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Running head: NEURAL SUBSTRATES OF SEMANTIC INTERFERENCE

Distinct loci of lexical and semantic access deficits in aphasia: Evidence from voxel-based lesion-symptom mapping and diffusion tensor imaging

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Abstract

Naming pictures and matching words to pictures belonging to the same semantic category negatively affects language production and comprehension. By most accounts, semantic interference arises when accessing lexical representations in naming (e.g., Damian, Vigliocco, & Levelt, 2001) and semantic representations in comprehension (e.g., Forde & Humphreys, 1997). Further, damage to the left inferior frontal gyrus (LIFG), a region implicated in cognitive control, results in increasing semantic interference when items repeat across cycles in both language production and comprehension (Jefferies, Baker, Doran, & Lambon Ralph, 2007). This generates the prediction that the LIFG via white matter connections supports resolution of semantic interference arising from different loci (lexical vs. semantic) in the temporal lobe. However, it remains unclear whether the cognitive and neural mechanisms that resolve semantic interference are the same across tasks. Thus, we examined which gray matter structures (using whole brain and region of interest approaches) and white matter connections (using deterministic tractography) when damaged impact semantic interference and its increase across cycles when repeatedly producing and understanding words in 15 speakers with varying lexical-semantic deficits from left hemisphere stroke. We found that damage to distinct brain regions, the posterior vs. anterior temporal lobe, was associated with semantic interference (collapsed across cycles) in naming and comprehension, respectively. Further, those with LIFG damage compared to those without exhibited marginally larger increases in semantic interference across cycles in naming but not comprehension. Lastly, the inferior fronto-occipital fasciculus, connecting the LIFG with posterior temporal lobe, related to semantic interference in naming, whereas the inferior longitudinal fasciculus, connecting posterior with anterior temporal regions related to semantic interference in comprehension. These neuroanatomical-behavioral findings have

implications for models of the lexical-semantic language network by demonstrating that semantic interference in language production and comprehension involves different representations which differentially recruit a cognitive control mechanism for interference resolution.

Keywords: Diffusion tensor imaging; language production and comprehension; lexical-semantic deficits; semantic interference; lesion-symptom mapping

1 Introduction¹

Producing a word is sometimes difficult, as evidenced by the fact that people say the wrong word or hesitate when speaking. Likewise, errors also occur when understanding a word. Investigating the way in which language processes fail has a long-standing tradition in informing models of the language system. The prevalence of semantic errors in patients with language impairments due to stroke (i.e., aphasia) (e.g., Dell, Schwartz, Martin, Saffran, & Gagnon, 1997; Forde & Humphreys, 1995) along with the finding that naming pictures (e.g., Kroll & Stewart, 1994) or matching words to pictures (Campanella & Shallice, 2011) belonging to the same semantic category hinders healthy participants' performance demonstrates that language production and comprehension are semantically driven processes. However, semantic interference in naming and word comprehension has been, for the most part, investigated separately, which has led to different assumptions about the locus of semantic interference in each language modality. By most accounts, semantic interference during picture naming arises when accessing the lexical representation for an intended meaning (at a lexical level) (e.g., Howard, Nickels, Coltheart, & Cole-Virtue, 2006; Oppenheim, Dell, & Schwartz, 2010; see also Damian & Als, 2005), whereas semantic interference during word-picture matching occurs when accessing the semantic representation for a given word form (at a semantic level) (e.g., Gotts & Plaut, 2002; see also Campanella & Shallice, 2011; Forde & Humphreys, 1997, 2007; Warrington & Cipolotti, 1996). Yet, neuropsychological evidence demonstrates that damage to neural regions involved in cognitive control results in exaggerated increases in semantic

¹ Abbreviations: ATL = anterior temporal lobe; AF = arcuate fasciculus; AWPV = auditory word-picture verification task; FA = fractional anisotropy; IFOF = inferior fronto-occipital fasciculus; ILF = inferior longitudinal fasciculus; LIFG = left inferior frontal gyrus; MTG = middle temporal gyrus; PNT = Philadelphia Naming Test; PPT = Pyramid and Palm Trees test; UF = uncinate fasciculus; WAB = Western Aphasia Battery; VLSM = voxel-based lesion-symptom mapping.

interference when items repeat across cycles regardless of language modality (i.e., language production or comprehension) (Jefferies, Baker, Doran, & Lambon Ralph, 2007), suggesting a shared mechanism serves to resolve interference arising at different loci. However, to our knowledge, previous research has yet to explore these hypotheses by investigating language production and comprehension performance using both behavioral and high-resolution neuroimaging approaches in the same participants with lexical-semantic processing deficits due to left-hemisphere stroke. Thus, the goal of this research was to examine the extent to which language production and comprehension processing stages overlap by exploring how, as a result of stroke, damage to neural regions and their white matter connections affect semantic interference and its increase across cycles in picture naming and word-picture matching tasks.

It is surprising that semantic interference in language production and comprehension is thought to arise at different levels in the language system (Howard et al., 2006; Levelt, Roelofs, & Meyer, 1999; Oppenheim et al., 2010; Roelofs, 1992, 2003; Campanella & Shallice, 2011; Forde & Humphreys, 1997, 2007; Gotts & Plaut, 2002; Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983, 1987) given that one must access a shared semantic system (e.g., Shelton & Caramazza, 1999) both to produce the word for a given meaning and to comprehend the meaning for a given word (see Figure 1). For example, subjects are slower and/or make more errors when naming pictures and matching words to pictures when trials are blocked in groups depicting items belonging to the same categories (related context: e.g., DOG, CAT, BEAR, COW) vs. different categories (unrelated context: e.g., DOG, TRAIN, SHIRT, DESK; e.g., Damian, Vigliocco, & Levelt, 2001; Biegler, Crowther, & Martin, 2008). Both naming and understanding words in these semantic blocking tasks are sensitive to semantic manipulations, where close vs. distant categorical relationships among items (e.g., DOG and CAT vs. DOG and

WHALE) results in greater semantic interference in naming (Vigliocco, Vinson, Damian, & Levelt, 2002) and word-picture matching tasks (Crutch & Warrington, 2005; Warrington & Cipolotti, 1996, Experiment 5). Likewise, semantic interference generalizes to novel category exemplars previously not named (Belke, Meyer, & Damian, 2005b, Experiment 3) or comprehended (Forde & Humphreys 1995, Experiment 12), providing evidence that semantic interference results from spreading activation across category members. These findings indicate that semantic interference in production and comprehension originates at the semantic level (see also Belke, 2013), where naming a picture (DOG) or comprehending a word (“dog”) activates its semantic representation, which then spreads activation to related representations sharing semantic features with the target (e.g., CAT/”cat”; e.g., Collins & Loftus, 1975; Levelt et al., 1999).

However, it is generally assumed that semantic interference in language production occurs at the lexical level (e.g., Levelt et al., 1999) while semantic interference in language comprehension occurs at the semantic level (e.g., Gotts & Plaut, 2002), despite the assumption that producing and comprehending words make use of shared lexical and semantic representations (reviewed in Levelt, 1999; Howard, 1995; cf. Caramazza, 1997; see Figure 1). In naming, semantic interference does not occur for tasks which tap the lexical level without access to semantics (i.e., written word naming; Belke, Brysbaert, Meyer, & Ghyselinck, 2005a; Kroll & Stewart, 1994; Vitkovitch & Humphreys, 1991) or the semantic level without lexical access (i.e., manually categorizing pictures; Belke, 2013; Damian et al., 2001). Evidence against an output level of interference in naming comes from the finding that naming phonologically related vs. unrelated pictures (e.g., BOAT, BONE vs. BOAT, CHAIR) facilitates language production (e.g., Damian & Bowers, 2003; Roelofs, 1999; Schnur et al., 2009). Semantic interference in naming is

computationally modeled as a result of co-activated lexical representations that compete for selection (Howard et al., 2006; Oppenheim et al., 2010; Roelofs, 1992, 2003; cf. Janssen, Carreiras, & Barber, 2011; Mahon, Costa, Peterson, Vargas, & Caramazza, 2007) which then delays naming and creates more errors. In contrast, theories of language comprehension assume that semantic interference occurs when accessing the semantic system (Forde & Humphreys, 1995, 1997, 2007; Warrington & Cipolotti, 1996) due to co-activation of shared semantic features that makes distinguishing the target amongst related non-target representations more difficult. Evidence for a semantic locus of interference in comprehension comes from studies demonstrating that the effect does not depend on the stimulus input modality (e.g., spoken word, written word, associatively matching picture, and/or environmental sound; Gardner et al., 2012), that the effect transfers both across input modalities (e.g., auditory word-written word matching and auditory word-picture matching; Forde & Humphreys, 1997, Experiment 11) and languages (i.e., English to French and vice versa; Ferrand & Humphreys, 1996), and that interference does not occur when accessing presemantic visual representations (i.e., unusual views matching; Forde & Humphreys, 1997, Experiment 5). Thus, repeatedly accessing semantic and lexical representations belonging to the same semantic category creates semantic interference by increasing competition amongst a target and co-activated categorically related representations, but most accounts assume a lexical locus in production and a semantic locus in comprehension.

A number of neuropsychological studies demonstrate that patients with aphasia show exaggerated semantic interference when naming (Biegler et al., 2008; McCarthy & Kartsounis, 2000; Schnur, Schwartz, Brecher, & Hodgson, 2006; Schnur et al., 2009; Wilshire & McCarthy, 2002) and comprehending semantically related stimuli (Campanella, Crescentini, Mussoni, & Skrap, 2013; Forde & Humphreys, 1995, 1997, 2007; Gardner et al., 2012; Jefferies et al., 2007;

Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983, 1987), which provides insight into the underlying processes that create semantic interference, and points to at least two sources of semantic interference. First, patients with aphasia often make more errors in the related compared to unrelated contexts in naming (McCarthy & Kartsounis, 2000; Schnur et al., 2005; Wilshire & McCarthy, 2002) and comprehension (Crutch & Warrington, 2005; Jefferies et al., 2007; Warrington & Cipolotti, 1996, Experiment 4) variants of the task (henceforth, *relatedness effect*). This is thought to reflect an impairment in accessing the representations themselves (i.e., lexical or semantic; see Figure 1) where damage creates noisy activation of representations, making them difficult to distinguish from one another in semantically blocked sets of trials. Second, in the cyclical version of the blocked naming and word-picture matching paradigms, target items appear multiple times in different orders for a number of cycles (Biegler et al., 2008; Damian & Als, 2005; Schnur et al., 2006), where some patients demonstrate increasingly worse performance with repetition of related compared to unrelated target items (henceforth, *increasing relatedness effect*; Schnur et al., 2006, 2009). Although repeating unrelated target items facilitates performance (i.e., repetition priming; e.g., Morton, 1969), this repetition priming is counteracted by interference when repeating target items belonging to the same semantic category (e.g., Oppenheim et al., 2010). This is thought to reflect impairments in recruiting a cognitive control mechanism that comes online to resolve semantic interference which increases as related vs. unrelated target stimuli are repeated, at either a lexical (Biegler et al., 2008; Schnur et al., 2006, 2009) and/or semantic level of representation (Jefferies et al., 2007). Consequently, poor performance in blocked-cyclic tasks is the result of damage to the representations themselves which creates noisy lexical or semantic activation (e.g., McCarthy & Kartsounis,

2000; Warrington & Cipolotti, 1996), and/or damage to a cognitive control mechanism involved in resolving interference (Biegler et al., 2008; Jefferies et al., 2007; Schnur et al., 2006, 2009).

Critically, because previous research has yet to examine semantic interference and its increase across cycles in blocked-cyclic production and comprehension tasks using lesion-symptom mapping within the same group of subjects, it is unclear whether these effects arise at different neural loci in language production and comprehension. Likewise, it is unclear whether cognitive control is required to resolve semantic interference regardless of language modality (i.e., as a result of the type of representations accessed: lexical vs. semantic). Although neuropsychological studies demonstrate behavioral dissociations between patients' language production and comprehension performance on tasks eliciting semantic interference (Biegler et al., 2008; McCarthy & Kartsounis, 2000; Wilshire & McCarthy, 2002; cf. Jefferies et al., 2007), these studies did not analyze the relationship between lesion location and behavior. The current study addresses these limitations by using voxel-based lesion symptom mapping (i.e., VLSM; Bates et al., 2003; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004) and region of interest (ROI) approaches within the same group of 15 subjects with brain damage, to our knowledge the largest group tested to date.

Because theories of production and comprehension assume that semantic interference arises at separate loci within the language system (e.g., Oppenheim et al., 2010; Forde & Humphreys, 2007), this suggests that the neural loci of the *relatedness effects* should differ across naming and word-picture matching tasks. The left temporal lobe is thought to support both lexical and semantic level processing (e.g., Indefrey, 2011; Jefferies, 2013; see also Cloutman et al., 2009), and indeed, damage here is associated with exaggerated *relatedness effects* in language production (Schnur, Lee, Coslett, Schwartz, & Thompson-Schill, 2005) and

comprehension (Campanella, Mondani, Skrap, & Shallice, 2009; Gardner et al., 2012) in the absence of *increasing relatedness effects*. However, these studies (Schnur et al., 2005; Campanella et al., 2009; Gardner et al., 2012) examined production or comprehension separately making it unclear whether damage to the same or different temporal lobe regions was associated with impaired performance across tasks. In a meta-analysis of neuroimaging studies on word production, Indefrey and Levelt (2004; see also Indefrey, 2011) identified the mid- to posterior middle temporal gyrus (MTG) as important for semantically driven lexical retrieval, suggesting a posterior temporal lobe (including the mid-posterior MTG) neural locus of the *relatedness effect* in naming. Semantic level processing, however, is thought to occur in more anterior regions of the temporal lobe. The anterior temporal pole is thought to serve as a semantic hub binding distributed features to form core semantic representations (reviewed in Patterson, Nestor, & Rogers, 2007; see also Jefferies, 2013; Visser, Jefferies, & Lambon Ralph, 2010), where regions located more anteriorly in the MTG serve as an interface between lexical input processing regions and the anterior temporal pole (e.g., Binney, Embleton, Jefferies, Parker, & Lambon Ralph, 2010), making the anterior temporal lobe (including the anterior MTG) one likely candidate for the neural locus of the *relatedness effect* in comprehension. Thus, the first aim of this study was to test whether damage to separate temporal lobe regions creates exaggerated *relatedness effects* in production vs. comprehension (i.e., posterior vs. anterior temporal lobe, respectively), as this would provide support for the assumptions that the competition creating semantic interference arises at different levels of the language system.

