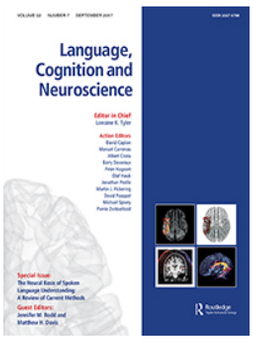

Routledge
Taylor & Francis Group

Language, Cognition and Neuroscience

ISSN: 2327-3798 (Print) 2327-3801 (Online) Journal homepage: http://www.tandfonline.com/loi/plcp21

Lesion-symptom mapping in the study of spoken language understanding

Stephen M. Wilson

To cite this article: Stephen M. Wilson (2017) Lesion-symptom mapping in the study of spoken language understanding, Language, Cognition and Neuroscience, 32:7, 891-899, DOI: 10.1080/23273798.2016.1248984

To link to this article: http://dx.doi.org/10.1080/23273798.2016.1248984

Published online: 01 Nov 2016.

LANGUAGE, COGNITION AND NEUROSCIENCE, 2017
VOL. 32, NO. 7, 891–899
https://doi.org/10.1080/23273798.2016.1248984

Routledge
Taylor & Francis Group

REVIEW ARTICLE

Lesion-symptom mapping in the study of spoken language understanding

Stephen M. Wilson

Department of Hearing and Speech Sciences, Vanderbilt University Medical Center, Nashville, TN, USA

ABSTRACT

Lesion-symptom mapping studies aim to make inferences about the functional neuroanatomy of spoken language understanding by investigating relationships between damage to different brain regions and the various speech perception and comprehension deficits that result. Voxel-based lesion-symptom mapping, voxel-based morphometry, and studies focused on specific cortical regions of interest or fibre pathways have all yielded insights regarding the localisation of different components of spoken language processing. Major challenges include the fact that brain damage rarely impacts just a single brain region or just a single processing component, and that neuroplasticity and recovery can complicate the interpretation of lesion-deficit correlations. Future studies involving large patient cohorts derived from multi-centre projects, and multivariate approaches to quantifying patterns of brain damage and patterns of linguistic deficits, will continue to yield new insights into the neural basis of spoken language understanding.

ARTICLE HISTORY
Received 6 January 2016
Accepted 4 October 2016

KEYWORDS
Lesion-symptom mapping; voxel-based morphometry; magnetic resonance imaging; spoken language understanding; language comprehension

Historical background

Lesion-symptom mapping studies seek to make inferences about the functional neuroanatomy of linguistic or cognitive processes by investigating relationships between damage to different brain regions and the behavioural deficits that result. This general approach dates back to the seminal contributions of Broca (1861) and Wernicke (1874), and some even earlier observations (Benton & Joynt, 1960). Although some early authors studied series of patients (Moutier, 1908), much of the early literature was dominated by case reports of single patients (Caplan, 1987). This was a significant limitation, because it was unclear how generalisable many of the findings were.

The emergence of computed tomography (CT) and magnetic resonance imaging (MRI) in the 1970s and 1980s made it possible to identify lesion locations before waiting potentially decades for patients to come to autopsy. This made it much more feasible to investigate brain-behaviour relationships in series of patients, so that common principles of functional organisation could be determined. The most prevalent approach in the first few decades of neuroimaging-based lesion-symptom mapping was to "overlay" representations of the lesions of patients with a common clinical syndrome, in order to determine which brain regions were invariably associated with the syndrome (Mohr, 1976).

In some of the earliest applications of this approach to disorders of spoken language understanding, Kertesz, Lesk, and Mccabe (1977) and Naeser and Hayward (1978) overlaid the lesions of patients with Wernicke's aphasia. Both studies demonstrated consistent involvement of the left superior temporal gyrus. Kertesz, Sheppard, and MacKenzie (1982) showed that transcortical sensory aphasia, which involves a comprehension deficit of a distinct nature to that of Wernicke's aphasia, was associated with a different lesion localisation, specifically posterior inferior temporal and occipital regions. The lesion overlay approach was not limited to focal damage caused by stroke. For instance, the neurodegenerative syndrome of semantic dementia, which involves impaired single word comprehension among other semantic deficits, was shown to be consistently associated with damage to the anterior temporal lobes (Hodges, Patterson, Oxbury, & Funnell, 1992; Mummery et al., 2000).

In the 1990s, researchers began to derive lesion overlays not just for clinical syndromes (that is, constellations of symptoms), but for specific functional deficits (that is, single symptoms). In the domain of language, expressive functions including naming (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996) and speech motor planning and programming (Dronkers, 1996) were investigated. Researchers also began to go beyond lesion overlays, for instance by presenting complementary lesion overlays of patients who lacked the deficit in question (Dronkers, 1996), by computing various statistics voxel-by-voxel to quantify the impact of damage to each voxel on performance (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000;

CONTACT Stephen M. Wilson stephen.m.wilson@vanderbilt.edu

Bates et al., 2003), and by using multivariate analyses to investigate the contributions of multiple brain regions (Caplan, Hildebrandt, & Makris, 1996; Caplan et al., 2007).

