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Support for Anterior Temporal Involvement in Semantic Error Production in Aphasia: New Evidence from VLSM

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Abstract

Semantic errors in aphasia (e.g., naming a horse as “dog”) frequently arise from faulty mapping of concepts onto lexical items. A recent study by our group used voxel-based lesion-symptom mapping (VLSM) methods with 64 patients with chronic aphasia to identify voxels that carry an association with semantic errors. The strongest associations were found in the left anterior temporal lobe (L-ATL), in the mid- to anterior MTG region. The absence of findings in Wernicke’s area was surprising, as were indications that ATL voxels made an essential contribution to the *post-semantic* stage of lexical access. In this follow-up study, we sought to validate these results by re-defining semantic errors in a manner that was less theory dependent and more consistent with prior lesion studies. As this change also increased the robustness of the dependent variable, it made it possible to perform additional statistical analyses that further refined the interpretation. The results strengthen the evidence for a causal relationship between ATL damage and lexically-based semantic errors in naming and lend confidence to the conclusion that chronic lesions in Wernicke’s area are not causally implicated in semantic error production.

Keywords

aphasia; voxel-based lesion-symptom mapping; naming; semantic; errors

1. Introduction

Incidental speech errors in otherwise healthy speakers have been used to comic effect in literature, film, and politics, as when the playwright William Shakespeare gave his bumbling constable Dogberry the line “O villain! thou wilt be condemned into everlasting *redemption* for this” (i.e., *damnation*; 1600/1905, IV.ii.51). Retrieving the wrong word becomes a more serious affair when the rate of error is high enough to disrupt fluent conversation. This can happen in the speech of healthy individuals, but it happens quite often in neurological

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conditions that disrupt the function of left hemisphere (LH) language networks, such as aphasia.

A common assumption is that lexical access errors in LH patients, while more frequent and more extreme than the errors of healthy speakers, do not differ from them in kind (Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Freud, 1891; Schwartz, Saffran, Bloch, & Dell, 1994). Among other things, both healthy speakers and patients are vulnerable to the two major classes of error: those that relate to the target in meaning (semantic errors) and those that relate to the target in sound (phonological errors). The high frequency with which these error types occur in patients has made them an important object of study for researchers interested in the neural underpinnings of semantic and phonological processes in language.

Studies of lexical access errors in patients necessarily begin with identification and classification of errors. With respect to the semantic-phonological distinction, some errors are unambiguous; for example, few would dispute that horse → dog is a semantic error, whereas horse → hearse is a phonological error. Problems arise in deciding how broadly or narrowly to define these categories, that is, when to lump and when to split. For example, should semantic errors be confined to taxonomically related nouns, e.g., horse → dog, animal, or pony? Or should the category also include errors that are thematically associated with the target (e.g., horse → cart)? Should noun (horse → cart) and non-noun (horse → trot) errors be lumped or split? And what about multi-word descriptions (horse → “it runs races”; “it goes ‘neigh’”)? Some errors with a clear semantic relation to the target also share some of its phonemes (e.g., horse → race); how should these “mixed” errors be classified? In the ideal case, scoring decisions like these are rationalized in relation to an explicit theory; more often, however, the rationale is idiosyncratic or unreported. Yet such decisions can have a major influence on the outcome of studies.

1.1. Schwartz et al. (2009)

We recently carried out voxel-based lesion-symptom mapping (VLSM) to identify brain regions associated with semantic picture naming errors in 64 patients with chronic left hemisphere stroke and aphasia (Schwartz et al., 2009). Motivated by the interactive two-step model of lexical access (Dell, 1986; Dell et al., 1997) and by the hypothesis that semantic error production is primarily the consequence of faulty mapping from semantics to abstract word entities (i.e., “lemmas”), this anatomical study sought to localize the lesions responsible for semantic errors that arise via this cognitive mechanism. Three VLSM analyses were carried out. In the first, unfiltered analysis, the dependent variable was semantic error proportion relative to total trials. In the second and third analyses, we regressed out the variance in the semantic error proportion that was shared with verbal and nonverbal comprehension measures, respectively. These secondary, filtered, analyses helped rule out the contribution to semantic errors of alternative mechanisms, such as failure to conceptualize the pictured target correctly, a shared requirement with nonverbal comprehension, or failure to edit out potential errors as a consequence of verbal comprehension deficits. There was only one brain region where the lesion status of voxels correlated with semantic errors in both the filtered and unfiltered analyses. That region was the left anterior temporal lobe (L-ATL), where we identified a large cluster of supra-threshold voxels occupying Brodmann areas (BA) 38 and 21, with peak t-values in mid-to-anterior middle temporal gyrus (MTG). Surprisingly, no effects were found in Wernicke’s area (posterior BA 22) or the angular gyrus (BA 39), even in the unfiltered analysis. These posterior areas feature prominently in classical and contemporary anatomical models of semantics and naming (e.g., Binder, Desai, Graves, & Conant, 2009; Cloutman et al., 2009; DeLeon et al., 2007; Hart & Gordon, 1990; Hillis et al., 2001a; Hillis et al., 2006; Hillis et al., 2001b; Mesulam, 1998; Noonan, Jefferies, Corbett, & Lambon Ralph, 2010), although

the anatomical claims have not gone unchallenged (e.g., Binder et al., 2009; Dronkers, Wilkins, Valin, Redfern, & Jaeger, 2004; Indefrey & Levelt, 2004; Mesulam et al., 2009a).

There is a growing literature looking at how left temporal regions anterior and inferior to Wernicke's area contribute to semantic processing. These newer studies demonstrate a contribution of anterior and lateral inferotemporal regions to narrative comprehension (Scott, Blank, Rosen, & Wise, 2000; Sharp, Scott, & Wise, 2004; Warren, Crinion, Lambon Ralph & Wise, 2009); word and picture comprehension (Antonucci, Beeson, Labiner, & Rapcsak, 2008; Pobric, Jefferies, & Lambon Ralph, 2010; Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996); amodal or supra-modal semantic processing (Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000; Lambon Ralph, Sage, Jones, & Mayberry, 2010; Patterson, Nestor, & Rogers, 2007; Rogers et al., 2004); naming, especially of categories and stimuli whose feature structure invites many perceptually-related competitors (e.g., living things; famous people; landmarks: Antonucci et al., 2008; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Gorno Tempini & Price, 2001; Grabowski et al., 2001; Mesulam et al., 2009b; Tranel, 2006; Tyler et al., 2004); and the mapping between semantics and lexical phonology (Cloutman et al., 2009; Foundas, Daniels & Vasterling, 1998; Hickok & Poeppel, 2004; Lüders et al., 1991; Mummery et al., 1999; Raymer, Maher, Foundas, Heilman, & Rothi, 1997; Trébuchon-Da Fonseca et al., 2009).

