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Uncovering the Neural Substrates of Language: A Voxel-Based Lesion–Symptom Mapping Approach

Juliana V. Baldo, Stephen M. Wilson, and Nina F. Dronkers

History of Lesion–Symptom Mapping in Aphasia

For many years, scientists have been attempting to uncover the neural substrates of language (Roth & Heilman, 2000; Whitaker, 1998). Early studies necessarily relied on postmortem analyses of patients with documented language impairment. Using this approach, Bouillaud (1825) described a large series of cases of patients with speech impairment who, upon autopsy, were revealed to have damage in the anterior portions of the brain. Broca's original cases (1861, 1865) further suggested that lesions in anterior portions of the left hemisphere in particular were most critical for producing such difficulties with articulation. Later, Wernicke (1874) described a left posterior region for processing sensory aspects of language related to the auditory word form. These early studies provided a basis for not only an understanding of the neural substrates of language, but also a scientific approach for answering a variety of brain–behavior questions.

The study of the neural basis of language had fallen out of favor in the scientific community by the middle of the twentieth century until Geschwind revived interest in aphasia in the 1960s (Damasio & Geschwind, 1984; Geschwind, 1972; Geschwind & Levitsky, 1968; Roth & Heilman, 2000). Along with his colleagues, Geschwind revisited the models put forward by the nineteenth-century aphasiologists and reasserted the usefulness of analyzing brain–behavior relationships. With the advent of computed tomography (CT) scanning in the 1970s, a whole new world opened up to allow for the detailed analysis of language–brain relationships that could be conducted on the living brain (Alexander, Naeser, & Palumbo, 1990; Basso, Lecours, Moraschini, & Vanier, 1985; Mazzocchi & Vignolo, 1979; Mohr, 1976;

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Naeser & Hayward, 1978; Pettit & Duffy, 1991; Yarnell, Monroe, & Sobel, 1976). Some of these studies confirmed long-held views of aphasia, such as the association of anterior lesions with nonfluent, Broca-like aphasia and the association of posterior lesions with fluent, Wernicke-like aphasia. However, a number of exceptions were also noted, such as the clinical presentation of global aphasia with relatively circumscribed lesions, anterior lesions causing fluent aphasia, posterior lesions causing nonfluent aphasia, and lesions to Broca's area alone that did not lead to a persisting Broca's aphasia (e.g., Basso et al., 1985; Mohr et al., 1978; Willmes & Poeck, 1993).

The next big advance in mapping language in the brain came with the expanded use of magnetic resonance imaging (MRI) in the 1980s (DeWitt, Grek, Buonanno, Levine, & Kistler, 1985; Kriesler et al., 2000). MRI images allowed for a much more fine-grained analysis of brain areas affected in aphasia given the greatly improved spatial resolution. These studies were an improvement over earlier research using CT, although they still often relied on grouping patients based on lesion site (e.g., anterior vs. posterior or frontal vs. temporal) in an attempt to draw conclusions about the types of language syndromes stemming from such damage. Alternatively, patients were grouped based on aphasia classification (e.g., Broca's, Wernicke's, etc.) or a specific aphasic symptom, and a common lesion site for patients belonging to the group was determined (Kertesz, 1979; Kertesz, Harlock, & Coates, 1979). An extension of this method was a lesion-overlapping approach whereby the lesions of patients with a particular symptom (e.g., apraxia of speech) were digitized and averaged together to identify regions of common overlap (Dronkers, 1996; Friedrich, Egly, Rafal, & Beck, 1998; Knight, Scabini, Woods, & Clayworth, 1988). Such methods are still commonly used and in some cases are preferable to newer voxel-based methods described below, such as when there is a clear-cut a priori hypothesis regarding a specific brain region and/or with smaller sample sizes.

While earlier lesion studies were critical to furthering our understanding of the brain basis of language, they were also constrained in a number of ways. First, finding language patients who neatly fit into a particular category (e.g., focal frontal or pure Broca's) is difficult, as often lesions cross neural boundaries and language syndromes are rarely pure. Therefore, many patients were often excluded from the analyses, and data were lost. Second, the boundaries often used to divide patients into groups (e.g., anterior vs. posterior) are somewhat arbitrary and may not reflect distinctions that are significant for the investigation of a particular linguistic behavior. Third, this approach required that patients be separable based on some binary distinction (e.g., patients with Broca's aphasia vs. those without), and thus patients' data could not be analyzed in a more quantitative manner (e.g., with more or less fluency). Another stumbling block has been the overreliance on syndrome labels (Broca's, Wernicke's, etc.), which often group together patients who may have quite distinct clinical symptoms. That is, the range of patients who might be labeled as Broca's can be quite broad, ranging from patients with little more than repetitive utterances to patients who can generate appropriate strings of words, albeit somewhat agrammatically. Despite these limitations, lesion studies following the advent

of structural imaging techniques not only resulted in an explosion of new research in the area of the neural basis of language, but also provided a coherent road map for future research.