The first large-scale application of a symptom-specific approach to spoken language understanding was a study by Bates et al. (2003), who investigated the neural correlates of auditory language comprehension in 101 patients with chronic aphasia due to left hemisphere stroke. Statistics were computed on a voxel-by-voxel basis, and the resulting map showed that damage to the left posterior middle temporal gyrus was most predictive of comprehension deficits, a more ventral lesion localisation than might have been expected based on the classical model of the neural organisation of language. Another contribution of this study was the proposal that continuous behavioural measures, rather than defined cut-off scores, should be used for lesion-symptom mapping, on the grounds that this makes best use of all available data.

Voxel-based approaches utilising continuous behavioural measures also proved effective in neurodegenerative populations. For instance, Amici et al. (2007) investigated sentence comprehension in 58 patients with primary progressive aphasia or other neurodegenerative syndromes, and showed that deficits in the comprehension of complex syntactic structures were associated with atrophy of specific left inferior frontal regions.

Overview of the method

Most modern studies use voxel-based approaches, in which statistical computations are carried out for each individual voxel to quantify the extent to which structural integrity of that voxel is associated with the language variable(s) of interest. Voxel-based lesion-symptom mapping (VLSM; Bates et al., 2003) and voxel-based morphometry (VBM; Ashburner & Friston, 2000) are two particularly widely used approaches, the most fundamental difference between them being whether the structural integrity of each voxel is modelled as binary, in the case of VLSM, or graded, in the case of VBM (Geva, Baron, Jones, Price, & Warburton, 2012). This section outlines the general steps that are common to VLSM and VBM analyses (several commonly used software packages are listed in Appendix 1). Then, other approaches are discussed which do not involve calculations for each voxel, but rather quantify the impact of damage to specific regions of interest (Caplan et al., 1996, 2007) or white matter pathways (Wilson et al., 2011).

In VLSM and VBM studies, the first step is to define a cohort of patients. In order to identify brain-behaviour relationships, the group of patients needs to exhibit variability in terms of the behavioural variable(s) of interest, and also in terms of whether or not brain regions hypothesised to be important for those function(s) are damaged. Most successful VLSM and VBM studies have been based on groups of at least 50–100 patients.

Second, brain damage needs to be quantified on a voxel-by-voxel basis. VLSM assumes that lesions are discrete, that is, each voxel is either lesioned or it is not. This is generally appropriate for neurological populations such as stroke and resective surgery in which lesions are largely discrete. Most researchers consider manual drawing of lesions to be the "gold standard" for lesion delineation. One method is to draw each patient's lesion on a template in a single, common space (e.g. Bates et al., 2003; Damasio et al., 1996). That way, the impact of large lesions on brain morphology (e.g. expansion of adjacent ventricles) can be considered and taken into account. However, drawing lesions on templates requires great expertise and invariably involves subjectivity. A alternative is to draw each patient's lesion on their own MRI or CT image, and then warp each brain (and associated lesion mask) to standard space (e.g. Wilson et al., 2015). This method is somewhat easier to implement, because the correspondence between the patient's brain and standard space is handled by the warping algorithm (e.g. Ashburner & Friston, 2005), but it may be less accurate, because normalisation algorithms do not always fare well in mapping distorted brains to standard space.

An alternative to manual delineation of lesions is the use of fully automated or semi-automated lesion segmentation algorithms (Leff et al., 2009; Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008; Tyler, Marslen-Wilson, & Stamatakis, 2005). This approach has the advantage of being objective and quick, which is important when studying large groups of patients. The correspondence between automatically and manually delineated lesions is presently only modest (Wilke, de Haan, Juenger, & Karnath, 2011), but continued advances in automated lesion delineation (Griffis, Allendorfer, & Szaflarski, 2016; Pustina et al., 2016) offer the promise of increasingly robust and valid methods that may in time perform as well if not better than manual delineation (Crinion, Holland, Copland, Thompson, & Hillis, 2013).

In contrast to VLSM, VBM is intended for neurological populations in which damage is graded. In the domain of spoken language understanding, patients with neurodegenerative disease have been particularly informative. Since damage is graded, only automated approaches are used. Segmentation algorithms are used to estimate grey matter, white matter and cerebrospinal fluid (CSF) proportions in each voxel, in order to identify regions

exhibiting parenchymal volume loss. The most widely used algorithm is the "unified segmentation" procedure implemented in statistical parametric mapping (SPM) (Ashburner & Friston, 2005), which estimates grey matter, white matter and CSF densities while simultaneously performing bias correction and warping to standard space. Many recent studies use the DARTEL algorithm (Ashburner, 2007) which performs more anatomically precise registration (Klein et al., 2009). Analyses are usually based on estimated grey matter density (e.g. Gorno-Tempini et al., 2004), but it is also possible to use VBM to look at white matter density (e.g. Rohrer et al., 2010), or to sum grey matter and white matter densities to obtain a general measure of parenchymal atrophy (Wilson et al., 2010).