The second aim of this study was to test whether the increase of semantic interference across cycles reflects the same underlying process in production and comprehension. According to Warrington and McCarthy (1983), *increasing relatedness effects* in patients' language

comprehension performance reflects a ‘refractory impairment,’ specifically “...a reduction in the ability to utilize the system efficiently for a period of time following activation” (p. 874).

Refractory impairments are also proposed to account for *increasing relatedness effects* in language production (McCarthy & Kartsounis, 2000; cf. Schnur et al., 2006). By this view, increasingly worse performance on tasks repeatedly probing the same semantic category results from residual spreading activation that makes disambiguating a target from related non-target representations increasingly difficult, whether at the semantic (Forde & Humphreys, 1997, 2007) or lexical level (McCarthy & Kartsounis, 2000).² In contrast, the semantic control hypothesis (Jefferies & Lambon Ralph, 2006) suggests that patients with aphasia perform poorly on semantic tasks in either language modality because of impairments in controlling the activation of lexical-semantic knowledge, instead of due to the refractory nature of the semantic or lexical representations themselves. Accordingly, Jefferies and colleagues (2007) suggest that patients exhibit *increasing relatedness effects* on both blocked-cyclic naming and comprehension tasks as a result of damage to a cognitive control mechanism (in left inferior prefrontal cortex) that serves to select the target representation, whether lexical or semantic, from amongst competing alternatives. This cognitive control mechanism is likely subserved by the left inferior frontal gyrus (LIFG), a region located within the left inferior prefrontal cortex that when damaged impedes competition resolution over lexical and semantic representations (see Novick, Trueswell, & Thompson-Schill, 2010 for a review). However, in Jefferies et al. (2007), the size of the patient group was small, as only four patients could perform both production and

²Note that other theories assume that semantic (e.g., Gotts & Plaut, 2002) and lexical representations (e.g., McCarthy & Kartsounis, 2000) undergo a period of inhibition following initial activation, which is thought to render them unavailable temporarily. Under both scenarios (hyperactivation vs. hyperinhibition), semantically related compared to unrelated representations suffer the most due to shared semantics.

comprehension tasks, and the reported *increasing relatedness effect* was weak or non-significant across the group (see Gardner et al., 2012, p. 781 for a similar discussion). Further, because some studies investigating semantic context effects using cyclical tasks – either in production or comprehension – did not contrast performance across cycles of related items with that of a baseline measure of performance (i.e., an unrelated condition; e.g., Jefferies et al., 2007; McCarthy & Kartsounis, 2000, Test 4a; Hamilton & Martin, 2010; Warrington & Cipolotti, 1996), it is unclear whether increasingly worse performance across cycles reflects a true impairment in cognitive control or a refractory effect that affects repeatedly accessing the same stimuli more generally (for evidence of increasingly worse performance when repeatedly naming unrelated items see McCarthy & Kartsounis, 2000, Test 1). Thus, in order to test the hypothesis that increasing semantic interference across cycles results from an inability to resolve competition arising at either lexical or semantic levels of representation (independent of a general deficit to repeatedly access representations), the current study calculated the *increasing relatedness effect* as the linear increase of the *relatedness effect* obtained at each cycle (following Biegler et al., 2008; Schnur et al., 2009).

If a shared mechanism in the LIFG resolves competition (Campanella et al., 2013; Schnur et al., 2009) arising at different temporal lobe loci for language production (access to lexical representations in left posterior temporal cortex) and comprehension (access to semantic representations in left anterior temporal cortex; Cloutman et al., 2009), this generates the prediction that white matter tracts play a key role in connecting regions supporting lexical and/or semantic processing with a cognitive control region important for resolving interference. Diffusion tensor imaging (DTI), a method that quantifies the integrity of white matter pathways allows us to investigate the connectional architecture of the language network, shedding light on

how disparate brain regions communicate with one another. DTI studies reveal at least four fiber tracts connecting the fronto-temporal language network described above (reviewed in Catani & Mesulam, 2008). The arcuate fasciculus (AF) projects from the inferior frontal lobe to the middle temporal gyrus (MTG), with additional projections through the parietal lobe. Both the uncinate fasciculus (UF) and the inferior longitudinal fasciculus (ILF) terminate in the anterior temporal lobe (ATL), where the former projects to the inferior frontal lobe and the latter projects through the temporal lobe terminating in the posterior temporal cortex. The inferior fronto-occipital fasciculus (IFOF) connects the posterior temporal cortex with the inferior frontal lobe, running medial and then superior to the ILF within the temporal lobe and medial to the UF in the inferior frontal lobe (Catani & Thiebaut de Schotten, 2008). Based on previous evidence (e.g., de Zubicaray, Rose, & McMahon, 2011; Duda, McMillan, Grossman, & Gee, 2010; Harvey, Wei, Ellmore, Hamilton, & Schnur, 2013; Han et al., 2013) and the anatomical terminations of each white matter tract, we hypothesize different tracts support separable aspects of language processing as revealed by semantic interference in the blocked-cyclic naming and word-picture matching tasks. Specifically, we predict that the AF and/or IFOF support interactions between the inferior frontal and MTG regions for semantic interference resolution at the lexical level, whereas the UF supports interactions between inferior frontal and anterior temporal cortices to resolve semantic interference arising at the semantic level. Thus, investigating the impact of damage to white matter pathways interconnecting regions hypothesized to be important for production and comprehension has the potential to reveal whether a shared semantic interference resolution mechanism serves to ameliorate competition arising at separate semantic interference loci.

To summarize, the aims of this study were threefold: (1) to examine whether semantic interference when naming and understanding semantically related vs. unrelated stimuli (i.e., a *relatedness effect*) in blocked-cyclic tasks results from damage to separate neural regions; (2) to investigate whether the increase in semantic interference across cycles (i.e., an *increasing relatedness effect*) results from damage to the LIFG regardless of language modality; and (3) to explore the impact of reduced white matter structural integrity interconnecting the LIFG with posterior and anterior temporal lobe regions on semantic interference and its increase across cycles in naming and comprehension.

1.1 Current study

The participants for this study were recruited from a database of persons diagnosed with a single left hemisphere stroke and enrolled in various studies in the Department of Psychology at Rice University. Inclusion criteria included a single left hemisphere stroke, ability to undergo magnetic resonance imaging (MRI), and intact input (auditory and visual) processing. Of 26 patients included in the database, 18 had high-resolution neuroimaging of whom 15 had intact auditory and visual processing. Critically, patients included in the study varied with regards to their lexical-semantic processing abilities in production and comprehension, which allows us to test the theoretical questions of whether semantic interference loci differ for production vs. comprehension (lexical vs. semantic) and whether a shared mechanism resolves interference across tasks. Thus, we examined the neural structures (both gray and white matter) that when damaged affect the magnitude of semantic interference and its increase across cycles (i.e., *relatedness* and *increasing relatedness effects*) in both production and comprehension.

We used two complementary methods for performing lesion-symptom mapping, a whole brain voxel-by-voxel approach (i.e., VLSM; Bates et al., 2003; Dronkers et al., 2004) and a

region of interest (ROI) analysis (see also Schnur et al., 2009). Similar to functional MRI (fMRI) methodological approaches, we combined whole-brain and ROI-based analyses to provide converging evidence for the functional role of different brain regions in language processing (e.g., Schnur et al., 2009) because a voxel by voxel approach reveals which voxels play a crucial role in the behavior of interest within a larger ROI but is subject to confounds such as total lesion volume and false negatives (type II errors) (Kimberg, Coslett, & Schwartz, 2007; Schnur et al., 2009) – confounds controlled for in an ROI-based approach. ROI-based analyses provide converging evidence for findings from the VLSM analyses, which is particularly relevant for the theoretical question tested regarding whether the posterior and anterior temporal lobes play different roles in lexical-semantic processing for production and comprehension. To quantify the integrity (i.e., fractional anisotropy (FA) value) of white matter pathways interconnecting the language network, we used DTI deterministic tractography (Ellmore et al., 2010; Harvey et al., 2013). We correlated pathway integrity with individual measures of *relatedness* and *increasing relatedness effects* to determine whether reduced structural connectivity accounts for behavior above and beyond the contribution from lesion location and/or total lesion volume.

If the competition creating semantic interference arises at different loci (access to lexical representations in production and access to semantic representations in comprehension), then damage to non-overlapping neural regions should relate to exaggerated *relatedness effects* when producing vs. comprehending words. Second, if competition arising at these different loci within the language system necessitates the recruitment of a shared cognitive control mechanism to resolve the interference, then damage to the same neural region should relate to *increasing relatedness effects* regardless of the task. Further, damage to separate white matter pathways connecting this control region to differing interference loci should relate to *relatedness* and

increasing relatedness effects in production vs. comprehension. In contrast, if semantic interference arises at the same level of the language system in production and comprehension, then *relatedness effects* should associate with damage to the same neural region across naming and word-picture matching tasks. To our knowledge, this is the first study to quantify in the same group of subjects how damage to gray and white matter impacts semantic interference and its resolution when accessing lexical and semantic representations for production and comprehension. By demonstrating separate neural loci for semantic interference and its resolution across modalities, these results inform cognitive models of language production and comprehension.

2 Method

2.1 Participants

We recruited 18 patients with left hemisphere damage as a result of a middle cerebral artery stroke. All patients were native English speakers, right-handed (as determined by self-report or reported by their caregiver), at least six months post stroke (chronic), and willing and able to undergo high-resolution MRI scanning. To draw the strongest brain-behavior conclusions we did not restrict subject inclusion to those who demonstrated semantic deficits (cf. Jefferies et al., 2007) as this allowed us to increase variability in both behavioral performance on tasks tapping lexical-semantic processing when producing vs. comprehending speech and location of neuroanatomical damage (see Schwartz et al., 2009 for similar motivation). However, patients were excluded if their lesions were not restricted to the left hemisphere and/or if they had suffered a second stroke in between scanning and behavioral testing sessions. Further, because the goal of this study was to assess lexical-semantic processing errors in production and comprehension, patients had to exhibit intact processing at input stages (see Figure 1) as assessed

by the Birmingham Object Recognition Battery (BORB; Riddoch & Humphreys, 1993) and an auditory or visual lexical decision task (adapted from Martin & Breedin, 1992).³ These inclusion criteria led to the exclusion of three patients where either input processing was impaired, a second stroke occurred or because structural MRI scans revealed that cortical damage was not restricted to the left hemisphere. The remaining 15 patients' mean (and range) age was 62 years (41-83); education 16 years (11-22); and months post-onset 58 (8-127). Aphasia subtypes were classified using the Western Aphasia Battery (WAB), and as indicated by the Aphasia Quotient, overall language impairment severity varied considerably across the patient group (Kertesz, 1982). See Table 1 for patient demographics, clinical information, and lesion information. Neuroimaging data from eight neurologically intact control participants (reported in Harvey et al., 2013), matched in age (mean 54, range 37-60; $t(21) = 1.68, p = .11$) and education (mean 19 years, range 16-20; $t(21) = 1.52, p = .14$) with the patients were also included in order to establish that the patient group had significantly reduced white matter integrity values compared to an older adult sample. All participants were native English speakers. Informed consent was obtained in accordance with the IRB of Rice University and the University of Texas Health Science Center at Houston.

As shown in Table 2, participants performed within the normal range on the BORB – a test of visual input form processing (Riddoch & Humphreys, 1993). Patients also demonstrated intact phonological and/or orthographic processing, as they performed at 90% correct or above

³ The blocked-cyclic word-picture matching task provided patients with both an auditory and visual probe word (see *Procedure, Blocked-cyclic word-picture matching*), and therefore allowed for the inclusion of patients with either intact phonological or orthographic input processing.

on either the auditory or visual lexical decision task (see Martin & Breedin, 1992).⁴ Also provided in Table 2 are scores on an assessment of non-verbal semantics (i.e., three picture Pyramid and Palm Trees (PPT) Test; Howard & Patterson, 1992). Eleven of the 15 patients scored within three standard deviations (SDs) of the mean performance of an older control group (mean (SD) = 98.5% (2.7%) correct as reported in Bozeat, Lambon Ralph, Patterson, Garrard, & Hodges, 2000), demonstrating relatively intact non-verbal semantic knowledge. Four patients scored below this range (N.K.C., B.B., W.F., and D.Z.), but were included because poor performance on this task also reflects poor control over semantic knowledge (see Jefferies & Lambon Ralph, 2006) – potentially increasing the likelihood of observing impairments on the tasks of interest. Lastly, to demonstrate variability in lexical-semantic processing for production and comprehension, we administered both the auditory word-picture verification task (AWPV; adapted from Martin, Lesch, & Bartha, 1999; see also Hillis, Rapp, Romani, & Caramazza, 1990; Breese & Hillis, 2004; Harvey et al., 2013) and the Philadelphia Naming Test (PNT; Dell et al., 1997). Patients demonstrated a wide-range of performance across tasks (AWPV range 7.4-98.1% correct; PNT range 44.6-97.7% correct).⁵ We excluded three patients from all naming analyses reported below (W.F., H.A., and D.Z.) because they showed marked impairments in naming single pictures (i.e., unable to perform the PNT).

2.2 Behavioral methods

2.2.1 Materials

⁴ For one patient (C.V.), scores were not available for the visual lexical decision task (adapted from Martin & Breedin, 1992), and they scored below the cut-off (69.7%) for the auditory lexical decision task (Martin & Breedin, 1992). However, this patient scored with 84.2% accuracy on the visual lexical decision task taken from the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA, subtest 25) (Kay, Lesser, & Coltheart, 1992), which is close to three SDs of control mean performance (mean: 96% correct; SD: 3.5% correct; 3SDs = 85.5% correct) reported in Nickels and Cole-Virtue (2004).

⁵ PNT range performance does not include three patients (W.F., H.A., and D.Z.) who were unable to complete the task.

Stimuli were 72 line drawings of familiar objects taken from Snodgrass and Vanderwart (1980). There were 12 semantic categories with six exemplars each (see Appendix A). In the related condition, same category exemplars appeared together in a set (e.g., animals: TIGER, MONKEY, PANDA, RABBIT, ZEBRA, ELEPHANT) to form 12 sets of semantically related items, whereas the unrelated condition consisted of 6-item sets comprising of semantically unrelated exemplars drawn from the different semantic categories (e.g., TIGER, HAND, BANANA, SOCK, BICYCLE, SPIDER) to form 12 sets of unrelated items (see Schnur et al., 2006). Picture names had a mean (and range) of 1.86 (1-4) syllables and 35.49 (1-431) lexical frequency counts (per million), as determined by an online database (http://websites.psychology.uwa.edu.au/school/MRCDatabase/uwa_mrc.htm; see also Wilson, 1988).