Voxel-based Lesion–Symptom Mapping

Recently, new lesion analysis techniques have become available that allow for a voxel-based statistical analysis of lesion data from stroke patients as they relate to speech and language changes (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000; Bates et al., 2003; Damasio & Frank, 1992; Kimberg, 2009; Rorden, Fridriksson, & Karnath, 2009; Rorden & Karnath, 2004; Rorden, Karnath, & Bonilha, 2007). This approach, called voxel-based lesion–symptom mapping (VLSM) has been applied to a number of questions regarding the brain basis of language as well as related areas of cognition (Baldo & Dronkers, 2007; Baldo et al., 2005; Baldo, Schwartz, Wilkins, & Dronkers, 2006; Bates et al., 2003; Borovsky, Saygin, Bates, & Dronkers, 2007; Bright, Moss, Longe, Stamatakis, & Tyler, 2007; Chatterjee, 2008; Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Damasio, Tranel, Grabowski, Adolphs, & Damasio, 2004; Glascher et al., 2009; Rudrauf, Mehta, Bruss, et al., 2008; Saygin, Wilson, Dronkers, & Bates, 2004; Tyler, Marslen-Wilson, & Stamatakis, 2005a, 2005b; Wilson & Saygin 2004; Wu, Waller, & Chatterjee, 2007). VLSM refers to techniques that calculate a test statistic at each voxel, relating the presence or absence of lesions and some cognitive measure, in order to make inferences about the brain regions necessary for the measured cognitive process. VLSM provides an alternative to the lesion overlapping method and allows one to answer different questions about the neural basis of language. A number of different VLSM software programs are freely available on the web (e.g., http://www.neuroling.arizona.edu/resources.html; and http://www.cabiatl.com/mricro/npm/). A related and very similar analysis technique, voxel-based morphometry (VBM), is used in cases of neurodegenerative disease and will not be discussed here (see Asburner & Friston, 2000, for a review).

Briefly, VLSM methodology identifies voxels or voxel clusters that are significantly related to a particular behavior of interest in a group of patients. The technique involves running a statistical test (e.g., a *t*-test for continuous data or a binomial test for a binary comparison) at every voxel, comparing patients' scores on a behavioral measure (e.g., auditory comprehension) in those patients with vs. without a lesion in that voxel. Voxels showing a significant relationship to the given behavioral measure are highlighted, and color-coded maps can be generated based on the relevant statistics (e.g., *t*-values), similar to functional neuroimaging. Noninferential statistics and nonparametric statistics (e.g., Brunner-Munzel rank order test) can also be used as a substitute for the traditional *t*-test statistic, depending on the sample size and distribution profile of the data (Rorden, Karnath, & Bonhila, 2007). Figure 28.1 illustrates the steps of the analysis technique.

Voxel-based analyses provide a number of advantages over prior lesion study approaches. First, the results from VLSM analyses can be directly compared to fMRI