The Schwartz et al., (2009) findings agree with this focus on semantic processing outside posterior temporal and temporo-parietal regions, but, here too, there are some surprises. First, according to Schwartz et al.'s (2009) filtered analyses, voxels in L-ATL play a role in naming that is independent of whatever role they might also play in verbal or nonverbal comprehension. At least at first blush, this does not fit well with the theory that neurons in this region code for amodal semantic information (e.g., Patterson et al., 2007; but see Discussion) or that they form convergence zones that mediate *two-way* mappings between words and concepts (Damasio et al., 1996; Damasio et al., 2004). Moreover, as errors in our study were gathered from the Philadelphia Naming Test (PNT), which assesses basic-level naming of non-unique categories of objects, the well-documented specialization of the left temporal pole for the naming of known people, landmarks, and other unique entities (e.g., Damasio et al., 2004; Gorno Tempini & Price, 2001; Grabowski et al., 2001; Tranel, 2006; Tyler et al., 2004) cannot explain the effects we obtained in this region.

Outside the ATL, Schwartz et al. (2009) identified clusters of voxels that were associated with semantic errors in the unfiltered analysis but not after controlling for nonverbal comprehension. One of these clusters was located in lateral, superior BA 37. Other research has linked BA 37 to "pure" anomia (Antonucci, Beeson, & Rapcsak, 2004; Benson & Ardila, 1996; Cloutman et al., 2009; Foundas et al., 1998; Raymer et al., 1997), which, by definition, does not derive from a semantic deficit. Questioning this, the Schwartz et al. (2009) data suggest that in the lateral superior division of BA 37, at least, lesions create semantic errors by virtue of their impact on conceptualization or other semantic processes shared with comprehension. We will return to the topic of pure anomia below.

It should be evident from even this cursory discussion that the Schwartz et al. (2009) study reached conclusions that are controversial on several grounds. Given this, we performed a new VLSM analysis, using a more inclusive definition of semantic errors. We explain the benefits of such a re-analysis below in detail, beginning with the consideration of how semantic errors were defined in the previous study, compared with others.

1.2. Semantic error coding reconsidered

The original study was motivated by the interactive two-step model of lexical access (Dell, 1986; Dell et al., 1997) and by the hypothesis that semantic error production is primarily the consequence of faulty mapping from semantics to abstract word entities (i.e., “lemmas”). The VLSM analyses were aimed at localizing lesions responsible for semantic errors that arise via this cognitive mechanism, with the filtered analyses used to control for alternative mechanisms. Semantic errors were obtained from the PNT

(<http://www.ncrrn.org/assessment/pnt>), using the error taxonomy and scoring rules that are standard for this test and that were used in many prior empirical tests of the interactive two-step model (e.g., Dell et al., 1997; Kittredge, Dell, Verkuilen, & Schwartz, 2008; Rumel, Caramazza, Capasso, & Miceli, 2005; Schwartz et al., 2006). The benefit of our having defined semantic errors in accordance with this scheme is that we could relate the findings directly to the model and this line of empirical research. There were also some significant downsides: The definition excluded other error types that bear directly on the broader question of how semantically-guided lexical access goes awry in aphasia. Other lesion-mapping studies have not been so restrictive in classifying semantic errors, and this could help explain discrepancies between those findings and ours (e.g., Antonucci et al., 2008; Cloutman et al., 2009). Moreover, using the more restrictive definition gave us fewer errors to analyze, which almost certainly affected the reliability of the dependent variable and, hence, power to detect smaller effects in the VLSM.

To be specific, the naming scores that Schwartz et al. (2009) mapped anatomically were comprised of pure semantic errors - substituted nouns that related to the target either taxonomically or associatively and that were not also phonologically related. Mixed (semantic plus phonological) errors were excluded to keep phonological influences from complicating the theoretical interpretation. This represents a departure from most prior studies. Moreover, by excluding mixed errors we undoubtedly underestimated patients' true semantic error rates, especially since the criteria for phonological overlap in the PNT scheme is biased toward identifying an error as phonologically related.¹ Consequently, many of the excluded mixed errors were likely relatively pure semantic errors.

The PNT scheme also excludes related non-noun responses (e.g., fish → swimming) and semantic descriptions/circumlocutions (e.g., cannon → “You shoot bullets, um bombs out of it”) from the count of semantic errors. In the interactive two-step framework, it is assumed that the grammatical component normally restricts the lexical choice set to single nouns, so non-noun and multi-word responses constitute off-task or “non-naming” responses. However, viewed from a different perspective, such non-naming responses might signal the loosening of executive control over task-appropriate semantic selection. This is in line with the well-known distinction between semantic access vs. representation (Cipolotti & Warrington, 1995; Ferrand & Humphreys, 1996; Forde & Humphreys, 1995, 1997; Warrington & McCarthy, 1983, 1987) and, more specifically, the re-interpretation of transcortical sensory aphasia (TSA) as a multi-modal semantic access disorder stemming from faulty semantic control and selection (Jefferies & Lambon Ralph, 2006; Jefferies, Baker, Doran, & Lambon Ralph, 2007; Noonan et al., 2010). Deviating from the view that standard picture naming taps *automatic* semantic retrieval processes (e.g., Moss et al., 2005a), Jefferies and colleagues postulate that in naming, as in all semantic tasks, a degree of semantic control is required to direct activation to the appropriate part of semantic space. Symptomatic of a naming deficit stemming from faulty control, they note the occurrence of semantic errors that are associatively rather than taxonomically related to the target

¹The minimum requirement for a response to be considered phonologically related to a target is sharing a single phoneme in the same word position (e.g., **plant** → **flower**), or two or more phonemes in any position (e.g., **train** → **engineer**).

(Jefferies & Lambon Ralph, 2006). A similar interpretation could apply to the production of semantic non-noun and multi-word naming responses: i.e., as a result of semantic dyscontrol, semantic features are activated that map better to a description of the target than to its name. According to this logic, the non-naming responses should be included among the semantic errors we map so as to increase sensitivity to voxels that carry an association with semantic errors by virtue of their involvement in semantic control. Research on the anatomy of TSA and semantic control processes predicts effects of this kind in ventrolateral prefrontal cortex, posterior lateral temporal cortex, and/or temporo-parietal junction (TPJ) (Bedny, McGill, & Thompson-Schill, 2008; Bookheimer, 2002; Nagel, Schumacher, Goebel, & D'Esposito, 2008; Noonan et al., 2010; Thompson-Schill, D'Esposito & Kan, 1999).

