Neuropsychologia 76 (2015) 208–219

Contents lists available at ScienceDirect

Neuropsychologia

journal homepage: www.elsevier.com/locate/neuropsychologia

# The ins and outs of meaning: Behavioral and neuroanatomical dissociation of semantically-driven word retrieval and multimodal semantic recognition in aphasia

Daniel Mirman [a,b,*], Yongsheng Zhang [c], Ze Wang [c], H. Branch Coslett [c], Myrna F. Schwartz [a]

[a] Moss Rehabilitation Research Institute, 50 Township Line Rd., Elkins Park, PA 19027, USA
[b] Department of Psychology, Drexel University, 3141 Chestnut St., Philadelphia, PA 19104, USA
[c] University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104, USA

ARTICLE INFO

*Article history:*
Received 29 September 2014
Received in revised form
30 January 2015
Accepted 10 February 2015
Available online 12 February 2015

*Keywords:*
Semantic memory
Comprehension
Semantic errors
Lesion-symptom mapping
Aphasia
White matter

ABSTRACT

Theories about the architecture of language processing differ with regard to whether verbal and nonverbal comprehension share a functional and neural substrate and how meaning extraction in comprehension relates to the ability to use meaning to drive verbal production. We (re-)evaluate data from 17 cognitive-linguistic performance measures of 99 participants with chronic aphasia using factor analysis to establish functional components and support vector regression-based lesion-symptom mapping to determine the neural correlates of deficits on these functional components. The results are highly consistent with our previous findings: production of semantic errors is behaviorally and neuroanatomically distinct from verbal and nonverbal comprehension. Semantic errors were most strongly associated with left ATL damage whereas deficits on tests of verbal and non-verbal semantic recognition were most strongly associated with damage to deep white matter underlying the frontal lobe at the confluence of multiple tracts, including the inferior fronto-occipital fasciculus, the uncinate fasciculus, and the anterior thalamic radiations. These results suggest that traditional views based on grey matter hub(s) for semantic processing are incomplete and that the role of white matter in semantic cognition has been underappreciated.



## 1. Introduction

A recurring theme in research on the neurology and neuropsychology of language centers on the co-occurrence of verbal and nonverbal comprehension deficits, that is, deficits affecting the extraction of meaning from words and from pictures or other nonverbal symbols (for a historical review see Gainotti, 2014). The fascination with this issue arises from the possibility that verbal and nonverbal comprehension have a common functional and neural substrate that is vulnerable to acquired cerebral damage. This common substrate has been variously characterized as the capacity for abstraction (Goldstein, 1948), label feedback (Lupyan, 2012; Lupyan and Mirman, 2013), amodal representations in semantic memory (Rogers et al., 2004), and mechanisms of cognitive control (Jefferies, 2013; Jefferies and Lambon Ralph, 2006; Mirman and Britt, 2014). A cross-cutting question is how meaning extraction in verbal and nonverbal comprehension relates to the ability to use meaning to drive verbal production. Much of the focus here has been on the picture naming task and measures of naming performance that reflect early semantic or semantic-lexical processes in word production (as opposed to later phonological or phonetic processes). The predominant such measure is the semantically-related word substitutions, such as CAT → "dog". Despite intensive study of the functional and neural basis of semantic errors and their relation to measures of verbal and nonverbal comprehension (e.g., Cloutman et al., 2009; Schwartz et al., 2006, 2009), the issue remains unsettled and debated.

Within neuropsychological studies, one approach is to recruit participants with a particular syndrome (e.g., multimodal semantic deficit) or contrasting syndromes (e.g., category-specific deficits for animals vs. tools) and to investigate those syndromes using case study or group comparison methods. An alternative approach, known as the case series method, involves testing a group of related patients in order to understand how and why they differ from one another. On the case series approach, it is not necessary for all participants to exhibit the syndrome of interest because the ones who do not exhibit it are critical comparison points for those that do. Regression methods are typically used to evaluate graded patterns of performance, which also eliminates the need for

* Corresponding author at: Moss Rehabilitation Research Institute, 50 Township Line Rd., Elkins Park, PA 19027, USA.
*E-mail addresses:* dan@danmirman.org (D. Mirman), mschwart@einstein.edu (M.F. Schwartz).

http://dx.doi.org/10.1016/j.neuropsychologia.2015.02.014
0028-3932/

participants to be categorically grouped according to whether they exhibit a particular deficit or not. Whereas case studies and group comparisons are primarily designed to assess deficit dissociations, such as deficits for animals vs. tools, (large) case series studies are also able to detect associations, such as the degree to which semantic production and comprehension deficits tend to co-occur (for a more detailed discussion see Patterson and Plaut, 2009; Schwartz and Dell, 2010; and related commentaries). Combining the behavioral case series method with high-quality neuroimaging (an anatomical case series) allows testing associations between deficits and lesion locations through lesion-symptom mapping. This approach led us to examine patterns of semantic deficits in post-stroke aphasia without restricting our sample to individuals with a specific semantic deficit profile (e.g., multimodal semantic deficit) or aphasia subtype.

We recently reported voxel-based lesion-symptom mapping (VLSM) of cognitive-linguistic factors derived by principal components analysis of test scores from individuals with post-stroke aphasia (Mirman et al., 2015; for related approaches see Butler et al. (2014); Glăscher et al., 2009). One key finding was a behavioral and neuroanatomical dissociation between production of semantic errors in picture naming and deficits on tests of semantic cognition. The factor analysis revealed a multimodal semantic recognition factor comprised of performance on the Camel and Cactus Test, the Peabody Picture Vocabulary Test, a Synonymy Judgment test, and other tests of verbal and nonverbal semantic recognition. Semantic errors in picture naming comprised a distinct factor, indicating a behavioral dissociation between deficits of semantically-driven word retrieval (semantic errors) and verbal and nonverbal semantic recognition. Anterior temporal lobe (ATL) lesions were associated with production of semantic errors, consistent with previous reports (e.g., Schwartz et al., 2009; Walker et al., 2011). The neuroanatomical correlate for deficits on tests of semantics was somewhat unexpected: deep white matter underlying the inferior and middle portions of the frontal lobe. We termed this white matter region a "white matter bottleneck" because it is at the confluence of multiple tracts, including the inferior fronto-occipital fasciculus (IFOF), the uncinate fasciculus (UNC), and the anterior thalamic radiations (ATR).

VLSM analyses consist of defining an anatomical region of interest (typically all voxels where a non-trivial number of participants had lesions) and testing whether performance on some behavioral measure differs as a function of damage in each voxel within that region (Bates et al., 2003). Each voxel is tested individually and a correction for multiple comparisons is applied. This "mass-univariate" approach can identify critical voxel-symptom associations, but it treats voxels independently and is, therefore, not well-suited to detecting *combinations* of voxels that contribute to behavior. It is also very sensitive to differences in lesion coverage: if a symptom can result from damage to either of two areas, all others things being equal, VLSM is more likely to identify the area with the better coverage (closer to approximately half of participants having lesions). Furthermore, according to a recent analysis of 581 ischemic stroke patients, the manner in which the vascular architecture shapes and constrains patterns of lesion distribution constitutes a systematic source of error in mass-univariate VLSM that can lead to mislocalization of deficit–symptom relationships (Mah et al., 2014). The argument, which derives from simulations, suggests in particular that when two distinct regions are involved in some cognitive task, deficits on that task can be mislocalized to underlying white matter. This raises the possibility that our "white matter bottleneck" was actually just a mislocalization of the distributed neural system supporting semantic cognition.

To address this mislocalization issue, Mah et al. (2014) recommended using multivariate analysis methods and demonstrated that one such method (support vector machine classification) was less susceptible to mislocalization of effects. Limitations of mass-univariate VLSM also motivated recent work by our group to develop and test a multivariate lesion-symptom method based on support vector regression (SVR-LSM, Zhang et al., 2014). Analyses conducted with real and simulated data revealed that SVR-LSM has higher sensitivity and specificity for detecting lesion-behavior relations, particularly when multiple regions contribute to behavior and when the lesion proportion differs substantially across voxels. Thus, SVR-LSM may offer a new lesion-symptom mapping method that is less susceptible to mislocalization (Mah et al., 2014) and better able to detect the contributions of multiple distinct brain regions. In the present report we re-visit the dissociation of semantic errors from other deficits of semantic cognition with a closer examination of the behavioral data and by re-analyzing the lesion data using SVR-LSM. The re-evaluation results are consistent with our previous results, providing further support for this functional and neural dissociation. We then consider how these data inform theories of the neural basis of semantic cognition.

## 2. Methods

Behavioral and lesion data were drawn from an ongoing project investigating the anatomical basis of psycholinguistic deficits in post-acute aphasia and were the same as in our previous report (Mirman et al., 2015).

### 2.1. Participants

To be included in this study, participants had to be at least 1 month post-onset of aphasia secondary to stroke, living at home, medically stable without major psychiatric or neurological comorbidities, and have been premorbidly right handed. Participants were also required to have English as their primary language, adequate vision and hearing (with or without correction) and left hemisphere cortical lesion confirmed by CT or MRI. Only participants who had data on all 17 measures were included in this study. All participants gave informed consent to take part in a multisession language assessment under protocols approved by the Institutional Review Boards at the Albert Einstein Medical Center and University of Pennsylvania School of Medicine. The sample consisted of 99 individuals: 43 women and 56 men; 48 African-Americans and 51 Caucasians. They averaged 58 years of age (SD=11; range=26–79), 14 years of education (SD=3; range=10–21), and 53 months post onset of stroke (SD=68; range=1–381). The vast majority (83%) were in the chronic phase ($>6$ months post onset). The predominant subtype diagnosis was anomic aphasia (44%), followed by Broca's aphasia (27%) and conduction aphasia (16%). The Aphasia Quotient, which rates overall severity on a scale from 1 (most severe) to 100, averaged 73 (SD=18.4; range=27.2–97.9).

