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SENTENCE PROCESSING IN LEWY BODY SPECTRUM DISORDER: THE ROLE OF WORKING MEMORY

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Abstract

Prior work has related sentence processing to executive deficits in non-demented patients with Parkinson's disease (PD). We extended this investigation to patients with dementia with Lewy bodies (DLB) and PD dementia (PDD) by examining grammatical and working memory components of sentence processing in the full range of patients with Lewy body spectrum disorder (LBSD). Thirty-three patients with LBSD were given a two-alternative, forced-choice sentence-picture matching task. Sentence type, working memory, and grammatical structure were systematically manipulated in the sentences. We found that patients with PDD and DLB were significantly impaired relative to non-demented PD patients and healthy controls. The deficit in PDD/DLB was most pronounced for sentences lengthened by the strategic placement of an additional prepositional phrase and for sentences with an additional proposition due to a center-embedded clause. However, there was no effect for subject-relative versus object-relative grammatical structure. An MRI voxel-based morphometry analysis in a subset of patients showed significant gray matter thinning in the frontal lobe bilaterally, and this extended to temporal, parietal and occipital regions. A regression analysis related sentence processing difficulty in LBSD to frontal neocortex, including inferiorprefrontal, premotor, and dorsolateral prefrontal regions, as well as right superior temporal cortex. These findings are consistent with the hypothesis that patients with PDD and DLB have difficulty processing sentences with increased working memory demands and that this deficit is related in part to their frontal disease.

Keywords

Lewy body; Parkinson's; sentence processing; working memory; MRI; prefrontal

INTRODUCTION

Parkinson's disease (PD) is thought to be primarily a motor disorder. However, it is increasingly recognized that non-motor aspects of PD can also be compromised (Rodriguez-Oroz, et al., 2009). Among the most disabling non-motor features is cognitive impairment (Aarsland, Bronnick, Larsen, Tysnes, & Alves, 2009; Elgh, et al., 2009; Foltynie, Brayne,

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Robbins, & Barker, 2004; Muslimovic, Post, Speelman, & Schmand, 2005). Indeed, cognitive symptoms in patients with PD are associated with more rapid disease progression (Starkstein, Bolduc, Mayberg, Preziosi, & Robinson, 1990), more frequent nursing home placement (Aarsland, Larsen, Tandberg, & Laake, 2000), greater caregiver burden (Aarsland, Larsen, Karlsen, Lim, & Tandberg, 1999), reduced quality of life (Siderowf, Ravina, & Glick, 2002), and increased mortality (Louis, Marder, Cote, Tang, & Mayeux, 1997). Perhaps the most commonly cited cognitive deficit in PD is a limitation in executive control (Brown & Marsden, 1990; Brown, Soliveri, & Jahanshahi, 2000; Dalrymple-Alford, Kalders, Jones, & Watson, 1994; Marie, et al., 1999; Price & Shin, 2009). By comparison, language difficulties have been examined rarely in PD and related disorders (Emre, et al., 2007; Tröster, 2008). In this study, we examined aspects of sentence processing that appear to depend on executive resources such as working memory.

Cognitive impairment in PD may be subtle at onset. Over time, progressive cognitive dysfunction reaches the level of dementia (PDD) in the majority of patients. Aarsland and colleagues (2003) measured the eight-year prevalence of dementia in a Norwegian community sample as 78.2% (95% CI, 71.1%–84.0%). This is a cumulative measure including PD patients with dementia at the baseline visit, as well as new cases of dementia among survivors at the eight-year visit (Aarsland, Andersen, Larsen, Lolk, & Kragh-Sorensen, 2003). In this population, Buter and colleagues (2008) showed that the cumulative incidence of dementia increased with age and duration of PD and, conditional on survival, increased to 80–90% by 90 years of age (Buter, et al., 2008). Hely and colleagues (2008) demonstrated dementia in 83% of 20-year survivors in a sample of Australian patients with newly diagnosed PD (Hely, Reid, Adena, Halliday, & Morris, 2008).

Dementia in PD is associated with the presence of Lewy bodies in the cerebral cortex, as well as in limbic and brainstem structures (Bertrand, et al., 2004; Goedert, 2001; Iwatsubo, 2003; M. E. Kalaitzakis, et al., 2009). Moreover, dopamine-producing cells in the substantia nigra pars compacta are prominently affected (Ehringer & Hornykiewicz, 1960), compromising projections to the striatum and ventral tegmental area, as well as disrupting frontal-striatal circuits. This histopathologic picture is similar to that seen in dementia with Lewy bodies (DLB). Indeed, patients with PDD and DLB both have variable degrees of parkinsonism, as well as cognitive impairment most prominent in frontal/executive and visuospatial domains (Aarsland, Litvan, et al., 2003; Horimoto, et al., 2003; Lippa, et al., 2007; Mosimann, et al., 2004; Weintraub, et al., 2005). DLB is distinguished clinically from PDD in its earlier onset of cognitive dysfunction relative to motor features (McKeith, et al., 2005). PD, PDD, and DLB thus can be considered to sit along a spectrum of disease characterized by overlapping extrapyramidal and cognitive features, unified by the presence of histopathologic Lewy bodies, and varying in the relative onset of motor and cognitive features (Lippa, et al., 2007). We refer to this family of conditions as Lewy body spectrum disorder (LBSD). We acknowledge that this view of PD, PDD, and DLB as a spectrum of cognitive and extrapyramidal motor disorders is not universally accepted. For example, other researchers have identified both similarities and differences in the cognitive consequences of PDD and DLB (Aarsland, Litvan, et al., 2003; Downes, et al., 1998). Others have demonstrated the presence of Alzheimer's disease pathology in some of these patients, suggesting that this process may also contribute to dementia (Hurtig, et al., 2000; M. Kalaitzakis, Graeber, Gentleman, & Pearce, 2008; Tsuboi, Uchikado, & Dickson, 2007).