A different argument for including semantic circumlocutions comes from studies of pure anomia. Traditionally characterized as a disconnection between semantics and phonology, both of which are preserved (Benson & Ardila, 1996; Geschwind, 1967), pure anomia can manifest in tip-of-tongue struggle, semantic errors, and, most commonly, semantic circumlocutions (Antonucci et al., 2008). Cognitive analysis has shown that patients of this type may have very mild deficits in semantic processing (Antonucci et al., 2008; Lambon Ralph, Sage, & Roberts, 2000) or unreliable access to the phonological output lexicon (Caramazza & Hillis, 1990). Both causal accounts have been linked to damage in BA 37 (Benson & Ardila, 1996; Cloutman et al., 2009; DeLeon et al., 2007), an area in which Schwartz et al. (2009) found only limited effects. Conceivably, stronger effects would be seen if semantic circumlocutions were aggregated with other semantic errors.

To help reconcile the discrepancies between findings in Schwartz et al. (2009) and prior lesion studies, and to create a more robust dependent variable, the current study added mixed errors, related non-nouns, and semantic circumlocutions to the category of mapped semantic errors. As an added benefit, this brought about a gain in statistical power that enabled us to perform several analyses that were not possible in the original study. Several of these relate to anatomical issues, as explained in the next section.

1.3. Anatomical considerations

As reported in the original study, and discussed more extensively in the sections below, lesion coverage in this patient sample is limited in regions of the left hemisphere that lie outside the territory of the middle cerebral artery. Relevant to present concerns, there is little or no coverage in anteromedial temporal cortex and inferolateral BA 20, regions known to be important for semantic processing (Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010; Bright, Moss, Stamatakis, & Tyler, 2005). Coverage is also poor in medial and inferolateral BA 37, which is implicated in pure anomia and systems that map between semantics and phonology (Antonucci et al., 2004, 2008; Hickok & Poeppel, 2004; Trébouchon-Da Fonseca et al., 2009). Consequently, our data cannot be used to assess the contributions of these regions to semantic error production.

It has been claimed that the ATL (referring to BA 38, anterior 20, 21 and 22) also is rarely affected in middle cerebral artery (MCA) strokes (e.g., DeLeon et al., 2007; Noonan et al., 2010; Wise, 2003). We previously observed that 34 of the current 64 subjects exhibited damage to this region (Schwartz et al., 2009). However, as the ATL is in the terminal distribution of the inferior division of the MCA, a reasonable concern is that the ATL involvement might have been restricted to the margins of very large lesions, and that it was the size of the lesion and not its locus that was responsible for associations in ATL. We attempted to address this in the original study but lacked statistical power to control for lesion size on a voxelwise basis. Using a more robust dependent variable allows us to overcome this limitation and demonstrate more persuasively that the ATL effect is not due

to a confound with lesion size. It also enables us to address, for the first time, the high correlation between lesion patterns in BA 21 and BA 22 and the concern that effects that Schwartz et al. (2009) attributed to BA 21 were in actuality due to BA 22, including Wernicke's area.

To summarize, this re-analysis now includes error types that other researchers consider critical to the understanding of semantically-driven speech production and controls for anatomical factors that may have confounded the original findings. As will be seen, the results from the current study corroborate and strengthen the conclusions from the earlier one.

2. Methods

2.1. Participants

Participants were 64 individuals (42% females; 48% African American) with confirmed left hemisphere stroke, who currently or initially presented with clinically apparent aphasia. Their mean age was 58 (range 26–78) and mean years of education was 14 (10–21). All were right handed (Oldfield, 1971), spoke English as their primary language, and had adequate vision and hearing (Ventry & Weinstein, 1983) without or with correction. Their mean number of months post-stroke at time of PNT performance was 68 (range 1–381). The most acute patient performed the PNT 6 weeks post-stroke and was imaged 8 weeks post-stroke; 59 of 64 subjects were at least 6 months post. None of the participants had major psychiatric or neurologic co-morbidities. All were living in the community at time of testing.

Participants performed an extensive language assessment battery, from which the experimental measures were extracted. All but two of them also underwent research quality structural MRI or CT imaging studies at the University of Pennsylvania School of Medicine. For the remaining two, a recently performed imaging study obtained for clinical purposes but judged to be of high quality (i.e., high resolution and free from artifacts) was used to map the lesions.

The participants were recruited from the Neuro-Cognitive Rehabilitation Research Patient Registry at the Moss Rehabilitation Research Institute (Schwartz, Brecher, Whyte, & Klein, 2005) or the Center for Cognitive Neuroscience Patient Database at the University of Pennsylvania. They gave informed consent under protocols approved by the Institutional Review Boards at Albert Einstein Medical Center and the University of Pennsylvania School of Medicine. Participants were paid for their participation and reimbursed for travel and related expenses.

2.2. Experimental language measures

2.2.1. Naming errors—The 175-item *Philadelphia Naming Test (PNT)* (Dell et al., 1997; Roach, Schwartz, Martin, Grewal, & Brecher, 1996) tests the naming of pictured objects from a variety of semantic categories, the largest being implements (41%) and animals (15%). Pictures have high familiarity, name agreement, and image quality. Names range in length from 1 to 4 syllables and in noun frequency from 1 to 2110 tokens per million (Francis & Kucera, 1982). The PNT was administered and scored according to standard procedures (<http://www.ncrn.org/assessment/pnt> see also Dell et al., 1997; Schwartz et al., 2006). However, for purposes of this re-analysis, errors were re-assigned to one of three categories: *SemPlus*, *PhonErr*, or *Other*.

The *SemPlus* category was broadly defined to include any language response other than the target name that indicated at least partial access to semantic knowledge of the target. Starting with the restrictive semantic error set analyzed in Schwartz et al. (2009) --

substituted nouns that were synonyms, category coordinates, superordinates, subordinates, or strongly associated responses to targets -- we added from the naming response corpus non-noun, single-word errors that named an associated action (verb) or non-pictured feature (adjective) of the target. Phonological overlap was not considered, so mixed (semantic plus phonological) errors were also included. Finally, circumlocutions and other multi-word descriptions were included in SemPlus if three experienced aphasia researchers agreed that the semantic content of the utterance indicated at least partial access to the semantic representation of the target.

The second error category, PhonErr, comprised word and non-word responses with phonological similarity to the target and no semantic connection. Non-nouns and circumlocutions are standardly excluded from this category, so broadening the scope of semantic errors did not affect this variable. PhonErr scores were entered into one analysis to control for confounding non-semantic influences on SemPlus scores.

The remaining errors were classified as Other. Included here were picture-part responses, personal comments (e.g. "I like that"), null responses, and all other responses with no semantic or phonological similarity to the target. Errors in the Other category were not examined in this study.

