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Dissociation of Quantifiers and Object Nouns in Speech in Focal Neurodegenerative Disease

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Abstract

Quantifiers such as *many* and *some* are thought to depend in part on the conceptual representation of number knowledge, while object nouns such as *cookie* and *boy* appear to depend in part on visual feature knowledge associated with object concepts. Further, number knowledge is associated with a frontal-parietal network while object knowledge is related in part to anterior and ventral portions of the temporal lobe. We examined the cognitive and anatomic basis for the spontaneous speech production of quantifiers and object nouns in non-aphasic patients with focal neurodegenerative disease associated with corticobasal syndrome (CBS, n=33), behavioral variant frontotemporal degeneration (bvFTD, n=54), and semantic variant primary progressive aphasia (svPPA, n=19). We recorded a semi-structured speech sample elicited from patients and healthy seniors (n=27) during description of the Cookie Theft scene. We observed a dissociation: CBS and bvFTD were significantly impaired in the production of quantifiers but not object nouns, while svPPA were significantly impaired in the production of object nouns but not quantifiers. MRI analysis revealed that quantifier production deficits in CBS and bvFTD were associated with disease in a frontal-parietal network important for number knowledge, while impaired production of object nouns in all patient groups was related to disease in inferior temporal regions important for representations of visual feature knowledge of objects. These findings imply that partially dissociable representations in semantic memory may underlie different segments of the lexicon.

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Keywords

corticobasal degeneration; frontotemporal dementia; speech; language; dementia aphasia; cognitive neuropsychology in dementia

1. Introduction

Many believe that there is a single, material-neutral system underlying both symbolic (e.g., “5” or “V”) and non-symbolic (e.g., “* * * *”) representations of numerosity (Dehaene, Spelke, Stanescu, & Tsivkin, 1999; Eger, Sterzer, Russ, Giraud, & Kleinschmidt, 2003; Fias, Lammertyn, Reynvoet, Dupont, & Orban, 2003; Hubbard, Piazza, Pinel, & Dehaene, 2005; Simon, Mangin, Cohen, Le Bihan, & Dehaene, 2002; Venkatraman, Ansari, & Chee, 2005). For example, “five,” “5,” “V,” and “* * * *” are several ways to represent the concept of “fiveness,” and all of these may derive their meaning in part from a deeper, material-neutral representation of quantity. One proposal suggests that numerosity is represented as a kind of mental number line (Dehaene, 1997). According to this view, the number line is a material-neutral logarithmic-like scale (e.g., with equal space allocated for the intervals between one and two, two and four, four and eight, etc.) that is the basis for the mental representation of quantity.

A characteristic feature of non-aphasic patients with corticobasal syndrome (CBS) is difficulty performing simple arithmetic operations. In one recent study, patients with CBS and posterior cortical atrophy (PCA) had significantly more difficulty than Controls with addition and subtraction of numbers as small as 2, and their error rate was correlated with the magnitude of the numbers (Spotorno, McMillan, Powers, Clark, & Grossman, 2014). This magnitude effect was correlated with atrophy in right superior and inferior parietal cortex. Another study (Koss, et al., 2010) assessed the representation of numerosity in non-aphasic patients with CBS by asking them to judge whether a target numerosity (e.g., “3”) falls between two bounding numerosities (e.g., “1” and “5”). Stimuli included Arabic numerals or dot arrays. CBS patients were significantly impaired (65.7% correct) compared to healthy seniors (96.6% correct), and patients required three times as much time as Controls to judge correct stimuli. This deficit was equally evident for Arabic numeral and dot array materials. Participants in this study had significant parietal cortex atrophy in comparison to healthy Controls.

The processing of numbers in the parietal lobe is also shown in studies of healthy adults. fMRI studies frequently show parietal activation, often centered in the intraparietal sulcus (IPS), for both symbolic (e.g., Arabic numerals) and non-symbolic (e.g., dot arrays) representations of numerosity (Dehaene et al., 1999; Eger et al., 2003; Fias et al., 2003; Hubbard et al., 2005; Piazza, Pinel, Le Bihan, & Dehaene, 2007; Simon et al., 2002; Venkatraman et al., 2005). One fMRI study showed increased activation in right IPS when comparing numeric magnitudes as opposed to simply reading numbers (Chochon, Cohen, van de Moortele, & Dehaene, 1999). Another fMRI study demonstrated activation of bilateral parietal regions during both active and passive viewing of numerosity stimuli,

indicating involvement of the IPS independent of task difficulty or attention (Ansari, Dhital, & Siong, 2006).

Several studies suggest that the deterioration of number knowledge in non-aphasic CBS patients co-occurs with impaired comprehension of quantifiers and parietal atrophy. Quantifiers – determiners or pronouns that express quantity, such as *some* and *many* – are extremely common in speech. Quantifier meaning is thought to depend in part on knowledge of quantity or magnitude (Keenan, Westersth, van Benthem, & ter Meulen, 1997; van Benthem, 1986). In a study of non-aphasic patients with CBS, behavioral variant frontotemporal degeneration (bvFTD), and Alzheimer's disease (AD), it was found that CBS patients were significantly more impaired than AD patients in their comprehension of quantifiers (McMillan, Clark, Moore, & Grossman, 2006). In addition, CBS patients were significantly more impaired on a dot magnitude comparison task, which assessed basic numeric abilities, than both bvFTD and AD patients. Finally, performance on the dot magnitude comparison task was correlated with quantifier comprehension in CBS. In another study, CBS and PCA patients were found to be impaired in their comprehension of cardinal quantifiers – those that depend directly on quantity knowledge, as in “There are more than two cows in the barn” – and their comprehension of this class of quantifiers was correlated with their accuracy in judging precise numbers (Morgan, et al., 2011). In a third study, the neural substrate of numerical quantifiers (e.g., “at least three”) was investigated in patients with CBS and healthy adults (Troiani, Peelle, Clark, & Grossman, 2009). CBS patients were significantly impaired in the comprehension of numerical quantifiers, and they displayed parietal disease involving the IPS. Converging data supporting the role of parietal cortex in quantifier processing was provided by an fMRI study of healthy adults using the same materials as were used with patients. In this part of the study, numerical quantifiers elicited significant bilateral activation of the IPS, right dorsolateral prefrontal cortex, and left precentral regions compared to logical quantifiers. In a further fMRI study, we used BOLD fMRI in healthy young adults to investigate the relative contribution of frontal and parietal components to quantifier comprehension (Olm, McMillan, Spotorno, Clark, & Grossman, 2014). Participants performed a sentence-picture verification task similar to that used with patients in another study (Morgan, et al., 2011) to determine whether a sentence containing a quantifier accurately described a real-world naturalistic scene. A whole-brain analysis demonstrated activation of a fronto-parietal network during quantifier comprehension, including bilateral inferior parietal, superior parietal and dorsolateral prefrontal cortices, along with right inferior frontal cortex. A region-of-interest (ROI) analysis found that inferior parietal cortex was equally activated across all classes of quantifiers, consistent with the hypothesis implicating inferior parietal cortex in quantifier comprehension due in part to its role in the representation of number knowledge.

Non-aphasic individuals with bvFTD have some difficulty with judgments of numerosity and simple numerical calculations, although they are not as impaired as patients with CBS (Halpern, McMillan, Moore, Dennis, & Grossman, 2003). These patients also exhibit impaired comprehension of quantifiers. They have been found to be particularly impaired on higher-order or majority quantifiers that require a mental comparison, and this has been correlated with reverse digit span performance, a test of working memory (McMillan, et al., 2006). Another study found that bvFTD patients were impaired on these as well as on

logical quantifiers, and their performance was correlated with executive measures (Morgan, et al., 2011). Deficits in quantifier comprehension in bvFTD were found to be related to disease in prefrontal regions. Despite these deficits in numerosity, CBS and bvFTD both appear to have relatively preserved object noun comprehension (McMillan, et al., 2006; Morgan, et al., 2011; Troiani, et al., 2009).

