sentence was initiated by the subject’s response. This also minimized grammatically irrelevant aspects of WM by not requiring subjects to retain their response until the end of sentence presentation.

In each run of stimulus presentation, longitudinal magnetization stabilized while subjects were acclimated to the MRI environment by viewing a blank screen for 20s and then an asterisk for 40s. These data were discarded. Eight randomly ordered blocks of sentences (including two blocks of each type of sentence) were presented for 40s each and without a break between blocks of different sentence types. Subjects were not informed that blocks of different types of sentences were being administered. Four runs of sentence stimuli were presented in total, and the rate of word presentation alternated across runs at 750 and 500ms/word for healthy seniors.1 Data were averaged across rate of presentation because we did not find a difference in activation patterns for these two presentation rates. For FTD patients, sentence presentation remained static across all four runs at either 750 or 1000ms/word, depending on the patients’ ability to maintain performance during pre-scan testing. Each run also included two baseline sensory-motor blocks of pseudofont stimuli designed to resemble the sentence material. The baseline task probed detection of one of two pseudofont targets in a sentence-like string of pseudofont “words,” resembling the two-choice probe of the sentences. These were presented analogously to the true sentences (each pseudofont word presented sequentially one at a time, each string containing 13 pseudofont words, identical presentation rates, the ability to respond as soon as the target was seen, a response triggered the next string). The targets were presented at the beginning of each of these baseline blocks for 1 s. Pauses in performance were included between runs (every 8 min 20 s).

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1 We had initially hoped to assess information processing speed in this study, but this design feature was subsequently eliminated when it proved uninformative in healthy seniors and too difficult for FTD patients.

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Table 2
Neuropsychological measures of healthy seniors (SENIOR), Progressive Non-Fluent Aphasics (PNFA) and dysexecutive/social patients (EXEC)

<table>
<thead>
<tr>
<th>Measure</th>
<th>SENIOR (n = 8)</th>
<th>PNFA (n = 3)</th>
<th>EXEC (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (max = 30)*</td>
<td>29.6 (7.4)</td>
<td>26.3 (3.1)</td>
<td>24.4 (4.3)</td>
</tr>
<tr>
<td>Stroop % accuracy</td>
<td>98.6 (2.2)</td>
<td>100 (0)</td>
<td>90.5 (12.4)</td>
</tr>
<tr>
<td>Trails B % accuracy</td>
<td>98 (3.0)</td>
<td>93.3 (8.3)</td>
<td>78.7 (19.5)</td>
</tr>
<tr>
<td>Tokens (max = 12)</td>
<td>11.3 (.88)</td>
<td>7.7 (3.8)</td>
<td>10.5** (2.1)</td>
</tr>
</tbody>
</table>

* MMSE, Mini Mental Status Exam.
* Indicates n = 4.
** Indicates n = 2.
An LCD projector (Epson PowerLite 5000) 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. A portable computer (Macintosh G3) outside the magnet room used PsychoScope presentation software (Cohen, MacWhinney, Flatt, & Provost, 1993) to present stimuli and record response accuracy.

Subjects were familiarized with the word-by-word presentation technique and the gender probe prior to entering the magnet bore, and each subject practiced the task. We monitored behavioral accuracy and latency while imaging data were being collected. A technical error prevented the collection of behavioral data in one healthy senior, so his behavioral data were obtained outside of the magnet. One PNFA patient was scanned for only one and one half of the four runs.

2.3. Imaging data acquisition and statistical analysis

This experiment was carried out at 1.5T 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 10–15 min acquisition of 5 mm thick adjacent slices for determining regional anatomy, including sagittal localizer images (TR = 500 ms, TE = 10 ms, 192–256 matrix), T2-weighted axial images (FSE, TR = 2000, TE = 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 echoplanar images were acquired for detection of alterations of blood oxygenation accompanying increased mental activity. All images were acquired with fat saturation, a rectangular FOV of 20 × 15 cm, flip angle of 90°, 5 mm slice thickness, an effective TE of 50 ms, and a 64 × 40 matrix, resulting in a voxel size of 3.75 × 3.75 × 5 mm. The echoplanar acquisitions consisted of 24 contiguous slices in the axial plane covering the entire brain every 2 s. A separate acquisition lasting 1–2 min was needed for phase maps to correct for distortion in echoplanar images (Alsop, 1995). Raw data were stored by the MRI computer on DAT tape and then processed off-line.