The third step in VLSM and VBM studies is to calculate statistical relationships between damage to each voxel and behavioural variable(s) of interest. VLSM and VBM are mass univariate approaches, similar to standard fMRI analyses. This means that each voxel is analysed independently of any other voxels. In VLSM, a *t*-test is performed at each voxel comparing patients with damage to the voxel to those without damage on the measure(s) of interest. In VBM, correlations are computed between grey matter density (or whatever metric of structural integrity is being used) and the behavioural measure(s) of interest.

Fourth, these statistical maps are corrected for multiple comparisons in order to avoid false positives due to the thousands of voxels in the brain. For VBM, Gaussian random field theory has been shown to effectively correct for multiple comparisons when using a corrected threshold, but not when using approaches based on cluster extent (Ashburner & Friston, 2000). For VLSM and VBM, many researchers have elected to control the false discovery rate (e.g. Bates et al., 2003), however it is unclear exactly how the non-independence of the multiple tests impacts this approach, and it does not control family-wise error. The author recommends the use of permutation-based thresholding methods, in which lesions and behavioural data are randomly reassigned many times in order to determine how likely the observed results would be under the null hypothesis that there is no relationship between lesion location and behaviour. This approach makes no problematic assumptions about the structure of the data, and is easy to implement now that the necessary computing power is readily available (Kimberg, Coslett, & Schwartz, 2007; Nichols & Holmes, 2002).

The line between VLSM and VBM is often blurred. For instance, Leff et al. (2009) used VBM in a study of stroke patients, assuming that lesions would be segmented as containing negligible grey matter, and that furthermore, there might be volume loss remote from the site of infarction that this approach would be sensitive to (see Geva et al. (2012) for an empirical comparison of VLSM and VBM in stroke patients, and a discussion of the advantages and disadvantages of each approach). In another study, Wilson et al. (2015) performed manual delineation of lesions, yet smoothed the resulting lesion masks in order to account for inter-individual variability. Because the lesion masks were smoothed, estimates of structural integrity were continuous rather than binary.

There are other approaches to lesion-symptom mapping that do not involve voxel-by-voxel computations. Some researchers quantify the extent to which anatomical regions of interest are lesioned, and then use these estimates as independent variables to predict behavioural measure(s) of interest (Caplan et al., 1996, 2007). With sufficient numbers of patients, multivariate analyses are then feasible, which could potentially show differential or interacting effects of damage to different regions. A limitation of this approach is that *a priori* hypotheses are required regarding which regions of interest to investigate. Another line of work investigates whether the integrity of white matter tracts are predictive of language deficits. Tract integrity can be quantified in terms of fractional anisotropy (Wilson et al., 2011) or other diffusion tensor imaging metrics (Galantucci et al., 2011), especially when damage is graded as in neurodegenerative disease. Alternatively, the integrity of tracts can be quantified by determining to what extent the tracts have been impacted by lesions (Griffiths, Marslen-Wilson, Stamatakis, & Tyler, 2013; Han et al., 2013).

Challenges and solutions for studying spoken language

The structural images and behavioural measures that go into lesion-symptom mapping analyses are both static, so there are no particular limitations on the experimental conditions under which deficits in spoken language understanding can be characterised. There are, however, general limitations to these approaches that need to be considered.

The most fundamental limitation of VLSM and VBM is that the statistic for each voxel is computed independently of any other voxel, yet behavioural deficit(s) are caused not by damage to a single voxel, but by damage to one or more brain regions, each of which contains many voxels. This implies that a statistically significant relationship between damage to a voxel and a behavioural deficit can never be taken at face value. It might be that the voxel in question really is important

for the behaviour, but alternatively, it could be that neighbouring structures, typically damaged simultaneously with the voxel, are really critical for the function in question. For instance, it has been argued that motor speech deficits are caused not by damage to the anterior insula (Dronkers, 1996), but rather by damage to the white matter pathways which run medial to it (Bonilha & Fridriksson, 2009). Or, it could be that the voxel does play a role, but that deficits only occur if other structures are damaged too. For instance, a small inferior frontal lesion does not cause persistent agrammatism, but a large fronto-parietal lesion does (Mohr, 1976). False negatives are possible too, especially for functions that are supported by both hemispheres. Even though primary auditory cortex in both hemispheres appears to be able to support early stages of spoken language understanding, an isolated lesion to left auditory cortex often does not result in any persistent deficits unless right auditory cortex is damaged too, so voxel-based methods may not show a significant relationship between left or right auditory cortex and any language measure.