In patients with LBSD, the most consistent neuropsychological deficit is executive dysfunction. This is a broad domain of cognition that supports on-going cognitive processes and includes attention, initiation of action and thought, working memory, planning and organizing, decision-making, and inhibitory control (Barbas, 2006; Kobayakawa, Tsuruya, & Kawamura, 2010; Muslimovic, et al., 2005; Uekermann, et al., 2004; Weintraub, et al.,

2005). It is difficult at times to identify unambiguously the nature of additional cognitive resources contributing to performance. During sentence processing, a lengthened sentence may be maintained in an enlarged processing space by increasing working memory resources. Alternately, more strategic organizational resources may be recruited while maintaining the same working memory capacity by optimizing processing strategies. Both of these approaches appear to recruit similar dorsolateral prefrontal regions during fMRI studies, for example (Braver, et al., 1997; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999; Smith, Marshuetz, Geva, & Grafman, 2002). In this paper, we use the phrase “working memory” to refer to a quantitative increase in processing load, and we use “executive functioning” to refer to potential processing strategies that may involve either increased working memory capacity (e.g. increased processing load) or optimized processing strategies. Regardless of the specific cognitive basis for these effects, executive dysfunction in patients with LBSD is likely related to compromised frontal-basal ganglia circuits (Lewis, Dove, Robbins, Barker, & Owen, 2003; Zgaljardic, Foldi, & Borod, 2004), and may be due in part to pathological changes in cortical regions including frontal cortex (Aarsland, Perry, Brown, Larsen, & Ballard, 2005; Gomperts, et al., 2008; Hurtig, et al., 2000). Volumetric MRI studies have shown frontal gray matter loss in LBSD, although there may also be extension to temporal, occipital, and parietal cortical areas, and deep gray matter structures also may be involved (Beyer, Larsen, & Aarsland, 2007; Burton, McKeith, Burn, Williams, & O'Brien, 2004; Whitwell, et al., 2007). Functional imaging has shown disturbance of frontostriatal metabolism in these disorders (Lewis, et al., 2003; Lozza, et al., 2004; Sawamoto, et al., 2008).

Evidence has been accumulating that cognitive deficits extend to language in LBSD (Bastiaanse & Leenders, 2009; Chenery, Angwin, & Copland, 2008; Colman, et al., 2009; Grossman, 1999; Hochstadt, 2009; Pereira, et al., 2009). This work has demonstrated sentence processing difficulty in LBSD using a variety of techniques. In the earliest of these studies, probes of sentences varying in grammatical complexity and length revealed a significant sentence processing deficit that was attributed to working memory limitations (Grossman, et al., 1991; Grossman, Carvell, Stern, Gollomp, & Hurtig, 1992). Reduced comprehension of lengthy, grammatically complex sentences was demonstrated as resource demands increased, such as performing a secondary task concurrently (Grossman, Kalmanson, Bernhardt, Stern, & Hurtig, 2000) or increasing sentence presentation speed (C. Lee, Grossman, Morris, Stern, & Hurtig, 2003). To dissociate task-related performance demands from the resources needed to process a sentence, an on-line procedure was used to demonstrate relative insensitivity to grammatical processing demands in lengthened sentences in PD (Grossman, Lee, Morris, Stern, & Hurtig, 2002).

The present study extended our investigation of sentence processing in LBSD from PD patients with mild cognitive deficits to patients with PDD and DLB. Sentence processing has been examined rarely in these patients. We manipulated three factors in the sentence stimuli used in this study. The first factor is *sentence type*. We administered control, cleft, and center-embedded sentences. Control sentences used in this study do not have a subordinate clause, while cleft sentences and center-embedded sentences have a subordinate clause. The presence or absence of a subordinate clause is a grammatical feature. In addition, because it can be related in part to the number of propositions in a sentence, sentence type also reflects a working memory feature. For instance, active control sentences like “The fast, green car suddenly hit the big truck” and cleft sentences like “It was the green car that hit the truck” contain two propositions. By comparison, conjoined control sentences like “The car hit the truck and it was green” and center-embedded sentences such as “The car that suddenly hit the truck is green” contain three propositions.