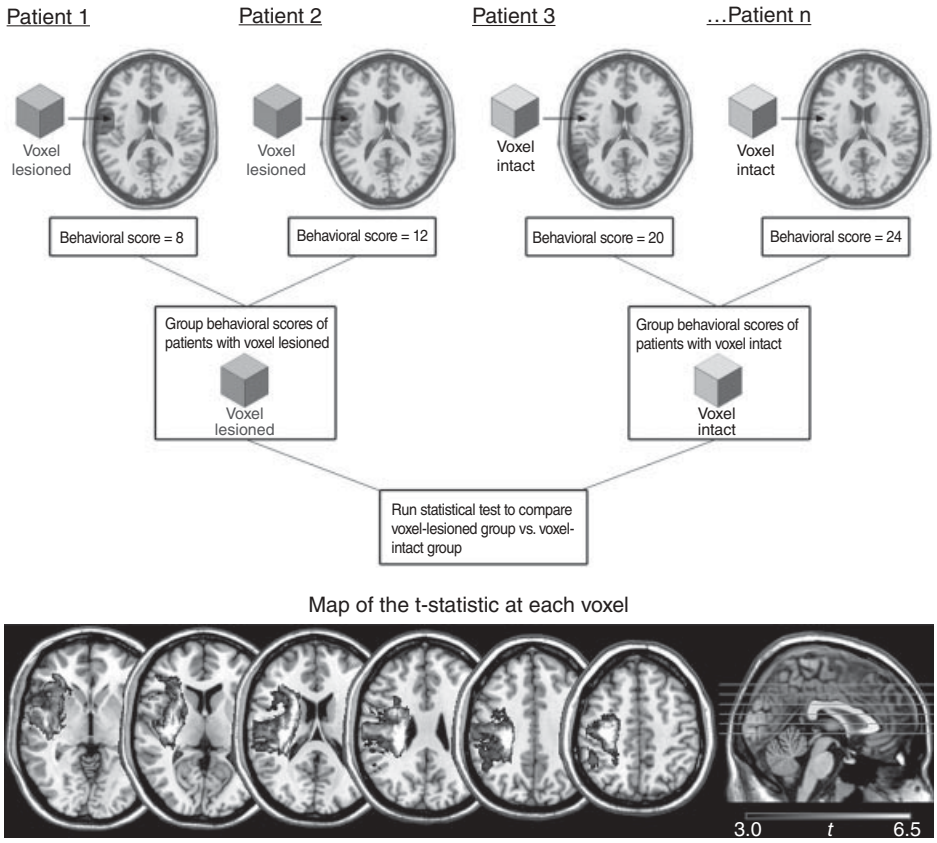

Figure 28.1 In the first stage, patients' lesions, which have been reconstructed onto a standardized template, are read into the analysis. Second, at every voxel, a statistical test is run to compare the behavioral scores (e.g., comprehension, fluency, etc.) of patients with and without a lesion in that voxel. The resulting test statistics (e.g., *t*-values) at every voxel are then color-coded and visualized as shown. In the next step (not shown), a statistical correction is applied (e.g., permutation testing) to correct for the large number of comparisons being done, so that only voxels meeting a pre-specified significance level are displayed.

and PET findings generated from normal participants, as the patients' lesions are digitally reconstructed in a common, standard stereotaxic space (e.g., MNI space). Such comparisons allow for a more comprehensive understanding of the behavior in question: Functional imaging in normal participants can tell us the range of brain regions involved in a particular cognitive operation, and VLSM analyses can tell us which part(s) of that network is (are) most critical to that operation (Rorden & Karnath, 2004; Tyler, Marslen-Wilson, & Stamatakis, 2005b). Second, the behavioral data in a VLSM analysis can be continuous (e.g., percent correct on an auditory comprehension task) rather than making a binary distinction (e.g., patients with

and without comprehension deficits), thus allowing for the inclusion of a wide range of patient performance and thereby increasing power and sensitivity. Third, VLSM analyses allow for a wide range of lesion size and location, and thus data are not lost to exclusion criteria (e.g., only those patients with focal frontal or temporal lesions). Furthermore, lesion size as well as other nuisance variables such as age and time post-onset can be formally accounted for as covariates in VLSM analyses (Kimberg, Coslett, & Schwartz, 2007). Last, VLSM allows one to observe the effects of lesions in a number of regions at once, such that a whole network can be visualized rather than focusing on one or two particular regions of interest.

Although VLSM represents a potentially more rigorous approach to lesion analysis, a number of constraints and caveats must be considered, many of which also apply to functional imaging modalities such as fMRI and PET (see Kimberg et al., 2007; Rorden et al., 2007). First, it is critical that statistical corrections be applied to the data, in order to control for the number of false positive results, given the large number of voxels being sampled. Studies that compare different types of corrections show that Bonferroni correction is the most conservative correction, permutation testing less so, and false discovery rate (FDR) correction, the most liberal (Kimberg et al., 2007). Bonferroni correction is often considered to be too severe a correction, because it corrects for all comparisons, when in fact lesions often affect neighboring voxels and thus they are not truly independent tests (Rorden et al., 2007). The FDR correction has the same problem of nonindependence. Another type of correction, Gaussian random field theory, is commonly used for fMRI but is not appropriate for structural studies, because of the greater degree of spatial dependence (see Ashburner & Friston, 2000).

Currently, statistical correction based on permutation testing is most accepted, because it accounts for the large number of multiple comparisons that are entailed when computing statistics at every voxel. Permutation testing involves randomly reassigning the behavioral data across the whole sample, thereby creating a simulation of how often extreme observations would be generated under the null hypothesis of no association between lesion site and behavioral score. For example, in a typical VLSM analysis, 1,000 permutations of the data may be run, which will then provide a critical *t*-value with *alpha* set to .05, that is, a *t*-value that we would only expect to occur 5% of the time by chance, based on the random permutations. Alternatively, one can use a cluster size threshold, based on the results of the permutation testing, such that only cluster sizes occurring <5% of the time are considered significant. Permutation testing is ideal in many ways because of the lack of assumptions made about the data and the fact that it preserves power (relative to Bonferroni correction; Rorden et al., 2007). As Kimberg et al. (2007) point out, this method probably would have been in widespread use a long time ago, except for the high degree of microcomputing cost necessary to run the permutations.