In contrast, patients with the semantic variant of primary progressive aphasia (svPPA, also known as semantic dementia) appear to have relatively intact number knowledge (Cappelletti, Butterworth, & Kopelman, 2001; Crutch & Warrington, 2002; Halpern, et al., 2004; Julien, Thompson, Neary, & Snowden, 2010). One case study describes relatively preserved quantifier comprehension (Cappelletti, Butterworth, & Kopelman, 2006). By comparison, these patients are generally thought to have difficulty with word comprehension and production. The most common assessments involve the comprehension and production of object nouns on measures of visual confrontation naming such as the Boston Naming Test and measures of object comprehension such as the Pyramids and Palm Trees test (Bonner, Ryan, & Epstein, 2015; Garrard & Carroll, 2006; Hodges & Patterson, 2007b; Libon, et al., 2013; Mion, et al., 2010; Patterson, Nestor, & Rogers, 2007; Warrington, 1975), and there is broad consensus that this lexical semantic domain is compromised in svPPA (Gorno-Tempini, et al., 2011). Indeed, several case studies and brief series of svPPA patients have emphasized difficulty with object nouns in descriptions of “reversal of the concreteness effect,” in which there is greater difficulty with concrete nouns than abstract nouns. One such report (Breedin, Saffran, & Coslett, 1994) describes the case of a patient with semantic dementia who was severely impaired on object nouns, with relative sparing of abstract nouns, in tasks such as providing definitions and judgments of synonymy. In another case, a longitudinal study of a semantic dementia patient was conducted over a period of 21 months, using tasks such as semantic similarity judgments of homophones, word-to-picture matching, word definition, spelling to dictation, and naming tasks (Macoir, 2009). A clear deficit for concrete words relative to abstract words was found; however, the difference between performance on tests of abstract and concrete word knowledge declined over time for some tests. A recent study used a two-alternative forced-choice procedure to demonstrate that svPPA patients are more impaired on concrete than abstract nouns (Cousins, York, Bauer, & Grossman, 2016). The deficit for word comprehension in svPPA has consistently been associated with disease in the anterior and inferior portions of the temporal lobe, particularly on the left (Amici, et al., 2007; Bonner, et al., 2009; Cousins, et al., 2016; Libon, et al., 2013; Mion, et al., 2010; Rogalski, et al., 2011; Wilson, et al., 2010). This parallels fMRI studies of healthy adults that associate noun representations of object knowledge with the ventral temporal lobe (Binder & Desai, 2011; Bonner, Price, Peelle, & Grossman, 2016; Fairhall & Caramazza, 2013).

These observations on the contrasting deficits in different neurodegenerative conditions suggest the hypothesis that quantifiers depend in part on a discrete semantic domain associated with number knowledge that is centered in parietal cortex and that this contrasts with the category of object nouns that may depend instead on visual feature knowledge which is represented in part in visual association cortex. While several reports have described quantifier comprehension deficits, assessments of quantifier production in spontaneous speech are lacking, despite the high frequency of these words in everyday

speech, and direct comparisons of different lexical domains during speech production are rare. In this study, we investigated a dissociation in quantifier and object noun portions of the lexicon in a semi-structured speech sample, and we assessed the neuroanatomic basis for these dissociated deficits in patients with focal neurodegenerative disease. Our findings support the hypothesis that the contrasting portions of the lexicon under study belong in part to different semantic domains and, correspondingly, they depend in part on different neural networks.

2. Materials and Methods

2.1 Participants

Participants were native English speakers with CBS (n=33), bvFTD (n=54), and svPPA (n=19), diagnosed by experienced neurologists (MG and DJI) in the Penn FTD Center of the Department of Neurology at the University of Pennsylvania. All participants met published criteria for their phenotype diagnosis (Armstrong, et al., 2013; Gorno-Tempini, et al., 2011; Rascovsky, et al., 2011). Exclusion criteria included vascular disease, structural brain abnormalities, medical diseases interfering with cognition, visual-perceptual impairment, and primary psychiatric disorders. Patients were assessed for object noun production using a 30-word version of the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983) and category naming fluency for animals during 60 seconds (Lezak, 1983), and for executive functioning with reverse digit span, a non-linguistic measure of working memory (Wechsler, 1987). We also studied 27 healthy seniors recruited from the community as control subjects. Demographic and clinical characteristics are summarized in Table 1. The four groups were matched for gender and age. The patient groups did not differ from Controls in years of education; however, the CBS group averaged about 2 years less education than bvFTD and svPPA ($p<.01$). We found no correlation between education and performance in our analyses. All participants completed an informed consent procedure in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the University of Pennsylvania.

2.2 Speech Evaluation

We performed a retrospective analysis utilizing materials collected from January, 2000 to December, 2014 that were acquired to support analyses of language beyond the current manuscript (e.g., grammatical features) that did not focus on quantifier and noun production (Ash, et al., 2013). We elicited a semi-structured speech sample by asking participants to describe the Cookie Theft picture from the Boston Diagnostic Aphasia Examination (Goodglass & Kaplan, 1972). This drawing depicts a boy and girl in a kitchen attempting to reach a cookie jar on a high shelf. Their mother, oblivious to their antics, is washing dishes at a sink that is overflowing onto the floor. This picture is suited to a study of quantifiers because there are numerous countable objects in the drawing: there are two cups on the counter, two plates in the picture, two children, several cookies, two shelves in the cabinet over the counter, and several cabinets under the counter. All of these objects were mentioned by the participants, and their quantity was available for explicit reference. Participants were instructed to describe the picture in as much detail as possible for a specified amount of time, either 90 seconds (n=75) or 60 seconds (n=58) (as the task duration changed during the

course of data collection; we found no difference in performance depending on duration, and data were normalized to tokens/100 words). Examiners minimized prompts to allow uninterrupted speech.

The spoken descriptions were recorded digitally, transcribed by trained transcribers using the signal processing software Praat (Boersma & Weenink, 1992-2014), and scored from the transcripts with reference to the sound files as necessary. All transcripts and coding were reviewed by an experienced linguist (SA). The speech was analyzed for features of speech rate, grammar, and lexicon, as described elsewhere (Ash, et al., 2013). These measures are summarized in Table 1.

Quantifiers included adjectives or phrases denoting a quantity and modifying a noun, e.g., *two, some, a few, another*. A pronoun was counted as a quantifier if it denoted a quantity, not merely serving as a pronominal replacement for “Determiner + Noun,” which does not express number knowledge.

A noun was judged to be an object noun if its referent could be perceived through the five senses, e.g., *girl, dishes, water, cookie*. Nouns denoting abstractions that cannot be perceived through the senses, e.g. *day, moment, attention, way*, were excluded.

One full Cookie Theft description representing each patient group is provided in Appendix A.

2.3 Statistical Considerations

Statistical analysis used SPSS v.22 (IBM). Levene's test indicated that most language measures did not meet the requirement of homogeneity of variances for parametric statistical tests. Therefore, we used non-parametric tests (e.g., Mann-Whitney U) to assess between-group differences.

2.4 Imaging Methods

High-resolution volumetric T1-weighted MRI was obtained within an average of 105 (± 110) days from the date of behavioral testing for 55 patients (CBS=11; bvFTD=32; svPPA=12). These patients did not differ from their phenotype cohort in demographic characteristics or behavioral performance, as summarized in Appendix B (all p-values $>.15$). Exclusion criteria included health and safety issues, including claustrophobia and metallic implants (e.g., pacemakers, shrapnel) in the body.

Gray Matter Image Acquisition & Processing—MRI volumes were acquired using an MPRAGE sequence from a SIEMENS 3.0T Trio scanner with an 8-channel head coil and the following acquisition parameters: repetition time=1620 msec; TE=3.09 msec; slice thickness=1.0 mm; flip angle=15°; matrix=192×256, and 1×1×1mm voxels. T1 MRI images were preprocessed using antsCorticalThickness (Tustison, et al., 2014), which uses a highly accurate Advanced Normalization Tools pipeline (ANTs). Each individual dataset was deformed into a standard local template space in a canonical stereotactic coordinate system. Registration used a diffeomorphic deformation that is symmetric to minimize bias toward the reference space for computing the mappings and also topology-preserving to capture the

large deformation necessary to aggregate images in a common space. The ANTs Atropos tool uses template-based priors to segment images into 6 tissue classes (cortex, white matter, CSF, deep gray structures, midbrain, and cerebellum) and to generate probability maps of each tissue. Gray matter probability (GMP) images including cortex, deep gray structures, and midbrain were then transformed into MNI space and smoothed using a 2 sigma full-width half-maximum Gaussian kernel. Resulting images were then downsampled to 2 mm resolution to account for variation in individual gyral anatomy.