2.2.2. Nonverbal comprehension—Two tests of nonverbal semantic comprehension were administered: *Pyramids and Palm Trees Test* (PPTT) (Howard & Patterson, 1992) and *Camel and Cactus Test* (CCT) (Bozeat et al., 2000; Lambon Ralph et al., 2001a). Both involve picture-picture matching based on thematic relatedness (e.g., wine-grape). The 52-item PPTT requires a two-choice match; the 64-item CCT requires a more demanding 4-choice match. These two tests were scored for accuracy (percent correct), standardized by z-scores, and averaged to create a nonverbal comprehension composite score, which we call *NVcomp*. *NVcomp* was used to control for difficulties in pre-lexical perceptual or conceptualization stages that might have resulted in a semantic error as here defined. As the aim was to localize semantic errors that arise in the mapping from concepts to words, specifically, it was important to eliminate confounding influences from these earlier stages of picture naming.

2.3. Ancillary behavioral tests and measures

Other tests were administered for the purpose of classifying the type and severity of aphasia (*Western Aphasia Battery*; Kertesz, 1982) and associated language deficits that are not of primary interest here. These include tests for verbal apraxia, word and nonword repetition, auditory input processing, short-term memory, syntactic comprehension, and verbal comprehension. Verbal comprehension was tested with the *Peabody Picture Vocabulary Test* (Third Edition-form A) (Dunn & Dunn, 1997), which involves spoken word to picture matching, and the *Synonym Judgment Test* (Martin, Schwartz, & Kohen, 2005), which requires the subject to pick the two of three words that are closest in meaning. Schwartz et al. (2009) entered verbal comprehension scores as a covariate in the analysis of semantic naming errors and found that this contributed little to the results. We refer readers to the original paper for further discussion.

2.4. Imaging methods

Structural images were acquired using magnetic resonance imaging (MRI; $n = 34$) or computed tomography (CT; $n = 30$). Thirty-two patients were scanned on a 3.0 Tesla Siemens Trio scanner. High-resolution whole brain T1-weighted images were acquired (TR = 1620ms, TE = 3.87ms, FOV = 192×256 mm, 1×1×1 mm voxels) using a Siemens 8 channel head coil. In accordance with established safety guidelines (MRI safety;

www.mrisafety.com), two patients were scanned on a 1.5 Tesla Siemens Sonata because of an implant that had not been approved for a 3T environment. Whole brain T1-weighted images were acquired (TR = 3000 msec, TE = 3.54, FOV = 24 cm, 1.25×1.25×1.2 mm voxels) with a slice thickness of 1mm using a standard radio-frequency head coil. MRI was contra-indicated for the remaining thirty patients. Twenty-eight patients underwent whole brain CT scans without contrast (60 axial slices, 3 mm thick) on a 64-Slice SOMATOM Sensation Scanner. As two patients declined undergoing a new scan, recent clinical CT scans were used with the participants' consent. In both instances, the scans were judged to be free of significant artifact and of sufficient quality such that the lesion could be readily identified.

2.5. Lesion registration to template

Lesions imaged with MRI (n = 34) were segmented manually on a 1×1×1 mm T1-weighted structural image. Lesion boundaries were identified on the basis of differences in signal characteristics between the infarcted and normal brain substance. Prior to warping, lesions were masked, and the structural scans and lesion maps were registered to a common template, constructed from images acquired on the same scanner, using a symmetric diffeomorphic registration algorithm (Avants, Schoenemann, & Gee, 2006; see also <http://www.picsl.upenn.edu/ANTS/>). A single mapping from this intermediate template to the 1 mm MNI-space "Colin27" volume (Holmes et al., 1998) was used to complete the mapping from subject space to MNI space. The final lesion map was quantized to produce a 0/1 map, using 0.5 as the cutoff value. Inevitably there is some degree of ambiguity at the border between normal and damaged brain. The effects of this uncertainty are unlikely to have contributed substantially to the data reported here, however, for at least two reasons. First, lesion boundaries were drawn by investigators who were naïve with respect to the behavioral data. Second, after being warped to MNI space, all of the manually drawn depictions of the lesions were compared to the original scan by HBC, an experienced neurologist who was naïve with respect to the behavioral data.

Lesions imaged with CT (n = 30) were drawn by HBC directly onto the Colin27 volume, after rotating (pitch only) the template to approximate the slice plane of the patient's scan. To this end, lesions were localized with respect to anatomic landmarks such as sulci, gyri, deep gray matter structures, ventricles and the cortical surface. Using these landmarks, the lesion was rendered on the 1 mm Colin27 volume. Because these images are sampled at a lower resolution than the template, we relied on the expertise of the neurologist to segment template slices that intervened between the corresponding image slices. We have previously demonstrated excellent intra- and inter-rater reliability with this method (Schnur et al., 2009).²

Lesion maps have much more intrinsic smoothness than the BOLD component of functional images, due to the spatial coherence of the lesions (the estimated smoothness of our lesion maps is $6.4 \times 7.0 \times 5.1$ mm FWHM). The reasons for smoothing in BOLD studies (e.g., spatially averaging noise) are less appropriate for lesion studies. For these reasons, we do not present analyses from smoothed data.

²Although this procedure produces maps with 1 mm isotropic resolution for all subjects, the effective resolution of lesion maps from subjects imaged in different modalities will be different. In fact, 1 mm³ certainly overstates the true resolution of our lesion drawings even for 3T MRI subjects. The decision to use 1 mm³ as a common target resolution was made to minimize the loss of information due to downsampling. The inclusion of lesion maps with varying effective resolutions is not ideal, but preferable to omitting large numbers of patients. The effect of mixing resolutions is minimized by the likelihood that few meaningful segmentation decisions are made at the 1 mm³ scale, and that the overall smoothness of lesion maps further reduces the meaningful differences between MRI and CT due to resolution alone (see Kimberg et al., 2007).

2.6. Voxel-based lesion-symptom mapping (VLSM)

Voxels in which fewer than 5 patients were lesioned were excluded from the VLSM analyses. A t-test comparing SemPlus scores between patients with and without lesions was performed at each voxel using the VoxBo brain imaging package (www.voxbo.org). The resulting t-map was thresholded to control the False Discovery Rate (FDR) (Genovese, Lazar, & Nichols, 2002) at $q = 0.01$, where q is the expected proportion of false positives among supra-threshold voxels.

Several additional analyses were performed to control for confounding factors. Unless stated otherwise, the procedure involved regressing the dependent variable (SemPlus) against the potential confound, and carrying out the VLSM analysis on the residuals. All imaging results reported use the FDR-controlled threshold ($q = 0.01$) as the standard for statistical significance.

3. Results

3.1. Behavioral measures

Aphasia severity, as measured by the WAB Aphasia Quotient (Kertesz, 1982), ranged from 33.3 (moderately severe) to 97.6 (recovered). The 6 (of 64) participants who performed above the aphasia cut-off (> 93.8) scored outside the control range on other tests in the battery. The WAB scheme classified the remaining 58 as follows: Anomic 24; Broca's 19; Conduction 10; Wernicke's 4; Transcortical Motor 1.