Another important consideration with VLSM is the issue of power. Given the strict corrections required, power to detect differences may be greatly diminished, especially with small sample sizes. It is recommended that power analyses be run prior to VLSM analyses in order to determine the ability of the analysis to detect

statistical differences across the different voxels/brain regions (Kimberg et al., 2007). Patient pools are a convenience sample, and thus do not include a randomized set of lesions that cover the entire brain. For example, certain regions, such as the left perisylvian region are often overrepresented due to the frequency and severity of strokes in the middle cerebral artery territory. Thus, it is important to determine the ability of a particular study to detect differences in voxels that may be less represented. For certain regions that are not well represented in typical stroke studies – for example, very inferior temporal areas – it is important not to make assumptions about null findings when in fact the null effects may be due to a reduced power profile in these regions. Rather, predictions must be confined to brain regions with sufficient power.

A third issue is that VLSM analyses should be limited to voxels with a reasonable number of patients with and without a lesion in that voxel, so that statistical tests are not based on, for example, 1 lesioned patient versus 50 nonlesioned patients, just as one would not run any type of statistical test with such unbalanced group sizes.

A final caveat to VLSM relates to the preprocessing stage. Prior to the VLSM analysis, patients' lesions must be reconstructed (digitally or manually) and standardized into a common stereotaxic space, such as MNI space, so that all images are in roughly equivalent correspondence. Generally, T1-weighted MRI scans are most appropriate when lesions are traced directly on to digital images. Lesion masks are recommended during the normalization process so that the lesion itself does not bias the transformation into normalized space (Brett, Leff, Rorden, & Ashburner, 2001). Alternatively, lesions may be reconstructed manually onto a standard template (e.g., Damasio & Damasio, 1980; Knight et al., 1988). Automatized programs for delineating lesions have been developed, but it is still argued whether such automated programs are sufficiently accurate and preferable to a skilled rater (Kimberg et al., 2007). Because it is very difficult to determine the exact border of a lesion, Kimberg et al. (2007) have suggested the use of probabilistic maps based on a range of scores (e.g., 0 for no lesion, 0.5 for possible lesion, and 1.0 for a certain lesion), where voxels would be more likely to be scored as 0 or 0.5 along the lesion border. Still, without functional data, it is impossible to be sure which voxels are truly lesioned and nonfunctional based on a structural MRI scan. Furthermore, this and other lesion-reconstruction techniques cannot capture diaschetic effects occurring at previously innervated targets of lesioned areas. Clearly, as methods for preprocessing lesion images improve, so will the accuracy of VLSM analyses applied to the data.

Application of VLSM to the Study of Language

The VLSM approach has been applied to the analysis of a number of different linguistic variables, in an effort to map brain networks critically involved in speech and language. In an early study using VLSM, Bates et al. (2003) tested a group of

101 chronic left hemisphere patients who suffered from a range of speech and language deficits. The dependent variables were patients' scores on fluency and comprehension subtests of the Western Aphasia Battery (WAB; Kertesz, 1982). Bates et al. found that fluency (in spontaneous speech) was most significantly associated with voxels in the left anterior insula and parietal white matter, specifically, the superior longitudinal fasciculus or SLF. Auditory comprehension, on the other hand, was most strongly associated with voxels in the left middle temporal gyrus (MTG). Although these findings were generally in keeping with an anterior–posterior dichotomy for fluency versus comprehension, the precise regions did not lie in the classical brain regions usually attributed to these functions, namely, Broca's area and Wernicke's area. Indeed, when voxels in these classic areas were used as covariates, the left insula and MTG were still found to be significantly associated with fluency and comprehension, respectively. In contrast, Broca's and Wernicke's area were not significantly associated with these functions once the insula and MTG were factored out. Therefore, this novel approach using VLSM enabled a more precise mapping of speech and language variables without having to rely on a priori regions of interest or arbitrary cut-off scores.

Since this report, a number of groups have made use of VLSM methodology to map speech and language networks in the brain. Many of these studies have used VLSM to characterize the network underlying language comprehension (Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Wilson & Saygin, 2004; Wu, Waller, & Chatterjee, 2007). In a detailed analysis of language comprehension, Dronkers et al. used VLSM to map brain regions in the left hemisphere critical for different aspects of auditory sentence comprehension. Overall, Dronkers et al. found that the following regions were most critical for auditory, sentence-level comprehension (sentence–picture matching): left MTG, anterior superior temporal gyrus (STG), superior temporal sulcus (STS)/angular gyrus (AG), and BA 46 and 47 (lateral prefrontal cortex). As before, the classical areas of Broca (BA 44/45) and Wernicke (BA 41/42) were not significantly associated with performance on these measures. When broken down into the types of syntactical structures, from simple (e.g., possession) to more complex (e.g., double embedding), a hierarchy of regions emerged. Specifically, the MTG was critical across all sentence structures, even the simplest subtests of possession and simple declaratives. The anterior STG was significantly involved in somewhat more complex structures, such as active voice and agentless passive. The most syntactically complex subtests relied on these basic comprehension areas but also showed reliance on BA 46 and 47, possibly due to the role of these areas in higher-level aspects critical for complex comprehension such as verbal rehearsal.