Each picture appeared an equal number of times in the related and unrelated sets. Within each context condition, the 6-item sets of pictures repeated four times (cycles) in a different pseudorandom order with the constraint that no two target items appeared consecutively, forming a block of 24 trials. There were 12 semantically related and unrelated blocks of 24 trials each for a total of 576 trials. The order of related and unrelated blocks was pseudorandom with the criterion that no more than two context conditions appeared consecutively. Each participant saw the same pictures in the blocked-cyclic naming and word-picture matching tasks, which combined constitutes a total of 1152 trials.

2.2.2 Procedure

Participants completed blocked-cyclic naming and word-picture matching in different sessions and always in this order. Participants took anywhere between two and four sessions to complete both tasks, as some participants required multiple sessions to complete the blocked-

cyclic naming task. We used errors as the dependent variable given that some subjects produced more than 15% error in blocked-cyclic naming ($n = 6$) and word-picture matching ($n = 8$), precluding an analysis of response times (cf. Schnur et al., 2006).

Blocked-cyclic naming. Before starting the experiment, each participant was familiarized with the picture stimuli and their names in a learning session. Subjects saw each of the 72 pictures once in a random order, and named them at a self-paced rate. The experimenter provided corrective feedback when necessary. Immediately following the learning session, the experiment began with the instructions to name each picture as quickly and accurately as possible. Participants pressed a button to begin the first block of trials, and a single picture appeared centrally on the screen. The picture remained on the screen for 10 seconds (s) or until the subject made a response. Then a fixation cross “+” appeared on the screen for 1 s, and the next trial began. In between each block of trials, the words “Get Ready...” appeared on the screen, giving subjects a brief rest before they pressed a key to start the next block. The first complete response made before the response deadline was scored as either correct or incorrect.

Blocked-cyclic word-picture matching. The experimental manipulations were identical to the blocked-cyclic naming task with the following exceptions. Participants did not complete a learning session prior to starting the experiment, as they were familiarized with the stimuli in the previous blocked-cyclic naming session(s). At the start of each trial, a target word (written and spoken) and 6-picture array appeared simultaneously. Written target words appeared at the top center of the screen in Times New Roman 18 point font size, and audio presentations of target words were presented through a headset. Below the visually presented word, the 6-item block sets appeared in a picture array comprised of two rows of three pictures. In each row, pictures were spaced at a distance of 9 centimeters (cm) from the center of each other, and a digit (1-6)

appeared underneath each picture in Times New Roman 12 point font size. Participants indicated the picture corresponding to the target word by pressing the keypad number (1-6) associated with the picture. Participants were free to choose the hand with which they responded (as some patients had dominant hand paresis). Numbers on the keypad were arranged in a way analogous to the presentation of the pictures on the screen. The visually presented word and picture array remained on the screen for 10 s or until the subject made a response.

2.2.3 Apparatus

Stimuli were presented using DMDX software (Forster & Forster, 2003). In blocked-cyclic naming, pictures appeared one-at-a-time, and a microphone headset triggered a voice key to record verbal responses and advance to the next trial. Two of the participants (C.V. and D.G.) made frequent false starts, and the voice trigger could not be used. For these patients, an experimenter pressed a key immediately following their first complete response made before the response deadline. If the subject did not respond within the deadline, the software automatically advanced to the next trial. An experimenter (D.Y.H.) and research assistant transcribed naming errors. In the blocked-cyclic word-picture matching task, the microphone headset presented auditory recordings of the target word stimuli, while written word target stimuli simultaneously appeared on the computer screen above a 6-item picture array, where one of the pictures corresponded to the target word. The DMDX software recorded participants' responses (i.e., button press indicating picture that corresponds to the target word), and following a response or at the end of the response deadline, the software advanced to the next trial.

2.2.4 Behavioral statistical analyses

At the group level, we performed within-subject (F_1) and within-item (F_2) repeated measures analyses of variance (ANOVA) using errors as the dependent variable. Fixed factors

included Task (Naming, Word-picture Matching), Condition (Related, Unrelated), and Cycle (1-4). We refer to the main effect of Condition (Related vs. Unrelated) as the *relatedness effect*, and a linear contrast reflecting the interaction between Condition (Related vs. Unrelated) and Cycle (1-4) as the *increasing relatedness effect*. Significant interactions were further tested for simple effects. Because three subjects were significantly impaired in naming (W.F., H.A., and D.Z.) we excluded them from this group level analysis. In order to determine the magnitude of individual participants' *relatedness* and *increasing relatedness effects* in blocked-cyclic naming and word-picture matching, we analyzed individual error rates across all 15 subjects separately for each task, using the same fixed factors as in the group analysis (excluding Task), including items as the random factor (following Biegler et al., 2008; Schnur et al., 2009). For each task, we obtained individual *t*-values for the main effect of condition (i.e., *relatedness effect*) and the linear contrast of the condition by cycle interaction (i.e., *increasing relatedness effect*). Accordingly, a larger and positive *t*-value indicated exaggerated *relatedness* and *increasing relatedness effects*, whereas a smaller *t*-value indicated weaker effects.

2.3 Neuroimaging methods

2.3.1 Image acquisition

Structural and diffusion-weighted images were collected on a 3 Tesla Philips Intera MRI scanner in a single session. We acquired two high-resolution T1-weighted structural images (TR/TE = 8.4/3.9 ms; FA = 8 degrees; matrix size = 256 x 256; FOV = 240 mm; slice thickness = 1.0 mm thick sagittal slices) and a 32-direction diffusion imaging sequence (high angular resolution, gradient overplus = on, TR/TE = 8500/67 ms; FA = 90 degrees; matrix size 128 x 128; FOV = 224 mm; 2mm thick axial slices, max. *b*-value of 800s/mm²) from each participant.

2.3.2 Lesion segmentation and template warping

The same experimenter segmented lesions manually on 2mm axial plane T1-weighted structural images (following Harvey et al., 2013; Schnur et al., 2009). Lesion masks and structural scans were warped and registered to an intermediate template using a symmetric diffeomorphic registration algorithm (Avants, Schoenemann, & Gee, 2006; see also <http://www.picssl.upenn.edu/ANTS/>). Scans were then mapped from the intermediate template to the 'N27 Colin' normalized template in MNI space (Holmes et al., 1998), and resampled to 1 mm axial resolution using AFNI's 3dresample (Cox, 1996). Total lesion volume and percent damaged to specific regions of interest (ROIs) was calculated in Automated Anatomical Labeling (AAL) space (Tzourio-Mazoyer et al., 2002) using VoxBo (<http://www.voxbo.org>).

2.3.3 VLSM analyses

Only voxels lesioned in at least three individuals were included in the statistical analyses (following Geva et al., 2011; see also Pazzaglia, Pizzamiglio, Pes, & Aglioti, 2008). At each voxel, a *t*-test comparing the behavioral scores for patients with and without lesions was conducted using the Nonparametric Mapping (NPM) tool in MRICron software package (Rorden, Karnath, & Bonilha, 2007), yielding a *t*-map of voxels that when damaged significantly relate to worse behavioral performance. To control for the false discovery rate (Genovese, Lazar, & Nichols, 2002), the *t*-map was thresholded at $q = 0.05$, where q reflects the probability of falsely identifying a positive relationship between lesion status and behavior among voxels exceeding the critical threshold. This threshold was used to determine significance in the VLSM results reported below. We also applied a cluster size threshold of 10 voxels following Magnúsdóttir et al. (2013).

2.3.4 DTI preprocessing

Processing of structural images and alignment of diffusion-weighted images were performed with AFNI (Cox, 1996). The T1-weighted images were aligned and averaged, and the skull was removed from the averaged T1-weighted images. AFNI's brain extraction algorithm was used to remove the skull from neuroimages with small lesions, but neuroimages with large lesions were skull-stripped by hand using MRICron (Rorden et al., 2007). Diffusion-weighted image volumes were then aligned to the individual's skull-stripped anatomical averaged T1-weighted MR image, and the gradient orientation vectors were rotated based on the individual angular motion parameters (Leemans & Jones, 2009). Diffusion tensor computations were carried out in native imaging space to preserve the reliability of calculated fiber tracts (Ellmore et al., 2010; Harvey et al., 2013).

2.3.5 DTI analysis

Pathways were delineated in DTI Query v1.1 (Akers, Sherbondy, Mackenzie, Dougherty, & Wandell, 2004; Sherbondy, Akers, Mackenzie, Dougherty, & Wandell, 2005) using deterministic tractography methods (following Ellmore et al., 2010; Harvey et al., 2013). A "seed" region, consisting of one or more volumes of interest (VOI), was placed at known anatomical terminations of fiber tracts (Mori, Crain, Chacko, & van Zijl, 1999; Catani, Howard, Pajevic, & Jones, 2002). Dissections of the inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UF) were determined using a 2-VOI approach. Following Harvey et al. (2013), the posterior terminations of the IFOF and ILF were defined in the same VOI located in the occipital lobe; however, the white matter projections that terminate at the frontal branches of the external/extreme capsule defined the anterior termination of the IFOF, and those that terminate in the anterior temporal lobe (ATL) defined the anterior terminations of the ILF. The UF was defined within the same frontal VOI as the IFOF, and the

same ATL VOI as the ILF (Catani & Thiebaut de Schotten, 2008). Only tracts with projections reaching their known anatomical terminations were included in the correlation analyses (following Agosta et al., 2010; see also Harvey et al., 2013), as tracts terminating early did not meet our criteria of connecting gray matter regions hypothesized to support language processes. Thus, the IFOF integrity values were not included for three patients (B.B., H.A., and D.Z.) and the UF integrity values were not included for another patient (D.G.). Extensive damage to the white matter in the left superior temporal and parietal lobes precluded investigations of the arcuate and superior longitudinal fasciculi, as only two of the patients (E.V. and Q.O.) had complete tracts. The same experimenter (D.Y.H.) delineated each pathway of interest for both the aphasic and control groups.

White matter pathway structural integrity was calculated using the fractional anisotropy (FA) value as a dependent measure. The FA value reflects the magnitude of water diffusion along white matter fibers relative to the diffusion of water across the fibers. This value ranges from zero to one, where FA values closer to one correspond to higher pathway integrity (Beaulieu, 2000). FA values are shown to correlate with different cognitive functions (reviewed in Chanraud, Zahr, Sullivan, & Pfefferbaum, 2010), and relate to changes in white matter that result from stroke (Ciccarelli, Catani, Johansen-Berg, Clark, & Thompson, 2008). Patients' mean (and range) FA values for the IFOF was .42 (.31-.50), ILF .38 (.30-.50), and UF .36 (.24-.43). Statistical comparisons between the FA values of patients and those of age- and education-matched controls established that the patient group has reduced white matter structural integrity for the three pathways of interest (IFOF: $t(18) = 3.74, p = .001$; ILF: $t(21) = 4.73, p < .001$; UF: $t(20) = 2.34, p = .03$).

3 Results

3.1 Behavioral

3.1.2 Group analysis

Table 3 displays mean error rates separated by Task (Naming and Word-picture Matching), Condition (Related and Unrelated), and Cycle (1-4) for the 12 patients who completed both tasks. The average error rate was 10% with a range of 1 to 27% across participants. Significant results ($p < .05$) with regards to *relatedness* and *increasing relatedness effects* are discussed below. See Table 4 for a complete summary of F_1 and F_2 statistics obtained in the group analysis.

Overall, participants made more errors in the Related (12.2%) vs. Unrelated (7.4%) conditions, where the *relatedness effect* was larger in the word-picture matching compared to the naming task (7.7% vs. 1.9%, respectively) (see *Individual Analyses* section and Appendix B). We observed a significant *increasing relatedness effect* demonstrating that semantic interference increased linearly across cycles (2.3, 3.6, 6.5, and 6.8%). However, this change was different between tasks (the 3-way interaction between Condition, Cycle, and Task was significant), where the *increasing relatedness effect* was significant in naming (Cycles 1-4: -3.2, -.3, 4.6, and 6.6%) but not word-picture matching (Cycles 1-4: 7.8, 7.5, 8.4, and 6.9%).⁶ The pattern of significant *relatedness* but not *increasing relatedness effects* in comprehension at the group-level did not change with the inclusion of three patients only able to perform blocked-cyclic word-

⁶It is currently a subject of debate as to whether semantic interference in naming increases across cycles (e.g., Belke, 2013; Belke & Stielow, 2013) or if the increase reflects short-term conceptual facilitation in the first cycle which is later counteracted by long-lasting interference effects across remaining cycles (Damian & Als, 2005; Navarrete, Del Prato, & Mahon, 2012; see also Wheeldon & Monsell, 1994; cf. Oppenheim et al., 2010). Analyses at the group-level in naming revealed a marginally significant first cycle facilitation effect (Related < Unrelated) ($t_1(11) = -2.34$, $p = .04$; $t_2(71) = -1.25$, $p = .22$). Critically, excluding the first cycle from the group-level analyses did not change the pattern of results. Even across cycles 2-4, we observed a significant *increasing relatedness effect* ($F_1(1, 11) = 9.02$, $p = .01$; $F_2(1, 71) = 13.17$, $p = .001$), indicating that increases in semantic interference across cycles in naming are not driven by a first cycle facilitation effect. This also suggests that *increasing relatedness effects* in naming vs. word-picture matching cannot be explained by differences in conceptual priming in the first cycle.

picture matching: The *relatedness effect* remained significant (Related: 4.7% vs. Unrelated .4%; $F_1(1, 14) = 16.78, p = .001$; $F_2(1, 71) = 87.97, p < .001$) and the *increasing relatedness effect* remained non-significant ($F_1(3, 42) = .15, p = .93$; $F_2(3, 213) = .21, p = .89$).

3.1.3 Individual analyses

Figure 1 displays participants' individual *t*-values for the *relatedness* (Figure 2a) and *increasing relatedness effects* (Figure 2b) in naming and word-picture matching, and notes whether these individual effects were significant. Appendix B shows individual mean errors rates for Task (Naming, Word-picture Matching), Condition (Related, Unrelated), and Cycle (1-4), and individual raw estimates for *relatedness* and *increasing relatedness effects* as calculated by error rate differences for the related vs. unrelated conditions (i.e., a *relatedness effect*) and the slope of these differences across cycles (i.e., an *increasing relatedness effect*). Individual *relatedness effects* in naming and word-picture matching varied considerably across patients. However, *increasing relatedness effects* were present at variable magnitudes in naming, but only one patient (D.Z.) exhibited a statistically significant *increasing relatedness effect* in word-picture matching.