Table 1 summarizes participants' performance on the language measures of interest. The breakdown of errors included in SemPlus is shown in Table 2. Relative to SemErr, the dependent variable mapped in Schwartz et al. (2009), SemPlus includes approximately twice as many errors, and the two measures are highly correlated ($r = .81$). It is therefore reasonable to conclude that SemPlus provides a more robust measure of patients' propensity to produce semantic errors in picture naming. Nevertheless, 34% of variance in SemPlus remains unexplained by SemErr, and this difference in measures may reasonably be expected to influence the outcome of anatomical mapping procedures.

3.2. Characterization of lesion data

After excluding voxels with fewer than five lesions, the number of voxels that qualified for analysis was 404,565, or 55% of the 738,535 voxels in the left hemisphere (using counts from the electronic AAL atlas) (Tzourio-Mazoyer et al., 2002). Examination of the coverage map in Figure 1 reveals good coverage, as expected, throughout the peri-Sylvian region. Maximal lesion counts in voxels in Broca's area (left inferior frontal cortex, LIFC; BA 44/45) and Wernicke's area (posterior superior temporal gyrus, pSTG) were 35 and 28, respectively. Critically, voxels with substantial numbers of lesions were also identified in the temporal pole (BA 38) and anterior middle temporal gyrus (BA 21); in the former, maximal lesion count was 19, in the latter, 16. On the other hand, coverage was limited in the posterior inferior temporal lobe, mesial temporal lobe, and occipital lobe. These brain regions lie outside the territory of the middle cerebral artery (MCA) and so are commonly spared in patient samples like this one, which was selected for post-stroke aphasia. We were thus unable to explore the contributions of these areas of low coverage.

3.3. Anatomic findings

3.3.1. SemPlus—This analysis identified 60,086 voxels in which there was a significant association between lesion status and increased production of SemPlus errors. Significant voxels were mostly clustered in three areas: ATL, posterior middle temporal gyrus (pMTG), and prefrontal cortex (BA 45 and 46) (see Fig. 2). There were also a few small clusters of

voxels reaching significance in the parietal lobe (predominately BA 40), and some scattered voxels in the deep white matter.

The strongest effects were concentrated in the ATL, with peak value ($t = 8.79$) occurring in 4 voxels in anterior MTG. Outside of the ATL, the peak t -value was 5.03. Within ATL, this extra-ATL peak value was exceeded by 22,981 voxels, representing damage to nearly half the patient sample ($n = 30$). The region that these voxels occupied was larger than the ATL cluster identified in Schwartz et al. (2009), extending further into the anterior portions of superior and inferior temporal gyri (BA 22, 20; see Figure 2).

3.3.2. SemPlus after controlling for PhonErr—Factoring out *PhonErr* from SemPlus had very little effect on the strength or pattern of results (Fig. 3), yielding 62,378 significant voxels. That the ATL effect remained strong confirms that the association with SemPlus is not due to confounding phonological influences or nonspecific naming difficulties.

3.3.3. SemPlus after controlling for NVcomp—The factoring out of NVcomp had a more substantial effect, reducing the number of significant voxels to 46,972. The majority of significant voxels were again clustered in the ATL, the location of peak voxels remaining unchanged from the unfiltered analysis. Few significant voxels remained in the previously identified PFC (BA 45, 46) and pMTG (BA 37) areas (see Fig 4). The presence of a strong ATL association after controlling for NVcomp indicates that the observed association with SemPlus is not due to the confounding influence of pre-lexical, conceptual processes.

3.3.4. SemPlus after controlling for total lesion volume—To assess whether lesion size was driving the effects we identified in ATL and elsewhere, we regressed SemPlus on total lesion volume and mapped lesions associated with the residualized SemPlus scores. 15,396 supra-threshold voxels were identified, all of them clustered in the anterior MTG (BA 21), anterior ITG (BA 20), and temporal pole (BA 38) (see Fig. 5). Thus, for the ATL cluster (but not those outside of ATL), confidence is warranted that the association with semantic errors is independent of lesion size.

3.3.5. Uncoupling effects in BA 21 and BA 22—Previous studies using ROI lesion analysis have implicated BA 22 (STG) in word-level semantic processing (Cloutman et al., 2009). Our voxelwise analysis also revealed significant and nearly significant effects in this region, primarily clustered in the anterior half of the STG (see Fig. 2). To investigate the independent contributions of BA 21 and BA 22, we factored out the percent of damage to each area separately, starting with BA 22. A total of 16,100 voxels showed a significant association with SemPlus when damage to BA 22 was factored out; 15,078 of these occupied a contiguous region in the ATL (see Fig. 6). In contrast, when the damage to BA 21 was factored out, we could no longer detect effects anywhere in the brain. Thus, the MTG, not the STG, is more likely the critical locus of the effect.

4.0. Discussion

4.1. Robustness of the ATL effect

We sought to determine whether the hypothesized association of semantic naming errors with lesions in the L-ATL would be demonstrated under a new, less theory dependent definition of semantic errors. The new definition admitted any response, noun or non-noun, single or multiword, that conveyed a taxonomic or associative relation, including responses related to the target in both meaning and form (so-called “mixed errors”; Dell et al., 1997). This broad definition better approximates what was used in prior patient studies that localized semantic error production more posteriorly in left temporal lobe (e.g., Antonucci et

al., 2004; Cloutman et al., 2009; Foundas et al., 1998; Raymer et al., 1997). The current study obtained strong confirmation that lesions in the L-ATL are associated with higher rates of semantic naming errors, and that voxels in this brain region carry this association independent of whatever role they might play in conceptualization processes. This assertion is justified by the analysis in which scores on nonverbal comprehension tests that assess conceptual knowledge were factored out of SemPlus using regression techniques. The surviving voxels, clustered in and around mid-to-anterior temporal lobe (Fig. 4), evidently play a critical role in achieving the correct mapping from concepts to words in production, specifically.

Importantly, expanding the criterion for classifying errors as semantic yielded a more robust dependent measure and greater power to control for confounding effects. The factoring out of total lesion volume is notable in this regard. As discussed in Schwartz et al. (2009), there is a strong association in this patient sample between total lesion volume and localized damage in most of the covered voxels, so factoring out lesion volume results in low statistical power to detect independent effects at a voxelwise level. With the original dependent variable, SemErr, it was not possible to generate an FDR threshold when lesion volume was controlled, and hence, in the original study, it was not possible to determine the extent to which lesion volume contributed to the associations involving SemErr. With SemPlus, a more robust estimator, that analysis was possible, and it yielded the most convincing evidence to date that our effects in the ATL are independent of lesion size.