### 2.2. Language tests

Participants completed a multi-session battery of psycholinguistic tests, primarily focused on word-level processing, from speech perception to verbal and non-verbal semantic processing. Here we provide a brief description along with mean, standard deviation, and range of performance for each test. A more detailed description of the battery is available elsewhere (Mirman et al., 2010).

#### 2.2.1. Camel and Cactus Test (Bozeat et al., 2000)

Test of non-verbal semantic processing in which a pictured

item must be matched to the closest associate among a set of four pictured choices (e.g., wine matched to: grapes, cherry, strawberry, orange). Performance is measured by percent correct of 64 trials: *M*=75.2, *SD*=15.0, *Range*=25–95.

*2.2.2. Pyramids and Palm Trees Test (Howard and Patterson, 1992)*

Test of non-verbal semantic processing in which a pictured item must be matched to the closest associate among a set of two pictured choices (e.g., fish matched to: cat, dog). Performance is measured by percent correct of 52 trials: *M*=87.4, *SD*=11.5, *Range*=46–100.

*2.2.3. Synonymy triplets (Martin et al., 2006)*

Test of verbal semantic processing in which participants must decide which two of three words are most similar in meaning. Half the trials involve nouns (e.g., violin, fiddle, clarinet), the other half verbs (e.g., to repair, to design, to fix). Performance is measured by percent correct of 30 trials: *M*=79.1, *SD*=16.9, *Range*=33–100.

*2.2.4. Semantic category probe test (Freedman and Martin, 2001)*

Test of semantic short-term memory in which participants listen to a list of three or more words and must determine whether the final word is from the same category as any of the preceding words by saying or pointing to "Yes" or "No". The list of words gradually increases and performance is measured as the maximum list length with 75% or higher accuracy: *M*=2.18, *SD*=1.28, *Range*=0.50–6.00.

*2.2.5. Peabody Picture Vocabulary Test (Dunn and Dunn, 1997)*

An untimed, norm-referenced spoken word-to-picture matching vocabulary test arranged in order of increasing difficulty and representing various parts of speech. Performance is measured by a standard score: *M*=79.9, *SD*=15.8, *Range*=40–115.

*2.2.6. Semantic category discrimination (based on Freedman and Martin, 2001)*

Test of verbal semantic processing in which participants must indicate whether two spoken words are members of the same semantic category by saying or pointing to "Yes" or "No". Performance is measured by percent correct of 40 trials: *M*=82.9, *SD*=13.2, *Range*=37–100.

*2.2.7. Philadelphia naming Test (Roach et al., 1996)*

A 175-item single-word picture naming test using black-and-white line drawings of minimal complexity and confusability. The target words cover a relatively wide range of word length, word frequency, and semantic category. The pictures are all familiar objects with high name agreement (97% correct naming performance by unimpaired controls). Three performance measures were included: overall percent correct (*M*=63.3, *SD*=29.1, *Range*=1.1–97.7), percent of semantic errors (e.g., naming *elephant* as *zebra*; *M*=5.4, *SD*=3.9, *Range*=1.1–18.3), and percent of phonological errors (e.g., naming *ghost* as *goath* or *horse* as *house*; *M*=13.2, *SD*=13.3, *Range*=0–49.1).

*2.2.8.. Philadelphia repetition Test*

A word repetition test using the same set of 175 targets as the Philadelphia Naming Test. Performance is measured by percent correct: *M*=85.9, *SD*=14.1, *Range*=39–100.

*2.2.9. Nonword repetition*

Pre-recorded nonword targets derived from Philadelphia Naming Test target words were presented to participants for repetition. Performance is measured by percent correct of 60 trials: *M*=47.3, *SD*=25.8, *Range*=0–98.

*2.2.10. Immediate serial recall span (Martin et al., 1994)*

Test of short term memory in which participants were required to repeat 10 lists of one-syllable words, starting with two-word lists ("wine–dream") and increasing up to five-word lists, if possible ("soul–fear–art–dream–shoe"). Performance is measured by *span length* of the form *X.Y*, where *X* is longest list that with at least 50% correct recall, and *Y* is the proportion correct on the next list out of 50%: *M*=2.70, *SD*=1.09, *Range*=0.50–5.00.

*2.2.11. Rhyme probe test (Freedman and Martin, 2001)*

Test of phonological short-term memory in which participants listen to a list of three or more words and must determine whether the final word rhymes with any of the preceding words by saying or pointing to "Yes" or "No". The list of words gradually increases and performance is measured as the maximum list length with 75% or higher accuracy: *M*=2.80, *SD*=1.69, *Range*=0.50–7.31.

*2.2.12. Rhyme discrimination (based on Freedman and Martin, 2001)*

Test of speech perception in which participants must indicate whether two spoken words rhyme by saying or pointing to "Yes" or "No". Performance is measured by percent correct of 30 trials: *M*=88.7, *SD*=12.1, *Range*=43–100.

*2.2.13. Auditory lexical decision*

(subtest of the Psycholinguistic Assessment of Language Processing in Aphasia, Kay et al., 1996). Test of spoken word recognition in which participants must indicate whether each item is a real English word or not (80 items of each type). Performance is measured as overall $d'$ (a measure of discrimination based on signal detection theory): *M*=2.48, *SD*=0.70, *Range*=0.33–3.88.

*2.2.14. Phoneme discrimination (Martin et al., 2006)*

Test of speech perception in which participants must indicate whether two spoken words ($n$=20) or nonwords ($n$=20) are the same or different. Non-identical pairs differ by a single onset or final phoneme. In the delay version, there is a 5-s interval between the two items in a pair. Performance is measured by percent correct. No delay: *M*=88.0, *SD*=11.6, *Range*=48–100. Delay: *M*=81.6, *SD*=12.8, *Range*=48–100.

### 2.3. Lesion data

Research brain scans were acquired for 87 participants (50 MRI, 37 CT). High-resolution whole-brain T1-weighted images [magnetization prepared rapid acquisition gradient echo (MPRAGE)] were acquired for the 50 participants undergoing MRI. Of these, 44 were scanned on a 3- T Siemens Trio scanner [repetition time (TR)=1,620 ms, echo time (TE)=3.87 ms, field of view (FOV)=192 × 256 $mm^2$, 1 × 1 × 1 $mm^3$ voxels]. Because medical implants were not approved for the higher strength magnetic field, 6 participants were scanned instead on a 1.5-T Siemens Sonata (TR=3000 ms, TE=3.54 ms, FOV=24 cm, 1.25 × 1.25 × 1.2-$mm^3$ voxels). For 37 participants who were not eligible for MRI scanning, whole-brain CT scans without contrast (60 axial slices, 3 mm thick) were acquired. Twelve additional participants declined scanning; for these participants, recent clinical scans [CT ($n$=8) and MRI ($n$=4)] with clearly delineated lesion boundaries were substituted in the lesion tracing procedure.

Lesion segmentation methods were those used in our previous studies (e.g., Schwartz et al., 2009). Lesions were manually segmented on the structural image by a trained technician or experienced neurologist (co-author H.B.C.) both of whom were blinded to the behavioral data. The lesion maps drawn by the technician were reviewed by H.B.C. The lesion overlap map for the 99 qualified participants is shown in Fig. 1. Only voxels with at

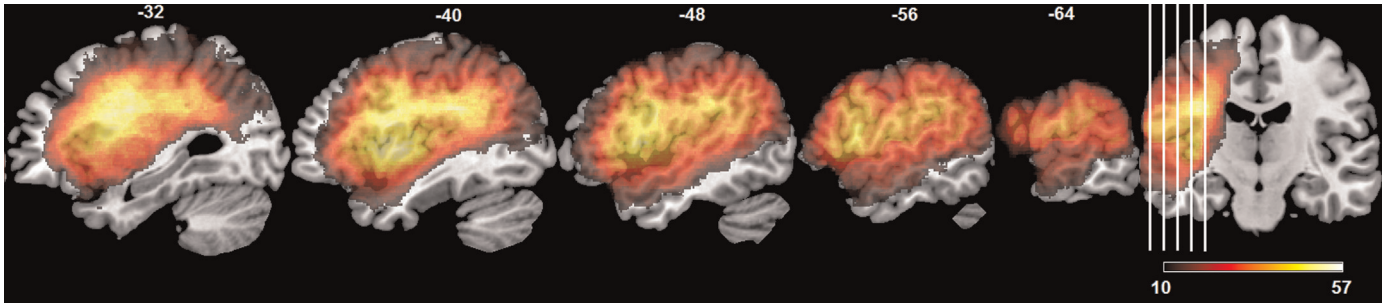


**Fig. 1.** Lesion overlap map for 99 participants in these analyses.

least 10 lesions are shown in the map because this threshold was used in the SVR-LSM analyses. The lesion overlap map indicates coverage throughout the left hemisphere middle cerebral artery territory, including the inferior parietal lobe (angular gyrus and supramarginal gyrus), the middle and superior temporal lobe, and the inferior and middle frontal lobe. Lesion counts confirmed adequate coverage of the inferior parietal lobe (BA 40: Median=26, range=6–45; BA 39: Median=26, range=5–45), inferior frontal gyrus (BA 44: Median=36, range=4–50; BA 45: Median=20, range=2–46), and anterior temporal lobe (operationally defined as BA 38: Median=13, range=0–38). That is, even in the anterior temporal lobe, the ventral surface of which is outside the MCA territory, most voxels had enough lesions for meaningful analysis.