Gray Matter Atrophy Analysis—To identify patterns of GM atrophy in each of the three patient groups we performed non-parametric permutation-based (10,000 iterations) t-tests using the Randomise tool in FSL (<http://fsl.fmrib.ox.ac.uk/fsl/randomise/>). GMP was compared in each patient group relative to healthy seniors (n=43) who were comparable to the patient group in age ($F(3,94)=1.831$, $p=.147$). Each permutation-based analysis was restricted to voxels containing GM using an explicit mask generated from the average GMP image of all patients and controls. We report clusters that survived a height threshold of $p<.001$ (FWE-corrected after using threshold-free cluster enhancement) and an extent threshold of 50 voxels.

Gray Matter Regression Analysis—To relate quantifier and object noun use to GMP we performed two whole-brain regression analyses using Randomise non-parametric tests (10,000 iterations). Specifically, for each behavioral score (quantifiers/100 words, object nouns/100 words) we related task performance across the entire patient cohort (CBS, bvFTD, svPPA) to GMP. Regression analysis was restricted to voxels containing GM using the same explicit mask as used for our whole-brain atrophy analyses. We considered only clusters that exceeded an extent threshold of 25 voxels and a height threshold of $p<.005$ (uncorrected) to be significant.

White Matter Image Acquisition & Processing—To evaluate white matter (WM), we acquired diffusion-weighted (DW) images in the same session as the T1-weighted MRI. DW images were available for 50 of the 55 patients included in the GM analysis. A total of 45 datasets were acquired with a 30-directional acquisition sequence and 5 were acquired with a 12-directional sequence. The former utilized a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (FOV=245mm; matrix size=128×128; number of slices=57; voxel size=2.2 mm isotropic; TR=6,700ms; TE=85ms; and fat saturation). In total, 31 volumes were acquired per subject, one without diffusion weighting ($b=0$ s/mm²) and 30 with diffusion weighting ($b=1,000$ s/mm²) along 30 noncollinear directions. The 12-directional DW sequence utilized a single-shot, spin-echo, diffusion-weighted echo planar imaging sequence (matrix size=128 × 128, number of slices=40, FOV=220mm; slice thickness=3mm; TR=6500ms, TE=99ms). In total, 13 volumes were acquired per subject, one without diffusion weighting ($b=0$ s/mm²) and 12 with diffusion weighting ($b=1000$ s/mm²) along 12 non-collinear directions. A nuisance covariate was included in all DWI analyses to minimize potential sequence bias.

For all DW images, the unweighted ($b=0$) images were first extracted and averaged. Then all DW images (including the individual $b=0$ volumes) were aligned to the average $b=0$ using ANTs (Tustison, et al., 2014). An affine transform was applied to capture distortion as well

as motion in the DW images. Diffusion tensors were computed using a weighted linear least squares algorithm in Camino (Cook, Bai, & Nadjati-Gilani, 2006). The corrected average $b=0$ image was aligned to the subject's T1 image from the same scanning session, first rigidly to correct for motion, then using a deformable diffeomorphic transformation with mutual information to correct for inter-modality distortion. The diffusion-to-T1-warp was composed with the T1-to-template warp (from the cortical thickness pipeline), producing a mapping from DWI space to the population T1 template in a single interpolation. Tensors were resampled into the template space using log-Euclidean interpolation (Arsigny, Fillard, Pennec, & Ayache, 2006) and reoriented to preserve the anatomical alignment of WM tracts (Alexander, Pierpaoli, Basser, & Gee, 2001).

White Matter Streamline Analysis—After preprocessing the diffusion data, we generated a healthy control diffusion tensor (DT) image tract template by averaging each DT image following spatial normalization to the local template. A population fractional anisotropy (FA) image was created from the DT image. We used Camino to generate streamline tracts based upon the average DT image. Streamlines were generated from all voxels in a seed image that consisted of voxels in the population FA image with $FA > 0.25$. Streamlines terminated in voxels with $FA < 0.25$, or if the streamline trajectory exceeded a 75° curve, in less than 5 millimeters.

For analysis we first identified the overlap between the GM atrophy and GM regression analyses to generate a mask for each of the 6 results (two behavioral conditions [quantifiers, object nouns] $\times$ three patient groups [CBS, bvFTD, svPPA]). Overlap was defined as GM clusters that had a minimum of 25 overlapping regression and atrophy voxels. This yielded 5 unique masks since there were no significant overlapping clusters between svPPA GM atrophy and the quantifiers regression. This procedure enabled us to use these masks to extract the WM streamlines connected to each of the GM regions associated with impaired performance on quantifiers and object nouns.

To identify whether patients had reduced WM integrity in identified streamlines we then used Randomise permutation-based (10,000 iterations) t-tests to evaluate patient FA in each streamline relative to controls. Each permutation-based analysis was restricted to voxels containing WM using the unique explicit masks generated from the tracts that connected the significant overlapping GM clusters of each patient group's atrophy and language (quantifier, noun) regressions. We report clusters that survived an extent threshold of $p < 0.05$ (FWE-corrected after using threshold-free cluster enhancement) and an extent threshold of 200 voxels for all groups.

3. Results

3.1 Speech Production

A summary of the participants' speech performance is provided in Table 1. Each patient group produced fewer words per minute (WPM) than Controls (all p -values < 0.01). With recalculation of speech rate after subtracting lengthy pauses (> 2 sec) that can occur during speech planning, only patients with CBS had a marginal reduction in their modified WPM.

The mean frequencies of quantifiers and object nouns in the speech of patients and Controls are displayed in Figure 1. CBS and bvFTD patients produced significantly fewer quantifiers/100 words than Controls and svPPA patients (all p-values <.05), while svPPA patients did not differ from Controls. In contrast, svPPA patients produced significantly fewer object nouns/100 words compared to CBS, bvFTD, and Controls (all p-values <.001), and these three groups did not differ from each other. The groups did not differ in production of inflected verbs/100 words.

We used Z-score analyses to evaluate individual patient performance profiles, quantifying each patient's performance for each word category relative to that of Controls. We found relatively greater difficulty with quantifiers than object nouns in the majority of patients with CBS (23/33) and bvFTD (31/54) and relatively greater difficulty with object nouns than quantifiers in patients with svPPA (16/19). These proportions differed significantly [$\chi^2(3)=14.7$, $p<.001$].

3.2 Imaging

Whole brain regression analyses across all patient groups identified a unique pattern of GM atrophy associated with quantifier and noun performance (summarized in Table 2 and Figure 2). For quantifiers, we observed a large-scale network of cortical regions related to reduced quantifier production, including bilateral frontal and right parietal cortex. For object nouns, we observed that cortical regions within left temporal cortex were related to reduced object noun production.

GM atrophy analyses revealed results largely consistent with previously reported regions of disease for each patient group (summarized in Table 3 and Figure 2). Briefly, both CBS and bvFTD had an extensive frontal, parietal, and temporal distribution of disease. CBS had more extensive parietal atrophy, while bvFTD had more extensive frontal and temporal atrophy. In contrast, svPPA had a bilateral temporal and ventral frontal distribution of GM atrophy that was most evident in the left hemisphere.

Of note, the overlap between language performance and the distribution of atrophy in each patient group is consistent with our behavioral results (summarized in Table 2 and Figure 2). Quantifier production was related to clusters overlapping areas of CBS atrophy in right inferior parietal, left inferior and medial frontal, and left caudate regions. Quantifier production for bvFTD was related to clusters which overlap areas of atrophy in regions similar to those in CBS, but additionally they exhibited overlap in more anterior regions in right superior frontal, right caudate, and right thalamus. In contrast, atrophy in svPPA did not overlap GM regions related to quantifier production; this is consistent with their preserved quantifier production. Object noun production in all groups was related to clusters that overlap temporal cortex, including left middle and left inferior temporal regions. svPPA additionally had overlap of clusters associated with object noun production encompassing atrophy in left fusiform gyrus.