3.2 Lesion and behavior correlations

3.2.1 VLSM results

Voxels lesioned in at least three of the 12 participants who performed the naming task consisted of 300841 voxels, or 30% of the 738535 left hemisphere voxels included in the AAL atlas (Tzourio-Mazoyer et al., 2002). In the VLSM analysis of semantic interference in comprehension ($n = 15$), voxels damaged in at least three participants consisted of 282370 voxels, or 38% of left hemisphere voxels. As shown in Figure 3, maximal lesion overlap at a given voxel was 12 patients. Power to detect an association between voxel status (lesion or no

lesion) and behavioral measures is greatest when lesion overlap in a particular voxel occurs in at least half of the patients (here, $n = 6$ in naming and $n = 7$ in word-picture matching; see Kimberg et al., 2007). Thus, regions with the greatest relative power to detect brain-behavior relationships in naming and word-picture matching included the middle and superior temporal gyri, the insula, and the precentral gyrus. In addition, word-picture matching analyses had good relative power in the LIFG (pars triangularis/opercularis).

To identify the voxels that when damaged were associated with exaggerated semantic interference effects in either blocked-cyclic naming or word-picture matching, we submitted individual t -values for patients' *relatedness* and *increasing relatedness effects* into separate VLSM analyses for naming and word-picture matching.

In blocked-cyclic naming we found a significant correlation between lesion status and naming *relatedness effects* (i.e., t -values for the comparison that exceeded the critical t -value: 3.07) in the posterior half of the left middle temporal gyrus (MTG) in a region corresponding to Brodmann area (BA) 21 (MNI coordinates: -52, -40, -5). There was also a smaller significant cluster in the MTG located more anterior and medial to the larger significant cluster (MNI coordinates: -49, -21, -8). Significant voxels are displayed in red in Figure 4.

Conversely, as displayed in blue in Figure 4, *relatedness effects* in blocked-cyclic word-picture matching significantly correlated with damage to two clusters of voxels located in the anterior portion of the temporal lobe (BA 20): t -values obtained in an anterior region of the MTG (MNI coordinates: -54, -16, -16 and -59, -35, -12) exceeded the critical t -value ($t = 3.74$). Other clusters significantly associated with word-picture matching *relatedness effect* magnitudes included two additional clusters located in the inferior temporal gyrus (ITG; BA 37), one cluster located in the precentral gyrus (BA 6), and one cluster in the middle occipital gyrus (BA 19). See

Table 5 for the list of regions and MNI coordinates for which we found significant relationships between lesion status and *relatedness effect* magnitudes.

Increasing relatedness effects, whether in naming or in word-picture matching, did not significantly correlate with lesion status in the VLSM – either across the 12 patients who performed both tasks or the 15 patients who performed the word-picture matching task only.

3.2.2 Region of interest (ROI)-based gray matter damage results

We conducted ROI based analyses to confirm the VLSM results while also controlling for total lesion volume (following Schwartz et al., 2009). Accordingly, we first divided the anterior and posterior temporal lobe in half (defined at the MNI coordinate: $y = 22$, cf. Schwartz et al., 2009), and then conducted four partial correlation analyses correlating percent damage to the anterior and posterior temporal lobe with *relatedness effect* magnitudes in each task while including total lesion volume as a covariate. In the blocked-cyclic naming task, percent damage to the posterior half of the temporal lobe significantly correlated with individual naming *relatedness effect t*-values (partial $r = .69$, $p = .01$; see Figure 5a), but not in word-picture matching (partial $r = .19$, $p = .51$). Likewise, percent damage to the anterior half of the temporal lobe significantly correlated with individual word-picture matching *relatedness effect t*-values (partial $r = .62$, $p = .02$; see Figure 5b), but not in naming (partial $r = .53$, $p = .09$). Thus, the ROI-based findings are consistent with those revealed by the VLSM analyses, and further demonstrate that greater lesion volume did not account for the pattern of the results.

3.2.3 Group comparisons based on LIFG damage

That the VLSM did not identify the LIFG as associated with *increasing relatedness effects* in the blocked-cyclic tasks is inconsistent with previous findings (Campanella et al., 2013; Gardner et al., 2012; Jefferies et al., 2007; Schnur et al., 2009). However, only nine patients in

our sample had lesions encompassing the LIFG (see Figure 3), and of those nine, six were able to perform the naming task. Of the patients who performed the naming task, few had damage to the same voxels within the LIFG. This suggests that in our patient sample we had relatively low power to detect an association between lesion status and naming performance at the voxelwise level in the LIFG, potentially resulting in a type II error. Thus, to examine the hypothesized role of the LIFG in resolving semantic interference arising in language production (e.g., Pisoni, Papagno, & Cattaneo, 2012; Schnur et al., 2009) and comprehension (e.g., Gardner et al., 2012; Jefferies et al., 2007), we split patients into two subgroups: those with and those without LIFG lesions.

We performed univariate ANOVAs with four different dependent variables (*t*-values representing individual *relatedness* and *increasing relatedness effects* for both naming and word-picture matching), using group (0% LIFG damage vs. > 0% LIFG damage) as the independent variable, and total lesion volume as a covariate. As shown in Figure 6, in blocked-cyclic naming patients with lesions encompassing the LIFG ($n = 6$) exhibited marginally larger *increasing relatedness effects* (mean *t*-value = 2.28) compared to those without LIFG damage (mean *t*-value = .55; $F(1, 9) = 4.55, p = .06$). Overall mean *relatedness effect* magnitudes in naming did not differ for those with and without LIFG damage (mean *t*-values = .64 vs. .25, respectively; $F(1, 9) = .01, p = .92$). Further, in blocked-cyclic word-picture matching, the magnitude of *relatedness effects* did not differ for those with LIFG damage ($n = 9$) vs. no damage ($n = 6$; mean *t*-values = 4.20 vs. 1.55, respectively; $F(1, 12) = 2.63, p = .13$), which was also true for *increasing relatedness effects* (mean *t*-values = -.31 vs. .06, respectively; $F(1, 12) = .60, p = .45$). Together, these findings suggest that LIFG damage results in the inability to recruit a cognitive control mechanism that serves to resolve interference by aiding in the selection of a target from amongst

semantically related competing lexical representations during production. However, that LIFG damage did not relate to measures of semantic interference (i.e., *relatedness* and *increasing relatedness effects*) in comprehension demonstrates that disrupting the selection mechanism required to resolve interference in naming (i.e., cognitive control underpinned by the LIFG) does not differentially affect performance in word-picture matching (cf. Jefferies et al., 2007; Gardner et al., 2012).

3.3 DTI and behavior correlations

We investigated whether the integrity of white matter pathways interconnecting frontal and temporal lobe regions related to the behavioral semantic interference measures. Partial correlations controlling for total lesion volume were performed to assess the relationship between FA values for the three pathways of interest (IFOF, UF, and ILF) and *relatedness* and *increasing relatedness effects* in the blocked-cyclic naming and word-picture matching tasks. As illustrated in Figure 7a, integrity of the IFOF significantly correlated with the *relatedness effect* in blocked-cyclic naming (partial $r = -.67$, $p = .03$), but not comprehension (partial $r = -.46$, $p = .16$). However, the UF FA values did not predict *relatedness effects* in either task (partial r 's $-.11$ – $-.25$, p 's $> .48$). Lastly, the ILF FA values correlated with the *relatedness effect* in blocked-cyclic word-picture matching (partial $r = -.60$, $p = .02$; see Figure 7b) but not blocked-cyclic naming (partial $r = -.54$, $p = .09$). The FA values of these three pathways did not predict *increasing relatedness effect* magnitudes in either task (partial r 's $-.39$ – $.14$, p 's $> .23$).

3.4 Summary of results & discussion

We found that the cognitive and neural mechanisms underpinning semantic interference in production and comprehension differ. First, the behavioral evidence demonstrated that although both language production and comprehension performance exhibited a *relatedness*

effect, only performance in language production revealed an *increasing relatedness effect*. While it is not entirely clear why the *increasing relatedness effect* in word-picture matching differs from that observed in naming, this difference suggests that either separate mechanisms are responsible for resolving interference in the two tasks (Biegler et al., 2008) or the same mechanism is involved but to different degrees (Jefferies et al., 2007). Second, the magnitude of individual *relatedness effects* in naming and word-picture matching varied, where critically, damage to separable temporal lobe regions accounted for the variation. While lesions to a posterior portion of the MTG correlated with *relatedness effect* magnitudes in blocked-cyclic naming, lesions to an anterior portion of the MTG correlated with *relatedness effect* magnitudes in blocked-cyclic word-picture matching, providing evidence for distinct loci of interference across language modalities. Although *increasing relatedness effect* magnitudes did not significantly relate to lesion status as identified in the VLSM analyses, ROI-based comparisons revealed that those with damage to the LIFG (compared to those without) exhibited marginally larger *increasing relatedness effects* in blocked-cyclic naming, but not word-picture matching consistent with previous evidence that the LIFG resolves competition in naming arising in posterior temporal lobe lexical processing regions (Pisoni et al., 2012; Schnur et al., 2009).

The correlation between the structural integrity of the IFOF connecting the LIFG with the posterior temporal cortex and the *relatedness effect* in naming is consistent with evidence elsewhere demonstrating that the regions the IFOF connects are involved in blocked-cyclic naming (Pisoni et al., 2012; Schnur et al., 2009) and that this pathway is critical in picture naming in general (Duffau, Gatignol, Mandonnet, Capelle, & Taillandier, 2008; Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007). However, that IFOF integrity correlated with individual *relatedness effects* and not

increasing relatedness effects in naming is prima facie in conflict with the argument that this pathway serves to communicate an LIFG-mediated selection mechanism to resolve lexical competition as it increases in the temporal lobe.

We propose that the distribution of lesion locations in our patient sample and the dynamic interaction between activations in the temporal lobe and control processing in the frontal lobe (see also Mirman, Yee, Blumstein, & Magnuson, 2011) account for why we did not find a correlation between IFOF FA values and *increasing relatedness effects* in naming. Only half of the patients who performed the naming task ($n = 6$) had LIFG damage, yet most patients ($n = 10$) had some posterior temporal lobe damage creating varying degrees of increased competition due to noisy lexical activation regardless of whether or not the LIFG was intact to resolve this interference. Thus, the finding that IFOF FA values correlated with *relatedness effects* (the lower the IFOF FA value the greater the *relatedness effect* magnitude) suggests that reduced IFOF structural integrity adds noise to the LIFG's ability to resolve competition arising at the lexical level. This generates the prediction that *increasing relatedness effects* should only relate to IFOF FA values in those patients with an intact LIFG, as patients with LIFG damage exhibited *increasing relatedness effects* whether or not the IFOF had enough structural integrity to communicate with posterior regions. We confirmed this prediction in the six patients with an intact LIFG, where increased IFOF FA values significantly and negatively correlated with *increasing relatedness effects* in naming, after partialing out percent damage to the temporal lobe (partial $r = -.94$, $p = .02$). Thus, the IFOF results provide novel evidence indicating that increasing semantic interference across cycles (i.e., an *increasing relatedness effect*) in blocked-cyclic naming arises either from damage to the cognitive control processes computed in the

LIFG or from an inability to communicate those processes to the posterior temporal lobe as a result of decreased IFOF structural integrity.

For blocked-cyclic word-picture matching, integrity of the white matter ILF tract predicted performance and not the UF.⁷ In previous work with nine of the 15 patients included in this study, we found that the degree to which the LIFG and ATL are functionally and structurally connected via the UF predicted patients' performance on two spoken word comprehension tasks requiring semantic control (Harvey et al., 2013; also see Duda et al., 2010). There are several possible explanations for this discrepancy, which for different reasons suggest that the control requirements in naming and comprehension are different. We discuss this further in the general discussion.

That decreased ILF integrity correlated with *relatedness effect magnitudes* in comprehension may be because neural damage results in noisy access to semantics from lexical representations. Structurally, the ILF connects the inferior posterior temporal lobe (a region thought to serve as an "entry point" affording access to lexical and semantic representations, e.g., Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Démonet, Thierry, & Cardebat, 2005; see also Bedny, McGill, & Thompson-Schill, 2008), with the ATL (a region thought to support semantic processing; Patterson et al., 2007; Mummery et al., 2000). Combined functional gray matter and structural white matter neuroimaging experiments of healthy subjects reveal that this pathway mediates mapping lexical with semantic representations during comprehension (Saur et al., 2008, 2010; Wong, Chandrasekaran, Garibaldi, & Wong, 2011). Campanella et al. (2009)

⁷ We also performed a post-hoc analysis similar to that conducted with the IFOF FA values of patients without LIFG damage to determine whether *increasing relatedness effect* magnitudes in word-picture matching related to UF FA values after controlling for temporal lobe damage, and found no relationship between the pathway and performance (partial $r = -.41$, $p = .50$).

found that patients who underwent left temporal lobe resection due to high grade gliomas exhibited exaggerated *relatedness effects* in the absence of *increasing relatedness effects* on a variant of the blocked-cyclic word-picture matching paradigm, where some of the underlying temporal lobe white matter, presumably the ILF, sustained damage during the surgery. Our results are consistent with this previous evidence suggesting that exaggerated *relatedness effects* in comprehension arise due to damage to left temporal regions and underlying white matter connections which subserve access to stored semantic knowledge from lexical representations.

In sum, the DTI results confirm that connectivity between the LIFG and left posterior temporal lobe regions via the IFOF is critical for resolving competition at a lexical level in naming (see Figure 4). However, the UF, which connects the LIFG with the anterior temporal lobe, did not relate to semantic interference in comprehension. Instead, connectivity between posterior and anterior temporal lobe regions via the ILF correlated with word-picture matching performance, suggesting that this pathway is critical for accessing semantics from a word in order to distinguish between semantically related representations.

It is worth noting that the relatively modest sample size in this study may present limitations – namely, the lack of significant VLSM findings for *increasing relatedness effects* and trending correlations between temporal lobe gray and white matter damage with behavioral performance in naming. However, we adopted several approaches to mitigate limitations due to sample size. First, we included several conservative measures in the lesion-behavior analyses to control for type I error (false discovery rate, excluding voxels with < 3 patient overlap, and cluster thresholding; see Rorden et al., 2007) and type II error (ROI analyses and subgroup behavioral comparisons of those with and without LIFG damage). Power in a VLSM study does not necessarily and/or exclusively depend on the number of subjects in the study, but instead

depends on both the variability of lesion location and behavioral performance (see Kimberg et al., 2007; Wu, Waller, & Chatterjee, 2007) – and in this patient sample, we demonstrate variability in both. Second, while trending temporal lobe (gray and white matter) effects in naming could become significant with the addition of more subjects, these effects if significant would be consistent with the conclusions we draw from the results. Specifically, because the *relatedness effect* in blocked-cyclic naming is hypothesized to be a semantically driven lexical process (e.g., Damian et al., 2001; Howard et al., 2006; Belke, 2013), damage to the anterior half of the temporal lobe and underlying white matter may also predict exaggerated *relatedness effects* in naming. Thus, this effect, if significant would not detract from the main findings presented here demonstrating that a critical difference between semantic interference in production and comprehension lies in where the competition takes its effect: during access to lexical vs. semantic representations, respectively.

