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The neural basis of inhibitory effects of semantic and phonological neighbors in spoken word production

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Abstract

Theories of word production and word recognition generally agree that multiple word candidates are activated during processing. The facilitative and inhibitory effects of these “lexical neighbors” have been studied extensively using behavioral methods and have spurred theoretical development in psycholinguistics, but relatively little is known about the neural basis of these effects and how lesions may affect them. The present study used voxel-wise lesion overlap subtraction to examine semantic and phonological neighbor effects in spoken word production following left hemisphere stroke. Increased inhibitory effects of near semantic neighbors were associated with inferior frontal lobe lesions, suggesting impaired selection among strongly activated semantically-related candidates. Increased inhibitory effects of phonological neighbors were associated with posterior superior temporal and inferior parietal lobe lesions. In combination with previous studies, these results suggest that such lesions cause phonological-to-lexical feedback to more strongly activate phonologically-related lexical candidates. The comparison of semantic and phonological neighbor effects and how they are affected by left hemisphere lesions provides new insights into the cognitive dynamics and neural basis of phonological, semantic, and cognitive control processes in spoken word production.

Keywords

lexical neighborhood; phonological neighborhood; semantic neighborhood; spoken word production; aphasia; lesion overlap

Theories of word production and word recognition generally agree that multiple word candidates are activated during processing and the degree of activation is based on their conceptual (semantic) and form (orthographic or phonological) similarity to the target. These similar words are typically called “lexical neighbors” and the consequences of this “parallel activation” are interestingly complex: neighbors can have both facilitative and inhibitory effects on target processing (for a recent review see Chen & Mirman, 2012). Chen and Mirman (2012) developed a computational model that provided a unified theory of these contrasting effects. As in other interactive activation and competition models (e.g., McClelland & Rumelhart, 1981), in the Chen and Mirman model, neighbors exert inhibitory effects through lateral inhibitory connections and facilitative effects through recurrent

excitatory connections to shared form or semantic units. Their novel development was that strongly active neighbors have net inhibitory effects and weakly active neighbors have net facilitative effects; that is, neighbors' facilitative effects are larger than their inhibitory effects when neighbor activation is low, but the inhibitory effect outweighs the facilitative effect when neighbor activation is high. Simulations of this model captured the qualitative pattern of neighbor effects across a wide range of neighbor types and tasks: (1) facilitative effects of orthographic neighbors on visual word recognition, (2) inhibitory effects of higher frequency neighbors on visual word recognition, (3) inhibitory effects of phonological neighbors on spoken word recognition, (4) facilitative effects of phonological neighbors on word production, (5) inhibitory effects of near semantic neighbors (words that share many semantic features) on word recognition and word production, and (6) facilitative effects of distant semantic neighbors (words that share a few semantic features) on word recognition and word production. All of these results stemmed from the same core principle: strongly active neighbors have a net inhibitory effect and weakly active neighbors have a net facilitative effect. Although lexical neighbor effects have been studied extensively using behavioral methods and have spurred much theoretical development in psycholinguistics, relatively little is known about the neural basis of these effects and how lesions in particular brain areas may affect neighbor effects.

To our knowledge, only one study has examined the neural correlates of phonological neighbor effects in spoken word production (Peramunage et al., 2010). This study used fMRI and found reduced activation for words with a minimal pair neighbor (e.g., *cape*, which has the onset minimal pair neighbor *gape*) compared to words without such a neighbor (e.g., *cake*, which has no such neighbor) in posterior superior temporal gyrus (pSTG), supramarginal gyrus (SMG), and inferior frontal gyrus (IFG). Studies that examined phonological neighbors in spoken word recognition have similarly implicated SMG and pSTG (Okada & Hickok, 2006; Prabhakaran et al., 2006; Righi et al., 2009), along with IFG (Righi et al., 2009; Zhuang et al., 2011).

In a study of semantic neighbor effects on word production in 62 participants with aphasia, Mirman (2011) reported an inhibitory effect of near semantic neighbors and, in a secondary analysis, that the size of this inhibitory effect was positively correlated with percent damage in IFG. More generally, semantic processing involves a distributed network of cortical regions (e.g., Binder & Desai, 2011; Patterson, Nestor, & Rogers, 2007) with the anterior temporal lobes (e.g., Patterson et al., 2007; Schwartz et al., 2009) and possibly temporo-parietal cortex (Binder & Desai, 2011; Mirman & Graziano, 2012) playing key integration or "hub" roles.

Lexical neighborhood effects have generally been considered specifically in the framework of language processing, but cognitive control is likely to be an important factor as well. Specifically, lexical neighbor effects in word recognition and word production arise because multiple lexical candidates are activated and, in most tasks (such as naming, word-to-picture matching, etc.), a single word must be selected from these activated candidates. The IFG has been identified as critical to selecting among competing alternatives, particularly in lexical processing tasks (e.g., Schnur et al., 2009; Snyder, Feigenson, & Thompson-Schill, 2007; Nozari, Schwartz, & Coslett, 2012).