WM analyses identified reduced FA for all patient groups in regions structurally connected to GM regions associated with language performance and disease-specific GM atrophy (summarized in Table 4 and Figures 3 and 4). For CBS, WM integrity was reduced in left

frontal tracts including uncinate fasciculus and a large cluster encompassing inferior and superior longitudinal fasciculus, and these tracts are connected to atrophied GM regions involved in quantifier production. Left inferior longitudinal fasciculus and left superior longitudinal fasciculus, exhibiting reduced WM integrity, also both project to regions of GM atrophy related to object noun production in CBS. Similarly, bvFTD had several regions of reduced WM integrity in frontal connections to GM regions involved in reduced quantifier production. While bvFTD had reduced WM integrity in left inferior longitudinal fasciculus, like CBS, they also had reduced WM integrity in fronto-temporal regions of the left uncinate fasciculus. svPPA did not have reduced WM integrity in any connections between regions related to quantifier production, since their pattern of GM atrophy did not overlap areas of the regression with quantifier production. We did, however, observe a large cluster of reduced WM integrity in inferior temporal cortex that was connected to atrophied GM regions involved in object noun production.

4. Discussion

In this study, we found a dissociation in the production of quantifiers and object nouns in the connected speech of non-aphasic patients with CBS and bvFTD compared to svPPA: CBS and bvFTD were impaired in the production of quantifiers but not object nouns, while svPPA had difficulty producing object nouns but not quantifiers. These findings mirror evidence from studies dissociating calculation and object naming in focal neurodegenerative disease (Halpern, et al., 2004). The dissociation in cognitive functioning was associated with a parallel neuroanatomic dissociation: quantifier production deficits in CBS and bvFTD were related to disease in a frontal-parietal network, and difficulty producing object nouns in svPPA was related to left temporal cortex. These findings are consistent with a multifocal model of lexical semantic representation that depends on a distributed network of concepts underlying lexical representations during the production of connected speech. Specifically, we have found evidence in spontaneous speech production that quantifiers and object nouns belong in part to discrete semantic categories which are served by relatively discrete neuroanatomic substrates. We discuss these issues below.

4.1 Quantifier Production in CBS and bvFTD

Previous work has demonstrated quantifier comprehension difficulty in non-aphasic patients with CBS and bvFTD (McMillan, et al., 2006; McMillan, Coleman, et al., 2013; Morgan, et al., 2011; Troiani, Clark, & Grossman, 2011; Troiani, et al., 2009). Here we have shown that these patients are less likely to produce quantifiers in speech during description of a picture. For example, a 77-year-old woman with CBS (MMSE=27) made the statement in (1):

(1) and the mother is wash- drying *the* dishes.

This exemplifies a plain determiner being used where a quantifier could have been used; in other cases, no determiner was expressed. Thus a 65-year-old man with bvFTD (MMSE=23) made the statement in (2) to describe the same part of the scene as above:

(2) And there are, dishes on the counter.

In contrast, a 60-year-old man with svPPA (MMSE=22) used the generalized quantifier *some* in (3) in describing the same element, although he had obvious word-finding difficulty for the depicted objects:

(3) And she's doing *some* washing in the uh w- washer or something.

Thus, in speech environments where svPPA and Controls tended to produce quantifiers, patients with CBS and bvFTD frequently used plain determiners or no determiner, resulting in a significantly reduced rate of quantifier production. The limited production of quantifiers in CBS and bvFTD cannot easily be attributed to a non-specific deficit in speech production, lexical retrieval, or executive functioning, since these patients spoke at the same rate, after correction for pauses, as Controls; they produced the same number of inflected verbs/100 words as Controls and patients with svPPA; they had relatively preserved confrontation naming and category naming fluency and the same reverse digit span as svPPA; and they produced significantly more object nouns than svPPA.

In previous work, we have reported relative difficulty understanding cardinal and majority subsets of quantifiers in CBS and logical and majority quantifiers in bvFTD (Morgan, et al., 2011). In the present study, we did not attempt to specify statistically a deficit for a particular class of quantifiers because of the relatively small speech samples. However, as we have seen (McMillan, Clark, Moore, Devita, & Grossman, 2005; McMillan, et al., 2006; Morgan, et al., 2011; Troiani, et al., 2011), cardinal quantifiers such as “at least three” depend in part on number knowledge. Majority quantifiers also rely on number knowledge as a prerequisite to the mental calculation needed to test the validity of an assertion that depends on a mental comparison or manipulation requiring working memory resources (McMillan, et al., 2005; McMillan, et al., 2006). Regardless of the distribution of quantifier subsets, we have argued that difficulty with quantifiers in CBS and bvFTD is related in part to their deficit for number knowledge and associated quantity knowledge (Koss, et al., 2010; Spotorno, et al., 2014). This is somewhat consistent with a broad interpretation of the grounded cognition approach to semantic memory (Barsalou, 2009) by which the representation of conceptual knowledge depends in part on processing associated sensory-motor features. In this view, the meaning of quantifiers depends in part on number and quantity knowledge (Clark & Grossman, 2007), which we take to be broadly analogous to the role of sensory-motor features in the representation of object knowledge. While knowledge of quantity is not a sensory-motor representation *per se*, the analogue spatial magnitude function underlying number knowledge and quantifier meaning appears to involve a fundamental type of representation analogous to that encompassed by sensory-motor representations underlying object knowledge and the meaning of object nouns.

The anatomic basis for quantifier comprehension in healthy adults appears to depend in part on a frontal-parietal network (McMillan, et al., 2005; McMillan, Coleman, et al., 2013; Olm, et al., 2014; Troiani, et al., 2009). In CBS and bvFTD, difficulty with quantifier comprehension has also been associated with this frontal-parietal network (McMillan, et al., 2006; Morgan, et al., 2011). This same network is associated with processing quantity and number knowledge in healthy adults (Pinel, Dehaene, Riviere, & Le Bihan, 2001; Simon, et al., 2002) and in patients with neurodegenerative disease (Koss, et al., 2010; Morgan, et al.,

2011; Spotorno, et al., 2014). We view this as an integrated bilateral network that is biased towards linguistic representations in the left hemisphere and magnitude vectors for quantity in the right hemisphere (Chochon, Cohen, van de Moortele, & Dehaene, 1999; Kadosh, et al., 2005). In the present study, we found that significantly reduced quantifier production in a semi-structured speech sample is associated with gray matter in the right inferior parietal cortex and bilateral frontal cortex. These regions overlap with patterns of atrophy observed in CBS and bvFTD and thus are consistent with our observation that CBS and bvFTD were selectively impaired in quantifier production relative to svPPA, who do not have atrophy in these fronto-parietal regions. Moreover, reductions in WM integrity in fronto-parietal projections were specific to the CBS and bvFTD patient groups. These projections may contribute to linking representations of number knowledge in parietal cortex to areas in the frontal lobe important for processing some aspects of quantifiers such as majority quantifiers, as well as lexical retrieval that is supported in part by inferior frontal cortex. The right-lateralized parietal bias in quantifier production may reflect in part a selection bias that attempted to minimize the inclusion of CBS patients with naming difficulty; additional work monitoring brain activation during production of quantifiers in speech by healthy adults is needed to evaluate the right laterality of this observed parietal involvement in quantifier production.