In a study that tested the notion that inferior frontal regions are critically important for syntactic processing, Wilson and Saygin (2004) used VLSM to study brain regions underlying patients' ability to make grammaticality judgments. Patients were presented with a series of sentences, half of which were not grammatical, and were asked to decide which items "sounded funny." Counter to prior notions of syntactic processing being associated primarily with inferior frontal cortex, Wilson

and Saygin found that performance on this task was most reliant on a region that encompassed the left posterior middle and superior temporal gyri, as well as the STS. However, a small number of anterior patients also performed poorly on the task, leading them to conclude that a network of perisylvian regions is involved in syntactic processing.

Tyler et al. (2005a) assessed the neural basis of regular versus irregular past tense verbs using VLSM and a lexical decision priming paradigm. They tested the hypothesis that the regular past tense is processed by brain regions which also subserve phonological processing, while irregular past tense verbs are processed by regions that subserve semantic processing. Counter to this theory, distinct regions were observed to subserve these processes: the regular past tense was significantly associated with the inferior frontal gyrus (BA 47), with little overlap with regions mediating phonological processing. The irregular past tense was associated with lesions in left inferior and superior parietal cortex, while semantics was associated with left fusiform hippocampus/parahippocampal regions. Therefore, they concluded that processing the regular and irregular past tense does not map directly on to phonological and semantic processing, respectively, and that regular and irregular past tense verbs are processed by distinct regions within a distributed but specific language network.

Testing a group of patients with aphasia, Saygin et al. (2004) compared comprehension of active sentences to nonverbal comprehension of the same actions. Patients had to choose the picture (e.g., an ice cream cone) that best completed a written sentence (e.g., *He is licking the . . .*) or a drawing of that pantomimed action (e.g., a boy licking something). They found that the sentence condition was associated with lesions in left anterior, superior temporal cortex, the anterior insula, and inferior parietal cortex. In contrast, poor pantomime interpretation was associated with lesions in left inferior frontal cortex, ventral pre-motor and motor cortex, and a portion of primary somatosensory cortex. Their findings, they concluded, were consistent with the embodiment notion of brain organization, such that processing actions (even without executing those actions) relies on motor regions in the brain.

Another set of papers has used VLSM to delineate the extent of regions involved in speech production. Borovsky et al. (2007) analyzed spontaneous speech data from 50 patients with aphasia using VLSM. Patients' speech samples from biographical interviews were scored on a number of parameters such as the number of tokens produced (i.e., fluency) and type–token ratio, which is a measure of semantic content. They found that fluency was associated most strongly with the left anterior insula, motor cortex, and superior longitudinal fasciculus. In contrast, the measure of semantic content was most significantly associated with the left middle and superior temporal gyri.

Another aspect of speech production, word retrieval, was tested by comparing brain regions associated with retrieval based on phonemic cues (i.e., letter fluency) vs. word retrieval from semantic categories (i.e., category fluency; Baldo et al., 2006). Prior research had suggested that letter fluency is dependent on anterior brain

regions, while category fluency is associated with temporal cortex. This prediction was based on studies in the literature looking at fluency in frontal patients who are reported to have difficulty primarily on letter fluency and separate studies on Alzheimer's patients who have marked difficulty on category fluency task. VLSM allowed for the analysis of both of these tasks in a single study with a single group of patients who were not selected based on any a priori groupings. The VLSM maps revealed significant foci in left frontal and temporal cortex for letter and category fluency, respectively, as predicted. However, additional voxels in inferior parietal cortex were significantly associated with performance on both types of tasks, suggesting a common role for this brain region in both tasks, perhaps due to its role in verbal working memory.

Voxel-based approaches have also been applied to the analysis of brain regions underlying conceptual knowledge. Bright et al. (2007) administered a property-verification task, in which patients had to answer yes/no questions such as, *Do cats have fur?* They found that anteromedial temporal cortex was critical for performance when the conceptual demands involved making a fine-grained analysis (e.g., when stimuli were animals, which have greater within-category similarity). Damasio et al. (2004) measured performance in a large group of patients, comparing object naming versus conceptual knowledge. They found that naming was most consistently associated with left temporal cortex, while conceptual knowledge (tested by recognition) relied more on the right hemisphere. Rudrauf, Mehta, Bruss, et al. (2008) used a type of VLSM to study deficits in naming and recognition across a range of semantic categories (e.g, animals, tools, faces, etc.). They calculated the relative proportion of patients with a particular symptom and a lesion at a particular voxel vs. patients with that symptom but no lesion at that voxel. They found a considerable degree of overlap in regions, for example, left anterior inferior temporal cortex was critical for naming across all five categories of concrete items they tested. However, they also found evidence of specific category-related regions in certain cases, such as the unique association of tools with left inferior parietal cortex.