A second factor that may contribute to sentence processing difficulty in LBSD is related only to *working memory*. Working memory is impaired in non-linguistic neuropsychological assessments of PDD and DLB (Calderon, et al., 2001; Collerton, Burn, McKeith, & O'Brien, 2003; Ferman, et al., 2006; Noe, et al., 2004; Salmon, et al., 1996). Aural sentences emerge over time, and working memory may be needed to maintain the initial portion of a sentence in an active mental state until later portions of the sentence are heard and can be linked to the earlier material. One way to assess the potential role of working memory in sentence processing is to stress working memory by inserting additional material strategically between sentence elements that must be linked. To exaggerate the working memory demands of these sentences, a prepositional phrase can be inserted between long-distance syntactically-linked dependencies, such as “The car with bright lights hit the truck that is dark green.”

The third factor is related only to a *grammatical feature*. Grammar involves a set of rules that defines the relationships between words in a sentence. In this study, we focused on the grammatical relationships that mediate long-distance syntactic dependencies so that a listener/speaker can appreciate “who is doing what to whom” within a sentence. Specifically, we manipulated grammatically the order of propositions in a sentence to examine whether LBSD patients are more impaired in their comprehension of sentences presented in an object-relative order compared to a subject-relative order. In subject-relative sentences like “The car that hit the truck is dark green,” the order of mention of propositions in the sentence corresponds to the order of occurrence of events in the real world. Here, the subject of the sentence “the car” is emphasized as the agent of the action. In object-relative sentences like “The car that the truck hit is dark green,” by comparison, the order of mention of propositions in a sentence does not correspond to the order of occurrence of events in the real world. Here, the subject of the sentence “the car” is the recipient of the action.

We used a two-alternative, forced-choice sentence-picture matching task to assess performance. This approach is analogous to that used in the Test for the Reception of Grammar (Bishop, 1989), but here we focus on a specific set of sentence factors with an adequate number of sentences involving each factor in order to understand the contribution of each factor to sentence comprehension performance. Since we use a repeated-measure design with the same sentence-picture matching methods across conditions, it is possible to minimize potential task-related effects by performing within-patient comparisons.

METHODS

Subjects

We studied 33 native Englishspeakers with LBSD, including 16 non-demented patients with PD and 17 patients with mild dementia due to PDD/DLB (8 with PDD and 9 with DLB). Patients were recruited from the University of Pennsylvania Health System cognitive neurology and movement disorders clinics. Patients were diagnosed with PD according to published criteria (Hughes, Daniel, Kilford, & Lees, 1992). Patients in the PDD/DLB group likewise met published criteria for these diagnoses (Emre, et al., 2007; McKeith, et al., 2005). The clinical distinction between PDD and DLB was based on the one-year rule: DLB is diagnosed if cognitive impairment occurs before or concurrently with parkinsonism (McKeith, et al., 2005). In addition, patients were classified as having dementia if (1) the Mini-Mental State Exam (MMSE) score was less than or equal to 24, or (2) the MMSE was greater than 24, but the patient performed in the demented range on the Mattis Dementia Rating Scale (DRS; age-adjusted scaled score less than or equal to 5) (Folstein, Folstein, & McHugh, 1975; Lucas, et al., 1998; Mattis, 1988). This latter criterion based on the DRS was implemented to capture patients with dementia largely on the basis of a dysexecutive syndrome, as the MMSE is relatively insensitive to executive deficits (Dubois, et al., 2007).

Clinical characteristics, demographic features, Hoehn and Yahr stage (Hoehn & Yahr, 1967), and Unified Parkinson's Disease Rating Scale (UPDRS) motor assessments (Fahn, Elton, & UPDRS Program Members, 1987) are summarized in Table 1. The PDD subgroup of patients was slightly older than controls, related to the fact that this condition tends to emerge over time in patients with longer-duration PD. However, we found no correlation between age and performance in the PDD/DLB group [$s = -0.22$; $p > 0.2$]. Exclusion criteria included a primary psychiatric disorder, structural brain lesion, and encephalopathy due to a medical condition. Some patients were taking stable doses of dopaminergic medications. Some patients were taking stable doses of a cholinesterase inhibitor, memantine, a non-sedating antidepressant, or a low dose of an atypical neuroleptic agent as clinically indicated. No patient showed evidence of sedation suggesting over-medication during testing. We also studied 12 healthy native Englishspeakers as controls. Control subjects were subject to a screening procedure to ensure absence of medication use or any neurologic, psychiatric, or medical condition that could compromise cognitive performance. In addition, control subjects had to score greater than or equal to 27/30 on the MMSE. This protocol was approved by the University of Pennsylvania Institutional Review Board. Written informed consent was obtained from all participants in this study. Some of these patients also participated in other studies from this lab during different testing sessions (Ash, et al., 2011; Grossman, et al., 2011).

Patients were characterized as well with a brief neuropsychological battery that included the following measures: episodic memory (verbal list learning delayed recall and recognition) (Libon, et al., 1996); executive functioning (reverse digit span (Wechsler, 1995), Trails B time to complete up to 180 msec (Reitan, 1958), and 50-trial Stroop color-word interference time to complete up to 180 msec (Stroop, 1935)); and semantic memory (Pyramids and Palm Tree semantic associativity for words) (Howard & Patterson, 1992). Performance on these measures is summarized in Table 2 as raw scores, as well as z-scores relative to 25 age- and education-matched controls who did not otherwise participate in this study. Comparisons between patient groups indicated that PDD/DLB patients are more impaired than non-demented PD patients for all measures at least at the $p < 0.01$ level, according to Mann-Whitney U tests, but PDD patients did not differ from DLB patients on any of these measures.