### 2.4. SVR-LSM

We (Zhang et al., 2014) developed SVR-LSM as a method for multivariate lesion-symptom mapping. In a typical whole-brain VLSM analysis the number of voxels (hundreds of thousands) is much greater than the number of patients (usually $< 1000$). This rules out a simple multiple regression approach to multivariate LSM because the number of model coefficients would be much greater than the number of observations, resulting in an under-determined model. In other words, a multiple regression-based multivariate lesion symptom model would have an infinite number of solutions. SVR-LSM extends support vector machines (SVM) —a machine learning method for classification—to predict continuous behavioral performance. That is, whereas SVM produces a binary classification of participants as "impaired" or "unimpaired", SVR-LSM produces a graded degree of participant's deficit.

SVR-LSM tries to solve the under-determination problem by adding a "flatness" constraint: the norm of the model coefficients (the square root of power) should be minimal. The consequence of this constraint is similar to a denoising process where high frequency (spike-like) signal components are suppressed by smoothing. An advantage of being "flat" is that the multivariate model is unlikely to be dominated by a few subjects (i.e., over-fitted to a few subjects' data) so the lesion-behavior relationship captured by the model reflects contributions from all subjects rather than several particular cases. Over-fitting (to all acquired data) is also avoided by setting a minimal error threshold so that errors smaller than the threshold are ignored during training. This trades off a small portion of fitting accuracy in exchange for substantial increases in prediction accuracy, thus making the model less sensitive to individual cases and more general to the population.

When a linear model is not sufficient to capture the lesion-symptom relationship, SVR-LSM uses a nonlinear transform to project the lesion data to a feature space so that a linear lesion-symptom association model can be built in the feature space rather than the original data space. Because the nonlinear transform contains interactive operations involving different voxels, it automatically takes the spatial correlations among voxels into account during model training, resulting in higher sensitivity for lesion-symptom relation detection as compared to a linear SVR-LSM as well as to VLSM (Zhang et al. 2014). To locate the symptom-associated brain regions, the multivariate parametric map of the nonlinear SVR-LSM is projected back to the original brain space. The parameter at each voxel after back-projection indicates the local lesion-behavior association strength.

Individual lesion maps were normalized to have a norm of 1 to stabilize data processing and to capture the effects of overall lesion volume. That is, for each participant, instead of coding the lesion status of each voxel as binary (0=no lesion, 1=lesion), it was 0 (no lesion on this voxel) or 1/(square root of total lesion volume). This captures the intuitive notion that the damage in a particular voxel is more informative for smaller lesions than for larger lesions. To provide a statistical inference for the local effects, the same SVR-LSM process can be repeated many times using randomly permuted behavior scores (2000 permutations for the analyses reported here). The proportion of times that the lesion-association strength from the permuted data is greater than the one from the original data provides a non-parametric $p$-value for the null hypothesis that the lesion-symptom association would occur at random. Correction for multiple comparisons is a critical (and controversial) issue in VLSM, but in SVR-LSM, the lesion-symptom associations at all voxels are identified simultaneously rather than as independent events, so there are no multiple comparisons involved in generating the statistical map. In addition, because the LSM betas are identified simultaneously for all voxels rather than from each voxel independently, SVR-LSM is less sensitive to differences in statistical power across voxels that result from differences in the proportion of participants with lesions in each voxel. These differences in power can have substantial effects on results of traditional VLSM analyses but are mitigated in SVR-LSM (this is discussed in more detail in Zhang et al., 2014). There is no single agreed-upon method for statistical thresholding in SVR-LSM (for some discussion see Zhang et al., 2014); however, our present goal is to evaluate the convergence between SVR-LSM and our previous VLSM analyses, so we thresholded the SVR-LSM maps to have the same number of supra-threshold voxels as the VLSM analyses, where the threshold was set based on false discovery rate (FDR) correction and a permutation-based cluster size threshold.

To quantify the convergence between results of SVR-LSM and our previous VLSM analyses, we computed a voxel overlap measure reflecting the proportion of overlapping voxels. Specifically, we computed the Sorensen-Dice index where the numerator was two times the number of supra-threshold voxels in the SVR-LSM analysis for which there was a supra-threshold voxel in the VLSM analysis within a 2 mm radius (i.e., within 2 voxels) and the denominator was the total number of supra-threshold voxels summed across the VLSM and SVR-LSM analyses.

## 3. Results

### 3.1. Behavioral data

Fig. 2 shows all pairwise correlations between behavioral measures and each measure's loading on each of the four factors, which we label "Semantic Recognition", "Speech Production", "Speech Recognition", and "Semantic Errors". The factor loadings (right side of figure) are based on a principal component analysis with varimax rotation (which produces orthogonal factors that, in the limit, would preserve all of the variance in the original data); the four factors accounted for.28, 21,.20, and.07 of the variance, respectively. Alternative analyses based on Kendall rank correlations instead of Pearson correlations and oblimin rotation instead of varimax rotation produced qualitatively identical results (e.g., oblimin and varimax rotations produced nearly identical factor loadings: for each factor, correlations between loadings were $r > 0.94$).

The pairwise correlations shown in Fig. 2 provide a closer look at how the behavioral measures clustered. Two patterns are noteworthy. First, the correlations among Semantic Recognition tests were quite high (all $r > 0.5$, most $r > 0.6$). These tests include verbal semantics (synonymy triplets, semantic category discrimination), nonverbal semantics (Camel and Cactus test, Pyramids and Palm trees Test), and both (Peabody Picture Vocabulary Test), which suggests a common functional system for verbal and non-verbal semantics in the left hemisphere. These data do not speak to the role of right hemisphere regions in semantic cognition (because we only tested participants with left hemisphere stroke), but they clearly demonstrate that unilateral left hemisphere stroke can cause multimodal (verbal and nonverbal) semantic deficits. The tests in this cluster all have minimal output demands (yes/no response or pointing), so the task demands emphasize semantic recognition or conceptualization rather than semantic knowledge driving other cognitive processes (such as word production).

The second noteworthy finding is that the correlation between semantic errors and deficits on semantic recognition tests was substantially lower. In fact, deficits on tests of semantic recognition correlated at least as strongly with deficits on *speech* recognition tests as with semantic errors. For example, performance on each of the semantic recognition tests correlated more strongly with Rhyme Discrimination ($r$ range 0.32–0.59) than with production of semantic errors in picture naming ($r$ range $-0.04$ to $-0.31$). Together, these two findings indicate that left hemisphere stroke can produce multimodal semantic deficits, but that this sort of deficit is not the primary cause of aphasic semantic errors in picture naming.

Fig. 3 shows average factor scores for each of the aphasia subtypes that were substantively represented in our sample.

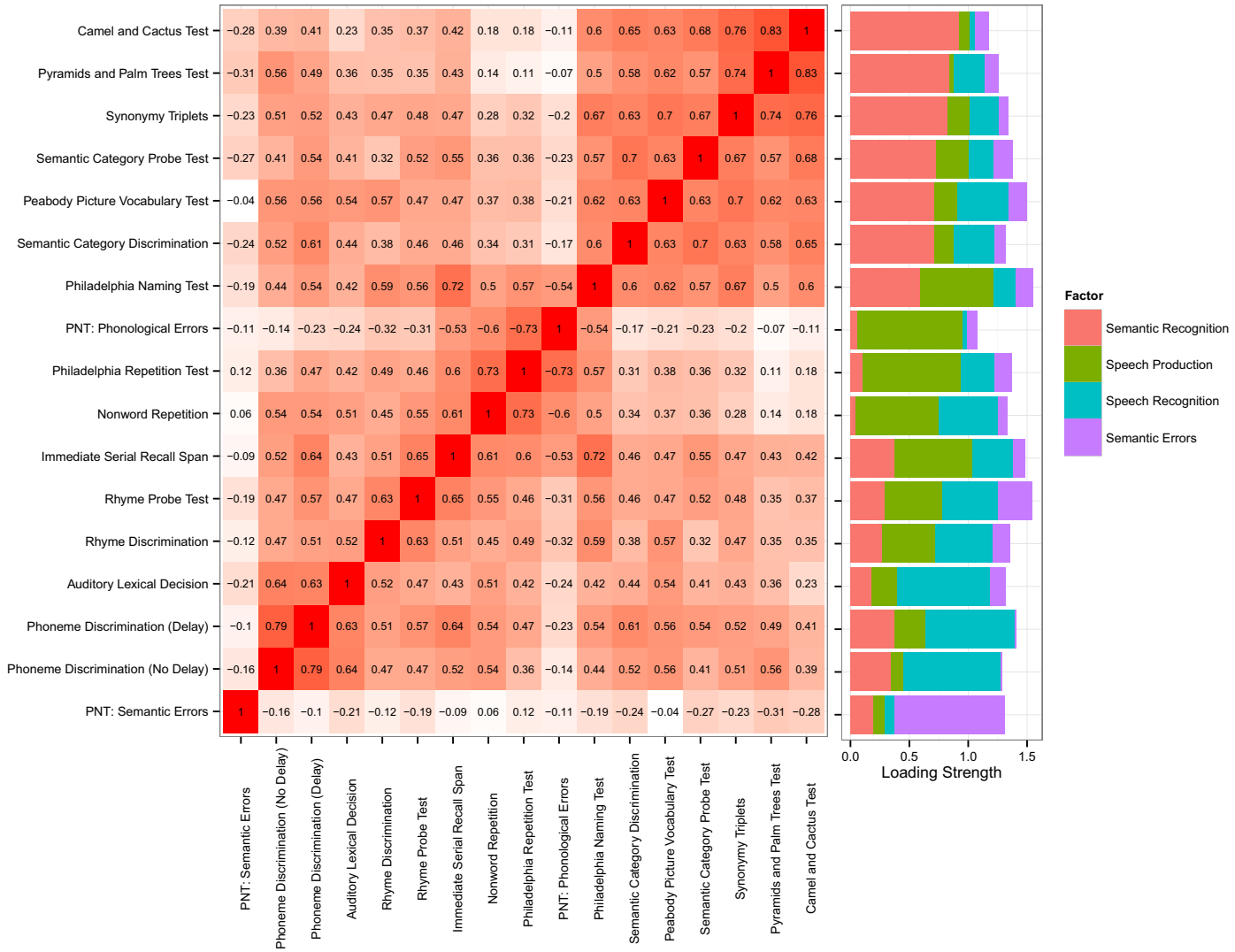


**Fig. 2.** Left: Pairwise correlations between behavioral measures. Darker colors indicate stronger correlations. Right: Factor loadings in a 4-factor solution.