4 General Discussion

We tested subjects with left hemisphere stroke using structural magnetic resonance and diffusion tensor imaging to investigate first, whether semantic interference in language production and comprehension arises at different brain loci as suggested by cognitive models (e.g., Belke, 2013; Damian et al., 2001; Howard et al., 2006; Levelt et al., 1999; Oppenheim et al., 2010; Roelofs, 1992, 2003; Gotts & Plaut, 2002; Warrington & Cipolotti, 1996) and second, whether interference in both modalities share a common neural mechanism that acts to resolve competition from co-activated same category representations (Badre, Poldrack, Paré-Blagoev, Insler, & Wagner, 2005; Badre & Wagner, 2007; Jefferies & Lambon Ralph, 2006; Jefferies et al., 2007; Novick, Trueswell, & Thompson-Schill, 2005, 2010; cf. Biegler et al., 2008; Hamilton & Martin, 2005; McCarthy & Kartsounis, 2000; Schnur et al., 2006, 2009; Wilshire &

McCarthy, 2002). Using the same blocked-cyclic paradigm for production and comprehension across subjects, we found that damage to the posterior middle temporal gyrus (MTG) created exaggerated *relatedness effects* in naming whereas damage to the anterior MTG created exaggerated *relatedness effects* in word-picture matching. However, we did not find a common neural mechanism which resolves competition in both production and comprehension, as only naming performance exhibited *increasing relatedness effects* which were marginally related to LIFG damage and significantly related to reduced structural integrity of the IFOF, a white matter pathway connecting the LIFG with the posterior temporal lobe. Instead, *relatedness effects* in word-picture matching correlated with the structural integrity of the ILF, a pathway connecting the inferior posterior with anterior temporal cortex. These results suggest a neuroanatomical language network for production and comprehension where posterior MTG subserves access to lexical representations that, when under conditions inducing competition, recruits the LIFG via the IFOF for competition resolution during production. The word-picture matching results suggest that the anterior MTG subserves mapping an input form (either phonological or orthographic) to its corresponding lexical representation and set of distinguishing semantic features via the ILF that, when under conditions maximizing semantic feature overlap creates difficult semantic discrimination – a process not requiring competition resolution via the LIFG. Critically, our results go beyond previous studies by using similar paradigms in a larger group of the same brain-damaged subjects to demonstrate which regions create and resolve semantic interference across language modalities. Thus, our results are an advance for cognitive models of language production and comprehension demonstrating that distinct neural regions within the left fronto-temporal language network govern retrieving words and meanings for production and comprehension.

4.1 Locus of semantic interference

Models of lexical access in language production assume that semantic interference in naming arises when accessing lexical representations from meanings (Damian et al., 2001; Howard et al., 2006; Levelt et al., 1999; Oppenheim et al., 2010; Roelofs, 1992, 2003), whereas theories of semantic interference in language comprehension assume that the effect arises when accessing semantic representations of a given word (Campanella & Shallice, 2011; Forde & Humphreys, 1997, 2007; Gotts & Plaut, 2002; Warrington & Cipolotti, 1996; Warrington & McCarthy, 1983, 1987). Our findings demonstrating separate neural loci of semantic interference in language production and comprehension provide support for this hypothesis. Converging evidence is also seen in other paradigms which elicit semantic interference. For example, when naming a picture while ignoring a superimposed semantically related word (i.e., picture-word interference paradigm) or after having named a semantically related word prompted by its definition (i.e., competitor priming task, Wheeldon & Monsell, 1994), healthy subjects show BOLD activation of the mid MTG (de Zubicaray, Wilson, McMahon, & Muthiah, 2001; see also de Zubicaray, McMahon, & Howard, 2013) to posterior MTG (de Zubicaray, McMahon, Eastburn, & Pringle, 2006). These regions correspond to the mid to posterior MTG locus we found, which is also close, though slightly inferior, to the region corresponding to the *relatedness effect* in blocked-cyclic naming using fMRI in healthy subjects (Schnur et al., 2009). Transcranial direct current stimulation (tDCS) evidence in healthy subjects also converges with this picture as tDCS to the posterior temporal lobe resulted in exaggerated *relatedness effects* in blocked-cyclic naming (Pisoni et al., 2012) presumably because stimulating this region heightened the activation levels of lexical representations. Further, our mid MTG region corresponds to a region identified by Schwartz et al. (2009) as critically involved in semantically

driven word retrieval, suggesting that MTG regions extending from the more anterior middle MTG to posterior MTG play a crucial role in mapping fine-grained semantic information with their corresponding lexical representations (see Walker et al., 2011 and Indefrey, 2011 for reviews). Our findings extend previous VLSM studies (Schwartz et al., 2009; Walker et al., 2011; see also Baldo, Arévalo, Patterson, & Dronkers, 2013) by demonstrating when naming under conditions inducing competition, both the mid and posterior MTG are necessary for successful lexical access.

In contrast, we found that damage to a left anterior temporal lobe region, distinct from the more posterior region associated with interference in naming, created exaggerated *relatedness effects* in word-picture matching. This is consistent with the anterior MTG BOLD activation found in healthy subjects for tasks tapping associative semantic relationship judgments (Vandenberghe, Price, Wise, Josephs, & Frackowiak, 1996) and for the comprehension of sentences ending in semantically anomalous nouns (e.g., I ordered a ham and cheese scissors) as compared to those ending in semantically appropriate nouns (e.g., when you go to bed turn off the living room lights; McCarthy, Nobre, Bentin, & Spencer, 1995). Because semantic relationships – especially those incongruous with a given sentence – elicit activation in the anterior MTG, this suggests that this region processes fine-grained semantic information as accessed from a given word form (e.g., Nobre & McCarthy, 1995; Rogers et al., 2006) and lines up with a number of studies demonstrating the role of anterior portions of the temporal lobe in processing semantic information (e.g., Binney et al., 2010; Pobric, Jefferies, Lambon Ralph, 2007, 2010; Rogers et al., 2006). Together, the picture that emerges illustrates that damage to the posterior MTG creates noisy access to lexical representations while damage to the anterior MTG produces noisy access to semantic representations, resulting in increased competition from

alternative same category representations when naming and difficulty to disambiguate a target word from those semantically related to it during comprehension.

4.2 Mechanism for resolving semantic interference

Our results suggest that a cognitive control mechanism in the LIFG operates to resolve lexical competition in language production, but interference resolution via this LIFG-mediated control mechanism is not involved in the analogous word-picture matching task. We hypothesize that the mechanisms generating and resolving semantic interference in naming fundamentally differ from those in word-picture matching comprehension tasks. Naming requires self-generated responses to target pictures that compete with previously named pictures for selection due to their relatively persistent increased activations levels (Howard et al., 2006; Damian & Als, 2006, Wheeldon & Monsell, 1994) especially in later cycles, generating significantly *increasing relatedness effects* as seen here and elsewhere (Biegler et al., 2008; Schnur et al., 2006, 2009). Thus, the LIFG comes online when competition increases in naming to bias activation for selection towards the target lexical representation and against non-target competitors (de Zubicaray et al., 2006; Pisoni et al., 2012; Schnur et al., 2006, 2009; Thompson-Schill & Botvinick, 2006). In turn, LIFG damage results in seemingly unimpaired performance on the first cycle of same category naming, but as selection demands increase on later cycles, performance becomes increasingly worse when compared to the repetition of items from different semantic categories (i.e., an *increasing relatedness effect*; Schnur et al., 2006, 2009; Biegler et al., 2008).⁸

⁸ Although cognitive control extends beyond the LIFG (i.e., temporo-parietal regions; see e.g., Noonan, Jefferies, Visser, & Lambon Ralph, 2013), it is currently unclear whether these areas perform the same control role as the LIFG (retrieval vs. selection, see Badre & Wagner, 2007; Snyder, Banich, & Munakata, 2011) and/or exert control over the same representations.

These results highlight how damage to the left frontal-temporal network impacts naming performance.

In contrast, although word-picture matching induces a *relatedness effect* in magnitudes larger than that observed in naming, damage to the LIFG and white matter tracts connected to the LIFG did not amplify individual measures of semantic interference in comprehension. There are several possible explanations for why damage to a cognitive control mechanism subserved by the LIFG did not affect semantic interference in blocked-cyclic word-picture matching. First, control demands in word comprehension may be more variable, depending on the task. For example, Wilshire and McCarthy (2002) proposed that semantic interference in word picture matching is less competitive, as "...word-picture matching involves generating semantic descriptions for the target word and picture(s), and evaluating the relative 'fit' of the different pairings – a task in which alternative plans may compete less strongly for output" (p. 182), similarly described more recently where "...WPM [word-picture matching] involves more straightforward identity matching and therefore might place fewer demands on semantic control" (Noonan, Jefferies, Eshan, Garrard, & Lambon Ralph, 2013, p. 15). This account has support from previous neuropsychological evidence demonstrating that semantic interference characteristics differ for blocked-cyclic naming as compared to the word-picture matching variant of the task. Biegler et al. (2008) demonstrated that both naming and word-picture matching tasks elicited *relatedness effects* in healthy older controls and patients. However, the control group only exhibited an *increasing relatedness effect* in blocked-cyclic naming, whereas patients exhibited weak *increasing relatedness effects* in comprehension when naming could be used as a strategy (i.e., direct word-picture matching; Experiment 2), which were eliminated when naming could not be used as a strategy (i.e., associative word-picture matching; Experiment 3). Similarly, our finding

that 14/15 patients did not exhibit an *increasing relatedness effect* in the comprehension task supports this notion of decreased control demands in word-picture matching vs. naming. These findings suggest a distinction between the underlying mechanisms involved in resolving competition when accessing lexical vs. semantic representations. Naming requires the recruitment of a selection mechanism (i.e., cognitive control) to select the appropriate response from amongst competing alternatives in high-competition situations, whereas comprehension in word-picture matching does not require cognitive control because the appropriate response can be identified without competition via selection from alternative responses.

Another possibility is that previous neuropsychological findings of impaired performance across cycles in the blocked-cyclic word-picture matching task arose not because of a deficit in recruiting a cognitive control selection mechanism (i.e., LIFG damage), but instead due to another impairment, such as a refractory impairment. Although a number of studies demonstrate increasingly worse performance on cyclical comprehension tasks, these ‘refractory effects’ appear regardless of the degree of cognitive control required, i.e., whether pictures were semantically blocked or not, thus reflecting a general difficulty to identify representations across repetitions (Campanella et al., 2013; Campanella & Shallice, 2011; Forde & Humphreys, 1997; Gardner et al., 2012; Warrington & McCarthy, 1987). For instance, neuropsychological studies taken as evidence in support of refractory impairments report increasingly worse performance across repetitions of unrelated items (patient F.A.S.; McCarthy & Kartsounis, 2000) and/or collapsed across repetitions of related and unrelated items (e.g., Hamilton & Martin, 2010). Likewise, other neuropsychological evidence of increasingly worse performance on cyclical comprehension tasks only included the semantically related condition (e.g., Gardner et al., 2012; Jefferies et al., 2007). This makes it difficult to discern whether the increase in error rates across

cycles reflected impairments due to greater control demands, or would have occurred more generally for both related and unrelated conditions, thus reflecting a generalized refractory impairment characterized by abnormally prolonged activation (or inhibition) of semantic representations which renders them temporarily inaccessible for a brief period of time following their initial activation (Warrington & Cipolotti, 1996; Warrington and McCarthy, 1983; see also Gotts & Plaut, 2002).⁹ We suggest then that (cognitive control) selection and refractory impairments reflect functionally distinct disorders. Future work should test these hypotheses in order to provide further support for a distinction between selection and refractory deficits.

4.3 Conclusions

We present the first study to examine semantic interference across both language production and comprehension within the same brain-damaged individuals using lesion-symptom mapping and white matter tractography neuroimaging techniques. We demonstrate that damage to distinct gray matter temporal lobe regions associates with worse performance on semantically related compared to unrelated items in picture naming and word-picture matching tasks, providing neuroanatomical evidence to support the assumption from cognitive models that semantic interference in language production and comprehension arises at different loci in the language system. Second, we provide evidence that the LIFG via the IFOF white matter tract supports cognitive control for selection over competing representations during naming. That LIFG damage and its white matter connections with the anterior temporal lobe did not relate to

⁹Consistent with this distinction between refractory vs. (cognitive control) selection impairments, patients with refractory impairments recover from semantic interference with long response stimulus intervals (RSIs) (15s; Warrington & Cipolotti, 1996; see also Forde & Humphreys, 1995, 1997), whereas those with selection impairments are not sensitive to temporal manipulations (Biegler et al. 2008; Schnur et al., 2006; see also Hsiao, Schwartz, Schnur, & Dell, 2009). Thus, an important direction for future research will be to explore the temporal dynamics of semantic interference effects in production and comprehension in order to disentangle these potentially dissociable deficits.

comprehension performance leaves open the question of whether there are different control mechanisms which resolve semantic interference in comprehension and production or instead whether it is the same control mechanism which differs in the degree to which it is recruited across tasks, potentially because control demands in word comprehension may be more variable. Together, these findings inform models of language production and comprehension by demonstrating the components required for successful lexical and semantic access.

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References

- Agosta, F., Henry, R. G., Migliaccio, R., Neuhaus, J., Miller, B. L., Dronkers, N. F., et al. (2010). Language networks in semantic dementia. *Brain*, 133, 286-299.
- Akers, D., Sherbondy, A., Mackenzie, R., Dougherty, R., & Wandell, B. (2004). Exploration of the brain's white matter pathways with dynamic queries. *Proceedings of IEEE Visualization*, 377-384.
- Avants, B. B., Schoenemann, P. T., & Gee, J. C. (2006). Lagrangian frame diffeomorphic image registration: Morphometric comparison of human and chimpanzee cortex. *Medical Image Analysis*, 10, 397-412.
- Badre, D., Poldrack, R. A., Paré-Blagoev, E. J., Insler, R. Z., & Wagner, A. D. (2005). Dissociable controlled retrieval and generalized selection mechanisms in ventrolateral prefrontal cortex. *Neuron*, 47, 907-918.
- Badre, D., & Wagner, A. D. (2007). Left ventrolateral prefrontal cortex and the cognitive control of memory. *Neuropsychologia*, 45, 2883-2901.
- Baldo, J. V., Arévalo, A., Patterson, J. P., & Dronkers, N. F. (2013). Grey and white matter correlates of picture naming: Evidence from a voxel-based lesion analysis of the Boston Naming Test. *Cortex*, 49(3), 658-667.
- 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. *Nature Neuroscience*, 6, 448-450.
- Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system – a technical review. *NMR in Biomedicine*, 15, 435-455.
- Bedny, M., McGill, M., & Thompson-Schill, S. L. (2008). Semantic adaptation and competition during word comprehension. *Cerebral Cortex*, 18, 2574-2585.