4.2 Object Noun Production in svPPA

Impaired confrontation naming is a core criterion for svPPA (Gorno-Tempini, et al., 2011). This emphasizes these patients' difficulty in retrieving nouns, and standardized tests of confrontation naming overwhelmingly involve retrieving the name of a visually depicted concrete object. A secondary criterion is impaired object knowledge (Garrard & Carroll, 2006; Hodges & Patterson, 2007a; Libon, et al., 2013; Patterson, 2007). Several reports have described greater semantic impairment for concrete than for abstract concepts in svPPA (Bonner, et al., 2009; Breedin, Saffran, & Schwartz, 1998; Cousins, et al., 2016; Papagno, Capasso, & Miceli, 2009; Reilly, Grossman, & McCawley, 2006; Warrington, 1975), a phenomenon known as reversal of the concreteness effect. In contrast, number and quantifier comprehension in svPPA have been reported to be relatively well preserved (Cappelletti, et al., 2001, 2006; Crutch & Warrington, 2002; Halpern, et al., 2004; Julien, et al., 2010).

In the present study of natural speech production, we elicited a semi-structured speech sample by asking individuals to describe a kitchen scene. This task maximizes the production of object nouns, as the speaker enumerates the elements shown in the drawing: two children, the mother, the sink, dishes, cookies, and so forth. Yet the patients with svPPA produced on average less than two-thirds the number of object nouns that were spoken by patients with CBS, bvFTD, and Controls. Pronouns were often substituted for object nouns, whether or not a required antecedent was present. For example, a 51-year-old man with svPPA (MMSE=24) made the statements in (4):

(4) And uh ... she's cleaning .. this

And uh .. right eh like the- like the water is on down.

Reference to the adult woman is reduced to “she,” and mention of the plate is reduced to “this.” “The water” is named, but the sink and the floor where a large puddle is

accumulating are not. This individual's overall rate of object noun production was 12.6 per 100 words, compared to the average rate of 17.5 for Controls. The production of object nouns in svPPA mirrors these subjects' impaired confrontation naming and semantic category fluency for object nouns such as *animals*. It is beyond the scope of this study to demonstrate that object noun production difficulty in these patients is comparable to their object noun comprehension deficit, but an impairment for word comprehension and production has been described elsewhere (Hodges & Patterson, 2007a; Patterson, et al., 2007). Their production deficit cannot easily be attributed to difficulty producing all word categories, since svPPA patients produced quantifiers as well as inflected verbs at rates comparable to those of Controls, paralleling their relatively preserved quantifier comprehension (Cappelletti, et al., 2006).

Several studies have related lexical retrieval difficulty to damage to visual association cortex in the inferior and anterior temporal lobes, the common location of disease in svPPA (Amici, et al., 2007; Mion, et al., 2010; Rogalski, et al., 2011; Wilson, et al., 2010). In the present investigation, we limited the examination of noun production to concrete object nouns because of observations that patients with svPPA have the most consistent deficit for this class of nouns. We confirmed the observation of difficulty with concrete object nouns in svPPA using common measures, the Boston Naming Test and the Pyramids and Palm Trees Test. While there is general agreement that svPPA patients have a deficit for object noun use, and while some observations indicate relative difficulty with concrete nouns compared to abstract nouns (Bonner, et al., 2016; Breedin, et al., 1994; Cousins, et al., 2016; Macoir, 2009; Papagno, et al., 2009), others advocate a domain-neutral deficit for all words in svPPA (Hoffman, Jones, & Lambon Ralph, 2012; Jefferies, Patterson, Jones, & Lambon Ralph, 2009; Patterson, et al., 2007), claiming that concrete nouns and verbs are both better preserved than abstract nouns and verbs in svPPA based on methodological issues (Hoffman, Jones, & Lambon Ralph, 2013). Further work is needed to illuminate the issues surrounding the contrast of words denoting concrete objects and abstract concepts. Regardless of the relative deficits for concrete and abstract nouns in svPPA, our findings demonstrate a dissociation for impaired object noun use in these patients compared to their relative preservation of quantifiers.

Regression studies have related impaired object noun comprehension in svPPA patients to atrophy in visual association cortex. The imaging results for svPPA in the present study are consistent with previous findings (Amici, et al., 2007; Bonner, et al., 2016; Cousins, et al., 2016; Libon, et al., 2013; Mion, et al., 2010; Rogalski, et al., 2011; Wilson, et al., 2010). In a regression analysis, we observed that performance on object noun production was related to several regions in the left temporal cortex, including inferior and middle temporal regions for all patient groups. Fusiform gyrus in ventral temporal cortex was a significant region for svPPA patients alone, consistent with other work emphasizing the role of this area in the lexical comprehension deficits of these patients (Bonner, et al., 2016; Cousins, et al., 2016; Mion, et al., 2010).

Object noun production difficulty was also associated with distinct regions of reduced WM integrity for each patient group. In svPPA, performance was related to regions constrained to inferior temporal WM. This is consistent with previous work showing reduced WM integrity

in these tracts in svPPA (Agosta, et al., 2010; Galantucci, et al., 2011). CBS object noun use was related to temporo-parietal projections in the superior longitudinal fasciculus, and bvFTD performance was related to fronto-temporal projections in the uncinate fasciculus. While CBS and bvFTD were not impaired on object noun performance, we view these results as evidence for a large-scale neuroanatomic network involved in object noun production. For example, uncinate fasciculus and superior longitudinal fasciculus may mediate projections of left temporal areas supporting lexical representations with inferior frontal areas important for speech production. These observations are consistent with the hypothesis that a distributed network of brain regions contributes to the representation of words from different semantic classes, in this case, words that depend in part on number knowledge as opposed to words that depend in part on the visual-perceptual feature knowledge of objects.

4.3 Conclusions

Our findings are subject to several limitations. The speech sample elicited in this study was brief, averaging less than 120 words in 72 seconds overall. While this appears to be a representative speech sample (Ash, et al., 2013), larger samples would increase confidence in our findings. In addition, the stimulus picture for the task did not strongly require the production of quantifiers or elicit a broad array of object nouns, and a stimulus prompting a wider variety of quantifiers and object nouns would be valuable. An activation study of speech production in healthy adults could provide converging evidence for the distributed anatomic network suggested by these patient studies. Lastly, while we observed anatomic overlap between object noun production and temporal regions in CBS and bvFTD despite their preserved performance with this word class, future work is necessary to tease apart the relative contributions of components of this large-scale network. For example, given that WM degeneration is relatively constrained in svPPA, often caused by TDP-43 pathology, and more distributed in CBS and bvFTD, often caused by tau pathology, it is possible that heterogeneity in the neuroanatomic distribution of disease may be related to pathological heterogeneity (McMillan, Irwin, et al., 2013).

With these caveats in mind, this study of quantifier and object noun production in connected speech provides evidence of a dissociation between CBS and bvFTD in contrast to svPPA. CBS and bvFTD appear to be impaired in the production of quantifiers relative to svPPA, while svPPA has difficulty producing object nouns compared to CBS and bvFTD. This parallels a previously documented dissociation between CBS and svPPA in an evaluation of simple calculations and confrontation naming (Halpern, et al., 2004). In the present study, difficulty with quantifiers was associated with disease in a frontal-parietal network in CBS and bvFTD, while object noun deficits were related to left temporal disease in all patient groups in conjunction with distinct patterns of reduced WM integrity. This dissociation emphasizes the presence of distributed and collaborative cognitive and neuroanatomic networks that contribute to the production of connected speech. Our observations appear to be consistent with the hypothesis that diverse semantic representations for word meaning contribute to retrieving the lexical representations needed during language expression, and this involves a distributed connectome that integrates several gray matter regions which form the neural basis for expressing word meaning in speech.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