4.2. Negative findings in Wernicke's area

An *a priori* expectation of positive effects in Wernicke's area was warranted on several grounds. Chief among them was Hillis and colleagues' innovative investigations of acute stroke that demonstrated strong correlations between perfusion abnormalities in BA 22 and presence and degree of lexical-semantic deficits in naming and comprehension (Cloutman et al., 2009; DeLeon et al., 2007; Hillis et al., 2001a; Hillis et al., 2006; Hillis et al., 2001b). In the present study, with good coverage in Wernicke's area and a more robust estimator of semantic errors, we were optimally positioned to corroborate their findings. Instead, as in Schwartz et al. (2009), we found that voxels in the pSTG/pMTG generally identified with Wernicke's area yielded very low t-values, indicating that lesions had no measurable impact on semantic error scores.

On the other hand, the current study did obtain effects in *anterior* sectors of STG (Figs. 2–5) that were not identified in the original analysis. This offers a potential explanation for the discrepancy between Hillis and colleagues' results and ours. Conceivably, the significant association they identified between regional dysfunction in BA 22 and scores on various lexical-semantic measures came from voxels in anterior STG more than Wernicke's area. However, further analysis casts doubt on even this possibility. At least in the present sample, there was a very high correlation ($r = .87$) between percent damage to BA 22 and BA 21, where the highest t-values were observed. When the percent damage to BA 21 was factored out, effects could not be detected by the present analysis anywhere in the brain. In contrast, factoring out percent damage to BA 22 revealed independent effects in BA 21, despite the proximity and high spatial coherence of some voxels within these two regions. It is therefore likely that the effects we observed in BA 22 were actually dependent on its shared variance with BA 21. The same may be true for other studies that reported correlations within BA 22 (see Dronkers et al., 2004 for a similar suggestion).

Hillis and colleagues studied patients within the first 24 hours of stroke, whereas we studied chronic patients. Possibly due to its importance for speech perception, Wernicke's area is richly interconnected, structurally and functionally, with anterior and posterior language centers (Crinion, Warburton, Lambon Ralph, Howard, & Wise, 2006; Hickok & Poeppel,

2000; Parker et al., 2005; Rauschecker & Scott, 2009; Warren et al., 2009). Consequently, acute damage here may ramify throughout the language network, impacting cognitive functions for which computations in Wernicke's area are not ultimately necessary. What we learn from the current analysis of chronic lesion correlates of semantic errors is that the L-ATL is indispensable for semantically guided naming, in the sense that the association with semantic errors persists even after recovery and reorganization have had a chance to take place (see Rafal, 2006 for discussion). The same cannot be said of Wernicke's area.

4.3. Findings outside ATL

Replicating Schwartz et al. (2009), the VLSM of unfiltered semantic errors turned up two clusters outside of ATL, one in lateral posterior temporal cortex (BA 37) and one in PFC (BA 45/46). In the original study, we argued that these were probably areas where lesions impact naming during conceptualization rather than lexical access. We based this on the fact that effects in these extra-ATL areas were eliminated by factoring out semantic comprehension, as well as prior evidence that these areas are involved in semantic processing or semantic control (for reviews, see Binder et al., 2009; Bookheimer, 2002; Devlin & Watkins, 2007).

We thought that by bringing our definition of semantic errors more in line with what others have used, we might see additional or different effects in these regions outside ATL. One possibility is that with the addition of semantic circumlocutions, the dominant commission error in pure anomia, we might identify voxels in BA 37 where the association with semantic errors was independent of semantic comprehension, in keeping with its hypothesized role in post-semantic lexical-phonological access (Cloutman et al., 2009; Raymer et al., 1997). Alternatively, we might see that the clusters in BA 45/46 and BA 37 now expanded into neighboring areas of LIFG (BA 44; 47) and inferior parietal cortex (BA 39 and 40) that are arguably the most strongly associated with semantic control and semantic processing (e.g., Binder et al., 2009; Hart & Gordon, 1990; Noonan et al., 2010). None of these expectations were confirmed. Instead, we learned that effects in both extra-ATL clusters were eliminated when we controlled for the correlation between SemPlus and total lesion volume. This result casts doubt on the localization of the SemPlus effect in the BA 45/46 and BA 37 clusters, pending further evidence.

4.4. Lesion coverage

Contradicting previous claims that lesions in stroke generally do not affect the ATL (e.g., Noonan et al., 2010), our lesion coverage was good in most of the anterolateral region superior to basal BA 20. Although this large sample of chronic aphasics might over-represent ATL damage, there is reason to think that ATL involvement is not, in fact, all that rare. This brain region is, on most accounts (e.g., Moeller & Rief, 2000; Mohr et al., 1998), supplied by the middle cerebral artery and, as illustrated by Mohr et al. (1998; Figures 19.17, 19.18), may be affected in middle cerebral artery strokes, particularly those involving the inferior division. Furthermore, Caviness et al. (2002) reported data delineating the specific brain regions damaged in 21 patients with stroke; in their unselected group, 5 of 21 (24%) had involvement of the temporal pole, 7 of 21 (33%) had involvement of the anterior portion of the middle temporal gyrus, and 9 of 21 (43%) had involvement of the anterior portion of the superior temporal gyrus. Thus, based on these considerations, it would appear that claims that anterior temporal involvement in stroke is "rare" are inaccurate for much of the lateral division. It is nonetheless true that in a small sample of patients with post-stroke aphasia, the probability of finding lesions in ATL is low, relative to finding them in the classical peri-Sylvian areas. Since much current wisdom about lesion-symptom correlations in aphasia comes from small-sample lesion overlap analyses, it is not surprising that the contribution of the L-ATL has been overlooked (Wise, 2003).

4.5. L-ATL anomia: Semantic or post-semantic?

In this final section, we delve more closely into what some view as our most controversial conclusion, namely that the causal basis for L-ATL semantic naming errors is post-semantic rather than semantic in nature. The opposing position stems primarily from the influential body of research on semantic dementia (SD) conducted by Hodges, Patterson, Rogers, Lambon Ralph and their colleagues. On the behavioral side, the argument is that the verbal and nonverbal semantic deficits in SD, including the anomia that is often the first and most profound symptom, have a unitary basis in the dissolution of core (amodal) semantic representations (e.g., Patterson et al., 2007; Rogers et al., 2004 and references therein; but for alternative views, see Graham, Patterson & Hodges, 1995; Mesulam et al., 2009b). Neurologically, the basis for this core semantic deficit is progressive focal atrophy and hypometabolism centered on the anterior and inferolateral temporal lobes bilaterally (e.g., Mummery et al., 2000). Of particular relevance to current interests is the proposal put forth by Lambon Ralph, McClelland, Patterson, Galton, and Hodges (2001b) that semantic representations in left and right ATLs are computationally distinct: The greater proximity of semantic units on the left (SU-L) to left-lateralized phonological representations means that in the course of learning to produce words, there comes to be a “division of labor” between SU-L and SU-R(ight), such that naming is more dependent on SU-L and, consequently, more impacted by lesions that disproportionately affect SU-L. We will have more to say about their computational account below. For now, let us spell out the premises of the argument as they bear on our data: (1) There are units in the L-ATL whose essential role is to represent core semantic information; (2) although semantic in nature, these units acquire specialization for production by virtue of their privileged access to output systems; (3) conceivably, it is these types of unit that our VLSM identified in L-ATL, in which case their function is better characterized as semantic than post-semantic.