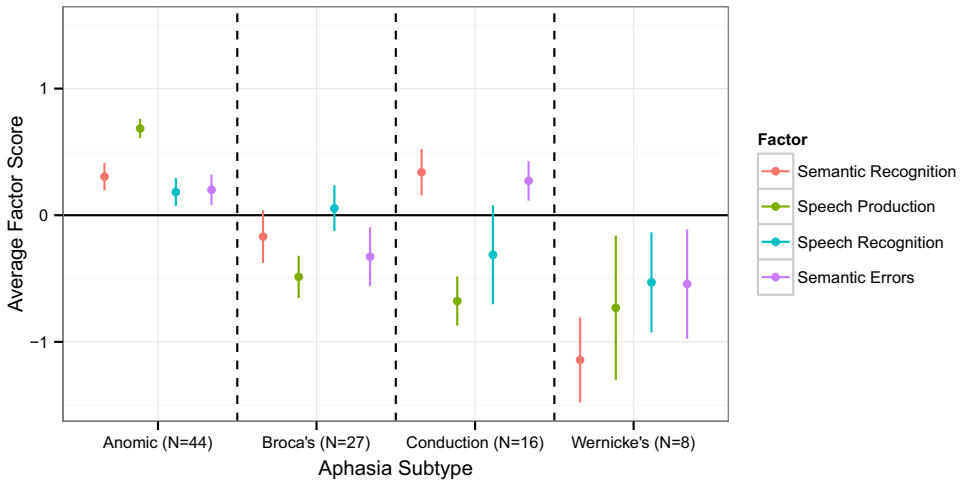


**Fig. 3.** Average factor scores by aphasia subtype (vertical lines indicate ±SE). Positive values indicate better performance. Global ($N=1$) and Transcortical Motor ($N=3$) aphasia are omitted due to their small sample size.

Positive values indicate better performance (including for the Semantic Errors factor, where positive values correspond to fewer semantic errors). These results broadly accord with clinical characterizations of these subtypes: anomic aphasia is generally mild with relatively spared performance in each domain; Wernicke's aphasia is the most severe of these four with poorer performance on all factors, especially the semantic recognition factor; Broca's aphasia is associated with deficits on both production factors (speech production and semantic errors in word production); and Condition aphasia is associated with deficits in both phonological processing factors – speech production and speech recognition. Note, however, that there is substantial overlap between the subtypes on many of the measures. Thus, although the expected aphasia subtype patterns generally hold at the group level, individual participant performance is likely to be only coarsely predicted by aphasia subtype.

Butler et al. (2014) used a very similar approach—data from a large group of individuals with chronic aphasia following left hemisphere were analyzed using principal component analysis with varimax rotation. Their results also revealed a dissociation of phonological and semantic factors, but not the recognition-production dissociation that we observe in our data (for both the

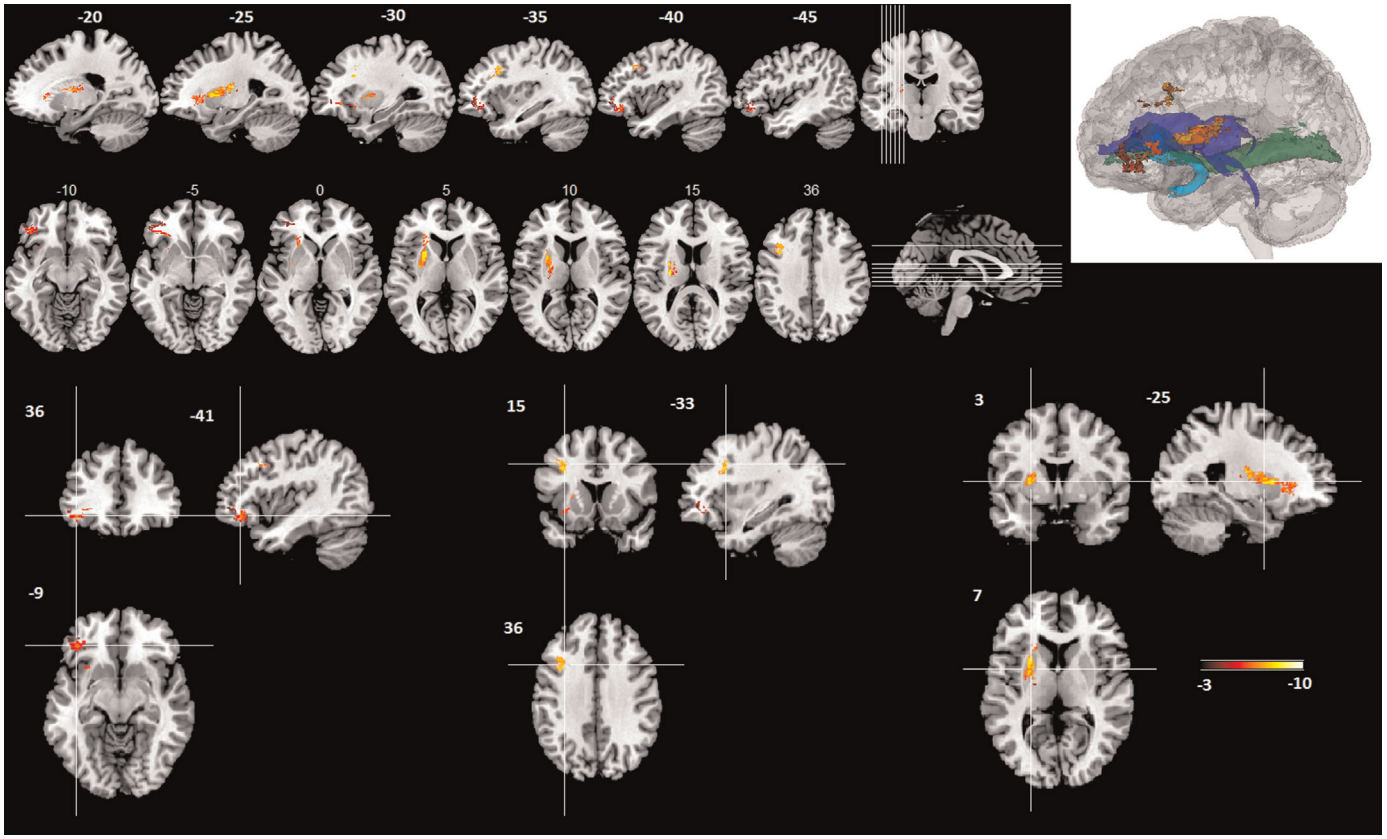


**Fig. 4.** SVR-LSM β-map for the Semantic Recognition factor. Inset in top right shows overlap between supra-threshold voxels (red-yellow) and three key white matter tracts: IFOF (green), UNC (light blue), and ATR (blue). The white matter tracts are based on the ICBM-DTI white-matter tractography atlas from FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases) using a 20% probability threshold. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

phonological and semantic factors). Two important differences between the studies may be responsible. First, Butler et al. included measures of accuracy in picture naming but not picture naming error types (i.e., phonological vs. semantic errors). This would, obviously, make it impossible to detect a dissociation of production of semantic errors from performance on tests of semantic recognition. Since production of phonological errors was the highest-loading measure for the Speech Production factor and the one that most uniquely contributed to it (tests of repetition and rhyme discrimination tended to load on both Speech Recognition and Speech Production), omitting this measure may have also limited their ability to distinguish production and recognition components of their "Phonology" factor. Second, our sample of participants was more than three times larger (99 vs. 31), providing substantially more statistical power to detect distinct factors.

### 3.2. Neuroanatomical data

The purpose of these analyses was to use a multivariate lesion-symptom mapping method (SVR-LSM) to re-evaluate (1) the association between multimodal semantic deficits following left hemisphere stroke and damage to white matter underlying the inferior and middle portions of the frontal lobe (the "white matter bottleneck"), and (2) the neuroanatomical dissociation of multimodal semantic deficits and production of semantic errors in picture naming. For completeness, we also report SVR-LSM reanalyses of the other two factors: Speech Production and Speech Recognition.

Fig. 4 shows the SVR-LSM β-map for the Semantic Recognition factor. The analysis revealed a cluster of voxels medial to the insula and lateral to the basal ganglia (with some voxels in the putamen). Using the FSL ICBM-DTI white-matter tractography atlas we found that several white matter tracts converge in this region, including the IFOF, UNC, and ATR. Recent studies have found that these white matter tracts are associated with semantic deficits in stroke (Han et al., 2013; Kümmerer et al., 2013) and neurodegenerative disease (Guo et al., 2013), as well as transient semantic disruption produced by intraoperative direct electrostimulation (Moritz-Gasser et al., 2013). Our analysis also revealed a second, more superior cluster of voxels in the white matter underlying the middle frontal gyrus. The overlap index between these results and our previous VLSM results was 0.92, indicating a high degree of convergence between the two analyses. These results also partly converge with the results Butler et al. (2014), who also found that deficits on their semantic factor were associated with damage to the IFOF and UNC in the temporal lobe, somewhat inferior to our finding.

The SVR-LSM analysis of the Semantic Error factor revealed two clusters of voxels: a larger one in the anterior portion of the superior and middle temporal gyri and a smaller one in the inferior frontal gyrus (Fig. 5). This also converged with our previous VLSM analysis, with an overlap index of 0.93.