Predictions

In sum, the available evidence suggests that lexical neighbor effects involve some combination of a network of regions including phonological (pSTG, SMG) and semantic (ATL) processing and competitive selection (IFG). Greater insight into the particular nature of that combination can inform cognitive theories of lexical processing as well as our understanding of the neural systems that support lexical processing. The present study used voxel-wise lesion analyses to examine semantic (Study 1) and phonological (Study 2) neighbor effects in spoken word production following left hemisphere stroke. Previous studies have used lesion analysis methods to examine semantic and phonological errors in picture naming in order to investigate the neural basis of semantic and phonological aspects of spoken word production. Here, we take a complementary approach of examining the neural correlates of different effects of semantic and phonological neighborhoods on picture naming accuracy. That is, previous studies have examined differences in output (errors), we examine differences in target properties (neighborhood density). By taking this complementary approach, we aim to provide new insights into the cognitive and neural processes involved in spoken word production.

Near semantic neighbors have been shown to exert inhibitory effects on spoken word production (Mirman, 2011; and visual word recognition: Mirman & Magnuson, 2008), which, according to Chen and Mirman (2012), is due to such neighbors being strongly activated and competing with the target word. Neuroanatomically, the activation of semantic neighbors should be most strongly associated with ATL and selection among lexical candidates should be most strongly associated with IFG. Thus, if IFG lesions are associated with increased inhibitory effects of semantic neighbors, that would indicate an effect of difficulty resolving lexical competition. If ATL lesions are associated with increased inhibitory effects of semantic neighbors, that would indicate that such lesions caused greater activation of semantic neighbors. In contrast, ATL lesions could be associated with facilitative effects of semantic neighbors (or reduced inhibitory effects), which would indicate that such lesions reduced activation of semantic neighbors.

Phonological neighbors have been shown to exert facilitative effects in spoken word production (e.g., Gordon, 2002; Kittredge, Dell, Verkuilen, & Schwartz, 2008; Vitevitch & Sommers, 2003), which, according to Chen and Mirman (2012), arises because the excitatory resonance between shared phonological representations and phonological neighbors outweighs their weak competition with the target word. On this view, the effect of phonological neighbors would be expected to become inhibitory if the neighbors become more strongly activated and their competition with the target begins to outweigh their facilitative effect. This pattern may arise if lesions in pSTG and SMG, which are associated with lexical-phonological deficits (e.g., Baldo, Katseff, & Dronkers, 2012; Fridriksson et al., 2010; Graves et al., 2008; Schwartz et al., 2012; Wilson, Isenberg, & Hickok, 2009), cause phonological neighbors to become more strongly activated. As for the semantic neighbors, IFG lesions may also cause increased inhibitory effect of phonological neighbors, but this is not as likely because phonological neighbors are only weakly activated and IFG is most important for selecting among strongly active competitors (e.g., Snyder et al., 2007). Finally, on the Chen and Mirman view, increased facilitative effects of phonological neighbors

should be difficult to detect because increased activation of phonological neighbors would make their effect inhibitory and reduced activation of phonological neighbors would reduce their effects. Although it is possible that this balance can be shifted to maximize their facilitative effect, it is not clear what kind of lesion would do this.

Analysis Strategy

Lesion analysis is a foundational method in cognitive neuroscience, although the specific techniques have evolved with the advancement of available participant recruitment, neuroimaging, and statistical methods (for historical summary see, e.g., Rorden & Karnath, 2004). One standard method is voxel-based lesion-symptom mapping (VLSM), in which a *t*-test is conducted at each voxel comparing the size of a behavioral effect (“symptom”) in participants with vs. without a lesion in that voxel. The many repeated *t*-tests inflate the probability of false positives, so it is customary to correct for the multiple comparisons (e.g., Bennett et al., 2009). This approach has been used successfully to study many aspects of cognition, including spoken word production (e.g., Baldo et al., in press; Cloutman et al., 2009; Schwartz et al., 2009, 2011, 2012; Walker et al., 2011). However, because of the nonrandom distribution and inherent spatial coherence of lesions, the power of a statistically rigorous VLSM analysis can be severely limited (e.g., Kimberg, Coslett, & Schwartz, 2007). That is, successful detection of effects requires that the effects be large relative to the size of the sample and detecting smaller or more subtle effects requires unrealistically large samples of participants with brain lesions.

One alternative to VLSM is lesion overlap (or overlay) analysis, in which lesions of individual participants who show a particular symptom are superimposed in order to find the location(s) that are most strongly associated with the symptom. This approach has a long history in cognitive neuroscience (e.g., Hayward, Naeser, & Zatz, 1977; Kertesz, Harlock, & Coates, 1979) and has continued to be used more recently (e.g., Badre et al., 2009; Buchsbaum et al., 2011; Damasio et al., 2004; Dronkers, 1996; Kemmerer et al., 2012; Shomstein, Lee, & Behrmann, 2010). The more recent applications of this method typically involve two important refinements. The first is use of a lesion control group: a particular lesion site may be frequently lesioned in participants with a particular symptom simply because it is more vulnerable for cerebrovascular reasons rather because of a functional link between that site and the behavior. Comparing relative frequency of lesions in a particular site between groups of participants who do vs. do not exhibit the symptom is critical for evaluating that site’s functional significance. The second is use of a principled difference threshold to define what it means for a lesion site to be more frequently lesioned in one group than the other.