In another naming study, Baldo, Arevalo, Wilkins, and Dronkers (2009) conducted a VLSM analysis of data from a large group of 92 patients on the Boston Naming Test (BNT), in order to determine regions critical for naming across different semantic categories (animals vs. tools, living vs. nonliving, and manipulable vs. nonmanipulable items). Counter to prediction, there were no major dissociations in the maps, as may have been predicted based on earlier case studies of impaired naming. Rather, performance across categories was associated with lesions in the left middle and superior temporal gyri. This study exemplifies the utility of a VLSM approach in its ability to analyze large datasets to identify commonly affected brain regions critical to a particular cognitive process.

The VLSM approach has also been used to look at the relationship between language and other cognitive processes, such as problem solving (Baldo et al., 2005) and arithmetic (Baldo & Dronkers, 2007), and has been applied to the analysis of nonlinguistic constructs such as IQ (Glascher et al., 2009) and visuospatial processing (Committeri et al., 2007; Karnath, Berger, Kuker, & Rorden, 2004).

Conclusion

In short, VLSM methodology represents a promising new method for analyzing lesion–behavior relationships. This approach allows for a more quantitative and statistically rigorous approach to lesion mapping that has already begun to further our understanding of the brain basis of speech and language processes and has produced a number of unique findings that illustrate the breadth of the speech/language network. Unlike traditional models that focus on Broca's and Wernicke's areas, we are learning that many regions of the left hemisphere outside these classical zones play a critical role in linguistic functions. VLSM has allowed for the visualization of these additional areas, as it does not rely on a priori regions of interest or specific language diagnoses, but rather allows for a relatively objective analysis of a large number of brain regions and their role in language.

Like functional neuroimaging methods, VLSM allows one to visualize a network of brain regions involved in a cognitive process of interest. Unlike functional neuroimaging, however, VLSM allows for a more direct, casual inference to be made, as regions implicated in the task can be viewed as *critical* to the task, rather than simply involved. Clearly, findings from VLSM analyses and functional neuroimaging are complementary and, considered in conjunction, these data can provide a more complete picture of the networks underlying speech and language in the normal brain (Chatterjee, 2005; Kimberg et al., 2007; Rorden et al., 2007). Moreover, very recent studies are now beginning to combine approaches such as fMRI and tractography with VLSM in a single study (e.g., see Dick et al., 2007; Rudrauf, Mehta, & Grabowski, 2008; Turken et al., 2008). The lesion–behavior mapping approach has endured for many years and, given the new tools available, it promises to continue to provide important insights into the neural underpinnings of language and cognition.

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References

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. (2000). A role for somatosensory cortices in the visual recognition of emotion as revealed by three-dimensional lesion mapping. *Journal of Neuroscience*, *20*, 2683–2690.

Alexander, M. P., Naeser, M. A., & Palumbo, C. (1990). Broca's area aphasias: Aphasia after lesions including the frontal operculum. *Neurology*, *40*, 35–362.

Ashburner, J., & Friston, K. (2000). Voxel-based morphometry – The methods. *NeuroImage*, *11*, 805–821.

Baldo, J. V., Arevalo, A., Wilkins, D. P., & Dronkers, N. (2009). Voxel-based lesion analysis of category-specific naming on the Boston Naming Test. *CRL Technical Report*, *21*, 1–2.

Baldo, J., & Dronkers, N. (2007). Neural correlates of arithmetic and language comprehension: A common substrate? *Neuropsychologia*, *45*, 229–235.

Baldo, J. V., Dronkers, N. F., Wilkins, D., Ludy, C., Raskin, P., & Kim, J. (2005). Is problem solving dependent on language? *Brain and Language*, *92*, 240–250.

Baldo, J., Schwartz, S., Wilkins, D., & Dronkers, N. (2006). Role of frontal versus temporal cortex in verbal fluency as revealed by voxel-based lesion symptom mapping. *Journal of the International Neuropsychological Society*, *12*, 896–900.

Basso, A., Lecours, A. R., Moraschini, S., & Vanier, M. (1985). Anatomoclinical correlations of the aphasias as defined through computerized tomography: Exceptions. *Brain and Language*, *26*, 201–229.

Bates, E., Wilson, S., Saygin, A., Dick, F., Sereno, M. I., Knight, R., et al. (2003). Voxel-based lesion–symptom mapping. *Nature Neuroscience*, *6*, 448–450.