These problems can be addressed by carrying out analyses which include the structural integrity of multiple brain regions as independent variables. One way to do this is to covary out the lesion status of other regions that might be important for the function of interest (e.g. Bates et al., 2003). Another possibility is to perform *post hoc* multiple regression analyses that model the function in terms of the potentially interacting contributions from multiple distinct brain regions (Rankin et al., 2009; Wilson et al., 2015). As mentioned above, some authors do not use voxel-based analyses at all, but rather skip straight to multivariate analyses involving multiple regions of interest (Caplan et al., 1996, 2007). The success of multivariate analyses depends on having very large numbers of patients, because the sample must contain patients representing different combinations of regions damaged, in order to determine which region(s) are actually important for the function of interest.

Another ubiquitous limitation of lesion-symptom mapping studies is that patients generally recover to varying extents from strokes and from other neurological insults, implying that there is considerable cortical plasticity, so a lesioned brain is not just a brain with some pieces missing: it is a brain with some pieces missing and with the remaining pieces reorganised to some unknown extent. The most obvious way to address this limitation is to study patients acutely. This is challenging from a practical standpoint, and also because there are often other factors at play early after a brain injury, such as oedema and hypoperfusion, that may complicate the picture in different ways. However, several lesion-symptom mapping studies have successfully demonstrated specific regions associated with various component processes of spoken language understanding in acute stroke patients (Kümmerer et al., 2013; Newhart, Ken, Kleinman, Heidler-Gary, & Hillis, 2007; Newhart et al., 2012; Race, Ochfeld, Leigh, & Hillis, 2012; Rogalsky, Pitz, Hillis, & Hickok, 2008; Tsapkini, Frangakis, & Hillis, 2011) or resective surgery patients in the immediate post-operative period (Wilson et al., 2015).

Key empirical contributions

Lesion-symptom mapping studies over the past decade or so have begun to paint a picture of the large-scale organisation of the brain regions involved in spoken language understanding.

The neural substrates of word-level comprehension have been investigated in a number of lesion-symptom mapping studies. In particular, VBM studies in patients with primary progressive aphasia and other neurodegenerative diseases have shown that comprehension of single words is associated with atrophy of left anterior temporal regions (Mesulam, Thompson, Weintraub, & Rogalski, 2015; Mummery et al., 2000; Rogalski et al., 2011; Sapolsky et al., 2010). While some authors have argued that the tip of the temporal lobe is the most critical region (Mesulam et al., 2013), a recent multivariate analysis in 110 patients who had undergone resective surgery showed that damage to a region in the fusiform gyrus approximately 6 cm posterior to the temporal pole is predictive of semantic deficits, not the temporal pole itself (Wilson et al., 2015; see also Mion et al., 2010). In stroke patients, single word comprehension specifically has rarely been investigated. Bates et al. (2003) used a composite measure of comprehension that included word-level and sentence-level components, however an analysis using only the word-level data (the auditory word recognition subscore from the Western Aphasia Battery) showed that damage to the posterior middle temporal gyrus is similarly associated with word-level comprehension deficits (Wilson and Dronkers, unpublished observations), that is, the same region that was associated with comprehension deficits in general (see also Saygin, Dick, Wilson, Dronkers, & Bates, 2003). Another study in acute stroke patients suggested that infarction or hypoperfusion of both anterior and posterior temporal regions contributes to word-level comprehension deficits (Newhart et al., 2007). These diverging findings from primary progressive aphasia and stroke remain to be reconciled; one recent proposal is that word-level comprehension deficits after posterior temporal damage in stroke are caused by lesion extension into the underlying white matter, which disconnects

anterior temporal regions from other perisylvian language regions (Mesulam et al., 2015).

Sentence-level comprehension has been investigated in a number of well-designed and relatively well-powered lesion-symptom mapping studies. The most commonly implicated regions have been left inferior frontal cortex, left superior temporal cortex, and left inferior parietal cortex, with many studies reporting one or more of these regions to be implicated in sentence-level comprehension (Amici et al., 2007; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Fridriksson, Fillmore, Guo, & Rorden, 2015; Leff et al., 2009; Newhart et al., 2012; Rogalski et al., 2011; Teichmann et al., 2015; Thothathiri, Kimberg, & Schwartz, 2012; Wilson et al., 2011; Wilson, Galantucci, Tartaglia, & Gorno-Tempini, 2012). Some studies have suggested that specific regions within this network have specific functions, such as a role for inferior frontal cortex in processing syntactically complex sentences (Amici et al., 2007), and a role for the posterior superior temporal gyrus in auditory short-term memory in support of sentence comprehension (Leff et al., 2009; Wilson et al., 2012). Damage to dorsal white matter fibre pathways connecting frontal and posterior language regions has also been shown to impair syntactic processing above and beyond damage to grey matter (Wilson et al., 2011). Not all studies have supported this general picture: some authors have argued that damage to anterior temporal regions (Dronkers et al., 2004; Magnusdottir et al., 2013) or ventral pathways (Griffiths et al., 2013) can result in syntactic processing deficits, and other authors have not observed any regions to be systematically associated with syntactic deficits (Caplan et al., 1996, 2007; Caplan, Michaud, Hufford, & Makris, 2015). For further discussion, see Wilson et al. (2012, 2014).