- Agosta F, Henry RG, Migliaccio R, Neuhaus J, Miller BL, Dronkers NF, Brambati SM, Filippi M, Ogar JM, Wilson SM, Gorno-Tempini ML. Language networks in semantic dementia. *Brain*. 2010; 133:286–299. [PubMed: 19759202]
- Alexander DC, Pierpaoli C, Basser PJ, Gee JC. Spatial transformations of diffusion tensor magnetic resonance images. *IEEE Trans Med Imaging*. 2001; 20:1131–1139. [PubMed: 11700739]
- Amici S, Ogar J, Brambati SM, Miller BL, Neuhaus J, Dronkers NL, Gorno-Tempini ML. Performance in specific language tasks correlates with regional volume changes in progressive aphasia. *Cogn Behav Neurol*. 2007; 20:203–211. [PubMed: 18091068]
- Armstrong MJ, Litvan I, Lang AE, Bak TH, Bhatia KP, Borroni B, Boxer AL, Dickson DW, Grossman M, Hallett M, Josephs KA, Kertesz A, Lee SE, Miller BL, Reich SG, Riley DE, Tolosa E, Troster AI, Vidailhet M, Weiner WJ. Criteria for the diagnosis of corticobasal degeneration. *Neurology*. 2013; 80:496–503. [PubMed: 23359374]
- Arsigny V, Fillard P, Pennec X, Ayache N. Log-Euclidean metrics for fast and simple calculus on diffusion tensors. *Magn Reson Med*. 2006; 56:411–421. [PubMed: 16788917]
- Ash S, Evans E, O'Shea J, Powers J, Bollner A, Weinberg D, Haley J, McMillan C, Irwin DJ, Rascovsky K, Grossman M. Differentiating primary progressive aphasia in a brief sample of connected speech. *Neurology*. 2013; 81:329–336. [PubMed: 23794681]
- Barsalou LW. Simulation, situated conceptualization, and prediction. *Philos Trans R Soc Lond B Biol Sci*. 2009; 364:1281–1289. [PubMed: 19528009]
- Binder JR, Desai RH. The neurobiology of semantic memory. *Trends Cogn Sci*. 2011; 15:527–536. [PubMed: 22001867]
- Boersma, P.; Weenink, D. Praat, v. 5.3.76. Institute of Phonetic Sciences, University of Amsterdam; 1992-2014.
- Bonner MF, Price AR, Peelle JE, Grossman M. Semantics of the Visual Environment Encoded in Parahippocampal Cortex. *J Cogn Neurosci*. 2016; 28:361–378. [PubMed: 26679216]
- Bonner MF, Ryan J, Epstein R. Neural coding of navigational affordances in the local visual environment. *J Vis*. 2015; 15:509.
- Bonner MF, Vesely L, Price C, Anderson C, Richmond L, Farag C, Avants B, Grossman M. Reversal of the concreteness effect in semantic dementia. *Cogn Neuropsychol*. 2009; 26:568–579. [PubMed: 20183015]
- Breedin SD, Saffran EM, Coslett HB. Reversal of a concreteness effect in a patient with semantic dementia. *Cogn Neuropsychol*. 1994; 11:617–660.
- Breedin SD, Saffran EM, Schwartz MF. Semantic factors in verb retrieval: an effect of complexity. *Brain Lang*. 1998; 63:1–31. [PubMed: 9642018]
- Cappelletti M, Butterworth B, Kopelman M. Spared numerical abilities in a case of semantic dementia. *Neuropsychologia*. 2001; 39:1224–1239. [PubMed: 11527560]
- Cappelletti M, Butterworth B, Kopelman M. The understanding of quantifiers in semantic dementia: a single-case study. *Neurocase*. 2006; 12:136–145. [PubMed: 16801149]
- Chochon F, Cohen L, van de Moortele PF, Dehaene S. Differential contributions of the left and right inferior parietal lobules to number processing. *J Cogn Neurosci*. 1999; 11:617–630. [PubMed: 10601743]

- Clark R, Grossman M. Number sense and quantifier interpretation. *Topoi: An International Review of Philosophy*. 2007; 26:51–62.
- Cook P, Bai Y, Nadjati-Gilani S. Camino: Open-source diffusion-MRI reconstruction and processing. *International Society for Magnetic Resonance in Medicine*. 2006:2759.
- Cousins KA, York C, Bauer L, Grossman M. Cognitive and anatomic double dissociation in the representation of concrete and abstract words in semantic variant and behavioral variant frontotemporal degeneration. *Neuropsychologia*. 2016; 84:244–251. [PubMed: 26944874]
- Crutch SJ, Warrington EK. Preserved calculation skills in a case of semantic dementia. *Cortex*. 2002; 38:389–399. [PubMed: 12146663]
- Dehaene, S. *The Number Sense*. New York, NY: Oxford University Press; 1997.
- Dehaene S, Spelke ES, Stanescu R, Tsivkin S. Sources of mathematical thinking: Behavioral and brain-imaging evidence. *Science*. 1999; 284:970–974. [PubMed: 10320379]
- Eger E, Sterzer P, Russ MO, Giraud AL, Kleinschmidt A. A supramodal number representation in human intraparietal cortex. *Neuron*. 2003; 37:719–725. [PubMed: 12597867]
- Fairhall SL, Caramazza A. Brain regions that represent amodal conceptual knowledge. *J Neurosci*. 2013; 33:10552–10558. [PubMed: 23785167]
- Fias W, Lammertyn J, Reynvoet B, Dupont P, Orban GA. Parietal representation of symbolic and nonsymbolic magnitude. *J Cogn Neurosci*. 2003; 15:47–56. [PubMed: 12590842]
- Galantucci S, Tartaglia MC, Wilson SM, Henry ML, Filippi M, Agosta F, Dronkers NF, Henry RG, Ogar JM, Miller BL, Gorno-Tempini ML. White matter damage in primary progressive aphasia: a diffusion tensor tractography study. *Brain*. 2011; 134:3011–3029. [PubMed: 21666264]
- Garrard P, Carroll E. Lost in semantic space: a multi-modal, non-verbal assessment of feature knowledge in semantic dementia. *Brain*. 2006; 129:1152–1163. [PubMed: 16585052]
- Goodglass H, Kaplan E. *Boston Diagnostic Aphasia Examination*. 1972
- Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar J, Rohrer JD, Black S, Boeve B, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, Grossman M. Classification of primary progressive aphasia and its variants. *Neurology*. 2011; 76:1006–1014. [PubMed: 21325651]
- Halpern C, Glosser G, Clark R, Gee J, Moore P, Dennis K, McMillan C, Colcher A, Grossman M. Dissociation of numbers and objects in corticobasal degeneration and semantic dementia. *Neurology*. 2004; 62:1163–1169. [PubMed: 15079017]
- Halpern C, McMillan C, Moore P, Dennis K, Grossman M. Calculation impairment in neurodegenerative diseases. *J Neurol Sci*. 2003; 208:31–38. [PubMed: 12639722]
- Hodges JR, Patterson K. Semantic dementia: A unique clinicopathological syndrome. *Lancet Neurol*. 2007a; 6:1004–1014. [PubMed: 17945154]
- Hodges JR, Patterson K. Semantic dementia: a unique clinicopathological syndrome. *Lancet Neurol*. 2007b; 6:1004–1014. [PubMed: 17945154]
- Hoffman P, Jones RW, Lambon Ralph MA. The degraded concept representation system in semantic dementia: damage to pan-modal hub, then visual spoke. *Brain*. 2012; 135:3770–3780. [PubMed: 23250888]
- Hoffman P, Jones RW, Lambon Ralph MA. Be concrete to be comprehended: consistent imageability effects in semantic dementia for nouns, verbs, synonyms and associates. *Cortex*. 2013; 49:1206–1218. [PubMed: 22721956]
- Hubbard EM, Piazza M, Pinel P, Dehaene S. Interactions between number and space in parietal cortex. *Nat Rev Neurosci*. 2005; 6:435–448. [PubMed: 15928716]
- Jefferies E, Patterson K, Jones RW, Lambon Ralph MA. Comprehension of concrete and abstract words in semantic dementia. *Neuropsychology*. 2009; 23:492–499. [PubMed: 19586212]
- Julien CL, Thompson JC, Neary D, Snowden JS. Understanding quantity in semantic dementia. *Cogn Neuropsychol*. 2010; 27:3–29. [PubMed: 20614353]
- Kadosh RC, Henik A, Rubinsten O, Mohr H, Dori H, van de Ven V, Zorzi M, Hendler T, Goebel R, Linden DEJ. Are numbers special?: The comparison systems of the human brain investigated by fMRI. *Neuropsychologia*. 2005; 43:1238–1248. [PubMed: 15949508]