- Belke, E. (2008). Effects of working memory load on lexical-semantic encoding in language production. *Psychonomic Bulletin and Review*, 15(2), 357-363.
- Belke, E. (2013). Long-lasting inhibitory semantic context effects on object naming are necessarily conceptually mediated: Implications for models of lexical-semantic encoding. *Journal of Memory and Language*, 69(3), 228-256.
- Belke, E., Brysbaert, M., Meyer, A. S., & Ghyselinck, M. (2005a). Age of acquisition effects in picture naming: Evidence for a lexical-semantic competition hypothesis. *Cognition*, 96, B45-B54.
- Belke, E., Meyer, A. S., & Damian, M. F. (2005b). Refractory effects in picture naming as assessed in a semantic blocking paradigm. *The Quarterly Journal of Experimental Psychology*, 58, 667-692.
- Belke, E., & Stielow, A. (2013). Cumulative and non-cumulative semantic interference in object naming: Evidence from blocked and continuous manipulations of semantic context. *The Quarterly Journal of Experimental Psychology*, 66(11), 2135-2160.
- Biegler, K. A., Crowther, J. E., & Martin, R. C. (2008). Consequences of an inhibition deficit for word production and comprehension: Evidence from the semantic blocking paradigm. *Cognitive Neuropsychology*, 25, 493-527.
- Binney, R. J., Embleton, K. V., Jefferies, E., Parker, G. J., & Ralph, M. A. L. (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. *Cerebral Cortex*, 20(11), 2728-2738.
- Bozeat, S., Lambon Ralph, M. A., Patterson, K., Garrard, P., & Hodges, J. R. (2000). Non-verbal semantic impairment in semantic dementia. *Neuropsychologia*, 38(9), 1207-1215.

- Breese, E. L., & Hillis, A. E. (2004). Auditory comprehension: Is multiple choice really good enough? *Brain and Language*, 89, 3-8.
- Campanella, F., Crescentini, C., Mussoni, A., & Skrap, M. (2013). Refractory semantic access dysphasia resulting from resection of a left frontal glioma. *Neurocase: The Neural Basis of Cognition*, 19, 27-35.
- Campanella, F., Mondani, M., Skrap, M., & Shallice, T. (2009). Semantic access dysphasia resulting from left temporal lobe tumours. *Brain*, 132, 87-102.
- Campanella, F., & Shallice, T. (2011). Refractoriness and the healthy brain: A behavioural study on semantic access. *Cognition*, 118, 417-431.
- Caramazza, A. (1997). How many levels of processing are there in lexical access? *Cognitive Neuropsychology*, 14(1), 177-208.
- Catani, M., Howard, R. J., Pajevic, S., & Jones, D. K. (2002). Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *Neuroimage*, 17, 77-94.
- Catani, M., & Mesulam, M. (2008). The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state. *Cortex*, 44(8), 953-961.
- Catani, M., & Thiebaut de Schotten, M. (2008). A diffusion tensor imaging tractography atlas for virtual in vivo dissections. *Cortex*, 44, 1105-1132.
- Chanraud, S., Zahr, N., Sullivan, E. V., & Pfefferbaum, A. (2010). MR diffusion tensor imaging: A window into white matter integrity of the working brain. *Neuropsychology Review*, 20, 209-225.
- Ciccarelli, O., Catani, M., Johansen-Berg, H., Clark, C., & Thompson, A. (2008). Diffusion-based tractography in neurological disorders: Concepts, applications, and future developments. *Lancet Neurology*, 7, 715-727.

Cloutman, L., Gottesman, R., Chaudhry, P., Davis, C., Kleinman, J. T., Pawlak, M., et al. (2009).

Where (in the brain) do semantic errors come from? *Cortex*, 45(5), 641-649.

Collins, A. M., & Loftus, E. F. (1975). A spreading-activation theory of semantic processing. *Psychological Review*, 82(6), 407-428.

Cox, R. W. (1996). AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Computational Biomedical Research*, 29, 162-173.

Crutch, S. J., & Warrington, E. K. (2005). Gradients of semantic relatedness and their contrasting explanations in refractory access and storage semantic impairments. *Cognitive Neuropsychology*, 22(7), 851-876.

Damasio, H., Tranel, D., Grabowski, T., Adolphs, R., & Damasio, A. (2004). Neural systems behind word and concept retrieval. *Cognition*, 92, 179-229.

Damian, M. F., & Als, L. C. (2005). Long-lasting semantic context effects in the spoken production of object names. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 31, 1372-1384.

Damian, M. F., & Bowers, J. S. (2003). Locus of semantic interference in picture-word interference tasks. *Psychonomic Bulletin and Review*, 10(1), 111-117.

Damian, M. F., Vigliocco, G., & Levelt, W. J. (2001). Effects of semantic context in the naming of pictures and words. *Cognition*, 81, B77-B86.

de Zubizaray, G., McMahon, K., Eastburn, M., & Pringle, A. (2006). Top-down influences on lexical selection during spoken word production: A 4T fMRI investigation of refractory effects in picture naming. *Human Brain Mapping*, 27, 864-873.

de Zubizaray, G., McMahon, K., & Howard, D. (2013). Perfusion fMRI evidence for priming of shared feature-to-lexical connections during cumulative semantic interference in spoken

- word production. *Language and Cognitive Processes*, doi:
10.1080/01690965.2013.848990.
- de Zubizaray, G. I., Rose, S. E., & McMahon, K. L. (2011). The structure and connectivity of semantic memory in the healthy older adult brain. *Neuroimage*, 54(2), 1488-1494.
- de Zubizaray, G. I., Wilson, S. J., McMahon, K. L., & Muthiah, S. (2001). The semantic interference effect in the picture-word paradigm: An event-related fMRI study employing overt responses. *Human Brain Mapping*, 14(4), 218-227.
- Dell, G. S., Schwartz, M. F., Martin, N., Saffran, E. M., & Gagnon, D. A. (1997). Lexical access in aphasic and nonaphasic speakers. *Psychological Review*, 104, 801-838.
- Démonet, J. F., Thierry, G., & Cardebat, D. (2005). Renewal of the neurophysiology of language: Functional neuroimaging. *Physiological Reviews*, 85, 49-95.
- Dronkers, N. F., Wilkins, D. P., Van Valin Jr, R. D., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition*, 92, 145-177.
- Duda, J. T., McMillan, C., Grossman, M., & Gee, J. C. (2010). Relating structural and functional connectivity to performance in a communication task. *Medical Image Computing and Computer-Assisted Intervention*, 13, 282-289.
- Duffau, H., Gatignol, P., Mandonnet, E., Capelle, L., & Taillandier, L. (2008). Intraoperative subcortical stimulation mapping of language pathways in a consecutive series of 115 patients with Grade II glioma in the left dominant hemisphere. *Journal of Neurosurgery*, 109, 461-471.

- Duffau, H., Gatignol, P., Moritz-Gasser, S., & Mandonnet, E. (2009). Is the left uncinate fasciculus essential for language? A cerebral stimulation study. *Journal of Neurology*, 256, 382-389.
- Ellmore, T. M., Beauchamp, M. S., Breier, J. I., Slater, J. D., Kalamangalam, G. P., O'Neill, T. J., et al. (2010). Temporal lobe white matter asymmetry and language laterality in epilepsy patients. *Neuroimage*, 49, 2033-2044.
- Ferrand, L., & Humphreys, G. W. (1996). Transfer of refractory states across languages in a global aphasic patient. *Cognitive Neuropsychology*, 13(8), 1163-1191.
- Forde, E., & Humphreys, G. W. (1995). Refractory semantics in global aphasia: On semantic organisation and the access-storage distinction in neuropsychology. *Memory*, 3, 265-307.
- Forde, E. M., & Humphreys, G. W. (1997). A semantic locus for refractory behaviour: Implications for access storage distinctions and the nature of semantic memory. *Cognitive Neuropsychology*, 14, 367-402.
- Forde, E. M., & Humphreys, G. W. (2007). Contrasting effects of repetition across tasks: Implications for understanding the nature of refractory behavior and models of semantic memory. *Cognitive, Affective, & Behavioral Neuroscience*, 7, 198-211.
- Forster, K. I., & Forster, J. C. (2003). DMDX: A Windows display program with millisecond accuracy. *Behavior Research Methods*, 35, 116-124.
- Gardner, H. E., Lambon Ralph, M. A., Dodds, N., Jones, T., Ehsan, S., & Jefferies, E. (2012). The differential contributions of pFC and temporo-parietal cortex to multimodal semantic control: Exploring refractory effects in semantic aphasia. *Journal of Cognitive Neuroscience*, 24, 778-793.

- Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage*, 15(4), 870-878.
- Geva, S., Jones, P. S., Crinion, J. T., Price, C. J., Baron, J. C., & Warburton, E. A. (2011). The neural correlates of inner speech defined by voxel-based lesion–symptom mapping. *Brain*, 134(10), 3071-3082.
- Gotts, S. J., & Plaut, D. C. (2002). The impact of synaptic depression following brain damage: A connectionist account of “access/refractory” and “degraded-store” semantic impairments. *Cognitive, Affective, & Behavioral Neuroscience*, 2, 187-213.
- Hamilton, A. C., & Martin, R. C. (2005). Dissociations among tasks involving inhibition: A single-case study. *Cognitive, Affective, & Behavioral Neuroscience*, 5(1), 1-13.
- 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(10), 2952-2965.
- 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, 789-801.
- Hillis, A. E., Rapp, B., Romani, C., & Caramazza, A. (1990). Selective impairment of semantics in lexical processing. *Cognitive Neuropsychology*, 7, 191-243.
- Holmes, C. J., Hoge, R., Collins, L., Woods, R., Toga, A. W., & Evans, A. C. (1998). Enhancement of MR images using registration for signal averaging, *Journal of Computer Assisted Tomography*, 22, 324-333.
- Howard, D. (1995). Lexical anomia: Or the case of the missing lexical entries. *The Quarterly Journal of Experimental Psychology*, 48(4), 999-1023.

- Howard, D., Nickels, L., Coltheart, M., & Cole-Virtue, J. (2006). Cumulative semantic inhibition in picture naming: Experimental and computational studies. *Cognition*, 100, 464-482.
- Howard, D., & Patterson, K. (1992). *Pyramids and palm trees: A test of semantic access from pictures and words*. Bury St Edmunds, UK: Thames Valley Test.
- Hsiao, E. Y., Schwartz, M. F., Schnur, T. T., & Dell, G. S. (2009). Temporal characteristics of semantic perseverations induced by blocked-cyclic picture naming. *Brain and Language*, 108, 133-144.
- Indefrey, P. (2011). The spatial and temporal signatures of word production components: a critical update. *Frontiers in Psychology*, 2, 1-16.
- Indefrey, P., & Levelt, W. J. M. (2004). The spatial and temporal signatures of word production components. *Cognition*, 92, 101-144.
- Janssen, N., Carreiras, M., & Barber, H. A. (2011). Electrophysiological effects of semantic context in picture and word naming. *Neuroimage*, 57, 1243-1250.
- Jefferies, E. (2013). The neural basis of semantic cognition: Converging evidence from neuropsychology, neuroimaging and TMS. *Cortex*, 49, 611-625.
- Jefferies, E., Baker, S. S., Doran, M., & Lambon Ralph, M. A. (2007). Refractory effects in stroke aphasia: A consequence of poor semantic control. *Neuropsychologia*, 45, 1065-1079.
- 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. (1992). *PALPA: Psycholinguistic assessments of language processing in aphasia*. Hove, England: Erlbaum.
- Kertesz, A. (1982). *Western aphasia battery*. New York: Grune & Stratton.

- Kimberg, D. Y., Coslett, H. B., & Schwartz, M. F. (2007). Power in voxel-based lesion-symptom mapping. *Journal of Cognitive Neuroscience*, 19(7), 1067-1080.
- Kroll, J. F., & Stewart, E. (1994). Category interference in translation and picture naming: Evidence for asymmetric connections between bilingual memory representations. *Journal of Memory and Language*, 33, 149-174.
- Leemans, A., & Jones, D. K. (2009). The B-matrix must be rotated when correcting for subject motion in DTI data. *Magnetic Resonance in Medicine*, 61, 1336-1349.
- Levelt, W. J. M. (1999). Models of word production. *Trends in Cognitive Sciences*, 3, 223-232.
- Levelt, W. J. M., Roelofs, A., & Meyer, A. S. (1999). A theory of lexical access in speech production. *The Behavioral and Brain Sciences*, 22, 1-75.
- Magnusdottir, S., Fillmore, P., den Ouden, D. B., Hjaltason, H., Rorden, C., Kjartansson, O., et al. (2013). Damage to left anterior temporal cortex predicts impairment of complex syntactic processing: A lesion-symptom mapping study. *Human Brain Mapping*, 34(10), 2715-2723.
- Mahon, B. Z., Costa, A., Peterson, R., Vargas, K. A., & Caramazza, A. (2007). Lexical selection is not by competition: A reinterpretation of semantic interference and facilitation effects in the picture-word interference paradigm. *Journal of Experimental Psychology: Learning, Memory, & Cognition*, 33(3), 503-535.
- Mandonnet, E., Nouet, A., Gatignol, P., Capelle, L., & Duffau, H. (2007). Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. *Brain*, 130, 623-629.
- Martin, R. C., & Breedin, S. D. (1992). Dissociations between speech perception and phonological short-term memory deficits. *Cognitive Neuropsychology*, 9(6), 509-534.