Materials and Procedure

We administered a two-alternative, forced-choice sentence-picture matching protocol to patients and control subjects. This protocol consisted of 72 items, with six stimuli in each cell (see below). Examples of sentence materials are provided in Table 3. The verbs used in these sentences were transitive, taking a subject and a direct object. The subject and the object were selected so that there was no semantic constraint or markedness associated with the materials. We manipulated three factors: 1) *sentence type*, including active control and conjoined control sentences (these were ultimately combined into a single set of controls, as performance on these two sentence types never differed), cleft sentences containing two propositions, and center-embedded sentences containing three propositions; 2) *sentence length*, including short sentences that are nine words in length and long sentences with an additional prepositional phrase that are 12 words in length; and 3) *sentence grammar*, including subject-relative and object-relative sentences.

Each sentence was paired with two colored pictures. One picture depicted the correct relationship between the subject and the object in the sentence, while the foil picture represented the reverse relationship between subject and object (e.g. a picture depicting a woman pushing a man in one picture, and the same man pushing the same woman in the second picture). In this task, the decision about matching a sentence to a picture is based on interpreting the actions of pictured individuals and not on the ability to discriminate a

property of a given individual. These pictures were displayed vertically one above the other, and the correct picture was the upper choice for half of each type of sentence. The stimuli types were randomly ordered. Sentences were read aloud at a comfortable rate with natural prosody while subjects viewed the pictures. Participants were given 15 seconds to point to the picture corresponding to the sentence. An item was considered incorrect if the subject did not respond within the allotted time (this occurred rarely).

A practice/training session was administered prior to the experimental task. This allowed participants to familiarize themselves with sentence presentation, the pairs of pictures, and the response modality. During this session, correct judgments were reinforced by the experimenter, saying “correct, the X is V-ing the Y.” Incorrect judgments were corrected by the experimenter, saying “no, the X is V-ing the Y” while the experimenter simultaneously pointed to the subject and the object depicted in the picture. All patients in the study demonstrated understanding of the procedure.

Statistical Analyses

There was a ceiling effect in healthy adults’ sentence comprehension performance, so we used nonparametric tests such as Friedman’s two-way analysis of variance by ranks, Mann-Whitney U to compare performance on specific aspects of sentence comprehension between groups, and the Wilcoxon signed-rank test to evaluate performance on specific aspects of sentence comprehension within groups.

Imaging Procedure

Twelve LBSD patients, including 5 patients with PD and 7 patients with PDD/DLB, had a volumetric T1-weighted brain MRI scan on average within 4.2 months of task administration. These patients did not differ statistically from the larger set of LBSD patients on any demographic or language measure. For eight patients (PD=2, PDD/DLB=6), as well as for 75 age-matched controls who comprised our local template for this study, images were collected using a SIEMENS Trio 3.0T scanner with 1-mm slice thickness using an MPRAGE protocol (TR = 1620 ms, TE = 3 ms, flip angle = 15°, resolution = .9766 × .9766 × 1 mm), and a 195 × 256 matrix. Four patients (PD=3, PDD/DLB=1) had MRI scans acquired using a GE 1.5T scanner with 1.2-mm slice thickness and the equivalent acquisition protocol with a 144 × 256 matrix. Images from both scanners were deformed into a standard local template space with a 1-mm³ resolution using Pipe Dream (<https://sourceforge.net/projects/neuropipedream/>) and Advanced Normalization Tools (ANTS, <http://www.picsl.upenn.edu/ANTS/>). These tools have been validated as stable and reliable for performing multivariate normalization (Avants, Epstein, Grossman, & Gee, 2008; Klein, et al., 2009). Both Pipe Dream and ANTS mapped T1 structural MRI images to an optimal template space, using diffeomorphic and symmetric registration methods (Avants & Gee, 2004; Avants, et al., 2010). The registered images were segmented into cortical and deep gray matter thickness maps using template-based priors and then registered to MNI-template space for statistical comparisons. Gray matter thickness images were smoothed in SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) using a 4-mm full-width half-maximum Gaussian kernel to minimize individual gyral variations.

In SPM5, a two-sample t-test contrasted gray matter thickness between patients with LBSD and healthy controls to identify regions of significant gray matter thinning, covarying for scanner. For this atrophy analysis, an explicit mask was defined by generating a mean gray matter image from the healthy controls in order to limit the analysis to voxel-wise comparisons within gray matter. The contrasts were performed at a $p < 0.005$ threshold (uncorrected). We accepted clusters with at least a 400-voxel extent and that contained peak voxels exceeding a height threshold of $p < 0.05$ (FDR-corrected).