SVR-LSM analyses of the Speech Production and Speech Recognition factors also converged with our previous VLSM results: overlap indexes 0.98 and 0.96, respectively. Lesions superior to the Sylvian fissure, primarily in the supramarginal gyrus and extending anteriorly into inferior postcentral, precentral, and premotor cortex were associated with lower scores on the Speech Production factor (Fig. 6, blue–green). That is, speech production deficits were associated with damage to the dorsal language pathway, consistent with claims that this region is involved in sensory-motor transformations that support speech production (e.g., Buchsbaum et al., 2011; Hickok and Poeppel, 2007; Schwartz et al., 2012). Lesions in a parallel region, inferior to the Sylvian fissure, primarily in the posterior superior temporal gyrus and extending deep into planum temporale were associated with lower scores on the Speech Recognition factor (Fig. 6, red-yellow). On one influential dual-pathways view (Hickok and Poeppel, 2007), the planum temporale is part of the dorsal route and the sensory-motor transformations performed by the dorsal route are critically involved in some laboratory speech recognition tasks (such as phoneme discrimination) because participants strategically engage speech production systems while performing these tasks. Our results are consistent with an alternative dual-pathways view, according to which the ventral language pathway includes Wernicke's area and planum temporale and supports speech comprehension in a hierarchical posterior-to-anterior system from speech sound recognition to phrase comprehension (e.g., Dewitt and Rauschecker, 2012; Rauschecker and Scott, 2009). The MNI coordinates for peak and center voxels and cluster sizes for each factor are summarized in Table 1.

## 4. Discussion

The results of these re-analyses are consistent with our previous report of a dissociation between production of semantic errors in picture naming and deficits on tests of semantic cognition. In further support of the behavioral dissociation, the bivariate correlation matrix revealed a tight clustering of tests of verbal and nonverbal semantics that have minimal output demands, but the production of semantic errors was not part of this cluster. Additionally, we mapped the factor scores for the orthogonal factors using a multivariate method based on support vector regression. This method was previously shown to be more sensitive than VLSM, particularly when the cognitive function is supported by multiple distinct brain regions (Zhang et al., 2014). A related multivariate method was shown by Mah et al. (2014) to be less susceptible to mislocalization arising from constraints of the cerebral vasculature. The SVR-LSM of factor scores confirmed our prior finding that semantic errors were most strongly associated with left ATL damage whereas deficits on tests of verbal and nonverbal semantic recognition were most strongly associated with

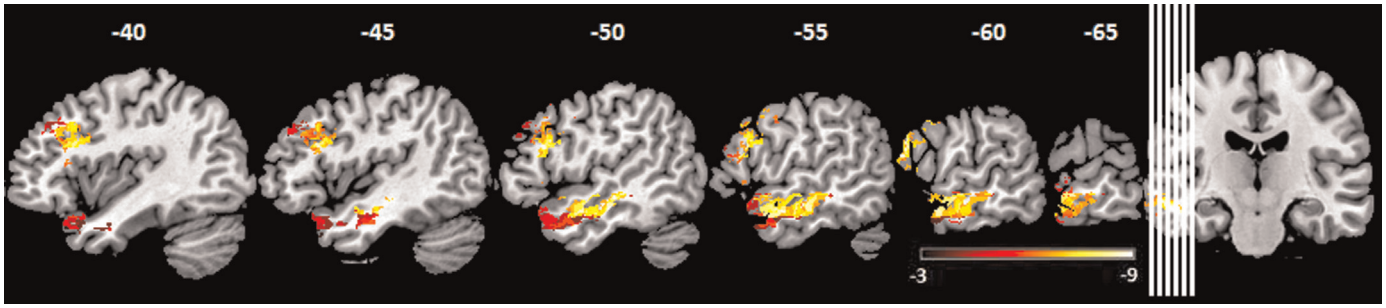


**Fig. 5.** SVR-LSM β-map for the Semantic Errors factor.

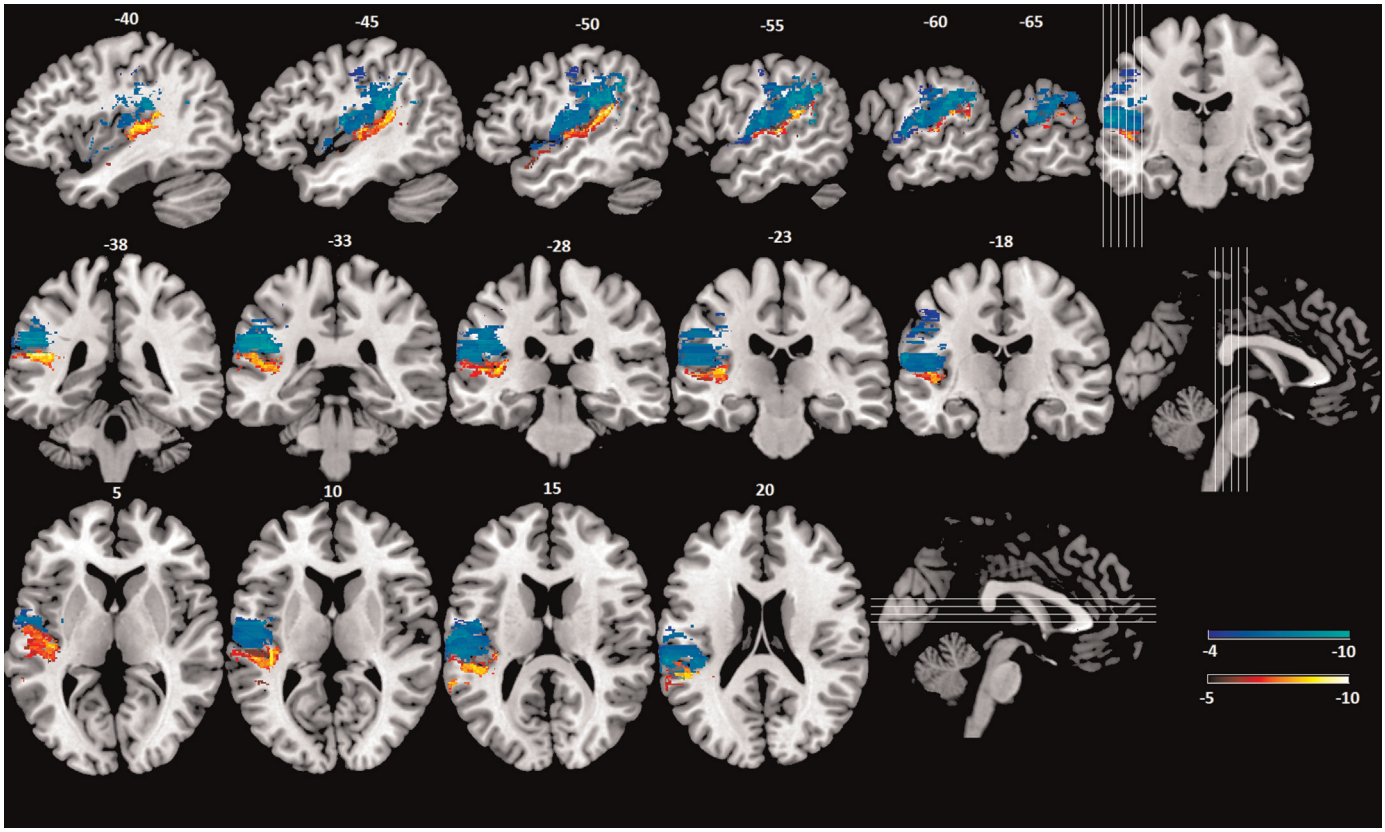


**Fig. 6.** SVR-LSM β-maps for the Speech Production (blue–green) and Speech Recognition (red–yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

damage to a frontal white matter bottleneck.

These results have strong bearing on debates about primary cause of semantic errors in naming. It has been argued that in post-stroke aphasia, such errors are symptomatic of a multi-modality semantic deficit arising from damage to semantic representations (Gainotti et al., 1984; Hillis et al., 1990) or to executive systems that control retrieval from semantic memory (Jefferies, 2013). Yet here, in a large group of stroke aphasics, the evidence is that semantic errors dissociate from multi-modal semantic comprehension behaviorally and neuroanatomically. This argues instead for a semantic deficit that is specific to verbal production (Lambon Ralph et al., 2001) or a deficit localized to a post-semantic stage of word production (i.e., access to lexical-semantic word forms, or "lemmas"). The post-semantic account is compatible with several psycholinguistic models of word production (e.g., Dell, 1986; Levelt et al., 1999) and receives support from large-scale computational and neuroanatomical analyses of naming errors in aphasia (Foygel and Dell, 2000; Schwartz et al., 2006; Dell et al., 2013).