- Martin, R. C., Lesch, M. F., & Bartha, M. C. (1999). Independence of input and output phonology in word processing and short-term memory. *Journal of Memory and Language*, 41, 3-29.
- McCarthy, G., Nobre, A. C., Bentin, S., & Spencer, D. D. (1995). Language-related field potentials in the anterior-medial temporal lobe: I. Intracranial distribution and neural generators. *The Journal of Neuroscience*, 15(2), 1080-1089.
- McCarthy, R. A., & Kartsounis, L. D. (2000). Wobbly words: Refractory anomia with preserved semantics. *Neurocase*, 6(6), 487-497.
- Mirman, D., Yee, E., Blumstein, S. E., & Magnuson, J. S. (2011). Theories of spoken word recognition deficits in aphasia: Evidence from eye-tracking and computational modeling. *Brain and Language*, 117(2), 53-68.
- Mori, S., Crain, B. J., Chacko, V. P., & van Zijl, P. C. M. (1999). Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology*, 45, 265-269.
- Morton, J. (1969). Interaction of information in word recognition. *Psychological Review*, 76(2), 165-178.
- Mummery, C. J., Patterson, K., Price, C. J., Ashburner, J., Frackowiak, R. S., & Hodges, J. R. (2000). A voxel-based morphometry study of semantic dementia: Relationship between temporal lobe atrophy and semantic memory. *Annals of Neurology*, 47, 36-45.
- Navarrete, E., Del Prato, P., & Mahon, B. Z. (2012). Factors determining semantic facilitation and interference in the cyclic naming paradigm. *Frontiers in Psychology*, 3, 1-15.

- Nickels, L., & Cole-Virtue, J. (2004). Reading tasks from PALPA: How do controls perform on visual lexical decision, homophony, rhyme, and synonym judgements? *Aphasiology*, 18(2), 103-126.
- Nobre, A. C., & McCarthy, G. (1995). Language-related field potentials in the anterior-medial temporal lobe: II. Effects of word type and semantic priming. *The Journal of Neuroscience*, 15(2), 1090-1098.
- Noonan, K. A., Jefferies, E., Garrard, P., Eshan, S., & Lambon Ralph, M. A. (2013). Demonstrating the qualitative differences between semantic aphasia and semantic dementia: A novel exploration of nonverbal semantic processing. *Behavioural Neurology*, 26(1), 7-20.
- Noonan, K. A., Jefferies, E., Visser, M., & Lambon Ralph, M. A. (2013). Going beyond inferior prefrontal involvement in semantic control: Evidence for the additional contribution of dorsal angular gyrus and posterior middle temporal cortex. *Journal of Cognitive Neuroscience*, 25(11), 1824-1850.
- Novick, J. M., Trueswell, J. C., & Thompson-Schill, S. L. (2005). Cognitive control and parsing: Reexamining the role of Broca's area in sentence comprehension. *Cognitive, Affective, and Behavioral Neuroscience*, 5, 263-281.
- Novick, J. M., Trueswell, J. C., & Thompson-Schill, S. L. (2010). Broca's Area and language processing: Evidence for the cognitive control connection. *Language and Linguistics Compass*, 10, 906-924.
- Oppenheim, G. M., Dell, G. S., & Schwartz, M. F. (2010). The dark side of incremental learning: A model of cumulative semantic interference during lexical access in speech production. *Cognition*, 114, 227-252.

- Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nature Reviews Neuroscience*, 8, 976-987.
- Pazzaglia, M., Pizzamiglio, L., Pes, E., & Aglioti, S. M. (2008). The sound of actions in apraxia. *Current Biology*, 18(22), 1766-1772.
- Pisoni, A., Papagno, C., & Cattaneo, Z. (2012). Neural correlates of the semantic interference effect: new evidence from tDCS. *Neuroscience*, 223, 56-67.
- Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2007). Anterior temporal lobes mediate semantic representation: Mimicking semantic dementia by using rTMS in normal participants. *Proceedings of the National Academy of Sciences*, 104(50), 20137-20141.
- Pobric, G., Jefferies, E., & Lambon Ralph, M. A. (2010). Amodal semantic representations depend on both anterior temporal lobes: Evidence from repetitive transcranial magnetic stimulation. *Neuropsychologia*, 48(5), 1336-1342.
- Riddoch, M. J., & Humphreys, G. W. (1993). *Birmingham object recognition battery (BORB)*. Hove (UK): Lawrence Erlbaum Associates Limited.
- Roelofs, A. (1992). A spreading-activation theory of lemma retrieval in speaking. *Cognition*, 42(1), 107-142.
- Roelofs, A. (2003). Goal-referenced selection of verbal action: modeling attentional control in the Stroop task. *Psychological Review*, 110(1), 88-125.
- Roelofs, A. (2003). Goal-referenced selection of verbal action: Modeling attentional control in the Stroop task. *Psychological Review*, 110(1), 88-125.
- Rogers, T. T., Hocking, J., Noppeney, U., Mechelli, A., Gorno-Tempini, M. L., Patterson, K., & Price, C. J. (2006). Anterior temporal cortex and semantic memory: Reconciling findings

- from neuropsychology and functional imaging. *Cognitive, Affective, & Behavioral Neuroscience*, 6(3), 201-213.
- Rorden, C., Karnath, H., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience*, 19, 1081-1088.
- Saur, D., Kreher, B. W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M., et al. (2008). Ventral and dorsal pathways for language. *Proceedings of the National Academy of Sciences USA*, 105, 18035-18040.
- Saur, D., Schelter, B., Schnell, S., Kratochvil, D., Küpper, H., Kellmeyer, P., et al. (2010). Combining functional and anatomical connectivity reveals brain networks for auditory language comprehension. *Neuroimage*, 49, 3187-3197.
- Schnur, T. T., Lee, E., Coslett, H. B., Schwartz, M. F., & Thompson-Schill, S. L. (2005). When lexical selection gets tough, the LIFG gets going: A lesion analysis study of interference during word production. *Brain and Language*, 95, 12-13.
- Schnur, T. T., Schwartz, M. F., Brecher, A., & Hodgson, C. (2006). Semantic interference during blocked-cyclic naming: Evidence from aphasia. *Journal of Memory and Language*, 54, 199-227.
- Schnur, T. T., Schwartz, M. F., Kimberg, D. Y., Hirschorn, 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. *Proceedings of the National Academy of Sciences USA*, 106, 322-327.
- Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2009). Anterior temporal involvement in semantic word retrieval: voxel-based lesion-symptom mapping evidence from aphasia. *Brain*, 132, 3411-3427.

- Shelton, J. R., & Caramazza, A. (1999). Deficits in lexical and semantic processing: Implication for models of normal language. *Psychonomic Bulletin & Review*, 6, 5-27.
- Sherbondy, A., Akers, D., Mackenzie, R., Dougherty, R., & Wandell, B. (2005). Exploring connectivity of the brain's white matter with dynamic queries. *IEEE Transactions on Visual and Computer Graphics*, 11, 419-430.
- Snodgrass, J. G., & Vanderwart, M. (1980). A standardized set of 260 pictures: norms for name agreement, image agreement, familiarity, and visual complexity. *Journal of Experimental Psychology: Human Learning and Memory*, 6(2), 174-215.
- Snyder, H. R., Banich, M. T., & Munakata, Y. (2011). Choosing our words: Retrieval and selection processes recruit shared neural substrates in left ventrolateral prefrontal cortex. *Journal of Cognitive Neuroscience*, 23(11), 3470-3482.
- Thompson-Schill, S. L., & Botvinick, M. M. (2006). Resolving conflict: A response to Martin and Cheng (2006). *Psychonomic Bulletin & Review*, 13(3), 402-408.
- Thompson-Schill, S. L., D'Esposito, M. D., Aguirre, G. K., & Farah, M. J. (1997). Role of the left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. *Proceedings of the National Academy of Sciences USA*, 94, 14792-14797.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage*, 15, 273-289.
- Vandenberghe, R., Price, C., Wise, R., Josephs, O., & Frackowiak, R. S. (1996). Functional anatomy of a common semantic system for words and pictures. *Nature*, 383(6597), 254-256.

- Vigliocco, G., Vinson, D. P., Damian, M. F., & Levelt, W. (2002). Semantic distance effects on object and action naming. *Cognition*, 85(3), B61-B69.
- Visser, M., Jefferies, E., & Lambon Ralph, M. (2010). Semantic processing in the anterior temporal lobes: A meta-analysis of the functional neuroimaging literature. *Journal of Cognitive Neuroscience*, 22(6), 1083-1094.
- Vitkovitch, M., & Humphreys, G. W. (1991). Perseverant responding in speeded naming of pictures: It's in the links. *Journal of Experimental Psychology. Learning, Memory, and Cognition*, 17, 664-680.
- Walker, G. M., Schwartz, M. F., Kimberg, D. Y., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2011). Support for anterior temporal involvement in semantic error production in aphasia: new evidence from VLSM. *Brain and Language*, 117, 110-122.
- Warrington, E. K., & Cipolotti, L. (1996). Word comprehension. The distinction between refractory and storage impairments. *Brain*, 119, 611-625.
- Warrington, E. K., & McCarthy, R. (1983). Category specific access dysphasia. *Brain*, 106(4), 859-878.
- Warrington, E. K., & McCarthy, R. A. (1987). Categories of knowledge further fractionations and an attempted integration. *Brain*, 110, 1273-1296.
- Wheeldon, L. R., & Monsell, S. (1994). Inhibition of spoken word production by priming a semantic competitor. *Journal of Memory and Language*, 33, 332-356.
- Wilshire, C. E., & McCarthy, R. A. (2002). Evidence for a context-sensitive word retrieval disorder in a case of nonfluent aphasia. *Cognitive Neuropsychology*, 19, 165-186.
- Wilson, M. (1988). MRC Psycholinguistic Database: Machine-usable dictionary, version 2.00. *Behavior Research Methods*, 20, 6-10.

Wong, F. C. K., Chandrasekaran, B., Garibaldi, K., & Wong, P. C. M. (2011). White matter anisotropy in the central language pathway predicts sound-to-word learning success.

Journal of Neuroscience, 31, 8780-8785.

Wu, D., Waller, S., & Chatterjee, A. (2007). The functional neuroanatomy of thematic role and locative relational knowledge. *Journal of Cognitive Neuroscience*, 19(9), 1542-1555.

Figures

Figure 1. Different levels of representation in the language system. Illustrated here are the hypotheses that semantic and lexical level representations are shared across language production and comprehension but output vs. input (i.e., phonological and phonological/orthographic) levels of representation differ for production vs. comprehension, respectively (Levelt et al., 1999; cf. Caramazza, 1997). Visual (structural) input processing is common to both production (picture naming) and comprehension (word-picture matching) tasks, and these input forms are thought to have privileged access to the semantic system (e.g., Hillis et al., 1990).

Figure 2. Individual *t*-values from ANOVA analyses assessing individual performance using items as a random factor. (a) Individual *relatedness effects* (Related vs. Unrelated) and (b) *increasing relatedness effects* (linear contrast for the Related vs. Unrelated comparison across the four cycles) for blocked-cyclic naming (red) and word-picture matching (blue). Patients are arranged from smallest to largest *relatedness effect t*-values for blocked-cyclic naming. Positive *t*-values signify interference and negative *t*-values signify facilitation. Note that “/” denotes inability to perform the task (patients W.F., H.A., and D.Z.) where no bar reflects no difference between conditions (i.e., *t*-value of 0; patient Q.O.). An * indicates significance at $p < .05$, and $\pm$ indicates marginal significance ($p < .10$).

Figure 3. Overlay map displaying the number of subjects with damage to a particular voxel, presented on 4mm 20 axial slices ranging from MNI z coordinates -16 to 60. Maximal overlap (dark red) is located in the midsection of the medial middle and superior temporal gyri (BA 22 and 48), where 12 of the 15 participants shared this site of damage. Regions

displayed in green represent voxels lesioned in half of the 15 subjects ($n = 7$). Maps depict only voxels lesioned in at least three participants. Each axial slice is labeled by its corresponding MNI z coordinate.

Figure 4. Results from the VLSM analyses examining the relationship between voxel lesion status and *relatedness effect t-values* in blocked-cyclic naming and word-picture matching. Voxels exceeding the false discovery rate ($q = .05$) indicate in red ($t > 3.07$) where posterior temporal lobe damage is associated with exaggerated *relatedness effects* in naming and in blue where anterior temporal lobe damage is associated with exaggerated *relatedness effects* in word-picture matching ($t > 3.74$). In green is an illustration of the IFOF anatomical trajectories, where it connects the posterior temporal cortex with the LIFG (see also *Figure 7*).

Figure 5. ROI-based analyses examining the relationship between percent damage to the posterior vs. anterior portions of the left temporal lobe and *relatedness effects* in naming and comprehension tasks when controlling for total lesion volume. The figure displays *relatedness effect t-value* residuals after accounting for total lesion volume (y-axis) plotted against residuals for percent damage (x-axis) to the posterior and anterior portions of the temporal lobe (divided at $y = -22$) after accounting for total lesion volume, reflecting the relationship between (a) posterior temporal lobe damage and naming and (b) anterior temporal lobe damage and word-picture matching.

Figure 6. The marginally significant difference ($p = .06$) in the magnitude of *increasing relatedness effects* in naming for patients with ($> 0\%$ damage) and without LIFG damage (0% damage). Individual naming *increasing relatedness effect t-values* appear on the mean bar graphs for those with (“+”) and without LIFG damage (“-”).

Figure 7. Partial correlations between FA values (integrity) and *relatedness effects* illustrating a significant relationship between (a) IFOF FA values and naming and (b) ILF FA values and word-picture matching, after controlling for total lesion volume. Plotted on the x-axes are residual FA values (IFOF and ILF), and plotted on the y-axes are residual individual *relatedness effect t*-values (naming and word-picture matching) after accounting for total lesion volume.

Table 1. Demographic, clinical, and neuroanatomical information for the aphasic participants.

Patient ID	Sex	Age	Education	Mos. Post Onset	Aphasia Quotient	Aphasia Subtype	Lesion Description	BA Regions
QO	M	67	20	24	95.0	A	L temporal	2, 20-22, 38, 40-42
DA	F	56	19	8	94.7	A	L inf. frontal	3-4, 6, 22, 38, 43-45
MB	M	65	13	84	94.4	A	L parietal, temporo-occipital (minor)	1-7, 18-19, 21-23, 37, 39-43
EV	F	52	16	107	93.6	A	L frontal, ant. temporal (minor)	6, 8-11, 32, 38, 44-47
SJ	F	62	13	40	88.8	A	L temporal, parietal	2-3, 7, 19-22, 37, 39-42
SH	M	82	11	73	84.8	A	L temporal, parietal	2, 7, 17-22, 36-42
NKC	M	54	14	28	83.6	C	L frontal, temporal, parietal (minor)	2-4, 6-7, 9, 11, 18-22, 28, 34, 36-42, 44-47
SL	M	62	21	68	83.3	C	L temporal, occipital (minor)	19-22, 37, 39, 41-42
BB	M	48	21	112	72.7	A	L frontal, sup. temporal, parietal	1-9, 11, 17-23, 32, 34, 37-47
BQ	M	67	16	127	71.8	A	L pos. frontal, temporal, parietal	1-9, 17-23, 37-47
DG	M	51	17	55	71.1	C	L pos. frontal, temporal	2-7, 17-23, 28, 30, 34-45
CV	M	73	13	28	64.1	C	L temporal, parietal, occipital	1-7, 17-23, 37-43
WF	M	74	15	22	30.7	W	L temporal, parietal, occipital	1-9, 17-23, 36-46
HA	M	83	16	41	19.4	B	L frontal, sup. temporal, parietal	1-7, 20-22, 28, 34, 36-47
DZ	F	41	22	51	14.7	B	L frontal, sup. temporal, parietal	1-9, 17-23, 28, 34, 36-47
Mean		62.5	16.5	57.9	70.8			

Patients are arranged in order of their Aphasia Quotient as determined by the Western Aphasia Battery (WAB; Kertesz, 1982), where lower numbers indicate greater severity of language impairments. BA regions were determined using MRICron (Rorden et al., 2007).