In this report we take a convergent approach using both uncorrected VLSM and voxel-wise lesion overlap subtraction. The uncorrected VLSM included the full set of participants and was meant as a preliminary, all-inclusive analysis to identify lesion locations that may be functionally relevant. For the lesion overlap subtraction we adapted the approach described by Kemmerer et al. (2012): we divided participants into two groups based on effect size and computed voxel-wise lesion probability difference maps. These maps show, at each voxel, the difference between (a) the proportion of participants with a large effect size who had a

lesion in that voxel and (b) the proportion of participants with a small effect size who had a lesion in that voxel. The maps were then thresholded at 40% to identify voxels that showed the largest group differences; that is, we considered only those voxels where at least 40% more participants in one group had a lesion than participants in the other group did. For the group sizes in this study, this threshold corresponds to a χ^2 test statistically significant at the 0.01 level. This threshold also imposes a minimum number of lesions that must be present in a voxel for it to be included in the analysis: at least 40% of one group must have lesions in a voxel for it to be included in the analysis. Given approximately equal group sizes, the analysis only included voxels where at least 20% of the overall sample (both groups combined) had a lesion. This lower limit is important for producing stable results, much like “effective coverage maps” (Kemmerer et al., 2012). In addition, the lesion overlap subtraction method has the advantage that the groups can be matched on various control variables, thus controlling for effects such as severity in a way that is more direct and effective than is possible in VLSM¹.

Finally, defining “high” vs. “low” effect size groups for the lesion overlap subtraction requires setting arbitrary boundaries. In general, this creates a trade-off between statistical power (higher power requires larger groups) and effect size (larger differences in effect sizes require more extreme boundaries, which produces smaller groups). We used a quantile approach and compared (approximately) the top and bottom 1/3rd of participants – that is, the participants who showed the largest neighborhood facilitation effects with those that showed the largest neighborhood inhibition effects. Dividing the sample into thirds and excluding the middle group represents a reasonable compromise between strength of the manipulation (focus on participants with the strongest facilitation or inhibition effects) and statistical power (maximize the number of participants in the analysis). To verify that the results were not due to peculiarities of that particular group definition, we repeated the analysis using a more extreme comparison: the 1/10th with the largest facilitation effects vs. the 1/10th with the largest inhibition effects and using a stricter probability difference threshold (60%).

Study 1: Semantic neighbors

Methods

Materials—The spoken word production data were drawn from the 175-item Philadelphia Picture Naming Test (PNT; Roach et al., 1996). Standard administration and scoring procedures were used². As in Mirman (2011), near semantic neighbors were defined as having greater than 0.4 cosine similarity between semantic feature vectors based on the McRae et al. (2005) semantic feature generation norms. The semantic feature norms were available for 95 of the 175 items in the PNT, so the analyses were restricted to these 95 items. From this set of 95 target words, two groups of words were selected such that they maximally differed in number of near semantic neighbors and were matched in log-

¹It is possible to enter control variables into VLSM but this tends to very severely reduce power and (typically) only controls for linear effects of the control variables, whereas it is quite possible that factors like overall severity, lesion size, etc. have non-linear effects on behavioral outcomes.

²Full test materials and procedures are available at <http://www.mrri.org/philadelphia-naming-test>.

transformed word frequency (based on the HAL frequency norms [Lund & Burgess, 1996; see also Balota et al., 2007] and the spoken portion of the American National Corpus [ANC, Ide & Suderman, 2004]), word length (number of phonemes), number of semantic features (e.g., Pexman, Holyk, & Monfils, 2003; see also Mirman & Magnuson, 2008), and number of phonological neighbors based on the one-phoneme-rule (i.e., number of words that can be formed by the addition, deletion, or substitution of a single phoneme; Luce, 1986; Luce & Pisoni, 1998; phonological neighborhoods were evaluated using the spoken portion of the ANC). There were 36 words in each set; the properties of the two sets of words are summarized in Table 1 and the full list of target words is provided in Appendix A.

Participants—The full sample of participants consisted of 106 individuals who had been diagnosed acutely with aphasia secondary to left hemisphere stroke, were at least 3 months post onset, and who had completed the PNT and CT or MRI imaging. Data from this sample have been previously reported in VLSM analyses of phonological (Schwartz et al., 2012) and omission (Chen et al., under review) errors in picture naming. Participants had no major psychiatric or neurologic co-morbidities, were premorbidly right handed, had English as their primary language, adequate vision and hearing (with or without correction), and some ability to name pictures (at least one correct response out of 175 PNT trials). For each of the participants, the near semantic neighbor effect size was computed as the picture naming accuracy difference between the items with few near semantic neighbors and the items with many near semantic neighbors. The distribution of this near semantic neighbor effect sizes is shown in Figure 1A.

To define groups for the lesion overlap subtraction analysis, first, eleven participants with unusually large lesions ($> 2SD$ above the mean lesion size) or unusually severe aphasia ($> 2SD$ below the mean Western Aphasia Battery Aphasia Quotient [WAB AQ; Kertesz, 1982]) were excluded from analyses. Then, the top and bottom 30 participants based on near semantic neighbor effect size were selected (i.e., approximately the top and bottom 1/3 of the overall group). Finally, participants were removed in order to maximize the effect size difference between groups and match the groups on lesion size and aphasia severity as measured by WAB AQ (both $t < 1$, $p > 0.5$). The groups also did not differ on overall picture naming accuracy or on the proportion of semantic, formal, or nonword errors (all $p > 0.25$). See Appendix B for group means and standard deviations. The group formation was done while blinded to lesion location so this information could not bias which participants were removed. The selected groups are represented by the shaded regions in Figure 1A. The resulting Inhibition group ($N = 25$) had higher accuracy on words with few near semantic neighbors than words with many near semantic neighbors ($M_{DIFF} = 13.1\%$, $SD_{DIFF} = 6.7\%$; i.e., near semantic neighbors inhibited performance in this group) whereas the Facilitation group ($N = 22$) showed the reverse effect: higher accuracy on words with many near semantic neighbors than words with few near semantic neighbors ($M_{DIFF} = 10.4\%$, $SD_{DIFF} = 4.9\%$; i.e., near semantic neighbors facilitated performance in this group). This group difference was highly statistically significant ($t = 13.81$, $p < 0.0001$).