In contrast to the rich findings on word-level and sentence-level comprehension, lesion-symptom mapping studies have made only modest contributions to our understanding of prelexical stages of spoken language understanding. This may be because much of this processing is bilaterally redundant, so genuine prelexical deficits are rare (Poeppel, 2001). Probably the most notable finding bearing on prelexical spoken language processing is a recent study of 99 stroke patients that showed that a derived factor reflecting measures including auditory lexical decision and phoneme discrimination was associated with damage to the left planum temporale and the dorsal part of the superior temporal gyrus (Mirman et al., 2015). This speech perception factor had clearly distinct neural correlates to a speech production factor which was affected by damage to immediately adjacent regions dorsal to the Sylvian fissure.

Many other aspects of spoken language understanding have been investigated using lesion-symptom mapping. Some examples include the relationship between regions involved in comprehending words and environmental sounds (Saygin et al., 2003), grammaticality judgement (Wilson & Saygin, 2004), narrative and discourse comprehension (Ash et al., 2012; Barbey, Colom, & Grafman, 2014), lexical and semantic access (Harvey & Schnur, 2015), and paralinguistic features such as voice identity, accent, and emotional prosody (Hailstone et al., 2011, 2012; Rankin et al., 2009; Rohrer, Sauter, Scott, Rossor, & Warren, 2012).

Future directions

One of the most exciting new directions in lesion-symptom mapping of spoken language understanding is Price and colleagues' "Predicting Language Outcome and Recovery After Stroke (PLORAS)" study (Price, Seghier, & Leff, 2010). This is a large multi-site study in the United Kingdom which had already recruited 750 patients as of early 2015 (Seghier et al., 2016). Structural scans and behavioural data are acquired from all patients, and functional imaging data are also acquired from some patients. The data will be made available for others in the research community to analyse. What makes this study groundbreaking is the size of the patient cohort, which is an order of magnitude larger than most of the large studies to date. Such a substantial patient cohort will ensure that there are enough patients with similar yet distinct lesions, so that subtle effects of lesion size and distribution on different aspects of language processing can be quantified. Multivariate analyses in which behaviour is predicted based on multiple regions of interest will become feasible when the sample size is large enough.

A second promising direction is the application of machine learning techniques and other multivariate approaches to lesion-symptom mapping. Machine learning algorithms such as support vector machines have been used to uncover relationships between distributed lesions and clinical syndromes including stroke (Saur et al., 2010), primary progressive aphasia (Wilson et al., 2009), and other neurodegenerative diseases (Klöppel et al., 2008). Recent studies have investigated relationships between lesions and specific symptoms using similar approaches (Xing et al., 2016; Yourganov, Smith, Fridriksson, & Rorden, 2015; Zhang, Kimberg, Coslett, Schwartz, & Wang, 2014). On the behavioural side, constellations of deficits have also been analysed from a multivariate perspective using principal components analysis (Butler, Ralph, & Woollams, 2014; Mirman et al., 2015). These new approaches should allow researchers

to overcome some of the limitations of the mass univariate approach that have been identified (Inoue, Madhyastha, Rudrauf, Mehta, & Grabowski, 2014; Mah, Husain, Rees, & Nachev, 2014).

Finally, lesion-symptom mapping needs to be used in conjunction with other cognitive neuroscience techniques such as task-based and connectivity-based functional MRI, perfusion imaging, and diffusion tensor imaging in order to probe the functionality of surviving tissue and its potential reorganisation (Saur & Hartwigsen, 2012; Specht et al., 2009; Warren, Crinion, Lambon Ralph, & Wise, 2009; Wilson et al., 2014). Combining structural and functional neuroimaging modalities will provide a more complete picture of which brain regions are critical for different aspects of spoken language understanding, as well as the potential of other regions to carry out these functions when the preferred regions are damaged.

Disclosure statement

No potential conflict of interest was reported by the author.

Funding

This work was supported by the National Institute on Deafness and Other Communication Disorders [NIH R01 DC013270].

ORCID

Stephen M. Wilson http://orcid.org/0000-0001-9884-2852

References

Adolphs, R., Damasio, H., Tranel, D., Cooper, G., & Damasio, A. R. (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.