Initial data processing was carried out with Interactive Data Language (Research Systems) on a Sun Ultra 60 workstation. Raw image data were reconstructed using a 2D FFT with a distortion correction to reduce artifact due to magnetic field inhomogeneities. Individual subject data were then prepared and analyzed statistically with a fixed-effects model using statistical parametric mapping (SPM99), operating on a MatLab platform, developed by the Wellcome Department of Cognitive Neurology (Frackowiak, Friston, Frith, Dolan, & Mazziotta, 1997). Briefly, 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 (Talairach & Tournoux, 1988). The data were scaled to equate global perfusion, and spatially smoothed with a 12 mm Gaussian kernel to account for small variations in the location of activation and subtle variability in gyral anatomy across subjects. Low-pass temporal filtering was implemented to control auto-correlation with a first-order auto-regressive method. The data were analyzed parametrically using t test comparisons converted to z-scores for each compared voxel. Unless noted otherwise, we tested our hypotheses by examining coordinates significant at p < .001 uncorrected for multiple comparisons.

3. Results

3.1. Behavioral data

Analysis of variance (ANOVA) with factors comparing group (EXEC, PNFA, control), grammatical structure (object-relative, subject-relative), and antecedent-gap length (short, long) revealed a significant group × grammatical structure interaction \( F[2, 14] = 8.79, p < .005 \). The results are summarized in Table 3. A planned t test confirmed that PNFA performance was worse than healthy seniors for object-relative sentences.

<table>
<thead>
<tr>
<th>Sentence type</th>
<th>Stimulus example</th>
<th>Accuracy: % correct (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject-relative—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>short antecedent-gap</td>
<td>[The strange man] in black who e, adored Sue was rather sinister in appearance</td>
<td>94.7 (5)</td>
</tr>
<tr>
<td>Subject-relative—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>long antecedent-gap</td>
<td>[The cowboy] with the bright gold front tooth who e, rescued Julia was adventurous</td>
<td>91.1 (6)</td>
</tr>
<tr>
<td>Object-relative—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>short antecedent-gap</td>
<td>[The flower girl] who Andy punched e, in the arm was five years old</td>
<td>88.5 (8)</td>
</tr>
<tr>
<td>Object-relative—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>long antecedent-gap</td>
<td>[The devoted boyfriend] who Carla from the doughnut shop loved e, was very content</td>
<td>90.8 (5)</td>
</tr>
</tbody>
</table>

Table 3

Example sentence material and mean percent (SD) accuracy during sentence comprehension tasks for healthy seniors (SENIOR), Progressive Non-Fluent Aphasics (PNFA) and dysexecutive/social patients (EXEC)
interaction effect [\( t(12) = 4.67, p < .001 \)], corresponding to their grammatical impairment. A second ANOVA contrasting EXEC and controls showed a significant group \( \times \) length interaction effect \([F(1, 14) = 5.79, p < .03]\). A planned \( t \) test showed that EXEC performance was worse than performance in healthy seniors for WM-demanding long antecedent-gap sentences \([t(14) = 3.01, p < .01]\), confirming their relative WM impairment.

### 3.2. Imaging data

Coordinates corresponding to the peak loci in activated areas are given in Table 4. Fig. 1 shows areas of recruitment during comprehension of object-relative sentences with a long antecedent-gap linkage relative to the baseline task. For background purposes, we show in Fig. 1, Panel A that healthy seniors recruited left vIFC and dIFC. They also activated left posterolateral temporal cortex and right temporal-parietal cortex. These findings are discussed in greater detail elsewhere (Grossman et al., 2002a). Fig. 1, Panel B shows that PNFA patients activated left dIFC (BA 6/44), like healthy seniors. However, vIFC activity did not exceed our statistical threshold. Fig. 1, Panel C shows that EXEC patients recruited left vIFC (BA 45/47), but they did not recruit left dIFC to a statistically significant degree.

### 4. Discussion

PNFA patients are thought to have difficulty processing grammatically complex sentences, while EXEC patients appear to have WM limitations that contribute to their sentence comprehension deficit. Analyses of FTD patients’ behavioral performance in the present study are consistent with these characterizations: PNFA patients were most impaired at understanding sentences that contain object-relative clauses, and EXEC patients encountered their greatest difficulty understanding sentences with a long antecedent noun-gap linkage. Previous fMRI studies of sentence comprehension in healthy subjects have begun to associate grammatical components of sentence processing with ventral portions of left IFC and WM components of sentence processing with dorsal portions of left IFC (Caplan et al., 1998; Cooke et al., 2002; Just et al., 1996; Kang, Constable, Gore, & Avrutin, 1999; Michael et al., 2001; Ni et al., 2000). Based on these observations, we hypothesized different patterns of left frontal activation during comprehension of sentences with an object-relative center-embedded clause and a lengthy antecedent noun-gap linkage in subgroups of FTD patients. In fact, fMRI activation patterns showed distinct profiles in FTD patient subgroups consistent with our predictions. PNFA patients had difficulty recruiting ventral portions of left inferior frontal cortex most closely associated with grammatical processing, while EXEC patients were impaired activating dorsal portions of left inferior frontal cortex associated with verbal WM. This may be related to the selective distribution of the histopathological abnormalities seen in FTD patients with distinct clinical presentations (Grossman, 2002; Harasty, Halliday, Code, & Brooks, 1996; Lieberman et al., 1998; Turner et al., 1996). Interruptions within the large-scale neural
network for sentence processing in FTD patient sub-
groups, reflecting relative difficulty with grammatical or
WM components of sentences, are consistent with a
model of sentence processing that includes partially
dissociable grammatical and WM components.