The anatomical findings also challenge the existence of a single cross-modal grey matter hub for semantic cognition within the covered territory (most of the left frontal, temporal, and parietal lobes, excluding the inferior temporal surface and the superior surface of the frontal and parietal lobes). In particular, the ATL, inferior parietal lobule (IPL), and temporo-parietal cortex (TPC) have been proposed to function as semantic hubs, yet neither emerged in our analyses (VLSM or SVR-LSM). Further, ATL damage was associated with a specific deficit—production of semantic

**Table 1**
Main clusters of identified voxels: MNI coordinates for peak and center voxels and number of voxels in each cluster.

| **Factor** Anatomical description of peak voxel location | Peak voxel | Center voxel | Num. voxels |
|---|---|---|---|
| **Semantic recognition** | | | |
| Region of external capsule underlying posterior insula | (−26, −15, 16) | (−30, 17, 3) | 3767 |
| Subcortical white matter of the MFG at the level of the head of the caudate | (−38, 10, 35) | (−36, 16, 34) | 560 |
| Cortex at the juncture of the anterior IFG and MFG | (−48, 29, 26) | (−51, 31, 27) | 96 |
| **Speech production** | | | |
| Region of precentral gyrus roughly corresponding to face/mouth | (−50, −16, 36) | (−53, −24, 22) | 18,352 |
| **Speech recognition** | | | |
| Posterior, medial STG | (−37, −24, 11) | (−49, −29, 11) | 4995 |
| Anterior STG | (−51, 0, −7) | (−51, 2, −7) | 89 |
| (More) anterior STG | (−49, 10, −12) | (−50, 11, −15) | 87 |
| **Semantic errors** | | | |
| Superior, lateral, anterior MTG | (−64, −3, −12) | (−55, −2, −17) | 10,970 |
| Cortex of posterior third of IFG | (−60, 22, 20) | (−48, 21, 18) | 7901 |
| Deep white matter between anterior, superior insula and caudate | (−26, 9, 18) | (−31, 11, 16) | 244 |
| Anterior, superior insula | (−32, 22, 12) | (−36, 22, 14) | 167 |

Note: IFG = inferior frontal gyrus, MFG = middle frontal gyrus, MTG = middle temporal gyrus, STG = superior temporal gyrus.

errors—so this null result cannot be attributed to lack of lesion coverage or statistical power. In other words, left ATL damage is more strongly associated with semantic errors than with multimodal semantic deficits. This does not preclude the ATL from contributing to multimodal semantic cognition, possibly through retrieval of verbal labels (e.g., Lupyan, 2012; Lupyan and Mirman, 2013) or in coordination with other semantic hubs, but not as a single semantic hub.

One might argue that we failed to find the hub because it is outside our covered territory, for example, because it is redundantly bilateral and therefore requires bilateral damage (Lambon Ralph, 2014) or because it is in ventral and inferolateral sectors of the anterior temporal lobe (Binney et al., 2010). In this case, we should not have observed the multimodal semantic deficit that is thought to reflect damage to the semantic hub. But we did observe this deficit—the semantic recognition factor reflects exactly this kind of deficit, affecting both verbal and nonverbal tasks. Another possibility is that the multimodal semantic deficit that we observed is a result of damaged communication between a ventral/inferolateral ATL hub (which is outside our lesion coverage) and other regions involved in semantic cognition. Specifically, damage to the uncinate fasciculus could disconnect an ATL hub from inferior frontal regions that may be critical for regulation or control of semantic cognition (e.g., Harvey, et al., 2013; Ueno et al., 2011). However, there is evidence that uncinate fasciculus damage is specifically associated with impaired label retrieval rather than semantic cognition deficits (e.g., Papagno et al., 2011) and the function of this fiber tract may extend beyond semantic memory and language (e.g., von Der Heide et al., 2013). Even if the function of the uncinate fasciculus were limited to communication between an ATL hub and frontal control systems, an account of our results based on specific damage to the uncinate is not quite consistent with our results.

Instead, our anatomical results identified a region of white matter convergence where a small amount of damage can have a large disruptive effect on connectivity patterns that are essential for the integration or control of elements of this system, thereby compromising semantic processing in a multi-modal fashion. These anatomical findings are consistent with recent evidence showing that semantic deficits in stroke (Han et al., 2013; Kümmerer et al., 2013) and primary progressive aphasia (Guo et al., 2013) are associated with damage to white matter tracts, particularly IFOF, ATR, and UNC, possibly among others. Further evidence from direct electrical brain stimulation that mimics the effect of white matter damage also demonstrated the critical role of IFOF in semantic processing (Moritz-Gasser et al., 2013). A unique property of our analyses is that the critical region they identified is a white matter "*bottleneck*" rather than a white matter tract. Since the tracts that pass through this bottleneck connect disparate cortical regions, it is their confluence that appears to be critical to semantic cognition rather than any one particular tract or cortical region. That is, disruption of integration or coordination of activity in disparate brain regions appears to be the critical factor that produces multimodal semantic recognition deficits following left hemisphere stroke.

The accumulating evidence of the importance of white matter for semantic cognition is consistent with the very general and widely-accepted view that semantic cognition draws on a widely distributed neural system. Before pursuing that point further, it is important to distinguish three related-but distinct-ideas about the neural and functional instantiation of this distributed system: (1) An early account emphasized distributed sensory-motor representation of concepts and categories (e.g., Allport, 1985; Saffran and Schwartz, 1994), particularly their relation to category-specific semantic deficits (e.g., Mahon and Caramazza, 2009; Warrington and Shallice, 1984), and more recent interpretations of patterns of activation in functional neuroimaging studies of object concepts (e.g., Binder and Desai, 2011; Martin, 2007). Integration and control systems have not been articulated within this framework, but are not specifically in conflict with it. (2) Building on the idea that semantic cognition involves primary sensory-motor areas, Damasio and colleagues (e.g., Damasio, 1989; Meyer and Damasio, 2009) proposed a convergence—divergence framework in which higher order cortices (convergence—divergence zones) capture correlations in lower-level zones during perception and, during recall, reinstate the activation patterns based on those correlations (see also Gainotti, 2011). (3) The observation of multimodal semantic deficits in the semantic variant of primary progressive aphasia (semantic dementia) has led to the proposal that there is a single semantic "hub" that integrates semantic information into an abstract form that supports generalization to non-similar instances of categories (e.g., Lambon Ralph, 2014; Patterson et al., 2007). A computational implementation of this "hub-and-spokes" view of the semantic system accounts for many key properties of semantic deficits in semantic dementia (Rogers et al., 2004). The theory locates this hub in the ATL, largely because of the association of semantic dementia with anterior temporal atrophy (e.g., Hodges and Patterson, 2007).

These views differ both architecturally and computationally. The architectural differences concern how the distributed sensory-motor information is integrated, either making no claims regarding integration (distributed view), or proposing multiple graded integration systems (convergence zones or systems), or proposing a single amodal (or transmodal) integration hub. The computational function is a (partly) separate issue from the architecture. Convergence–divergence zones are proposed to have a very limited computational function: capturing correlations in lower zones during perception and reinstating those correlated activation patterns during recall (e.g., Meyer and Damasio, 2009). In contrast, the hub in the hub-and-spokes model (Rogers et al., 2004) performs a substantially more sophisticated computational function, though a single hub may not be the only way to accomplish this computational function (e.g., McNorgan et al., 2011).

### 4.1. Hub models reconsidered

A fully distributed view of semantic cognition, one in which all areas are connected to one another with no hub, predicts that there should not be a brain region where focal damage would produce a multimodal semantic deficit. On this view, focal damage could produce modality-specific or category-specific deficits depending on the location of the lesion, but it would require multiple distributed lesions, or one very large one, to compromise semantic processing across a range of modalities and categories. Since the Semantic Recognition factor taps semantic processing on a range of modalities and categories, it would be expected to correlate with lesion volume and show no effect of lesion location. In fact, the Semantic Recognition factor had only a moderate correlation with lesion volume ($r = -0.30$) and the SVR-LSM controlled for this relationship yet still identified a focal neural correlate. Given this, the distributed-no-hub view can be rejected.

Our data provide no support for a grey matter processing hub, either in the ATL or in the IPL/TPC. A hub in the prefrontal cortex (PFC) would be consistent with the present data on the assumption that white matter bottleneck damage would disconnect this hub from the rest of the semantic system. This view could connect with the emerging consensus that semantic cognition involves dissociable elements for storage or representation of semantic knowledge and control or access systems for manipulation of that knowledge (e.g., Jefferies, 2013; Jefferies and Lambon Ralph, 2006; Mirman and Britt, 2014) and that the latter semantic control system involves inferior (ventrolateral) prefrontal cortex. However,

this perspective requires several qualifications. First, if the critical semantic control hub were in the IFG/VLPFC grey matter, then multimodal semantic deficits should have been most strongly associated with damage to that region rather than to the underlying white matter as we observed. In fact, stroke damage to the left IFG/VLPFC has been associated with a more specific deficit of lexical selection in the context of semantic competition (e.g., Mirman and Graziano, 2013; Schnur et al., 2006, 2009; for related fMRI evidence see also Snyder et al., 2014). Second, although some of the tests that loaded strongly on the Semantic Recognition factor have substantial semantic control demands (e.g., Camel and Cactus Test), others do not (e.g., Semantic Category Discrimination is a simple AX semantic discrimination task), so it is not simple to argue that the Semantic Recognition factor was rather a Semantic Control factor. Finally, frontal damage was more strongly associated with performance on the Semantic Errors factor than on the Semantic Recognition factor. Insofar as semantic errors in picture naming reflect errors of semantically-driven lexical selection, this association again points to this region's involvement in lexical selection processes rather than broader semantic control functions involved in tasks like the Camel & Cactus Test. More generally, a semantic control account of the white matter bottleneck effect requires an explanation of why the effect was specific to semantic recognition tasks rather than semantic production errors and was subcortical rather than cortical.

One alternative to a grey matter processing hub is a white matter "transit" hub. Just as it would be impractical to build rail lines from every city to all other cities, it is anatomically impossible for every functional brain region to be connected to all other possibly relevant brain regions. This idea of a hub is closely related to the idea of network hubs coming from efforts to map the human "connectome" (e.g., van den Heuvel and Sporns, 2013) or more specifically the language connectome (e.g., Dick et al., 2014). This sort of hub could arise simply as a result of the anatomical constraint that each brain regions cannot have a direct connection to all other regions and serve no additional role beyond allowing them to communicate with one another. This would make it a variant of the distributed multimodal semantics view (e.g., Allport, 1985) with the additional anatomical constraint on connections between regions. Since the convergence–divergence zones are proposed to have a very simple computational role, this simple white matter hub idea may also be framed as a version of the convergence–divergence zones view. Computationally, this may be similar to the "Jets and Sharks" model (McClelland, 1981)—an early connectionist model of semantic memory that used a hub-and-spoke architecture in which the hub merely connected associated elements in different spokes, as a convergence—divergence zone is proposed to do.