Amici, S., Brambati, S. M., Wilkins, D. P., Ogar, J., Dronkers, N. L., Miller, B. L., & Gorno-Tempini, M. L. (2007). Anatomical correlates of sentence comprehension and verbal working memory in neurodegenerative disease. *Journal of Neuroscience*, *27*, 6282–6290. doi:10.1523/jneurosci.1331-07.2007

Ash, S., Xie, S. X., Gross, R. G., Dreyfuss, M., Boller, A., Camp, E., … Grossman, M. (2012). The organization and anatomy of narrative comprehension and expression in Lewy body spectrum disorders. *Neuropsychology*, *26*, 368–384. doi:10.1037/a0027115

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*, 95–113. doi:10.1016/j.neuroimage.2007.07.007

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry – The methods. *NeuroImage*, *11*, 805–821. doi:10.1006/nimg.2000.0582

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, *26*, 839–851. doi:10.1016/j.neuroimage.2005.02.018

Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. *Medical Image Analysis*, *12*, 26–41. doi:10.1016/j.media.2007.06.004

Barbey, A. K., Colom, R., & Grafman, J. (2014). Neural mechanisms of discourse comprehension: A human lesion study. *Brain*, *137*, 277–287. doi:10.1093/brain/awt312

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. doi:10.1038/nn1050

Benton, A. L., & Joynt, R. J. (1960). Early descriptions of aphasia. *Archives of Neurology*, *3*, 205–222. doi:10.1001/archneur.1960.00450020085012

Bonilha, L., & Fridriksson, J. (2009). Subcortical damage and white matter disconnection associated with non-fluent speech. *Brain*, *132*, e108. doi:10.1093/brain/awn200

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 Serie*, *6*, 330–357.

Butler, R. A., Ralph, M. A. L., & Woollams, A. M. (2014). Capturing multidimensionality in stroke aphasia: Mapping principal behavioural components to neural structures. *Brain*, *137*, 3248–3266. doi:10.1093/brain/awu286

Caplan, D. (1987). *Neurolinguistics and linguistic aphasiology: An introduction*. Cambridge: Cambridge University Press.

Caplan, D., Hildebrandt, N., & Makris, N. (1996). Location of lesions in stroke patients with deficits in syntactic processing in sentence comprehension. *Brain*, *119*, 933–949. doi:10.1093/brain/119.3.933

Caplan, D., Michaud, J., Hufford, R., & Makris, N. (2015). Deficit-lesion correlations in syntactic comprehension in aphasia. *Brain and Language*, *152*, 14–27. doi:10.1016/j.bandl.2015.10.005

Caplan, D., Waters, G., Kennedy, D., Alpert, N., Makris, N., Dede, G., … Reddy, A. (2007). A study of syntactic processing in aphasia II: Neurological aspects. *Brain and Language*, *101*, 151–177. doi:10.1016/j.bandl.2006.06.226

Crinion, J., Holland, A. L., Copland, D. A., Thompson, C. K., & Hillis, A. E. (2013). Neuroimaging in aphasia treatment research: Quantifying brain lesions after stroke. *NeuroImage*, *73*, 208–214. doi:10.1016/j.neuroimage.2012.07.044

Damasio, H., Grabowski, T. J., Tranel, D., Hichwa, R. D., & Damasio, A. R. (1996). A neural basis for lexical retrieval. *Nature*, *380*, 499–505. doi:10.1038/380499a0

Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature*, *384*, 159–161. doi:10.1038/384159a0

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*, 145–177. doi:10.1016/j.cognition.2003.11.002

Fridriksson, J., Fillmore, P., Guo, D., & Rorden, C. (2015). Chronic Broca's aphasia is caused by damage to Broca's and Wernicke's areas. *Cerebral Cortex*, *25*, 4689–4696. doi:10.1093/cercor/bhu152

Friston, K. J., Ashburner, J. T., Kiebel, S. J., Nichols, T. E., & Penny, W. D. (Eds.). (2007). *Statistical parametric mapping: The analysis of functional brain images*. Amsterdam: Elsevier.

Galantucci, S., Tartaglia, M. C., Wilson, S. M., Henry, M. L., Filippi, M., Agosta, F., … Gorno-Tempini, M. L. (2011). White matter

damage in primary progressive aphasias: A diffusion tensor tractography study. *Brain*, *134*, 3011–3029. doi:10.1093/brain/awr099

Geva, S., Baron, J.-C., Jones, P. S., Price, C. J., & Warburton, E. A. (2012). A comparison of VLSM and VBM in a cohort of patients with post-stroke aphasia. *NeuroImage: Clinical*, *1*, 37–47. doi:10.1016/j.nicl.2012.08.003