Lesion analysis—Image acquisition, lesion segmentation, and template registration methods followed the procedures established in previous work by our research group

(Schnur et al., 2009; Schwartz et al., 2009, 2011, 2012) and detailed descriptions are available there (particularly Schwartz et al., 2012, who reported data from the same sample). Briefly, lesion location was assessed based on MRI (N=60) or CT (N=46) brain scans. Lesions imaged with MRI were manually segmented on each participant's T1-weighted structural image by a trained technician blinded to the behavioral data and registered to the Montreal Neurological Institute (MNI) space Colin27 template by an automated process (Avants, Schoenemann, & Gee, 2006). Lesions imaged with CT were drawn by an experienced neurologist directly onto the Colin27 template after rotating it (pitch only) to match the approximate slice plane of the participant's scan. Lesion volume was calculated by using the digital Brodmann atlas available with MRICron and using tools available in the VoxBo software package. The VLSM analysis consisted of a *t*-test at every voxel comparing the semantic neighbor effect size of participants with vs. without a lesion in that voxel.

Voxel-wise lesion overlap subtraction—Figure 1B shows the coverage map (number of lesions in each voxel) for the 47 participants in the lesion overlap subtraction analysis (25 in the Inhibition group and 22 in the Facilitation group). The lesions covered essentially the entire left hemisphere, with particular concentration in the peri-Sylvian region. Note, however, that coverage was comparatively poor in the anterior temporal lobe, indicating that there was limited power to evaluate the predictions regarding ATL involvement in semantic neighborhood effects. As described above, for each voxel, we computed the difference between the proportion of the Facilitation group participants who had a lesion in that particular voxel compared to the proportion of the Inhibition group participants who had a lesion in that particular voxel (and vice versa). In order to focus on just the voxels where this proportion difference was large, we only consider voxels where this difference was at least 40% of group size (i.e., 9 participants for the Facilitation group, 10 participants for the Inhibition group). To further reduce the likelihood of interpreting possibly spurious findings and to take into consideration the fact that the inherent spatial coherence of lesions emphasizes contiguous effects, we focus our discussion on brain regions where at least 10% of the voxels in the region met the 40% difference threshold. Brain regions were defined by the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

Results and Discussion

Figure 2 shows the results of the uncorrected VLSM analysis that included the entire set of participants (N = 106) and the continuous measure of effect size (i.e., not dividing participants into Inhibition and Facilitation groups). These results suggested that the primary inhibitory effects were in the frontal lobe (Figure 2A) and that the facilitative effects were in posterior parietal, occipital, and superior medial frontal regions (the latter two are likely to reflect artifacts of very large lesions). The lesion overlap subtraction analyses examined this more closely.

The voxel-wise lesion overlap subtraction results are shown in Figure 3. A total of 20,522 voxels met the 40% threshold for the “Inhibition > Facilitation” comparison (i.e., Inhibition group more likely to have lesion than Facilitation group, Figure 3A). The largest concentration of these voxels was in the precentral gyrus (8,543 voxels, 30.3% of region) and neighboring regions, including the inferior frontal gyrus pars opercularis (2,866 voxels,

34.7% of region), the postcentral gyrus (3,929 voxels, 12.7% of region), and the Rolandic operculum (1,567 voxels, 19.7% of region). For the reverse contrast (Facilitation > Inhibition, Figure 3B), only 914 voxels met the 40% threshold with no clusters meeting the 10%-of-region threshold (the largest cluster was in the angular gyrus: 617 voxels, 6.6% of region; the arrow in Figure 3B highlights this small cluster). As an internal replication, we repeated the analysis using a more restrictive group definition (upper and lower 10% of effect size) and a higher difference threshold (60% of group size). The results showed the same qualitative pattern: increased inhibitory effects associated primarily with inferior frontal lesions and increased facilitative effects not substantively associated with any lesion location.

These results indicate that damage to inferior frontal lobe structures (and perhaps the anterior inferior parietal lobe) increases the inhibitory effect of near semantic neighbors on word production. As discussed in the Predictions section above, this result suggests that the increased inhibitory effect of near semantic neighbors was due to decreased ability to select among competing alternatives resulting from IFG lesions. This result converges with the previous report of a positive correlation between inhibitory effects of near semantic neighbors and percent damage in IFG (Mirman, 2011).

We did not observe an effect of ATL lesion, but only 11 of the 47 participants had substantive lesions in ATL (i.e., including at least 10% of either the superior or middle temporal pole; see Figure 1B) and our 40% difference threshold required a group difference of at least 9–10 participants, so it was difficult to detect an ATL effect with so few ATL lesions (nearly all of the participants with ATL lesions would have had to be in one group or the other). Thus, the present data cannot rule out the possibility that ATL lesions do modulate semantic neighborhood effects, either in a facilitative or inhibitory direction, but the results can shed light on the role of IFG in word production. Related investigations of semantically-related errors in picture naming (e.g., *cow* - *horse*) have reported that lesions in anterior and middle temporal lobe increase the likelihood of such errors (Schwartz et al., 2009; Walker et al., 2011). These studies also found weaker effects of IFG lesions that were eliminated after controlling for non-verbal semantic deficits, which they interpreted as indicating that IFG is involved in conceptualization whereas the ATL is involved in lexical-semantic access (for related findings from omission errors, see also Chen et al., under review).