The regression module in SPM5 was used to relate gray matter thinning to the sentence comprehension measure that most reflected the patients' sentence processing deficits, in particular, lengthened sentences containing three propositions (i.e., sentences with center-embedded clauses; see Results below). We performed a whole-brain analysis, and then used an explicit mask so that we could examine the relationship between comprehension performance and gray matter thinning specifically in brain areas known to be significantly atrophied from the prior analysis of whole-brain gray matter thinning. We interpreted only regions where comprehension performance was related to atrophied gray matter because we knew that these implicated regions are diseased and because it would be difficult to explain with confidence significant associations between non-atrophied regions and patients' performance. For the regression analysis, we used a statistical height threshold of $p < 0.01$ and accepted clusters containing a peak with z -score > 3.09 ($p < 0.001$) and an extent greater than 200 voxels. Coordinates for all accepted clusters were converted to Talairach space (Talairach & Tournoux, 1988) using mni2tal (<http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach>).

RESULTS

Behavioral results

Friedman's two-way analysis of variance by ranks demonstrated significant differences between groups depending on the sentence materials ($p < 0.001$). Subsequent nonparametric statistical comparisons revealed worse overall performance in PDD/DLB patients ($\mu \pm \text{correct} = 86.8 \pm 13.4$) compared to controls ($\mu \pm \text{correct} = 99.1 \pm 1.1$) and compared to non-demented patients with PD ($\mu \pm \text{correct} = 95.6 \pm 9.8$; all comparisons significant at $p < 0.001$). These findings were true for both patients with PDD ($\mu \pm \text{correct} = 91.8 \pm 3.5$) and patients with DLB ($\mu \pm \text{correct} = 82.4 \pm 17.4$; $p < 0.001$ for all comparisons).

Figure 1 suggests that between-group differences are not equal across all sentence types. Statistical analyses indicated that PDD/DLB patients are significantly impaired relative to controls and non-demented patients with PD for all types of sentences except for short control sentences without an additional phrase to stress working memory (all contrasts significant at least at $p < 0.05$). We found no differences between the PDD and DLB groups.

We performed within-patient analyses to investigate the basis for this deficit in greater detail. Control subjects were equally accurate for all types of sentences. Likewise, non-demented patients with PD were equally accurate for all sentence types, except for marginally worse performance for short center-embedded sentences compared to short cleft sentences ($p < 0.05$). In the PDD/DLB group, however, we observed greater difficulty for the short cleft and short center-embedded sentences compared to the short control sentences, and greater difficulty for the long center-embedded sentences compared to the long control sentences and the long cleft sentences (all comparisons significant at least at $p < 0.05$). We did not observe an effect for subject-relative compared to object-relative sentences, suggesting that grammatical manipulation alone had minimal impact on sentence comprehension performance in patients with PDD/DLB. In sum, these findings suggest that the insertion of either an additional phrase or an additional proposition stresses working memory and leads to impaired sentence comprehension in PDD/DLB patients.

Image Analyses

A gray matter thickness analysis in the LBSD cohort relative to healthy seniors revealed significant cortical thinning in frontal regions, extending into temporal, parietal, and occipital regions. Areas of thinning are illustrated in Figure 2, and the anatomic locations of peak voxels in these clusters are summarized in Table 4.

We performed regression analyses relating patients' sentence comprehension performance to gray matter thinning. Significant regressions are also illustrated in Figure 2, and the locations of peaks in significant regressions are summarized in Table 5. This analysis revealed areas of cortical thinning related to comprehension of lengthened sentences containing three propositions in inferior frontal, premotor, dorsolateral prefrontal, and right temporal regions.

DISCUSSION

Patients with LBSD have sentence comprehension difficulty, most evident in patients with DLB and PDD. Impairment was most prominent for lengthened sentences and sentences with a subordinate clause that contain three propositions. Object-relative sentences were not more difficult than subject-relative sentences, suggesting that grammatical complexity per se did not worsen patient performance. This pattern of sentence comprehension accuracy is related to disease in frontal brain regions bilaterally. We discuss these findings in greater detail below.

Sentence comprehension difficulty has been demonstrated previously in non-demented patients with PD. This work showed significantly impaired processing of resource-demanding sentences that stress working memory (Grossman, et al., 1991; Grossman, et al., 1992), as well as difficulty understanding grammatically complex sentences in the setting of increased resource demands such as speeded presentation (C. Lee, et al., 2003) or concomitant performance of a secondary task (Grossman, et al., 2000). This pattern of difficulty was equally evident in an on-line study of sentence processing (Grossman, et al., 2002), emphasizing that these findings could not be easily attributed to task-related demands. In the present study, we observed a similar pattern of performance in patients with mild dementia due to PDD and DLB. We found that the subgroup of LBSD patients with PDD/DLB has difficulty understanding sentences that are lengthened by the addition of a prepositional phrase strategically placed between sentence elements that must be linked prior to comprehension. Likewise, complex sentences containing three propositions are more difficult than complex sentences containing two propositions.

Both the addition of a prepositional phrase and the inclusion of three propositions stress working memory during sentence processing. Working memory is known to be impaired in LBSD (Calderon, et al., 2001; Collerton, et al., 2003; Ferman, et al., 2006; Noe, et al., 2004; Salmon, et al., 1996). It is important to point out in this context that task-related demands associated with performing an off-line task such as sentence-picture matching cannot fully explain patients' performance in this study. Indeed, PDD/DLB patients differed in their performance between sentence types despite the fact that task-related properties were otherwise matched (e.g. in both cases, patients were asked to listen to a sentence and point to one of two pictures). Moreover, the specificity of the deficit in PDD/DLB is emphasized by the observation that these patients were not impaired in processing object-relative sentences compared to subject-relative sentences.