A recent study of patients with focal left inferotemporal lesions generated findings consistent with the SU-L hypothesis. Antonucci et al. (2008) studied 16 patients, half with L-ATL resection for treatment of epilepsy, the remaining half with L posterior cerebral artery (PCA) strokes. Through extensive and detailed cognitive testing, the authors established that the group of 16 had subtle deficits in nonverbal comprehension (e.g., *Pyramids and Palms* test) and impaired knowledge of object attributes, worse for sensory/perceptual attributes than functional ones (Borgo & Shallice, 2003; Breedin, Saffran, & Coslett, 1994; Gainotti & Silveri, 1996; Moss, Rodd, Stamatakis, Bright, & Tyler, 2005b). On word retrieval tests, including picture naming, performance was more seriously impaired. While the naming deficit manifested in most respects as “pure” anomia (i.e., patients produced informative and relevant circumlocutions for unnamed targets and benefited from phonological cuing), it proved to be worse for living things than non-living things. Alongside the semantic knowledge decrement for sensory/perceptual attributes, this suggests that the naming deficit was not post-semantic, as suggested by the resemblance to pure anomia, but instead was semantic in nature (Lambon Ralph, Moriarty, & Sage, 2002). Interestingly, there were no appreciable differences between the ATL and PCA groups, whose lesions overlapped maximally in anterolateral temporal cortex (BA 20). A plausible conclusion is that this anterolateral region houses SU-L that represent core knowledge of the sensory attributes of objects, yet when lesioned have their major impact on semantically-guided word retrieval.

Recent evidence from repetitive transcranial magnetic stimulation further supports the existence of units in L-ATL that represent core semantics (Lambon Ralph, Pobric, & Jefferies, 2009; Pobric et al., 2007, 2010). In these studies, low-frequency repetitive transcranial magnetic stimulation (rTMS) was applied to a common site in left and/or right ATL, localized to anterior MTG, 10 mm back from the pole. Task performance immediately after stimulation (during the “refractory period”) was compared to performance outside this

period. Relevant to current concerns, stimulation applied to this common site in L-ATL prolonged latencies to name pictures and judge similarity relations among words and pictures, but had no comparable effects on non-semantic control tasks of comparable difficulty. Here, too, a reasonable assumption is that the L-ATL units that were affected, in this case by “virtual” lesions, were semantic in nature (SU-L) and essential to both comprehension and production.

Are these the units that our methods picked out in the L-ATL? If they were, one would have expected the NVcomp control to have eliminated the association with semantic errors. Instead, the association persisted in a large cluster of ATL voxels. Before fleshing out the implications of this finding, it is useful to consider some relevant methodological issues.

Firstly, was our measure of nonverbal comprehension sufficiently sensitive to pick up the overlapping semantic requirements of nonverbal comprehension and semantically-guided lexical access? We believe it was. The two tests that went into our comprehension composite score – *Pyramids and Palms* and *Camel and Cactus* – have been shown to be sensitive to the subtle comprehension deficits associated with L-ATL dysfunction (e.g., Antonucci et al., 2008). Patients in our sample produced an adequate range of scores on both tests, and their mean scores differed significantly from control norms (Table 1). Most importantly, the filtering of NVcomp eliminated any significant voxelwise associations outside the ATL, thereby demonstrating that this measure’s psychometric properties and cognitive overlap with semantically guided naming were well suited to the purposes of this investigation.

One might also question whether limitations of lesion coverage prevented us from detecting an NVcomp filtering effect in ATL. It is true with no coverage in anteromedial temporal cortex and limited coverage in the inferior aspects of BA 20 and 37, we are unable to make any claims about these areas. However, this qualification does not apply to the site near the pole that Pobric and colleagues stimulated (e.g., Pobric et al., 2007) or to the anterolateral region of BA 20 picked out by Antonucci et al.’s (2008) overlap analysis. These were areas in which we identified supra threshold voxels in both unfiltered and filtered analyses.

In light of these considerations, the conclusion seems clear that the L-ATL plays a critical role at a post-semantic stage of lexical access. This is *not* to say that the L-ATL plays no role in core semantics. The rTMS and neuropsychological evidence reviewed above (see also Crinion et al., 2006; Warren et al., 2009) shows convincingly that L-ATL dysfunction has a negative impact on semantic representation and/or processing. Moreover, this impact, however subtle, is likely to be magnified in a task as sensitive as word retrieval. But this cannot be the whole story. Based on the current findings, a complete account of how the L-ATL contributes to semantic cognition must allow that it makes a contribution to production that is independent of its contribution to comprehension and, more generally, conceptualization.

Our theoretical explanation for the independent contribution of the L-ATL invokes lemmas -- the abstract (pre-phonological) lexical entities that syntactic-combinatorial processes manipulate (e.g., Dell, 1986; Garrett, 1975; Levelt et al., 1991). Lemmas collect activation from the semantic level, and shared semantics creates competition among lemmas. Semantic errors occur when a competitor wins out over the target. Brain damage in aphasia weakens the integrity of lemma selection, making semantic errors more likely. This account finds strong empirical support in computational case-series investigations of aphasic naming (Foygel & Dell, 2000; Schwartz et al., 2006) and repetition (Dell, Martin, & Schwartz, 2007). It also comports with a meta-analysis of neuroimaging studies of word production (Indefrey & Levelt, 2000, 2004) and with a large body of findings in the psycholinguistic and neurolinguistic literature on speech production (see reviews in Dell et al., 1997; Rapp &

Goldrick, 2000; Schwartz et al., 2006). Melding the cognitive and anatomical data together, we postulate that the L-ATL, specifically the mid-to-anterior middle temporal gyrus, subserves lemma selection (see also Indefrey & Levelt, 2004).