Our results further clarify the role of IFG in word production, namely its involvement in selecting among competing alternatives. Although the competitive selection demands of picture naming are relatively low, they are increased when naming a target with many near semantic neighbors, which is why individuals with IFG lesions show particularly large inhibitory effects of near semantic neighbors. Because selection errors will frequently – but not always – lead to semantic errors and semantic errors can be produced in other ways, examination of semantic errors provides a less direct window on the consequences of competitive selection deficits. Nevertheless, due to impaired competitive selection, IFG lesions should tend to increase the likelihood of semantic errors, which converges with more recent analyses of a larger group of participants in which the IFG lesion effect on semantic

errors survived controlling for non-verbal semantic deficits (Schwartz et al., 2012, particularly their Figure 7).

To interpret these findings fully, it is important to examine whether inhibitory and facilitative effects of a different sort of lexical neighbors have similar or different lesion correlates. To this end, Study 2 used the same approach to examine phonological neighbor effects.

Study 2: Phonological neighbors

Methods

Materials—The spoken word production data were drawn from the same set of PNT data. Phonological neighborhood density was defined as the summed log frequency of the target word and all words that share the word onset (i.e., same initial two phonemes; called “cohort density”; see Magnuson et al., 2007). This measure was selected because word onsets have particular importance in word production (e.g., Goldrick, Folk, & Rapp, 2010) and because preliminary studies suggested that this phonological neighborhood measure had the biggest impact on picture naming performance in a large group of participants with aphasia. The full set of PNT target words was divided based on a median split on cohort density and then a few words were removed in order to create two equal-sized ($N = 85$) groups of words that were matched on (log-transformed) word frequency, word length, and, when available, number of near semantic neighbors (using the same definition and norms as in Study 1). Measures of phonological neighborhood density tend to be highly correlated, so these two sets of words also differed in number of phonological neighbors as defined by the one-phoneme rule and the summed log frequency of the target word and its one-phoneme-rule neighbors. In other words, the two groups of words differed based on just about any measure of phonological neighborhood and were matched on word frequency, word length, and semantic neighborhood. The properties of the two sets of words are summarized in Table 2 and the full list of items is provided in Appendix A.

Participants—The full sample of participants consisted of the same 106 individuals as Study 1 and groups for the lesion overlap subtraction analysis were defined using the same approach. Phonological neighbor effect size was computed as the difference between picture naming accuracy for words with many phonological neighbors and words with few phonological neighbors. The top and bottom 30 participants based on this effect size were selected and then participants were removed in order to maximize the effect size difference between groups and match the groups on lesion size ($t < 1$, $p > 0.8$) and aphasia severity ($t = 1.58$, $p > 0.1$). The groups also did not differ on overall picture naming accuracy or on the proportion of semantic, formal, or nonword errors (all $p > 0.1$). See Appendix B for group means and standard deviations. The groups were formed while blinded to lesion location. The overall distribution of phonological neighbor effect sizes is shown in Figure 4A, with the shaded regions corresponding to the selected groups. The resulting Inhibition group ($N = 27$) had higher accuracy on words with few phonological neighbors than words with many phonological neighbors ($M_{\text{DIFF}} = 3.5\%$, $SD_{\text{DIFF}} = 3.7\%$; i.e., phonological neighbors inhibited performance in this group) whereas the Facilitation group ($N = 30$) showed the reverse effect: higher accuracy on words with many phonological neighbors than words with

few phonological neighbors ($M_{\text{DIFF}} = 8.2\%$, $SD_{\text{DIFF}} = 3.4\%$; i.e., phonological neighbors facilitated performance in this group). This difference was highly statistically significant ($t = 12.42$, $p < 0.0001$). These groups did not differ in their near semantic neighbor effect size (both groups exhibited an approximately 2% inhibition effect, $t < 1$, $p > 0.9$); nor did the groups in Study 1 differ in the cohort density effect size (both groups exhibited an approximately 2% facilitation effect, $t < 1$, $p > 0.9$).

Lesion analysis and voxel-wise lesion overlap subtraction—Image acquisition, lesion segmentation, and template registration methods were the same as in Study 1, as was the voxel-wise lesion overlap subtraction method. Figure 4B shows the coverage map for the full set of 57 participants in this analysis, which was nearly identical to Study 1. As in Study 1, we only report voxels where the subtraction difference was at least 40% of group size (11 for the Inhibition group, 12 for the Facilitation group) and focus our discussion on brain regions where at least 10% of voxels met this 40% threshold.

Results and Discussion

Uncorrected VLSM analysis examining the entire set of participants ($N = 106$) and the continuous measure of effect size (i.e., not dividing participants into Inhibition and Facilitation groups) suggested that the primary inhibitory effects were in the posterior superior temporal and inferior parietal lobes (Figure 5A) and there were virtually no voxels that showed a facilitative effect difference even at the uncorrected threshold (Figure 5B).