A white matter hub could play an additional computational role beyond simply allowing communication between regions. This additional role may be to integrate feature information and to capture more complex relationships between features than the simple correlations of the convergence—divergence framework. For example, whereas the "hub-and-spokes" model (e.g., Rogers et al., 2004) critically involves processing units organized into a hub, it is possible to accomplish the same cognitive processing using connections rather than units (e.g., O'Connor et al., 2009; Rabovsky and McRae, 2014). Alternatively, the additional role may be a cognitive or semantic control function, namely, biasing activiation within the distributed semantic system toward task-relevant information (e.g., Jefferies and Lambon Ralph, 2006). As discussed above, this control function is not likely to be conferred by the PFC alone—the control system itself must be distributed, such that the white matter connections play a critical role in its function beyond simply transmitting the control signal.

### 4.2. Limitations and future directions

The analyses presented here tested associations between structural damage due to left hemisphere stroke and deficits in phonological and semantic processing. Numerous other neural factors may contribute to language (dis)function following stroke, such as hypoperfusion of perilesional areas, Wallerian degeneration, and changes in neural activity in the contralesional hemisphere. More generally, complex cognitive tasks are supported by overlapping distributed neural networks, so damage to one node in a network can alter function throughout the network, including distal nodes. Therefore, lesion-symptom mapping analyses such as the ones presented here demonstrate that damage in a particular neural region is associated with a particular deficit, but the functional disruption may extend beyond this region. In other words, the identified region must have been part of a network or functional system that carried out this cognitive task. The challenge for future research is to move beyond identifying nodes in order to understand the functional systems.

To that end, our results suggest that earlier neural claims about semantic hubs may have been overly focused on grey matter and insufficiently concerned with white matter. This may due to methodological limitations (fMRI is primarily sensitive to grey matter) or to theoretical predispositions, such as the assumption that grey matter does the information processing and white matter just transmits the information. In any case, methods to study anatomical and functional connectivity are developing rapidly and they seem likely to provide very new and different insights into the neural basis of semantic cognition.

## Acknowledgements

This research was supported by National Institutes of Health Grants R01DC010805 to D.M. and R01DC000191 to M.F.S. We thank Adelyn Brecher and Gabriella Garcia for their contributions to participant recruitment and testing, Grant Walker and Kristen Graziano for their work on lesion segmentation, and Dan Kimberg, Qi Chen, Olufunsho Faseyitan, Grant Walker, and Gary Dell for contributions to earlier versions of these analyses.

## References

Allport, D.A., 1985. Distributed memory, modular systems and dysphasia In: Newman, S.K., Epstein, R. (Eds.), Current Perspectives in Dysphasia. Churchill Livingstone, Edinburgh, pp. 32–60.

Bates, E., Wilson, S.M., Saygin, A.P., Dick, F., Sereno, M.I., Knight, R.T., Dronkers, N.F., 2003. Voxel-based lesion-symptom mapping. Nat. Neurosci. 6 (5), 448–450. http://dx.doi.org/10.1038/nn1050.

Binder, J.R., Desai, R.H., 2011. The neurobiology of semantic memory. Trends Cognit. Sci. 15 (11), 527–536. http://dx.doi.org/10.1016/j.tics.2011.10.001.

Binney, R.J., Embleton, K.V., Jefferies, E., Parker, G.J.M., Lambon Ralph, M.A., 2010. The ventral and inferolateral aspects of the anterior temporal lobe are crucial in semantic memory: evidence from a novel direct comparison of distortion-corrected fMRI, rTMS, and semantic dementia. Cereb. Cortex 20 (11), 2728–2738. http://dx.doi.org/10.1093/cercor/bhq019.

Bozeat, S., Lambon Ralph, M.A., Patterson, K.E., Garrard, P., Hodges, J.R., 2000. Non-verbal semantic impairment in semantic dementia. Neuropsychologia 38 (9), 1207–1215.

Buchsbaum, B.R., Baldo, J.V., Okada, K., Berman, K.F., Dronkers, N.F., D'Esposito, M., Hickok, G.S., 2011. Conduction aphasia, sensory-motor integration, and phonological short-term memory-an aggregate analysis of lesion and fMRI data. Brain Lang. 119 (3), 119–128. http://dx.doi.org/10.1016/j.bandl.2010.12.001.

Butler, R.A., Lambon Ralph, M.A., Woollams, A.M., 2014. Capturing multidimensionality in stroke aphasia: mapping principal behavioral component to neural structures. Brain 137 (12), 3248–3266. http://dx.doi.org/10.1093/brain/awu286.

Cloutman, L., Gottesman, R., Chaudhry, P., Davis, C., Kleinman, J.T., Pawlak, M., Hillis, A.E., 2009. Where (in the brain) do semantic errors come from? Cortex 45 (5), 641–649. http://dx.doi.org/10.1016/j.cortex.2008.05.013.