The SU-L hypothesis (Lambon Ralph et al., 2001b), which we discussed earlier, offers an interesting explanation for how the L-ATL comes to serve this role: Reflecting its spatial proximity to left lateralized phonological units, the semantic units in L-ATL become specialized for language production, meaning that they develop privileged links to phonological representations. Differences between our account and Lambon Ralph's (2001b) centers on how these privileged links are conceptualized, but we see much common ground between our two proposals, and also with the theory of convergence zones, as developed by Damasio and colleagues (e.g., Damasio et al., 1996; Tranel, 2006). Specifically, if one allows that the privileged linkage to production is accomplished by L-ATL units that compute representations intermediate between semantics and output phonology (in the manner of hidden units in neural network models), then whether one conceives of these as additional semantic units, the units of convergence zones, or lemma-like lexical representations comes down to theoretical commitments that go beyond this particular issue.

4.5. Summary

Regardless of whether we choose to model these errors as semantic or post-semantic, our analyses clearly demonstrate that patient variability in semantic error production that is independent of semantic comprehension is associated with the L-ATL (BA 38, 21, 20) and not with BA 22, including Wernicke's area. These findings are robust with respect to the definition of semantic errors, and they do not depend on the correlation of ATL lesions with total lesion volume or the overlap of lesions in BA 21 and BA 22. Much literature suggests that core semantic representations depend on both anterior temporal lobes. According to our results, the L-ATL also contains the means by which semantics is conveyed to the lexical system for purposes of production. It is damage to this system that leads to semantic errors in production that are independent of comprehension.

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Fig. 1. Maps depicting lesion overlaps of the 64 subjects in the left hemisphere. Maps A–D are at MNI x coordinates of -64 , -58 , -52 , and -46 respectively. Map E is a single axial slice at $z=-24$. The regions of maximal overlap (bright yellow) are in the peri-Sylvian regions, particularly anterior. Only voxels lesioned in at least five subjects were included, yielding 404,565 total voxels to be tested.

Fig. 2.

Maps of the reliability (t statistic) of the difference in SemPlus between patients with and without lesions in each voxel (rendered on the MNI-space ch2 volume). Voxels exceeding the FDR threshold ($q=0.01$) are rendered in a red ($t=3.09$) to yellow ($t>6.18$) scale, while nonsignificant values are rendered on a scale from green (t just below threshold) to blue ($t=0$ or below). Maps A–D are at MNI x coordinates of -64 , -58 , -52 , and -46 respectively. Map E is a single axial slice at $z=-24$. The peak value of 8.79 was held in common by four contiguous voxels centered at MNI coordinates -64.5 , -3.75 , -24.5 – the anterior cortex of the middle temporal gyrus (Maps A and E show crosshairs at -64 , -4 , -24). There were 9 (of 64) subjects who had lesions encroaching the peak voxels.

Fig. 3. Maps of the reliability (t statistic) of the difference in SemPlus, after factoring out PhonErr, between patients with and without lesions in each voxel (rendered on the MNI-space ch2 volume). Voxels exceeding the FDR threshold ($q=0.01$) are rendered in a red ($t=3.08$) to yellow ($t>6.16$) scale, while non-significant values are rendered on a scale from green (t just below threshold) to blue ($t=0$ or below). Maps A–D are at MNI x coordinates of -64, -58, -52, and -46 respectively. Map E is a single axial slice at $z=-24$. The centroid of the peak voxels ($t=8.54$) in the map were at -64.5, -3.75, -24.5 (exactly the same region as in the unfiltered analysis).

Fig. 4. Maps of the reliability (t statistic) of the difference in SemPlus, after factoring out NVcomp, between patients with and without lesions in each voxel (rendered on the MNI-space ch2 volume). Voxels exceeding the FDR threshold ($q=0.01$) are rendered in a red ($t=3.18$) to yellow ($t>6.35$) scale, while non-significant values are rendered on a scale from green (t just below threshold) to blue ($t=0$ or below). Maps A–D are at MNI x coordinates of -64, -58, -52, and -46 respectively. Map E is a single axial slice at $z=-24$. The centroid of the peak voxels ($t=7.25$) in the map were at -64.5, -3.75, -24.5 (exactly the same region as in the unfiltered analysis).

Fig. 5. Maps of the reliability (t statistic) of the difference in SemPlus, after factoring out total lesion volume, between patients with and without lesions in each voxel (rendered on the MNI-space ch2 volume). Voxels exceeding the FDR threshold ($q=0.01$) are rendered in a red (t=3.54) to yellow (t>7.09) scale, while non-significant values are rendered on a scale from green (t just below threshold) to blue (t=0 or below). Maps A-D are at MNI x coordinates of -64, -58, -52, and -46 respectively. Map E is a single axial slice at z=-24. The peak statistical value of 5.95 is held by four contiguous voxels at MNI coordinates -62.5, -3, -27.75 (a very slight shift from the unfiltered analysis).

Fig. 6. Maps of the reliability (t statistic) of the difference in SemPlus, after factoring out percent damage to BA22, between patients with and without lesions in each voxel (rendered on the MNI-space ch2 volume). Voxels exceeding the FDR threshold ($q=0.01$) are rendered in a red ($t=3.53$) to yellow ($t>7.06$) scale, while non-significant values are rendered on a scale from green (t just below threshold) to blue ($t=0$ or below). Maps A-D are at MNI x coordinates of -64, -58, -52, and -46 respectively. Map E is a single axial slice at $z=-24$. The peak statistical value of 5.86 is held by four contiguous voxels at MNI coordinates -62.5, -3, -27.75 (the same as the total lesion volume filtered analysis).

Behavioral measures

Table 1

Test/Measure	Participants with aphasia (n = 64)				Norms for healthy participants	
	Mean (SD)	Median	Low	High	Mean (SD)	
Philadelphia naming test (PNT):						
Prop. Correct	0.69 (.26)	0.80	0.02	0.97	.97 (.03) ^a	
Prop. SemErr ^b	0.03 (.03)	0.03	0.00	0.12	.01 (.01) ^a	
Prop. SemPlus	0.08 (.06)	0.05	0.01	0.25	.02 (.02) ^a	
Nonverbal Comprehension:						
Pyramids and palm trees test (pictures; max. 52)	46.4 (5.0)	47.8	24	52	51.2 (1.4) ^c	
Camel and cactus test (pictures; max. 64)	50.1 (7.6)	51.8	23	61	58.4 (3.4) ^d	
Composite measure (NVcomp; mean of z-scores)	-.04 (1.04)	0.16	-4.0	1.16	n/a	

^aUnpublished; N = 20 healthy participants; Mean age = 58.9 (13.6)

^bDependent measure in Schwartz et al., 2009

^cBozeat et al., 2000

^dLambon Ralph et al., 2001a

Table 2

Error types included in SemPlus

Error type	Sum
Taxonomic or associative noun	391
Mixed (semantic and phonological) noun	222
Semantic circumlocutions	184
Associated action	49
Non-pictured feature	28
Total (SemPlus)	874