Gorno-Tempini, M. L., Dronkers, N. F., Rankin, K. P., Ogar, J. M., Phengrasamy, L., Rosen, H. J., … Miller, B. L. (2004). Cognition and anatomy in three variants of primary progressive aphasia. *Annals of Neurology*, *55*, 335–346. doi:10.1002/ana.10825

Griffis, J. C., Allendorfer, J. B., & Szaflarski, J. P. (2016). Voxel-based Gaussian naïve Bayes classification of ischemic stroke lesions in individual T1-weighted MRI scans. *Journal of Neuroscience Methods*, *257*, 97–108. doi:10.1016/j.jneumeth.2015.09.019

Griffiths, J. D., Marslen-Wilson, W. D., Stamatakis, E. A., & Tyler, L. K. (2013). Functional organization of the neural language system: Dorsal and ventral pathways are critical for syntax. *Cerebral Cortex*, *23*, 139–147. doi:10.1093/cercor/bhr386

Hailstone, J. C., Ridgway, G. R., Bartlett, J. W., Goll, J. C., Buckley, A. H., Crutch, S. J., & Warren, J. D. (2011). Voice processing in dementia: A neuropsychological and neuroanatomical analysis. *Brain*, *134*, 2535–2547. doi:10.1093/brain/awr205

Hailstone, J. C., Ridgway, G. R., Bartlett, J. W., Goll, J. C., Crutch, S. J., & Warren, J. D. (2012). Accent processing in dementia. *Neuropsychologia*, *50*, 2233–2244. doi:10.1016/j.neuropsychologia.2012.05.027

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*, 2952–2965. doi:10.1093/brain/awt205

Harvey, D. Y., & Schnur, T. T. (2015). Distinct loci of lexical and semantic access deficits in aphasia: Evidence from voxel-based lesion-symptom mapping and diffusion tensor imaging. *Cortex*, *67*, 37–58. doi:10.1016/j.cortex.2015.03.004

Hodges, J. R., Patterson, K., Oxbury, S., & Funnell, E. (1992). Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain*, *115*, 1783–1806. doi:10.1093/brain/115.6.1783

Inoue, K., Madhyastha, T., Rudrauf, D., Mehta, S., & Grabowski, T. (2014). What affects detectability of lesion-deficit relationships in lesion studies? *NeuroImage: Clinical*, *6*, 388–397. doi:10.1016/j.nicl.2014.10.002

Kertesz, A., Lesk, D., & Mccabe, P. (1977). Isotope localization of infarcts in aphasia. *Archives of Neurology*, *34*, 590–601. doi:10.1001/archneur.1977.00500220024004

Kertesz, A., Sheppard, A., & MacKenzie, R. (1982). Localization in transcortical sensory aphasia. *Archives of Neurology*, *39*, 475–478. doi:10.1001/archneur.1982.00510200017002

Kimberg, D. Y., Coslett, H. B., & Schwartz, M. F. (2007). Power in voxel-based lesion-symptom mapping. *Journal of Cognitive Neuroscience*, *19*, 1067–1080. doi:10.1162/jocn.2007.19.7.1067

Klein, A., Andersson, J., Ardekani, B. A., Ashburner, J., Avants, B., Chiang, M.-C., … Parsey, R. V. (2009). Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. *NeuroImage*, *46*, 786–802. doi:10.1016/j.neuroimage.2008.12.037

Klöppel, S., Stonnington, C. M., Chu, C., Draganski, B., Scahill, R. I., Rohrer, J. D., … Frackowiak, R. S. (2008). Automatic classification of MR scans in Alzheimer's disease. *Brain*, *131*, 681–689. doi:10.1093/brain/awm319

Kümmerer, D., Hartwigsen, G., Kellmeyer, P., Glauche, V., Mader, I., Klöppel, S., … Saur, D. (2013). Damage to ventral and dorsal language pathways in acute aphasia. *Brain*, *136*, 619–629. doi:10.1093/brain/aws354

Leff, A. P., Schofield, T. M., Crinion, J. T., Seghier, M. L., Grogan, A., Green, D. W., & Price, C. J. (2009). The left superior temporal gyrus is a shared substrate for auditory short-term memory and speech comprehension: Evidence from 210 patients with stroke. *Brain*, *132*, 3401–3410. doi:10.1093/brain/awp273

Magnusdottir, S., Fillmore, P., den Ouden, D. B., Hjaltason, H., Rorden, C., Kjartansson, O., … Fridriksson, J. (2013). Damage to left anterior temporal cortex predicts impairment of complex syntactic processing: A lesion-symptom mapping study. *Human Brain Mapping*, *34*, 2715–2723. doi:10.1002/hbm.22096

Mah, Y.-H., Husain, M., Rees, G., & Nachev, P. (2014). Human brain lesion-deficit inference remapped. *Brain*, *137*, 2522–2531. doi:10.1093/brain/awu164