- Kaplan, E.; Goodglass, H.; Weintraub, S. The Boston naming test. Philadelphia: Lea and Febiger; 1983.
- Keenan, EL.; Westersthl, D.; van Bentham, J.; ter Meulen, A. Handbook of Logic and Language. Cambridge, MA: MIT Press; 1997. Generalized quantifiers in linguistics and logic; p. 837-893.
- Koss S, Clark R, Vesely L, Weinstein J, Powers C, Richmond L, Farag C, Gross R, Liang TW, Grossman M. Numerosity impairment in corticobasal syndrome. *Neuropsychology*. 2010; 24:476–492. [PubMed: 20604622]
- Lezak, M. Neuropsychological assessment. Oxford; Oxford University Press; 1983.
- Libon DJ, Rascovsky K, Powers J, Irwin DJ, Boller A, Weinberg D, McMillan CT, Grossman M. Comparative semantic profiles in semantic dementia and Alzheimer's disease. *Brain*. 2013; 136:2497–2509. [PubMed: 23824492]
- Macoir J. Is a plum a memory problem? Longitudinal study of the reversal of concreteness effect in a patient with semantic dementia. *Neuropsychologia*. 2009; 47:518–535. [PubMed: 18973766]
- McMillan CT, Clark R, Moore P, Devita C, Grossman M. Neural basis for generalized quantifier comprehension. *Neuropsychologia*. 2005; 43:1729–1737. [PubMed: 16154448]
- McMillan CT, Clark R, Moore P, Grossman M. Quantifier comprehension in corticobasal degeneration. *Brain Cogn*. 2006; 62:250–260. [PubMed: 16949714]
- McMillan CT, Coleman D, Clark R, Liang TW, Gross RG, Grossman M. Converging evidence for the processing costs associated with ambiguous quantifier comprehension. *Front Psychol*. 2013; 4:153. [PubMed: 23565102]
- McMillan CT, Irwin DJ, Avants BB, Powers J, Cook PA, Toledo JB, McCarty Wood E, Van Deerlin VM, Lee VM, Trojanowski JQ, Grossman M. White matter imaging helps dissociate tau from TDP-43 in frontotemporal lobar degeneration. *J Neurol Neurosurg Psychiatry*. 2013; 84:949–955. [PubMed: 23475817]
- Mion M, Patterson K, Acosta-Cabronero J, Pengas G, Izquierdo-Garcia D, Hong YT, Fryer TD, Williams GB, Hodges JR, Nestor PJ. What the left and right anterior fusiform gyri tell us about semantic memory. *Brain*. 2010; 133:3256–3268. [PubMed: 20952377]
- Morgan B, Gross RG, Clark R, Dreyfuss M, Boller A, Camp E, Liang TW, Avants B, McMillan CT, Grossman M. Some is not enough: quantifier comprehension in corticobasal syndrome and behavioral variant frontotemporal dementia. *Neuropsychologia*. 2011; 49:3532–3541. [PubMed: 21930136]
- Olm CA, McMillan CT, Spotorno N, Clark R, Grossman M. The relative contributions of frontal and parietal cortex for generalized quantifier comprehension. *Front Hum Neurosci*. 2014; 8:610. [PubMed: 25147520]
- Papagno C, Capasso R, Miceli G. Reversed concreteness effect for nouns in a subject with semantic dementia. *Neuropsychologia*. 2009; 47:1138–1148. [PubMed: 19350708]
- Patterson K. The reign of typicality in semantic memory. *philos Trans R Soc Lond B Biol Sci*. 2007; 362:813–821. [PubMed: 17400539]
- Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat Rev Neurosci*. 2007; 8:976–987. [PubMed: 18026167]
- Pinel P, Dehaene S, Riviere D, Le Bihan D. Modulation of parietal activation of semantic distance in a number comparison task. *Neuroimage*. 2001; 14:1013–1026. [PubMed: 11697933]
- Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prileau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011; 134:2456–2477. [PubMed: 21810890]
- Reilly J, Grossman M, McCawley G. Concreteness effects in lexical processing of semantic dementia. *Brain Lang*. 2006; 99:157–158.

- Rogalski E, Cobia D, Harrison TM, Wieneke C, Thompson CK, Weintraub S, Mesulam MM. Anatomy of language impairments in primary progressive aphasia. *J Neurosci*. 2011; 31:3344–3350. [PubMed: 21368046]
- Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron*. 2002; 33:475–487. [PubMed: 11832233]
- Spotorno N, McMillan CT, Powers JP, Clark R, Grossman M. Counting or chunking? Mathematical and heuristic abilities in patients with corticobasal syndrome and posterior cortical atrophy. *Neuropsychologia*. 2014; 64c:176–183. [PubMed: 25278132]
- Troiani V, Clark R, Grossman M. Impaired verbal comprehension of quantifiers in corticobasal syndrome. *Neuropsychology*. 2011; 25:159–165. [PubMed: 21381823]
- Troiani V, Peelle JE, Clark R, Grossman M. Is it logical to count on quantifiers? Dissociable neural networks underlying numerical and logical quantifiers. *Neuropsychologia*. 2009; 47:104–111. [PubMed: 18789346]
- Tustison NJ, Cook PA, Klein A, Song G, Das SR, Duda JT, Kandel BM, van Strien N, Stone JR, Gee JC, Avants BB. Large-scale evaluation of ANTs and FreeSurfer cortical thickness measurements. *Neuroimage*. 2014; 99:166–179. [PubMed: 24879923]
- van Benthem, J. *Essays in Logical Semantics*. Dordrecht, the Netherlands: D. Reidel Publishing Company; 1986.
- Venkatraman V, Ansari D, Chee MWL. Neural correlates of symbolic and non-symbolic arithmetic. *Neuropsychologia*. 2005; 43:744–753. [PubMed: 15721187]
- Warrington EK. The selective impairment of semantic memory. *Q J Exp Psychol*. 1975; 27:635–657. [PubMed: 1197619]
- Wechsler, D. *Wechsler memory scale - revised*. San Antonio: The Psychological Corporation; 1987.
- Wilson SM, Henry ML, Besbris M, Ogar JM, Dronkers NF, Jarrold W, Miller BL, Gorno-Tempini ML. Connected speech production in three variants of primary progressive aphasia. *Brain*. 2010; 133:2069–2088. [PubMed: 20542982]

Highlights

- Corticobasal syndrome (CBS) and behavioral variant FTD (bvFTD) are not aphasic.
- CBS and bvFTD have calculation deficits.
- We find that CBS and bvFTD produce fewer quantifiers in their speech.
- Reduced quantifier production is related to frontal-parietal disease.
- Object noun deficits are related to left temporal disease in CBS, bvFTD and svPPA.

Figure 1. Mean (S.E.) quantifier and noun production in patients with corticobasal syndrome (CBS), behavioral variant frontotemporal dementia (bvFTD), semantic variant primary progressive aphasia (svPPA), and elderly Controls¹

1. * differs from Controls, $p < .01$; + differs from CBS, $p < .001$; ^ differs from bvFTD, $p < .001$; # differs from svPPA, $p < .05$

Figure 2.

Results of gray matter analyses illustrating whole-brain regressions for quantifiers (orange) and nouns (red) across all patient groups. Each row also illustrates patterns of gray matter atrophy for CBS (purple), bvFTD (blue), and svPPA (green).

Figure 3.

Regions of reduced white matter integrity that are connected to atrophied GM regions associated with quantifier production. Reduced FA in CBS is shown in purple; reduced FA in bvFTD is shown in blue.

Figure 4.

Regions of reduced white matter integrity that are connected to atrophied GM regions associated with object noun production. Reduced FA in CBS is shown in purple, reduced FA in bvFTD is shown in blue, and reduced FA in svPPA is shown in green.