Several researchers have observed dissociations in
language-related processes involving specific sub-regions
of left frontal cortex in healthy subjects that may help
explain our observations in FTD patient subgroups.
Semantic processing may preferentially activate vIFC
(BA 47/45), while phonological processing may activate
more dorsal portions of IFC (BA 44/45) (Poldrack et al.,
1999). Similarly, anterior aspects of ventrolateral pre-
frontal cortex (PFC) (BA 45/47) may support access and
maintenance of semantic representations, while posteri-
or aspects of IFC (BA 44/6) may support phonological
access and maintenance (Wagner, Maril, Bjork, & Sch-
acter, 2001). Others have contrasted ventral IFC with
dorsolateral PFC. An fMRI study during Wisconsin
Card Sorting Task performance attributed the mainte-
nance of a contingency set to dorsolateral prefrontal
cortex (BA 46/9), and the shifting of attentional set to
mid-ventrolateral IFC (BA 47/12) (Monchi, Petrides,
Petre, Worsley, & Dagher, 2001). Smith and Jonides
(1999) reviewed functional neuroimaging evidence that
short-term storage of verbal material (i.e., subvocal re-
hearsal) is supported by ventrolateral IFC (BA 45/47),
Broca’s area (BA 44), and left supplementary motor
and premotor areas (BA 6), while active manipulation
of verbal material is supported by dorsolateral PFC.

Petrides and coworkers integrated data from lesioned
monkeys and functional neuroimaging studies in hu-
mans to put forth a two-level hypothesis that distin-
guishes active strategic encoding and long-term memory
retrieval processes supported by mid-ventrolateral IFC
(i.e., BA 45, 47/12) from monitoring and manipulation
processes supported by dorsolateral PFC (Petrides,
1996; Petrides, Alivisatos, & Evans, 1995). Others have

Fig. 1. Areas of significant activation during comprehension of sentences with an object relative clause and a long antecedent-gap linkage in
comparison to a pseudofont baseline, illustrated with lateral projections. (A) Healthy seniors (n = 11), (B) progressive-non-fluent aphasics (n = 3), (C)
dysexecutive/social patients (n = 5).
emphasized modality-based functional specialization in dorsal and ventral frontal regions (Owen, 1997).

Functional distinctions along the dorsal-ventral axis of inferior frontal cortex in this work honor an anatomic distinction based on cytoarchitectonic studies of these areas (Amunts et al., 1999). However, the fMRI results reported above should be interpreted with caution. Dorsal and ventral regions of the frontal lobe have been recruited by a wide variety of cognitive tasks, emphasizing that these regions appear to support multiple cognitive functions (Duncan & Owen, 2000). Our data can be directly compared with this literature only cautiously, moreover, because of the linguistically rich nature of the sentence stimuli used in the current study. We can nevertheless attempt to relate our findings to existing non-linguistic work on frontal executive functions to examine the hypothesis that some aspects of sentence processing are an emergent property of phylogenetically older, non-linguistic processes. The association between dorsal prefrontal activity and active manipulation of stimulus material suggested by the process-based “two-level” hypothesis (Petrides, 1996) and studies of WM (Smith & Jonides, 1999) is consistent with our view of left dIFC as a WM resource for sentence processing. Dorsal (BA 44/45) activation for phonological processing (Poldrack et al., 1999) is not inconsistent with our results to the extent that the information contained in long antecedent-gap linkages may be processed phonologically and held transiently in a phonological WM store (Wagner et al., 2001).