Abbreviations: ID (identification code), F (female), M (male), Mos. (months), A (Anomic), B (Broca), C (Conduction), W (Wernicke), ant. (anterior), inf. (inferior), L (Left), pos. (posterior), sup. (superior), BA (Brodmann Area).

Table 2. Individual performance on standard tests of visual input processing (Birmingham Object Recognition Battery; Riddoch & Humphreys, 1993), phonological and orthographic input processing (Martin & Breedin, 1992), non-verbal semantic knowledge (Pyramid and Palm Trees task; Howard & Patterson, 1992), single word comprehension (Auditory Word-Picture Verification; Martin et al., 1999; see also Hillis et al., 1990; Breese & Hillis, 2004), and picture naming (Philadelphia Naming Test; Dell et al., 1997).

Patient ID	BORB	Lexical Decision		PPT	AWPV		PNT	
	Percent Correct	Auditory (Percent Correct)	Visual (Percent Correct)	Percent Correct	Percent Correct	Proportion Semantic Errors	Percent Correct	Proportion Semantic Errors
QO	84.4	90.0	NA	98.1	98.1	100.0	97.7	50.0
DA	87.5	85.0	99.2	94.2	90.7	100.0	89.7	44.4
MB	100.0	72.5	98.3	100.0	92.6	25.0	96.0	71.4
EV	84.4	89.2	95.0	92.3	79.6	81.8	86.3	62.5
SJ	90.6	86.7	96.7	98.1	90.7	60.0	96.6	66.7
SH	87.5	84.2	94.2	98.1	81.5	40.0	93.1	66.7
NKC	84.4	85.8	96.7	80.8	87.0	57.1	93.7	27.3
SL	NA	73.3	96.7	100.0	44.4	33.3	80.0	22.9
BB	NA	93.3	96.7	88.5	74.1	100.0	74.9	40.9
BQ	84.4	87.5	96.7	94.2	66.7	77.8	95.4	50.0
DG	78.1	91.7	NA	90.4	51.9	96.2	49.7	39.8
CV	87.5	69.2	84.2*	92.3	64.8	52.6	44.6	13.4
WF	NA	NA	NA	69.2	7.4	88.0	0.0	NA
HA	78.1	70.0	91.7	94.2	51.9	92.9	0.0	NA
DZ	87.5	55.8	92.5	84.6	51.9	96.4	0.0	NA
Mean	86.2 ^a	81.0 ^b	94.9	91.7 ^c	68.9 ^d	73.4	83.1 ^e	46.3

Note. Scores on the BORB task (Riddoch & Humphreys, 1993) reflect percent correct out of 32 trials (16 real and nonreal objects).

Lexical decision scores were calculated as percentage correct out of 120 trials (per task), where the items comprised of 60 real and 60 pronounceable nonwords that differed from the real words by one phoneme (see Martin & Breedin, 1992). The auditory and visual variants of the task took place on separate testing sessions. Scores on the three picture version of the PPT task (Howard & Patterson, 1992) reflect the percentage of correct responses out of the 52 target items. In the AWPV task, patients heard a word and saw one of four pictures: a target match, semantically related foil, phonologically similar foil, or an unrelated foil (i.e., 54 words presented 4 times each with a different foil = 216 trials). Patients had to correctly accept the target word and picture match, and reject the target word when paired with a foil in order to get the item correct. Percent Correct on the AWPV reflects performance scored by item, and Proportion Semantic Error reflects the proportion of error responses that were made on the semantic foils compared to the other conditions. Scores on the PNT (Dell et al., 1997) are based on the proportion of accurate naming responses for the 175 pictures (Percent Correct) and the proportion semantic errors out of all error responses (Proportion Semantic Errors). Note that mean PNT Percent Correct does not reflect scores for three patients (W.F., H.A., and D.Z.) unable to perform the task.

*Visual lexical decision performance was assessed with the PALPA battery (subtest 25) (Kay et al., 1992).

Abbreviations: AWPV (auditory word-picture verification), BORB (Birmingham Object Recognition Battery), NA (Not Available), PALPA (Psycholinguistic assessments of language processing in aphasia), PNT (Philadelphia Naming Test), PPT (Pyramid and Palm Trees), *SD* (standard deviation)

^a Mean (and range) performance on the BORB from an older control group was 84.4% (68.8-93.8%) correct (reported in Riddoch & Humphreys, 1993).

^b Mean (and range) performance on the auditory variant of the lexical decision task from an older control group was 94% (90-98%) correct (reported in Martin & Breedin, 1992).

^c Mean (*SD*) performance on the three picture PPT from an older control group was 51.2 (*1.4*) items correct, or 98.5% (*2.7*%) correct (reported in Bozeat et al., 2000).

^d Mean (*SD*) performance on a version of the AWPV task similar to that used in the present study obtained from an older adult control group (mean age 64.7 years $\pm$ 10.7 *SD*) was 99.9% (*.9*) correct (reported in Cloutman et al., 2009). Control performance on the semantic foils was not available.

^e Mean (*SD*) performance on the PNT task from an older control group was 97% (*1.8*) correct (reported in Schwartz et al., 2009).

Information concerning the proportion of semantic errors in naming was not available for controls.

Table 3. Mean percent error rate and standard deviations (*SD*) separated by Task (Naming, Word-picture Matching), Condition (Related, Unrelated), and Cycle (1-4).

Cycle	Condition				Effect	
	Related		Unrelated		R - U	95% CI
	Mean %	SD	Mean %	SD		
<i>Naming</i>						
1	14.0	11.9	17.2	14.4	-3.2	±5.0%
2	13.1	14.6	13.4	11.8	-0.3	±2.9%
3	14.1	12.8	9.5	9.5	4.6	±1.9%
4	14.6	15.0	8.0	7.3	6.6	±2.8%
<i>Word-picture Matching</i>						
1	10.1	9.6	2.3	2.8	7.8	±2.6%
2	10.8	10.4	3.2	3.9	7.5	±1.3%
3	10.9	10.9	2.4	3.8	8.4	±3.0%
4	9.8	11.4	2.9	3.8	6.9	±2.9%

Note. Effect refers to the difference in mean percentage errors for Related (R) – Unrelated (U) and associated 95% Confidence Intervals (95% CI) for the group comparison (n = 12).

Table 4. Summary of F statistics for the group ANOVA results (and linear contrasts) examining mean error rates for Task (Naming, Word-picture Matching), Condition (Related, Unrelated), and Cycle (1-4) using subjects (F_1) and items (F_2) as random factors. An * indicates significant main effects and interactions where $* = p < .05$, $** = p < .01$, and $*** = p < .001$.

Variables	Subject			Item		
	df		F_1	df		F_2
	Num	Den		Num	Den	
Task	1	11	5.60*	1	71	27.41***
Condition	1	11	7.34*	1	71	74.70***
Cycle	3	33	4.70**	3	213	3.49*
Task x Condition	1	11	9.33*	1	71	23.79***
Prod: Condition	1	11	2.57	1	71	6.19*
Comp: Condition	1	11	8.90*	1	71	80.83***
Task x Cycle	3	33	2.97*	3	213	3.82*
Prod: Cycle	3	33	5.01**	3	213	6.53***
Comp: Cycle	3	33	0.37	3	213	0.40
Condition x Cycle	3	33	5.98**	3	213	4.59**
Linear Contrast	1	11	9.74**	1	71	11.66**
Task x Condition x Cycle	3	33	4.99**	3	213	5.74**
Prod: Condition x Cycle	3	33	7.41**	3	213	8.79***
Comp: Condition x Cycle	3	33	0.36	3	213	0.38
Linear Contrast	1	11	9.19*	1	71	13.92***
Prod: Condition x Cycle	1	11	11.59**	1	71	19.08***
Comp: Condition x Cycle	1	11	0.10	1	71	0.19

Abbreviations: Comp (comprehension, as in Word-picture Matching), Den (denominator), df (degrees of freedom), Num (numerator),

Prod (production, as in Naming).

Table 5. VLSM results. Significant regions associated with exaggerated *relatedness effects* in blocked-cyclic naming (critical *t*-value: 3.07) and word-picture matching (critical *t*-value: 3.74). There were no voxels significantly associated with *increasing relatedness effects* in either task.

Naming <i>Relatedness Effect</i> (n = 12)						Word-picture Matching <i>Relatedness Effect</i> (n = 15)					
X	Y	Z	Cluster Size (Voxels)	BA	AAL	X	Y	Z	Cluster Size (Voxels)	BA	AAL
-52	-40	-5	7515	21	L MTG	-54	-16	-16	643	20	L MTG
-49	-21	-8	17	21	L MTG	-45	4	41	117	6	L precentral
						-45	-38	-14	37	37	L inf. temporal
						-59	-35	-12	21	20	L MTG
						-44	-45	-11	10	37	L inf. temporal
						-42	-72	-1	10	19	L middle occipital gyrus

Abbreviations: AAL (Automated Anatomical Labeling), BA (Brodmann Area), inf. (inferior), L (left), MTG (middle temporal gyrus).

a.*Relatedness Effects* **b.***Increasing Relatedness Effects*

a. **b.**

a. **b.**

Appendix A

		Unrelated Sets					
Related Sets	<i>Body Parts</i>	hand	foot	eye	mouth	ear	nose
	<i>Insects</i>	spider	bee	ant	fly	butterfly	grasshopper
	<i>Fruit</i>	banana	coconut	apple	pineapple	watermelon	grapes
	<i>Animals</i>	tiger	elephant	zebra	panda	rabbit	monkey
	<i>Vehicles</i>	motorcycle	boat	airplane	bicycle	bus	train
	<i>Clothing</i>	sock	scarf	tie	skirt	pants	hat
		Unrelated Sets					
Related Sets	<i>Birds</i>	rooster	swan	duck	peacock	penguin	owl
	<i>Appliances</i>	fan	TV	camera	refrigerator	washing machine	telephone
	<i>Vegetables</i>	onion	eggplant	cabbage	corn	mushroom	carrot
	<i>Tools</i>	pliers	scissors	screwdriver	axe	hammer	saw
	<i>Food</i>	pizza	popcorn	cake	turkey	hamburger	cookie
	<i>People</i>	fireman	nurse	chef	police	teacher	painter

Appendix B

Patients' mean percent error rates for each Task (Naming, Word-picture Matching), Condition (Related, Unrelated), and Cycle (1-4).

Relatedness and increasing relatedness effects are also displayed.

Task	Patient ID	Related				Unrelated				Effects	
		1	2	3	4	1	2	3	4	<i>Relatedness Effect</i>	<i>Increasing Relatedness Effect</i>
<i>Naming</i>	QO	2.8	1.4	1.4	1.4	4.2	9.7	1.4	5.6	-3.5	0.0
	DA	1.4	0.0	2.8	0.0	4.2	2.8	2.8	1.4	-1.7	0.7
	MB	8.3	2.8	2.8	5.6	19.4	12.5	1.4	5.6	-4.9	4.4
	EV	2.8	6.9	11.1	8.3	8.3	9.7	5.6	4.2	0.3	3.8
	SJ	4.2	0.0	2.8	0.0	1.4	0.0	0.0	0.0	1.4	-0.6
	SH	12.5	6.9	13.9	11.1	8.3	5.6	4.2	5.6	5.2	1.3
	NKC	12.5	9.7	20.8	12.5	18.1	4.2	11.1	2.8	4.9	5.0
	SL	11.1	8.3	5.6	9.7	8.3	5.6	6.9	6.9	1.7	-0.4
	BB	25.0	22.2	15.3	20.8	30.6	20.8	12.5	8.3	2.8	5.6
	BQ	19.4	22.2	23.6	30.6	22.2	31.9	19.4	12.5	2.4	7.6
	DG	38.9	48.6	44.4	51.4	48.6	36.1	31.9	25.0	10.4	10.8
	CV	29.2	27.8	25.0	23.6	33.3	22.2	16.7	18.1	3.8	3.2
<i>Word-picture Matching</i>	QO	4.2	1.4	1.4	4.2	5.6	1.4	1.4	1.4	0.3	1.3
	DA	9.7	11.1	12.5	12.5	1.4	8.3	9.7	11.1	3.8	-2.1
	MB	1.4	0.0	2.8	0.0	0.0	0.0	1.4	0.0	0.7	-0.3
	EV	8.3	8.3	6.9	1.4	1.4	0.0	1.4	0.0	5.6	-1.9
	SJ	2.8	1.4	0.0	1.4	2.8	0.0	0.0	0.0	0.7	0.3
	SH	4.2	6.9	4.2	1.4	1.4	0.0	0.0	0.0	3.8	-0.7
	NKC	19.4	30.6	31.9	31.9	2.8	9.7	2.8	6.9	22.9	3.3
	SL	1.4	0.0	1.4	0.0	0.0	0.0	0.0	0.0	0.7	-0.3
	BB	0.0	8.3	8.3	2.8	1.4	4.2	1.4	5.6	1.7	-0.1
	BQ	20.8	13.9	13.9	13.9	0.0	1.4	0.0	1.4	14.9	-2.4
	DG	27.8	26.4	30.6	22.2	1.4	4.2	0.0	1.4	25.0	-0.8
	CV	20.8	20.8	16.7	26.4	9.7	9.7	11.1	6.9	11.8	1.9
	WF	63.9	61.1	50.0	58.3	31.9	38.9	45.8	29.2	21.9	-2.6
	HA	22.2	19.4	22.2	22.2	5.6	5.6	16.7	12.5	11.5	-2.9
	DZ	13.9	22.2	23.6	26.4	6.9	5.6	4.2	5.6	16.0	4.4

Note: For the rows labeled *Naming* and *Word-picture Matching*, *Relatedness Effect* refers to mean error rate differences between the Related and Unrelated Conditions, and the *Increasing Relatedness Effect* reflects the slope of this difference across the four cycles.