There are two potential accounts of working memory difficulty, depending on the architecture of working memory resources. One possibility is that the form of working memory recruited during sentence processing is highly specialized and is dedicated to supplementing resource demands as they interact with other aspects of language such as syntax (Santi & Grodzinsky, 2007). A second possibility is that sentence processing is not a modular, self-contained process. Instead, sentence processing may take advantage of material-neutral resources like working memory to facilitate comprehension of lengthy sentences. This latter account would be consistent with previous work examining sentence

comprehension in PD during concurrent administration of various non-linguistic secondary tasks (Grossman, et al., 2000). Additional work is needed to resolve this issue.

Regardless of the nature of working memory, an important finding of the present study is that sentence comprehension in PDD/DLB patients was not compromised by manipulating a specific grammatical feature. Specifically, sentences with an object-relative structure were not more difficult than sentences with a subject-relative structure. The subject-relative or object-relative structure of a sentence depends on a rule that is specific to the grammatical structure of a language. Since this aspect of sentence processing appeared to be unimpaired in these patients, our observations lend credence to the claim that grammatical rules may be a distinct property of language that cannot be easily processed by material-neutral problem-solving algorithms.

PD patients without dementia were unimpaired overall in this study relative to controls. However, they did have some difficulty with center-embedded sentences. This resembles the pattern observed in previously published studies of non-demented patients with PD (Grossman, et al., 1991; Grossman, et al., 1992). The magnitude of the deficit may have been less in the present study compared to previous work because of the careful way in which we minimized cognitive difficulty in the PD group of LBSD patients. This may be clarified in the future by including LBSD patients with mild cognitive impairment, that is, an intermediate level of cognitive difficulty not sufficiently severe to constitute dementia (Litvan, et al., 2011; Tröster, 2008).

There has been considerable debate about the relationship between PDD and DLB. Patients with PDD and DLB are distinguished clinically according to the one-year rule: PDD is diagnosed when motor features precede the onset of cognitive difficulties by at least one year, while DLB is diagnosed when cognitive features precede or begin within one year of motor features (McKeith, et al., 2005). While most previous studies have failed to demonstrate a difference between these groups on measures of executive functioning (Aarsland, Litvan, et al., 2003; Noe, et al., 2004), others have reported a difference between these groups. For example, some described worse performance on executive measures assessing working memory, attention and organization (Aarsland, Ballard, & Halliday, 2004; Downes, et al., 1998). We did not find a difference in sentence comprehension between PDD and DLB patients. We had an opportunity to study only a small number of patients, and additional work with larger sample sizes will be needed to examine differences between these LBSD subgroups.

Few studies have examined the neuroanatomical basis of sentence comprehension difficulty in LBSD. Patients with LBSD are known to have frontal gray matter disease, as demonstrated using structural (Beyer, et al., 2007; Burton, et al., 2004; J. E. Lee, et al., 2010) and functional (Lewis, et al., 2003; Lozza, et al., 2004; Sawamoto, et al., 2008) imaging. This corresponds to histopathologic observations relating cortical Lewy bodies seen at autopsy to the presence of dementia (Hurtig, et al., 2000), although other deep gray matter structures also are implicated in PDD and DLB (Colosimo, Hughes, Kilford, & Lees, 2003; M. Kalaitzakis, et al., 2008; Tsuboi, et al., 2007). Imaging abnormalities also extend into parietal, temporal and occipital brain regions (Burton, et al., 2004), also observed at autopsy (Hurtig et al., 2000). The present study used volumetric MRI to obtain a detailed assessment of gray matter thickness. We found significant gray matter thinning in frontal regions bilaterally, and this extended to temporal, parietal and occipital regions. We did not observe significant hippocampal atrophy in the present study, although hippocampal atrophy has been reported elsewhere (Whitwell et al., 2007), consistent with the finding of varying degrees of Alzheimer's disease pathology in cases of PDD and DLB (Hurtig et al., 2000; Kalaitzakis et al., 2008; Tsuboi et al., 2007). We observed semantic memory difficulty in

some of the demented patients that may be due to co-occurring Alzheimer's disease. However, our observation of poor free recall with relatively preserved recognition memory suggests that a true episodic memory deficit is unlikely and that Alzheimer's disease pathology, if present, is relatively mild.