There is less clear overlap, however, between our observations and the role played by ventral IFC in these non-linguistic studies. One possibility is that vIFC contributes to an aspect of our procedure that is related only indirectly to sentence processing, such as the ordered nature of the word-by-word method of sentence presentation. Some work in patients with frontal insult has shown difficulty appreciating order information, even though the content of the information may be preserved (Shimamura, Janowsky, & Squire, 1991). However, functional neuroimaging studies of healthy young subjects appear to have associated order information with dorsal portions of IFC and with dorsolateral PFC (Cabeza et al., 1997; Marshuetz, Smith, Jonides, DeGutis, & Chenevert, 2001). Other studies have associated ventral IFC activation with processing semantic representations (Demb et al., 1995; Thompson-Schill, D’Esposito, Aguirre, & Farah, 1997; Wagner, Desmond, Demb, Glover, & Gabrieli, 1997), although this approach is not compatible with other work showing selective vIFC activation for specific grammatical structures despite similar lexical semantic content (Cooke et al., 2002; Kang et al., 1999; Ni et al., 2000). Additional work is needed to establish whether one role of left vIFC in cognition is uniquely related to the interpretation of long-distance grammatical relations in sentences, or can be reduced in part to a process that suberves non-grammatical, phylogenetically older cognitive functions.

Regardless of the specific contribution of left vIFC to sentence interpretation, our work demonstrates one method for investigating the collaboration between dorsal and ventral portions of left inferior frontal cortex during the processing of sentences that involve grammatically structured material that varies in its WM demands. In healthy seniors with age-related WM limitations, we previously observed increased recruitment of WM-related left dIFC brain regions to help support sentence comprehension, although left vIFC activation apparently does not change with age during sentence comprehension (Grossman et al., 2002a, 2002b). The present study provides additional converging evidence concerning the critical relationship between grammatical and WM functions during sentence processing that is consistent with this approach. Specifically, we show that FTD patients have selectively impaired comprehension of sentences when a neural component contributing to grammatical or WM processes is not contributing effectively to the large-scale neural network underlying sentence comprehension. One potential confound associated with this approach is that FTD patient subgroups and healthy seniors were not equated for sentence comprehension accuracy. Differences in activation profiles thus could be related directly to the different patterns of comprehension difficulty that we find, or to the fact that poor sentence comprehension may also be associated with non-specific increases in resource-related task difficulty for more difficult sentences. Our approach nevertheless emphasizes that sentence comprehension should not totally fall apart during the interruption of the large-scale neural network that supports this complex real-world activity. Instead, there should be qualitative changes that yield subtle deficits with particular aspects of sentence processing. We believe that this converging approach, involving data from multiple sources, will ultimately lead to a clearer understanding of brain-behavior relationships.

While selective differences in left IFC recruitment in subgroups of FTD patients are consistent with our hypothesis, there are other changes in activation that could also contribute to some of the observed behavioral profiles seen in PNFA and EXEC subgroups of FTD patients. For example, PNFA patients additionally recruited medial frontal regions. This activation may support components of attention important for selecting and maintaining sensitivity to specific features of sentences (Benedict et al., 1998; Corbetta, Miezin, Shulman, & Petersen, 1993; Coull, Frith, Frackowiak, & Grasby, 1996; George et al., 1994), compatible with Posner’s executive component of attention (Posner & Petersen, 1990), or help control the implementation of
response selection during task performance (Botvinick, Braver, Barch, Carter, & Cohen, 2001). For example, several recent fMRI studies of the Stroop effect suggest that anterior cingulate cortex is activated in situations where competition between response choices must be resolved (Barch et al., 2001; Braver, Barch, Gray, Molfese, & Snyder, 2001; Carter et al., 1998; MacDonald, Cohen, Stenger, & Carter, 2000). Patterns of activation change such as this may reflect the development of a conscious, alternate behavioral strategy to support sentence comprehension. Alternately, this may reflect neural reorganization that is also observed in stroke patients (Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Rosen et al., 2000) and in studies of Alzheimer’s disease (Becker et al., 1996; Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001; Grossman et al., in press; Grossman et al., submitted; Saykin et al., 1999) that may support the emergence of alternate processing strategies. Regardless of the specific basis for this change, the increased activation of this medial frontal area in FTD suggests that changes in patients’ activation cannot be attributed entirely to a global reduction in FTD recruitment.

Another difference relative to healthy seniors is that left PLTC was not recruited in a statistically significant manner in EXEC patients. Similarly, we observed limited right PLTC activation in PNFA patients. We assessed small numbers of patients in this study, and we cannot rule out that there was insufficient power to demonstrate PLTC activation in FTD patients. Several studies of healthy young subjects have demonstrated activation of right PLTC during comprehension of resource-demanding sentences (Just et al., 1996; Keller, Carpenter, & Just, 2001). Our work suggests the possibility that this recruitment may be related to a material-specific form of WM (Cooke et al., 2002; Grossman et al., 2002a), and thus we cannot rule out that PNFA patients also have a material-specific WM limitation during sentence processing. Additional work is needed to establish the precise contribution of these right hemisphere regions to sentence processing difficulty in FTD.


Reference:  