Borovsky, A., Saygin, A. P., Bates, E., & Dronkers, N. F. (2007). Lesion correlates of conversational speech production deficits. *Neuropsychologia*, *45*(11), 2525–2533.

Bouillaud, M. J. (1825). Recherches cliniques propres a démontrer que la perte de la parole correspond a la lésion des lobules antérieurs du cerveau, et a confirmer l'opinion de M. Gall, sur le siège de l'organe du langage articule. *Archives Generales de Medecine*, *3*, 25–45.

Brett, M., Leff, A. P., Rorden, C., & Ashburner, J. (2001). Spatial normalization of brain images with focal lesions using cost function masking. *Neuroimage*, *14*, 486–500.

Bright, P., Moss, H. E., Longe, O., Stamatakis, E. A., & Tyler, L. K. (2007). Conceptual structure modulates anteromedial temporal involvement in processing verbally presented object properties. *Cerebral Cortex*, *17*, 1066–1073.

Broca, P. (1861). Remarques sur le siège de la faculté du langage articulé, suivies d'une observation d'aphémie (perte de la parole). *Bulletins de la Société d'Anatomie (Paris), 2e série*, *6*, 330–357.

Broca, P. (1865). Sur le siège de la faculté du langage articule. *Bulletin de la Société d'Anthropologie*, *6*, 337–93.

Chatterjee, A. (2005). A madness to the methods in cognitive neuroscience? *Journal of Cognitive Neuroscience*, *17*, 847–849.

Chatterjee, A. (2008). The neural organization of spatial thought and language. *Seminars in Speech and Language*, *29*, 226–238.

Committeri, G., Pitzalis, S., Galati, G., Patria, F., Pelle, G., Sabatini, U., et al. (2007). Neural bases of personal and extrapersonal neglect in humans. *Brain*, *130*, 431–441.

Damasio, H., & Damasio, A. R. (1980). The anatomical basis of conduction aphasia. *Brain*, *103*, 337–50.

Damasio, H., & Frank, R. (1992). Three-dimensional in vivo mapping of brain lesions in humans. *Archives of Neurology*, *49*, 137–143.

Damasio, A. R. & Geschwind, N. (1984). The neural basis of language. *Annual Review of Neuroscience*, *7*, 127–47.

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. (1996). A neural basis for lexical retrieval. *Nature*, *380*, 499–505.

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

DeWitt, L. D., Grek, A. J., Buonanno, F. S, Levine, D. N., & Kistler, J. P. (1985). MRI and the study of aphasia. *Neurology*, *35*, 861–865.

Dick, F., Saygin, A. P., Galati, G., Pitzalis, P., Bentrovato, S., D'Amico, S., et al. (2007). What is involved and what is necessary for complex linguistic and non-linguistic auditory processing: Evidence from fMRI and lesion data. *Journal of Cognitive Neuroscience*, *19*, 799–816.

Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature*, *384*, 159–161.

Dronkers, N. F., Wilkins, D. P., Van Valin, R. D., Jr., Redfern, B. B., & Jaeger, J. J. (2004). Lesion analysis of the brain areas involved in language comprehension. *Cognition*, *92*(1–2), 145–77.

Friedrich, F. J., Egly, R., Rafal, R. D., & Beck, D. (1998). Spatial attention deficits in humans: A comparison of superior parietal and temporal-parietal junction lesions. *Neuropsychology*, *12*, 193–207.

Geschwind, N. (1972). Language and the brain. *Scientific American*, *226*, 76–83.

Geschwind, N., & Levitsky, W. (1968). Human brain: Left–right asymmetries in temporal speech region. *Science*, *161*, 186–187.

Gläscher, J., Tranel, D., Paul, L. K., Rudrauf, D., Rorden, C., Hornaday, A., et al. (2009). Lesion mapping of cognitive abilities linked to intelligence. *Neuron*, *61*, 681–691.

Karnath, H., Berger, M., Kuker, W., & Rorden, C. (2004). The anatomy of spatial neglect based on voxelwise statistical analysis: A study of 140 patients. *Cerebral Cortex*, *14*, 1164–1172.

Kertesz, A. (1979). *Aphasia and associated disorders*. New York: Grune & Stratton.

Kertesz, A. (1982). *Western aphasia battery*. New York: Grune & Stratton.

Kertesz, A., Harlock, W., & Coates, R. (1979). Computer tomographic localization, lesion size, and prognosis in aphasia and nonverbal impairment. *Brain and Language*, *8*, 34–50.

Kimberg, D. (2009). Voxel-based mapping of lesion–behavior relationships. http://www.ncrrn.org/papers/methodology_papers/voxel_based_mapping.pdf.

Kimberg, D. Y., Coslett, H. B., & Schwartz, M. F. (2007). Power in voxel-based lesion–symptom mapping. *Journal of Cognitive Neuroscience*, *19*, 1067–1080.