We were particularly interested to examine the neuroanatomic basis of the sentence processing difficulties seen in LBSD patients. Regression analyses implicated several regions in the frontal lobe that have been related to working memory. The inferior frontal lobe (Brodmann area 45) has been implicated in many studies of sentence processing and associated particularly with processing grammatical and working memory aspects of sentences (Friederici & Kotz, 2003; Grodzinsky & Santi, 2008). A related area identified in the regression analysis was the premotor region (Brodmann area 6), which has been associated with working memory (Smith, et al., 2002; Wager & Smith, 2003). A final region associated with sentence processing in LBSD was dorsolateral prefrontal cortex, an area associated with both increased working memory capacity demands and strategic decision-making (Badre & D'Esposito, 2007; Houde & Tzourio-Mazoyer, 2003; Koechlin & Hyafil, 2007; Sanfey, Hastie, Colvin, & Grafman, 2003). Both increased working memory capacity and strategic planning and organization appear to recruit similar dorsolateral prefrontal regions during fMRI studies of healthy adults (Braver, et al., 1997; Rypma, et al., 1999; Smith, et al., 2002). Thus, multiple areas of frontal cortex with significant gray matter thinning in LBSD appear to be related to sentence processing deficits in these patients that have been implicated in working memory. Although not often associated with working memory, fMRI studies have related activity in ventral prefrontal cortex (Brodmann area 11) to uncertainty during decision-making (Hsu, Bhatt, Adolphs, Tranel, & Camerer, 2005). We did not predict that regression analyses would relate sentence processing to right temporal thinning. However, previous work in stroke patients has related right temporal-parietal disease to grasping the spatial and configurational aspects of agents in sentences such as these (Caramazza, Gordon, Zurif, & DeLuca, 1976; Grossman, 1982).

Several caveats should be kept in mind when considering our findings. We studied only a small number of patients. We investigated a limited range of sentence features. We used a sentence-picture matching task, an off-line measure that involves processing resources. Because the sentence-picture matching task is relatively easy for controls, they showed a ceiling effect, and despite the pattern of within-patient differences seen in PDD/DLB, the ceiling effect may have limited the ability to detect impaired processing of purely grammatical features in patients. With these limitations in mind, our findings suggest that LBSD patients have difficulty with sentence processing, particularly for aspects of sentences that depend in part on working memory resources. By comparison, grammatical aspects of sentence processing related to the subject-relative or object-relative properties of a sentence were relatively preserved. This pattern of sentence processing difficulty in LBSD was related to frontal disease bilaterally.

HIGHLIGHTS

- We examined sentence-picture matching in Lewy body spectrum disorder.
- Comprehension was impaired by working memory demands but not grammatical factors.
- Sentence processing difficulty was related to MRI prefrontal thinning.

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FIGURE 1.
Sentence comprehension accuracy in lewy body spectrum disorder

FIGURE 2.

Significant cortical thinning in lewy body spectrum disorder compared to healthy controls with overlaid areas of significant regression relating cortical thinning to comprehension accuracy for lengthened sentences containing three propositions¹

NOTE

1. Colored areas indicate significant cortical thinning; blue areas indicate significant cortical thinning related to comprehension accuracy for lengthened sentences containing three propositions.

Mean ($\pm$ S.D.) demographic and clinical features of patients with Lewy body spectrum disorder and healthy elderly controls

TABLE 1

	PD	PDD	DLB	PDD/DLB	LBSD	Controls
Age	70.2 (6.5)	74.9 (7.2)*	70.6 (9.0)	72.6 (8.2)*	71.4 (7.0)	66.0 (7.2)
Education	15.7 (3.4)	14.5 (2.8)	14.0 (2.1)	14.3 (2.4)	15.0 (3.0)	15.7 (3.1)
MMSE	28.2 (1.9)	25.7 (1.7)	23.9 (4.6)	24.7 (3.7)	26.4 (3.4)	29.0 (1.3)
Hoehn & Yahr stage	2.2 (0.6)	2.8 (.07)	1.3 (0.5)	2.2 (0.9)	2.1 (0.8)	--
UPDRS total motor score	25.5 (9.1)	33.0 (8.7)	11.6 (7.4)	25.4 (13.5)	23.9 (11.4)	--

NOTE

* p<0.01 (relative to PD) (relative to PD and/or controls)

PD = Parkinson's disease; PDD = Parkinson's disease dementia; DLB = dementia with Lewy bodies; PDD/DLB = Parkinson's disease dementia/dementia with Lewy bodies; LBSD = Lewy body spectrum disorder; MMSE = Mini-Mental State Exam score; UPDRS = Unified Parkinson's Disease Rating Scale

TABLE 2

Mean ($\pm$ S.D.) raw score/z-score on neuropsychological measures in patients with Lewy body spectrum disorder relative to healthy elderly controls[/]

	PD	PDD	DLB	PDD/DLB	LBSD
EXECUTIVE					
Digit span reverse	4.79(1.4)/-0.49(1.0) [14]	3.50(1.2)/-1.36(0.8) [8]	3.67(0.7)/-1.24(0.5) [9]	3.59(0.9)/-1.30(-.6) [17]	4.13(1.3)/-0.93(0.9) [31]
Stroop	67.09(15.0)/-2.96(1.9) [11]	123(48.4)/-10.13(6.2) [4]	132(54.2)/-11.28(6.9) [6]	128.4(49.3)/-10.82(6.3) [10]	96.29(46.8)/-6.70(6.0) [21]
Trails B	102.47(41.2)/-0.72(1.0) [15]	162.88(28.1)/-2.25(0.7) [8]	179.60(0.9)/-2.67(0.1) [5]	169.31(23.0)/-2.41(0.6) [13]	133.50(47.6)/-1.51(1.2) [28]
MEMORY					
Delayed recall	6.88(2.30)/0.05(1.5) [16]	2.38(1.5)/-2.75(0.9) [8]	3.22(1.3)/-2.22(0.8) [9]	2.82(1.4)/-2.47(0.9) [17]	4.79(2.8)/-1.25(1.7) [33]
Recognition	8.56(0.5)/0.24(0.6) [16]	7.87(1.2)/-0.66(1.5) [8]	8.33(1.1)/-0.12(1.3) [9]	8.12(1.2)/-0.37(1.4) [17]	8.33(0.9)/-0.13(1.1) [33]
SEMANTIC MEMORY					
Pyramids & Palm	51.0(1.3)/-0.25(1.0) [11]	49.0(1.5)/-1.84(1.2) [8]	47.8(4.4)/-2.82(3.5) [9]	48.35(3.3)/-2.36(2.7) [17]	49.39(3.0)/-1.53(2.4) [28]