The voxel-wise lesion overlap subtraction results for cohort density effect size are shown in Figure 6. A total of 6,362 voxels met the 40% threshold for the “Inhibition > Facilitation” comparison (i.e., Inhibition group more likely to have lesion than Facilitation group, Figure 6A). Almost all (89.4%) of these voxels were in the posterior superior temporal and inferior parietal lobes, including the pSTG (2,189 voxels, 12.0% of the region), SMG (1,786 voxels, 18.0% of the region), and Heschl’s gyrus (462 voxels, 25.6% of the region) and extending into the Rolandic operculum (1,250 voxels, 15.8% of the region). For the reverse contrast (Facilitation > Inhibition, Figure 6B), only 82 voxels met the 40% threshold with no region substantially affected (no region had more than 0.5% of voxels that met this threshold). As in Study 1, this qualitative pattern was replicated using a more restrictive group definition (upper and lower 10% of effect size) and a higher difference threshold (60% of group size): increased inhibitory effects were associated with pSTG and SMG lesions and increased facilitative effects not substantively associated with any lesion location.

These results indicate that damage to posterior superior temporal lobe and inferior parietal lobe structures increases the inhibitory effect of phonological neighbors on word production. This finding is consistent with prior evidence that SMG and pSTG are sensitive to effects of phonological neighborhood density (Okada & Hickok, 2006; Peramunage et al., 2010; Prabhakaran et al., 2006; Righi et al., 2009) and converges with evidence that lesions in these regions correlate with phonological impairments in aphasia (e.g., Baldo et al., 2012; Fridriksson et al., 2010; Graves et al., 2008; Schwartz et al., 2012; Wilson et al., 2009). This region is also associated with mapping between phonological representations and articulatory representations in speech perception and speech production (e.g., Gow, 2012;

Hickok, 2012; Hickok & Poeppel, 2007). In the framework developed by Chen and Mirman (2012), the current results suggest that posterior superior temporal and inferior parietal lesions increased activation of phonological neighbors. This increase in phonological neighbor activation caused their lateral inhibition effect to outweigh their recurrent facilitation effect, thus making their net effect on target processing inhibitory (see also Chen & Mirman, under review, for behavioral evidence of this sort of reversal in spoken word comprehension). In addition, increased activation of phonological neighbors is consistent with recent voxel-based lesion-symptom mapping evidence that lesions in this region are associated with increased production of phonologically-related errors in picture naming (Schwartz et al., 2012).

General Discussion

Voxel-wise lesion overlap subtraction was used to examine how brain lesions impact the effects of semantic and phonological lexical neighbors on spoken word production. Starting with a large group of individuals with aphasia secondary to left hemisphere stroke, for each type of neighborhood effect, two severity-matched groups of individuals were identified: a group that exhibited maximal facilitation effects and a group that exhibited maximal inhibition effects. A lesion overlap subtraction method was then used to identify brain regions where lesions tended to produce inhibition or facilitation effects. No lesion locations convincingly corresponded to facilitation effects. Inferior frontal lobe lesions tended to increase the inhibitory effect of near semantic neighbors, posterior superior temporal and inferior parietal lobe lesions tended to increase the inhibitory effect of phonological neighbors (summarized in Figure 7). This pattern also emerged when a more restrictive group definition was used and in uncorrected VLSM analyses using a continuous measure of effect size in the full set of 106 participants. Given the convergence between all three analysis methods, the results are unlikely to be due to peculiarities of the group assignment or comparison procedure.

We interpret these results in the context of the Chen and Mirman (2012) computational model account of lexical neighbor effects. The core principle of that account is that lexical neighbors exert both inhibitory and facilitative effects, with facilitative effects dominating when neighbor activation is low and inhibitory effects dominating when neighbor activation is high. Because picture naming is a semantically-driven task, near semantic neighbors are expected to be highly activated and already exerting a net inhibitory effect (Mirman, 2011). A large body of evidence indicates that inferior frontal damage impairs cognitive control mechanisms involved in selection among competing alternatives (e.g., Schnur et al., 2009; Snyder et al., 2007; Nozari et al., 2012); the current evidence suggests that this cognitive control impairment exacerbates the inhibitory effect of near semantic neighbors.

Several functional imaging studies have documented the involvement of posterior superior temporal and inferior parietal regions in phonological-lexical processing, including phonological neighbor effects (Okada & Hickok, 2006; Peramunage et al., 2010; Prabhakaran et al., 2006; Righi et al., 2009). Further, damage to pSTG and SMG is known to cause phonological processing deficits (Baldo et al., 2012; Fridriksson et al., 2010; Schwartz et al., 2012; Wilson et al., 2009). Efforts to develop a theoretical framework for

speech processing have cast this region as a “dorsal lexicon” that is involved in mapping between phonological and articulatory representations (e.g., Gow, 2012; Hickok, 2012; Hickok & Poeppel, 2007). The present finding that damage to this region increases the inhibitory effect of phonological neighbors in spoken word production is consistent with these past findings in the general sense that it reflects a phonological-lexical impairment. In the context of the theoretical and computational framework developed by Chen and Mirman (2012), the increased inhibitory effect provides additional elaboration: when these brain regions are lesioned, phonological-lexical feedback more strongly activates phonological neighbors, causing their inhibitory effect to outweigh their facilitative effect. Although the specific reason for this increased activation is not clear, one possibility is that the downstream mapping from phonological targets to articulatory motions is impaired, resulting in a build-up of phonological-lexical feedback that increases activation of phonological neighbors. This possibility is consistent with Hickok’s (2012) recent proposal that this region (which he calls Spt: Sylvian fissure at the parieto-temporal boundary) is involved in mapping between phonological targets and motor syllable programs.