Knight, R. T., Scabini, D., Woods, D. L., & Clayworth, C. (1988). The effects of lesions of superior temporal gyrus and inferior parietal lobe on temporal and vertex components of the human AEP. *Electroencephalography and Clinical Neurophysiology*, *70*, 499–509.

Kreisler, A., Godefroy, O., Delmaire, C., Debachy, B., Leclercq, M., Pruvo, J. P., et al. (2000). The anatomy of aphasia revisited. *Neurology*, *54*, 1117–1123.

Mazzocchi, F., & Vignolo, L. A. (1979). Localisation of lesions in aphasia: Clinical–CT scan correlations in stroke patients. *Cortex*, *15*(4), 627–653.

Mohr, J. P. (1976). Broca's area and Broca's aphasia. In H. Whitaker & H. Whitaker (Eds.), *Studies in neurolinguistics* (vol. 1, pp. 201–233), New York: Academic Press.

Mohr, J. P., Pessin, M. S., Finkelstein, S., Funkenstein, H. H., Duncan, G. W., & Davis, K. R. (1978). Broca aphasia: Pathologic and clinical. *Neurology*, *28*, 311–324.

Naeser, M. A., & Hayward, R. W. (1978). Lesion localization in aphasia with cranial computed tomography and the Boston Diagnostic Aphasia Exam. *Neurology*, *28*, 545–551.

Pettit, J. M., & Duffy, J. R. (1991). Left-hemisphere lesions: A comparison of subjects with and without aphasia. In *Clinical Aphasiology*: Pro-Ed, pp. 55–68.

Rorden, C., Fridriksson, J., & Karnath, H. O. (2009). An evaluation of traditional and novel tools for lesion behavior mapping. *Neuroimage*, *44*(4), 1355–1362.

Rorden, C., & Karnath, H. O. (2004). Using human brain lesions to infer function: A relic from a past era in the fMRI age? *Nature Neuroscience*, *5*, 813–819.

Rorden, C., Karnath, H. O., & Bonhila, L. (2007). Improving lesion–symptom mapping. *Journal of Cognitive Neuroscience*, *19*, 1081–1088.

Roth, H., & Heilman, K. (2000). Aphasia: A historical perspective. In S. E. Nadeau, B. A. Crosson, & L. Gonzalez-Rothi (Eds.), *Aphasia and language: Theory to practice* (vol. 1, pp. 3–30). New York: Guilford Press.

Rudrauf, D., Mehta, S., Bruss, J., Tranel, D., Damasio, H., & Grabowski, T. J. (2008). Thresholding lesion overlap difference maps: Application to category-related naming and recognition deficits. *Neuroimage*, *41*, 970–984.

Rudrauf, D., Mehta, S., & Grabowski, T. (2008). Disconnection's renaissance takes shape: Formal incorporation in group-level lesion studies. *Cortex*, *44*, 1084–1096.

Saygin, A. P., Wilson, S. M., Dronkers, N., & Bates, E. (2004). Action comprehension in aphasia: Linguistic and non-linguistic deficits and their lesion correlates. *Neuropsychologia*, *42*, 1788–1804.

Turken, A., Whitfield-Gabrieli, S., Bammer, R., Baldo, J., Dronkers, N., & Gabrieli, J. (2008). Cognitive processing speed and the structure of white matter pathways: Convergent evidence from normal variation and lesion studies. *NeuroImage*, *42*, 1032–1044.

Tyler, L. K., Marslen-Wilson, W. D., & Stamatakis, E. A. (2005a). Differentiating lexical form, meaning, and structure in the neural language system. *Proceedings of the National Academy of Sciences*, *102*, 8375–8380.

Tyler, L. K., Marslen-Wilson, W. D., & Stamatakis, E. A. (2005b). Dissociating neuro-cognitive component processes: Voxel-based correlational methodology. *Neuropsychologia*, *43*, 771–778.

Wernicke, C. (1874) *Der aphasische Symptomenkomplex*. Breslau: Cohn, Weigert.

Whitaker, H. A. (1998). Neurolinguistics from the middle ages to the pre-modern era: Historical vignettes. In B. Stemmer & H. A. Whitaker (Eds.), *Handbook of neurolinguistics* (pp. 27–54). San Diego: Academic Press.

Willmes, K., & Poeck, K. (1993). To what extent can aphasic syndromes be localized? *Brain*, *116*, 1527–1540.

Wilson, S. M., & Saygin, A. P. (2004). Grammaticality judgment in aphasia: Deficits are not specific to syntactic structures, aphasic syndromes or lesion sites. *Journal of Cognitive Neuroscience*, *16*, 238–252.

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

Yarnel, F., Monroe, P., & Sobel, L. (1976). Aphasia outcome in stroke. *Stroke*, *7*, 516–522.