NOTE

[/] PD = Parkinson's disease; PDD = Parkinson's disease dementia; DLB = dementia with Lewy bodies; PDD/DLB = Parkinson's disease dementia/dementia with Lewy bodies; LBSD = Lewy body spectrum disorder;

TABLE 3

Examples of sentence materials

SENTENCE TYPE	WORKING MEMORY	GRAMMATICAL STRUCTURE	
CONTROL ACTIVE	SHORT		The humble and generous man chased the beautiful dog.
	LONG		The shy and unhappy cow on the hill shoved the talkative child.
CONTROL CONJOINED	SHORT		The cow followed the girl and it was upbeat.
	LONG		The child with a smile was kind and she observed the kitten.
CLEFT	SHORT	SUBJECT-REL	It was the creepy woman that kicked the cow.
		OBJECT-REL	It was the forceful horse that the lady shoved.
	LONG	SUBJECT-REL	It was the hungry cow in the meadow that pulled the man.
		OBJECT-REL	It was the juvenile child with poor hearing that the sheep chased.
CENTER	SHORT	SUBJECT-REL	The giraffe that trailed the carefree lion was quiet.
		OBJECT-REL	The pig that the friendly dog pushed was playful.
	LONG	SUBJECT-REL	The snake with deceiving eyes that bit the pretty puppy was upset.
		OBJECT-REL	The woman with blond hair that the odd man shoved was annoying.

TABLE 4

Gray matter thinning in lewy body spectrum disorder

Anatomic Locus (Brodmann Area)	Coordinates			Z-Score	Cluster Size (Voxels)
	X	Y	Z		
L inferior frontal (44)	-55	17	16	5.38	678
L inferior frontal (45)	-59	14	4	4.93	1067
L dorsolateral prefrontal (46)	-50	38	16	4.21	463
L dorsolateral prefrontal (10)	-40	47	0	4.12	654
L dorsolateral prefrontal (10)	-9	63	4	4.10	966
L premotor (6)	-64	-1	20	3.76	564
L medial prefrontal (10)	-12	50	-7	3.73	487
L anterior cingulate (32)	-6	41	17	3.83	647
R inferior frontal (45)	56	19	5	4.84	3667
R inferior frontal (47)	47	26	-9	4.06	507
R dorsolateral prefrontal (46)	42	42	17	4.32	1157
R dorsolateral prefrontal (10)	24	49	21	4.05	1966
R dorsolateral prefrontal (10)	35	48	-2	4.01	1099
R medial prefrontal (10)	11	63	1	3.56	732
R ventral lateral frontal (11)	28	56	-10	4.26	707
R ventral medial frontal (11)	3	31	-22	3.93	660
L lateral temporal (22)	-58	0	-5	4.26	1411
L lateral temporal (21)	-64	-44	-2	4.38	534
L lateral temporal (21)	-59	-1	-23	3.79	463
R lateral temporal (22)	64	-22	2	4.31	710
R lateral temporal (21)	64	-30	-6	4.81	1503
R lateral temporal (21)	57	-3	-6	3.74	673
R lateral temporal (21)	38	2	-14	3.62	522
R lateral temporal (20)	53	-15	-27	3.76	427
L inferior parietal (40)	-66	-15	18	4.24	404
L lateral occipital (19)	-47	-76	9	4.22	743

Anatomic Locus (Brodmann Area)	Coordinates			Z-Score	Cluster Size (Voxels)
	X	Y	Z		
R medial occipital (18)	13	-97	8	4.04	586
R occipital-temporal (19)	46	-68	14	3.84	646

Regression analyses relating comprehension of lengthened sentences containing three propositions to gray matter thinning in lewy body spectrum disorder

TABLE 5

Anatomic Locus (Brodmann Area)	Coordinates			Z-Score	Cluster Size (Voxels)
	X	Y	Z		
L dorsolateral prefrontal (10)	-18	61	6	4.16	725
L premotor (6)	-64	-1	17	3.96	267
L inferior frontal (6)	-61	8	8	3.42	240
R dorsolateral prefrontal (10)	3	63	1	3.32	231
R inferior frontal (45)	55	18	5	3.86	421
R ventromedial prefrontal (11)	3	32	-18	3.11	189
R superior temporal (22)	64	-22	5	3.15	346
R middle temporal (21)	58	1	-3	3.29	394