Unlike the inhibitory effect of semantic neighbors, IFG lesions did not appear to increase the inhibitory effects of phonological neighbors, suggesting that the inhibitory effect of phonological neighbors was not due to deficits of selection among competing alternatives. As discussed in the Introduction, in typical (neurologically intact) spoken word production, phonological neighbors are weakly activated by phonological-to-lexical feedback. This weak activation may only weakly engage competitive selection mechanisms supported by IFG, which are thought to be particularly important for resolving competition among strongly activated candidates (e.g., Snyder et al., 2007). It is possible that the conjunction of SMG/pSTG and IFG damage would cause particularly strong inhibitory effects of phonological neighbors if phonological neighbors were more strongly activated due to SMG and pSTG damage and competitive selection mechanisms were deficient due to IFG damage. However, the present subtraction methodology is not well-suited to detecting such conjunctions. A multivariate or multi-voxel pattern analysis method would be necessary, but such methods are only beginning to be developed for voxel-wise lesion analysis (e.g., Smith et al., 2013). More importantly, lesions that include both posterior temporal and inferior frontal regions would be quite large and would likely cause severe word processing deficits, so it is not clear that such a conjunction could be distinguished from an overall effect of lesion size and/or cognitive deficit severity.

We did not observe any lesion location that was convincingly associated with increased facilitative effects of either semantic or phonological neighbors. In the case of phonological neighbors, this may be due to the very narrow window for increasing their typical facilitative effect. Increasing the facilitative effect of phonological neighbors requires optimizing the balance between more neighbor activation, which would make their effect inhibitory, and less neighbor activation, which would eliminate their effect. In the present data, there is no evidence that lesions in a particular location optimize this balance. In the case of semantic neighbors, ATL – due to its association with semantic deficits – was the primary candidate for a lesion location that might reduce the activation of semantic neighbors, thus making their effect less inhibitory and more facilitative. First, it is also possible that ATL lesions would cause the opposite result because semantic deficits may equalize the activation

between the target and its semantic neighbors, thus making their effect more inhibitory. Second, there were relatively few participants in the semantic neighbor analysis with substantive lesions in ATL, so it was difficult to detect an ATL effect with so few ATL lesions³. Thus, the present data cannot rule out the possibility that ATL lesions do modulate semantic neighborhood effects, either in a facilitative or inhibitory direction.

Parallel activation of multiple related candidates is a core principle of lexical processing theories. The present results demonstrate the different ways that lesions can disrupt the dynamics of this process. The inhibitory effects of semantic neighbors were increased by inferior frontal lobe lesions, suggesting impaired competitive selection mechanisms. Inferior frontal lesions did not cause comparable increases in inhibitory effects of phonological neighbors because phonological neighbors are only weakly activated during spoken word production. Rather, posterior superior temporal and inferior parietal lesions caused an increase in inhibitory effects of phonological neighbors, indicating that this sort of damage allows phonological-to-lexical feedback to more strongly activate lexical items that are phonologically similar to the target. These findings further refine our understanding of the functional and neural coordination of interactive activation, competition, and response selection mechanisms in spoken word production.

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³There was good coverage throughout the peri-Sylvian regions, including IFG, STG, angular gyrus, and SMG, so the contrast between the IFG effect for semantic neighbors and pSTG/SMG effect for phonological neighbors cannot be due simply to power differences.

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Appendix A: Complete target word lists

All items are taken from the Philadelphia Naming Test (Roach et al., 1996). Test administration and scoring details, along with the complete set of pictures are available at: <http://www.mrri.org/philadelphia-naming-test>.

Study 1: Semantic neighbors

Few: anchor, balloon, bed, belt, bench, book, bread, bridge, camel, candle, carrot, clock, closet, comb, corn, crown, desk, drum, football, fork, hose, key, kite, lamp, pencil, pig, pyramid, rake, rope, ruler, skis, slippers, table, tent, tractor, whistle.

Many: apple, ball, banana, bottle, bowl, broom, bus, cake, cannon, celery, chair, church, dog, door, elephant, frog, hammer, horse, knife, necklace, octopus, owl, pear, pen, piano, pie, pillow, pumpkin, scarf, scissors spider, squirrel, train, turkey, van, wagon.

Study 2: Phonological neighbors

Few: ambulance, anchor, apple, ball, binoculars, book, boot, bread, bride, bridge, broom, chair, cheerleaders, chimney, church, clock, closet, clown, cow, cowboy, cross, crown, crutches, dinosaur, dog, door, dragon, drum, ear, elephant, eskimo, eye, flashlight, flower, foot, football, frog, garage, ghost, glass, glove, goat, grapes, hair, house, iron, key, kite, knife, mountain, nail, necklace, nurse, octopus, owl, pie, pineapple, pipe, pirate, plant,

queen, ruler, saw, scale, scarf, shoe, skis, skull, slippers, snake, sock, spider, spoon, squirrel, strawberries, toilet, towel, train, tree, vase, vest, volcano, wagon, whistle, zipper.

Many: baby, balloon, banana, basket, bat, beard, bed, bell, belt, bench, bone, bottle, bowl, bus, butterfly, cake, calendar, camel, camera, can, candle, cane, cannon, carrot, cat, celery, comb, corn, desk, dice, duck, fan, fireman, fireplace, fish, fork, hammer, hand, harp, hat, heart, helicopter, horse, hose, king, kitchen, lamp, leaf, letter, lion, man, map, microscope, monkey, mustache, nose, pear, pen, pencil, piano, pig, pillow, pumpkin, pyramid, rake, ring, rope, saddle, sailor, sandwich, scissors, seal, star, suit, sun, table, tent, top, tractor, turkey, typewriter, van, waterfall, well, window.