Table 1

Mean (SD) demographic, neuropsychological, and language characteristics of Cookie Theft participants with corticobasal syndrome (CBS), behavioral variant frontotemporal dementia (bvFTD), and semantic variant primary progressive aphasia (svPPA) and elderly Controls.^{1, 2}

	CBS	bvFTD	svPPA	Controls
Sex (M/F)	15/18	31/23	14/5	9/18
Age	65.3 (16.8)	63.7 (8.9)	64.6 (8.8)	67.1 (8.2)
Education (yr)	13.9 (2.1) ^{#^}	15.7 (2.9)	16.2 (3.1)	14.9 (2.2)
Disease duration (yr)	4.2 (2.0)	4.2 (2.9)	4.3 (2.2)	--
MMSE	23.2 (6.0) [*]	23.4 (5.0) [*]	21.1 (4.7) [*]	29.2 (1.2)
Boston Naming Test (max=30)	21.0 (7.9) [21] [*]	20.5 (7.7) [46] [*]	5.3 (5.3) [15] ^{*+^}	27.4 (2.6) [19]
Semantic fluency (animals)	10.4 (4.5) [23] [*]	9.0 (6.0) [47] [*]	5.7 (4.6) [15] ^{*+}	19.3 (6.0) [20]
Reverse digit span	3.8 (1.6) [32] [*]	3.5 (1.5) [51] [*]	3.8 (1.7) [19] [*]	5.6 (1.4) [16]
Language features				
WPM	82 (35) [*]	87 (38) [*]	102 (44) [*]	138 (36)
Modified WPM ³	127 (41) [*]	137 (37)	146 (48)	155 (29)
Inflected verbs/100 words	14.5 (2.9)	14.5 (3.7)	13.8 (2.1)	13.7 (1.9)

¹ Statistical significance for demographic characteristics is calculated using Student's *t*; statistical significance for other variables is calculated using Mann-Whitney U. Because of multiple comparisons, we accepted as significant p-values <.01.

^{*} differs from Controls;

⁺ differs from CBS;

[^] differs from bvFTD;

[#] differs from svPPA.

² For neuropsychological tests, the number of participants with available data for each group is given in square brackets.

³ Modified WPM is words per minute recalculated after subtracting the total duration of extended pauses (2.0 sec) from the total duration of the Cookie Theft description.

Table 2

Significant whole brain regression analyses of quantifiers/100 words and object nouns/100 words across all patient groups. The three rightmost columns indicate clusters which overlap (+) or do not overlap (-) with patterns of gray matter atrophy in each group.

Regression	Neuroanatomic Region (Brodmann Area)	MNI coordinates of Peak Voxel			P value of Peak Voxel	Cluster Size (voxels)	CBS Overlap	bvFTD Overlap	svPPA Overlap
		x	y	z					
Quantifiers	L caudate (48)	-12	12	7	0.001	199	-	+	-
	R caudate (48)	10	14	7	0.001	188	+	+	-
	L retrosplenial cortex (30)	-8	-42	-30	0.001	150	-	-	-
	L frontal medial gyrus (11)	-8	25	-13	0.001	127	+	-	-
	R Thalamus (50)	4	-19	6	0.001	115	-	+	-
	L Inferior frontal gyrus (44)	-55	7	18	0.001	73	+	+	-
	R superior frontal gyrus (10)	28	48	23	0.001	68	-	+	-
	R retrosplenial cortex (30)	10	-32	-24	0.001	65	-	-	-
	L medial frontal gyrus (8)	-22	16	42	0.001	43	-	+	-
	R inferior parietal (40)	40	-27	49	0.001	38	+	+	-
	R cingulate gyrus (23)	8	-44	19	0.001	36	-	-	-
	L superior temporal gyrus (22)	-38	-36	17	0.001	28	-	-	-
	L superior frontal gyrus (6)	-24	9	59	0.001	27	-	-	-
	R superior frontal gyrus (8)	26	14	47	0.001	27	-	+	-
Object Nouns	L cingulate gyrus (32)	-4	15	38	0.001	27	-	-	-
	L middle frontal gyrus (9)	-40	21	27	0.001	27	-	-	-
	R inferior frontal gyrus (45)	42	25	2	0.001	25	-	-	-
	L fusiform gyrus (37)	-44	-46	-18	0.001	313	-	+	+
	L middle temporal gyrus (21)	-55	-3	-13	0.001	205	+	+	+
	L superior temporal gyrus (38)	-46	12	-31	0.001	158	-	-	-
	L inferior temporal gyrus (20)	-34	-2	-40	0.001	120	+	+	+
	L cingulate gyrus (23)	-6	-12	26	0.001	67	-	-	-
	L fusiform gyrus (20)	-63	-36	-15	0.001	65	-	-	-
	L caudate (48)	-6	17	19	0.001	45	-	-	-
	L middle temporal gyrus (21)	-63	-13	-21	0.001	45	-	-	-
	L fusiform gyrus (20)	-34	-24	-19	0.001	41	-	-	-

Regression	Neuroanatomic Region (Brodmann Area)	MNI coordinates of Peak Voxel	P value of Peak Voxel	Cluster Size (voxels)	CBS Overlap	bvFTD Overlap	svPPA Overlap
	R retrosplenial cortex (30)	10 -41 -40	0.001	36	-	-	-
	R parahippocampal gyrus (36)	28 -39 -5	0.001	25	-	-	-

Table 3

Significant gray matter atrophy in patients with corticobasal syndrome (CBS), behavioral variant frontotemporal dementia (bvFTD), and semantic variant primary progressive aphasia (svPPA).

Group Comparison	Neuroanatomic Region (Brodmann Area)	MNI coordinates of Peak Voxel	P value of Peak Voxel	Cluster Size (voxels)
CBS < Eld	L middle frontal gyrus (38)	x -26 y 4 z -44	0.001	13832
	R inferior temporal gyrus (21)	x 64 y -4 z -24	0.001	4283
	R parahippocampal gyrus (28)	x 26 y -8 z -14	0.001	323
	R superior frontal gyrus (8)	x 32 y 18 z 54	0.001	198
	L precuneus (7)	x -4 y -66 z 44	0.001	194
bvFTD < Eld	L cingulate gyrus (31)	x -12 y -24 z 44	0.001	152
	R precentral gyrus (6)	x 44 y -2 z 48	0.001	91
	R inferior temporal gyrus (20)	x 42 y -2 z -48	0.001	40883
	L parahippocampal gyrus (30)	x -18 y -34 z -6	0.001	82
	L uncus (20)	x -24 y -4 z -50	0.001	9292
svPPA < Eld	R inferior temporal gyrus (20)	x 36 y -8 z -48	0.001	4287
	R putamen	x 14 y 6 z -12	0.001	62

Table 4

Peak anatomic locations of reduced fractional anisotropy (FA) in white matter tracts connected to significant gray matter quantifier and noun regression clusters in corticobasal syndrome (CBS), behavioral variant frontotemporal dementia (bvFTD), and semantic variant primary progressive aphasia (svPPA).

	Neuroanatomic Region	MNI coordinates of Peak Voxel			P value of Peak Voxel	Cluster Size (voxels)
		x	y	z		
CBS < Eld (quantifier connections)	R corticospinal tract	9	-12	-14	0.001	9188
	L central corpus callosum	-2	-8	27	0.002	2349
	L inferior longitudinal fasciculus	-44	-46	1	0.002	1223
	L uncinate fasciculus	-9	43	-15	0.027	541
	R straight gyrus white matter	10	34	-16	0.026	205
bvFTD < Eld (quantifier connections)	R frontal corpus callosum	20	-10	46	0.012	201
	L uncinate fasciculus	-13	38	-17	0.001	12434
	R cerebrosplinal tract	4	-37	-18	0.001	4014
	L inferior longitudinal fasciculus	-38	-34	-7	0.001	1829
	R parieto-occipital corpus callosum	3	-37	20	0.001	973
	R inferior longitudinal fasciculus	37	-11	-18	0.001	890
	R fornix	2	0	3	0.001	511
CBS < Eld (noun connections)	L inferior longitudinal fasciculus	-46	-44	-2	0.001	4064
	L superior longitudinal fasciculus	-44	-39	29	0.012	461
bvFTD < Eld (noun connections)	L inferior longitudinal fasciculus	-48	-26	-21	0.001	11494
	L uncinate fasciculus	-15	28	-14	0.001	351
svPPA < Eld (noun connections)	L inferior temporal gyrus white matter	-34	1	-37	0.001	9904