Damasio, A.R., 1989. Time-locked multiregional retroactivation: A systems-level

proposal for the neural substrates of recall and recognition. Cognition 33 (1), 25–62.
Dell, G.S., 1986. A spreading-activation theory of retrieval in sentence production. Psychol. Rev. 93 (3), 283–321.
Dell, G.S., Schwartz, M.F., Nozari, N., Faseyitan, O., Coslett, H.B., 2013. Voxel-based lesion-parameter mapping: identifying the neural correlates of a computational model of word production. Cognition 128 (3), 380–396. http://dx.doi.org/10.1016/j.cognition.2013.05.007.
DeWitt, I., Rauschecker, J.P., 2012. Phoneme and word recognition in the auditory ventral stream. Proc. Natl. Acad. Sci. USA 109 (8), E505–E514. http://dx.doi.org/10.1073/pnas.1113427109.
Dick, A.S., Bernal, B., Tremblay, P., 2014. The language connectome: new pathways, new concepts. Neuroscientist 20 (5), 453–467. http://dx.doi.org/10.1177/1073858413513502.
Dunn, L.M., Dunn, L.M., 1997. Examiner's Manual for the Peabody Picture Vocabulary Test-III (PPVT-III). American Guidance Service, Circle Pines, MN.
Foygel, D., Dell, G.S., 2000. Models of impaired lexical access in speech production. J. Mem. Lang. Spec. Issue: Disord. Lang. Mem.: Implic. Cognit. Theory 43 (2), 182–216.
Freedman, M.L., Martin, R.C., 2001. Dissociable components of short-term memory and their relation to long-term learning. Cognit. Neuropsychol. 18 (3), 193–226. http://dx.doi.org/10.1080/02643290042000080.
Gainotti, G., 2011. The organization and dissolution of semantic-conceptual knowledge: is the "amodal hub" the only plausible model? Brain Cognit. 75 (3), 299–309. http://dx.doi.org/10.1016/j.bandc.2010.12.001.
Gainotti, G., 2014. Old and recent approaches to the problem of non-verbal conceptual disorders in aphasic patients. Cortex J. Devot. Study Nerv. Syst. Behav. 53, 78–89. http://dx.doi.org/10.1016/j.cortex.2014.01.009.
Gainotti, G., Silveri, C., Villa, G., Miceli, G., 1984. Anomia with and without lexical comprehension disorders. Brain Lang. 29, 18–33.
Gläscher, J., Tranel, D., Paul, L.K., Rudrauf, D., Rorden, C., Hornaday, A., Adolphs, R., 2009. Lesion mapping of cognitive abilities linked to intelligence. Neuron 61 (5), 681–691. http://dx.doi.org/10.1016/j.neuron.2009.01.026.
Goldstein, K., 1948. Language and Language Disturbances; Aphasic Symptom Complexes and their Significance for Medicine and Theory of Language. Grune & Stratton, Oxford, England, p. 374.
Guo, C.C., Gorno-Tempini, M.L., Gesierich, B., Henry, M., Trujillo, A., Shany-Ur, T., Seeley, W.W., 2013. Anterior temporal lobe degeneration produces widespread network-driven dysfunction. Brain 136 (Pt 10), 2979–2991. http://dx.doi.org/10.1093/brain/awt222.
Han, Z., Ma, Y., Gong, G., He, Y., Caramazza, A., Bi, Y., 2013. White matter structural connectivity underlying semantic processing: evidence from brain damaged patients. Brain 136 (Pt 10), 2952–2965. http://dx.doi.org/10.1093/brain/awt205.
Harvey, D.Y., Wei, T., Ellmore, T.M., Hamilton, A.C., Schnur, T.T., 2013. Neuropsychological evidence for the functional role of the uncinate fasciculus in semantic control. Neuropsychologia 51 (5), 789–801. http://dx.doi.org/10.1016/j.neuropsychologia.2013.01.028.
Hickok, G.S., Poeppel, D., 2007. The cortical organization of speech processing. Nat. Rev. Neurosci. 8 (May), 393–402.
Hillis, A.E., Rapp, B., Romani, D., Caramazza, A., 1990. Selective impairment of semantics in lexical processing. Cognit. Neuropsychol. 7 (3), 191–243.
Hodges, J.R., Patterson, K.E., 2007. Semantic dementia: a unique clinicopathological syndrome. Lancet Neurol. 6 (11), 1004–1014. http://dx.doi.org/10.1016/S1474-4422(07)70266-1.
Howard, D., Patterson, K.E., 1992. Pyramids and palm trees: A test of semantic access from pictures and words. Bury St. Edmunds, UK: Thames Valley Test Company.
Jefferies, E., 2013. The neural basis of semantic cognition: converging evidence from neuropsychology, neuroimaging and TMS. Cortex 49 (3), 611–625. http://dx.doi.org/10.1016/j.cortex.2012.10.008.
Jefferies, E., Lambon Ralph, M.A., 2006. Semantic impairment in stroke aphasia versus semantic dementia: A case-series comparison. Brain 129, 2132–2147.
Kay, J., Lesser, R., Coltheart, M., 1996. Psycholinguistic assessments of language processing in aphasia (PALPA): An introduction. Aphasiology 10 (2), 159–180. http://dx.doi.org/10.1080/02687039608248403.
Kümmerer, D., Hartwigsen, G., Kellmeyer, P., Glauche, V., Mader, I., Klöppel, S., Saur, D. (2013). Damage to ventral and dorsal language pathways in acute aphasia. Brain, 136(2), 619–629. 10.1093/brain/aws354.
Lambon Ralph, M.A., 2014. Neurocognitive insights on conceptual knowledge and its breakdown. Philos. Trans. R. Soc. B: Biol. Sci. 369 (1634), 20120392. http://dx.doi.org/10.1098/rstb.2012.0392.
Lambon Ralph, M.A., McClelland, J.L., Patterson, K.E., Galton, C.J., Hodges, J.R., 2001. No right to speak? The relationship between object naming and semantic impairment: neuropsychological evidence and a computational model. J. Cognit. Neurosci. 13 (3), 341–356.
Levelt, W.J.M., Roelofs, A., Meyer, A.S., 1999. A theory of lexical access in speech production. Behav. Brain Sci. 22 (1), 1–75, Retrieved from.
Lupyan, G., 2012. What do words do? Toward a theory of language-augmented thought. Psychol. Learn. Motiv. 57, 255–297. http://dx.doi.org/10.1016/B978-0-12-394293-7.00007-8.
Lupyan, G., Mirman, D., 2013. Linking language and categorization: evidence from aphasia. Cortex 49 (5), 1187–1194. http://dx.doi.org/10.1016/j.cortex.2012.06.006.
Mah, Y.-H., Husain, M., Rees, G., Nachev, P., 2014. Human brain lesion-deficit inference remapped. Brain . http://dx.doi.org/10.1093/brain/awu164.
Mahon, B.Z., Caramazza, A., 2009. Concepts and categories: a cognitive neuropsychological perspective. Annu. Rev. Psychol. 60, 27–51. http://dx.doi.org/10.1146/annurev.psych.60.110707.163532.
Martin, A., 2007. The representation of object concepts in the brain. Annu. Rev. Psychol. 58, 25–45. http://dx.doi.org/10.1146/annurev.psych.57.102904.190143.
Martin, N., Schwartz, M.F., Kohen, F.P., 2006. Assessment of the ability to process semantic and phonological aspects of words in aphasia: a multi-measurement approach. Aphasiology 20 (2–4), 154–166.
Martin, R.C., Shelton, J.R., Yaffee, L.S., 1994. Language processing and working memory: neuropsychological evidence for separate phonological and semantic capacities. J. Mem. Lang. 33 (1), 83–111. http://dx.doi.org/10.1006/jmla.1994.1005.
McClelland, J.L., 1981. Retrieving general and specific information from stored knowledge of specifics. In: Proceedings of the 3rd Annual Conference of the Cognitive Science Society, pp. 170–172.
McNorgan, C., Reid, J., McRae, K., 2011. Integrating conceptual knowledge within and across representational modalities. Cognition 118 (2), 211–233. http://dx.doi.org/10.1016/j.cognition.2010.10.017.
Meyer, K., Damasio, A., 2009. Convergence and divergence in a neural architecture for recognition and memory. Trends Neurosci. 32 (7), 376–382. http://dx.doi.org/10.1016/j.tins.2009.04.002.
Mirman, D., Britt, A.E., 2014. What we talk about when we talk about access deficits. Philos. Trans. R. Soc. B: Biol. Sci. 369 (1634). http://dx.doi.org/10.1098/rstb.2012.0388.
Mirman, D., Graziano, K.M., 2013. The neural basis of inhibitory effects of semantic and phonological neighbors in spoken word production. J. Cognit. Neurosci. 25 (9), 1504–1516. http://dx.doi.org/10.1162/jocn.
Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O.K., Coslett, H.B., Schwartz, M. F., 2015. Neural organization of spoken language revealed by lesion–symptom mapping. Nat. Commun. 6 (6762), http://dx.doi.org/10.1038/ncomms7762.
Mirman, D., Strauss, T.J., Brecher, A.R., Walker, G.M., Sobel, P., Dell, G.S., Schwartz, M. F., 2010. A large, searchable, web-based database of aphasic performance on picture naming and other tests of cognitive function. Cognit. Neuropsychol. 27 (6), 495–504. http://dx.doi.org/10.1080/02643294.2011.574112.
Moritz-Gasser, S., Herbet, G., Duffau, H., 2013. Mapping the connectivity underlying multimodal (verbal and non-verbal) semantic processing: a brain electrostimulation study. Neuropsychologia 51 (10), 1814–1822. http://dx.doi.org/10.1016/j.neuropsychologia.2013.06.007.
Papagno, C., Miracapillo, C., Casarotti, A., Romero Lauro, L.J., Castellano, A., Falini, A., Bello, L., 2011. What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval.. Brain 134 (2), 405–414. http://dx.doi.org/10.1093/brain/awq283.
Patterson, K.E., Nestor, P.J., Rogers, T.T., 2007. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat. Rev. Neurosci. 8, 976–987. http://dx.doi.org/10.1038/nrn2277.
Patterson, K.E., Plaut, D.C., 2009. . Shallow draughts intoxicate the brain: lessons from cognitive science for cognitive neuropsychology. Top. Cognit. Sci. 1, 39–58.
Rauschecker, J.P., Scott, S.K., 2009. Maps and streams in the auditory cortex: nonhuman primates illuminate human speech processing. Nat. Neurosci. 12 (6), 718–724. http://dx.doi.org/10.1038/nn.2331.
Roach, A., Schwartz, M.F., Martin, N., Grewal, R.S., Brecher, A.R., 1996. The Philadelphia naming test: scoring and rationale. Clin. Aphasiol. 24, 121–133.
Rogers, T.T., Lambon Ralph, M.A., Garrard, P., Bozeat, S., McClelland, J.L., Hodges, J.R., Patterson, K.E., 2004. Structure and deterioration of semantic memory: a neuropsychological and computational investigation. Psychol. Rev. 111 (1), 205–235.
Saffran, E.M., Schwartz, M.F., 1994. Of cabbages and things: semantic memory from a neuropsychological perspective—A tutorial review In: Umiltà, C. (Ed.), Attention and Performance XV. MIT Press, Cambridge, MA, USA, pp. 507–536.
Schnur, T.T., Schwartz, M.F., Brecher, A.R., Hodgson, C., 2006. Semantic interference during blocked-cyclic naming: Evidence from aphasia. J. Mem. Lang. 54 (2), 199–227. http://dx.doi.org/10.1016/j.jml.2005.10.002.
Schnur, T.T., Schwartz, M.F., Kimberg, D.Y., Hirshorn, E., Coslett, H.B., Thompson-Schill, S.L., 2009. Localizing interference during naming: convergent neuroimaging and neuropsychological evidence for the function of Broca's area. Proc. Natl. Acad. Sci. USA 106 (1), 322–327.
Schwartz, M.F., Dell, G.S., 2010. Case series investigations in cognitive neuropsychology. Cognit. Neuropsychol. 27 (6), 477–494. http://dx.doi.org/10.1080/02643294.2011.574111.
Schwartz, M.F., Dell, G.S., Martin, N., Gahl, S., Sobel, P., 2006. A case-series test of the interactive two-step model of lexical access: evidence from picture naming. J. Mem. Lang. 54 (2), 228–264. http://dx.doi.org/10.1016/j.jml.2005.10.001.
Schwartz, M.F., Faseyitan, O., Kim, J., Coslett, H.B., 2012. The dorsal stream contribution to phonological retrieval in object naming. Brain 135 (12), 3799–3814. http://dx.doi.org/10.1093/brain/aws300.
Schwartz, M.F., Kimberg, D.Y., Walker, G.M., Faseyitan, O., Brecher, A.R., Dell, G.S., Coslett, H.B., 2009. Anterior temporal involvement in semantic word retrieval: voxel-based lesion-symptom mapping evidence from aphasia. Brain 132 (12), 3411–3427. http://dx.doi.org/10.1093/brain/awp284.
Snyder, H.R., Banich, M.T., Munakata, Y., 2014. All competition is not alike: neural mechanisms for resolving underdetermined and prepotent competition. J. Cognit. Neurosci. 26 (11), 2608–2623. http://dx.doi.org/10.1162/jocn_a_00652.
Ueno, T., Saito, S., Rogers, T.T., Lambon Ralph, M.A., 2011. Lichtheim 2: synthesizing aphasia and the neural basis of language in a neurocomputational model of the dual dorsal-ventral language pathways. Neuron 72 (2), 385–396. http://dx.doi.org/10.1016/j.neuron.2011.09.013.
Van den Heuvel, M.P., Sporns, O., 2013. Network hubs in the human brain. Trends

Cogn. Sci. 17 (12), 683–696 http://dx.doi.org/10.1016/j.tics.2013.09.012.
von Der Heide, R.J., Skipper, L.M., Klobusicky, E., Olson, I.R., 2013. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. Brain 136 (6), 1692–1707. http://dx.doi.org/10.1093/brain/awt094.
Walker, G.M., Schwartz, M.F., Kimberg, D.Y., Faseyitan, O., Brecher, A.R., Dell, G.S., Coslett, H.B., 2011. Support for anterior temporal involvement in semantic error production in aphasia: new evidence from VLSM. Brain Lang. 117 (3), 110–122.
Warrington, E.K., Shallice, T., 1984. Category specific semantic impairments. Brain 107, 829–854.
Zhang, Y., Kimberg, D.Y., Coslett, H.B., Schwartz, M.F., Wang, Z., 2014. Multivariate lesion-symptom mapping using support vector regression. Hum. Brain Mapp. 35 (12), 5861–5876.