Appendix B: Participant group means (standard deviations in parentheses)

	Study 1: Semantic neighbors		Study 2: Phonological neighbors	
	Inhibition	Facilitation	Inhibition	Facilitation
N	25	22	27	30
WAB AQ	75.4 (14.8)	76.8 (15.8)	71.8 (16.6)	78.3 (14.1)
Lesion Volume (cc)	99.8 (69.5)	87.8 (59.4)	86.7 (71.5)	83.0 (62.3)
Picture Naming (PNT)				
% Correct	70.0 (20.8)	63.2 (25.5)	62.0 (28.1)	69.4 (21.6)
% Semantic errors	3.4 (2.0)	4.0 (2.5)	3.1 (2.2)	3.7 (2.8)
% Formal errors	3.4 (4.2)	5.2 (6.5)	5.6 (6.6)	3.3 (3.9)
% Nonword errors	8.5 (7.7)	9.7 (10.8)	11.7 (11.4)	8.7 (8.9)

Figure 1.

A: Distribution of semantic neighbor effect sizes in proportion correct picture naming (i.e., negative values correspond to inhibitory effect of neighbors). Shaded bars correspond to participants selected for lesion overlap subtraction analysis. B: Coverage map for semantic neighbor lesion overlap subtraction at $x = -52$, $y = 7$, $z = 4$.

Figure 2.

VLSM of near semantic neighbor effects (uncorrected t -maps). Larger t -values (brighter colors) correspond to larger inhibitory (A; $x = -55$, $y = -25$, $z = 17$) or facilitative (B; $x = -44$, $y = 42$, $z = 21$) effects of near semantic neighbors in participants with a lesion in that voxel than participants without a lesion in that voxel. Only $t > 1.66$ ($p < 0.05$) values are shown.

Figure 3.

Voxel-wise lesion overlap subtraction maps of near semantic neighbor effects. A: Voxels where Inhibition group had at least 40% more lesions than Facilitation group did; at $x = -53$, $y = -25$, $z = 20$. B: Voxels where Facilitation group had at least 40% more lesions than Inhibition group did (arrow highlights the small cluster of voxels meeting this threshold); at $x = -44$, $y = 42$, $z = 21$.

Figure 4.

A: Distribution of phonological neighbor effect sizes in proportion correct picture naming (i.e., positive values correspond to facilitative effect of neighbors). Shaded regions correspond to participants selected for lesion overlap subtraction analysis. B: Coverage map for phonological neighbor lesion overlap subtraction at $x = -52$, $y = 7$, $z = 4$.

Figure 5.

VLSM of near phonological neighbor effects (uncorrected t -maps). Larger t -values (brighter colors) correspond to larger inhibitory (A; $x = -55$, $y = 16$, $z = 1$) or facilitative (B; $x = -35$, $y = -18$, $z = 3$) effects of phonological neighbors in participants with a lesion in that voxel than in participants without a lesion in that voxel. Only $t > 1.66$ ($p < 0.05$) values are shown.

Figure 6.

Voxel-wise lesion overlap subtraction maps of phonological neighbor effects. A: Voxels where Inhibition group had at least 40% more lesions than Facilitation group did; at $x = -50$, $y = 12$, $z = 6$. B: Voxels where Facilitation group had at least 40% more lesions than Inhibition group did; at $x = -35$, $y = -18$, $z = 3$.

Figure 7.
Voxel-wise lesion overlap subtraction proportion difference maps (at $x = -52$, $y = 12$, $z = -2$) of inhibitory effects of semantic (red-yellow) and phonological (blue-white) neighbors in spoken word production.

Table 1

Mean (SD) target word properties for near semantic neighborhood manipulation.

	Few	Many	t	p
Num. words	36	36	-	-
Num. semantic neighbors	0 (0)	3.3 (3.9)	5.14	< 0.0001
Num. features	14.4 (2.3)	14.9 (2.4)	0.95	n.s.
HAL word frequency	8.7 (1.3)	8.8 (1.4)	0.23	n.s.
ANC word frequency	1.0 (0.5)	1.1 (0.5)	0.86	n.s.
Num. phonemes	4.2 (1.2)	4.2 (1.4)	0.0	n.s.
Phonological neighborhood density	13.3 (13.2)	12.7 (13.8)	0.18	n.s.
Cohort density	50.4 (42.6)	43.1 (40.8)	0.74	n.s.

Table 2

Mean (SD) target word properties for phonological neighborhood manipulation.

	Few	Many	t	p
Num. words	85	85	-	-
Cohort density	14.9 (8.7)	73.2 (36.0)	14.5	< 0.0001
Num. phonological neighbors	10.2 (8.8)	14.1 (11.3)	2.51	< 0.05
Phonological neighborhood density	11.8 (12.8)	16.2 (15.2)	2.05	< 0.05
HAL word frequency	8.7 (1.5)	9.1 (1.6)	1.51	n.s.
ANC word frequency	1.1 (0.7)	1.2 (0.7)	0.94	n.s.
Num. phonemes	4.3 (1.7)	4.4 (1.5)	0.09	n.s.
Num. semantic neighbors	2.0 (3.7)	1.6 (3.7)	0.59	n.s.

Note: Number of semantic neighbors data were only available for 92 of the 170 words (43 in the Few condition, 49 in the Many condition).