Mesulam, M.-M., Thompson, C. K., Weintraub, S., & Rogalski, E. J. (2015). The Wernicke conundrum and the anatomy of language comprehension in primary progressive aphasia. *Brain*, *138*, 2423–2437. doi:10.1093/brain/awv154

Mesulam, M.-M., Wieneke, C., Hurley, R., Rademaker, A., Thompson, C. K., Weintraub, S., & Rogalski, E. J. (2013). Words and objects at the tip of the left temporal lobe in primary progressive aphasia. *Brain*, *136*, 601–618. doi:10.1093/brain/aws336

Mion, M., Patterson, K., Acosta-Cabronero, J., Pengas, G., Izquierdo-Garcia, D., Hong, Y. T., … Nestor, P. J. (2010). What the left and right anterior fusiform gyri tell us about semantic memory. *Brain*, *133*, 3256–3268. doi:10.1093/brain/awq272

Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O. K., Coslett, H. B., & Schwartz, M. F. (2015). Neural organization of spoken language revealed by lesion-symptom mapping. *Nature Communications*, *6*, 6762. doi:10.1038/ncomms7762

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

Moutier, F. (1908). *L'aphasie de Broca*. Paris: Steinheil.

Mummery, C. J., Patterson, K., Price, C. J., Ashburner, J., Frackowiak, R. S. J., & 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. doi:10.1002/1531-8249(200001)47:1<36::AID-ANA8>3.0.CO;2-L

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. doi:10.1212/WNL.28.6.545

Newhart, M., Ken, L., Kleinman, J. T., Heidler-Gary, J., & Hillis, A. E. (2007). Neural networks essential for naming and word comprehension. *Cognitive and Behavioral Neurology*, *20*, 25–30. doi:10.1097/WNN.0b013e31802dc4a7

Newhart, M., Trupe, L. A., Gomez, Y., Cloutman, L., Molitoris, J. J., Davis, C., … Hillis, A. E. (2012). Asyntactic comprehension, working memory, and acute ischemia in Broca's area versus angular gyrus. *Cortex*, *48*, 1288–1297. doi:10.1016/j.cortex.2011.09.009

Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping*, *15*, 1–25. doi:10.1002/hbm.1058

Poeppel, D. (2001). Pure word deafness and the bilateral processing of the speech code. *Cognitive Science*, *25*, 679–693. doi:10.1207/s15516709cog2505_3

Price, C. J., Seghier, M. L., & Leff, A. P. (2010). Predicting language outcome and recovery after stroke: The PLORAS system. *Nature Reviews Neurology*, *6*, 202–210. doi:10.1038/nrneurol.2010.15

Pustina, D., Coslett, H. B., Turkeltaub, P. E., Tustison, N., Schwartz, M. F., & Avants, B. (2016). Automated segmentation of chronic stroke lesions using LINDA: Lesion identification with neighborhood data analysis. *Human Brain Mapping*, *37*, 1405–1421. doi:10.1002/hbm.23110

Race, D. S., Ochfeld, E., Leigh, R., & Hillis, A. E. (2012). Lesion analysis of cortical regions associated with the comprehension of nonreversible and reversible yes/no questions. *Neuropsychologia*, *50*, 1946–1953. doi:10.1016/j.neuropsychologia.2012.04.019

Rankin, K. P., Salazar, A., Gorno-Tempini, M. L., Sollberger, M., Wilson, S. M., Pavlic, D., … Miller, B. L. (2009). Detecting sarcasm from paralinguistic cues: Anatomic and cognitive correlates in neurodegenerative disease. *NeuroImage*, *47*, 2005–2015. doi:10.1016/j.neuroimage.2009.05.077

Rogalski, E., Cobia, D., Harrison, T. M., Wieneke, C., Thompson, C. K., Weintraub, S., & Mesulam, M. (2011). Anatomy of language impairments in primary progressive aphasia. *Journal of Neuroscience*, *31*, 3344–3350. doi:10.1523/jneurosci.5544-10.2011

Rogalsky, C., Pitz, E., Hillis, A. E., & Hickok, G. (2008). Auditory word comprehension impairment in acute stroke: Relative contribution of phonemic versus semantic factors. *Brain and Language*, *107*, 167–169. doi:10.1016/j.bandl.2008.08.003

Rohrer, J. D., Ridgway, G. R., Crutch, S. J., Hailstone, J., Goll, J. C., Clarkson, M. J., … Warren, J. D. (2010). Progressive logopenic/phonological aphasia: Erosion of the language network. *NeuroImage*, *49*, 984–993. doi:10.1016/j.neuroimage.2009.08.002

Rohrer, J. D., Sauter, D., Scott, S., Rossor, M. N., & Warren, J. D. (2012). Receptive prosody in nonfluent primary progressive aphasias. *Cortex*, *48*, 308–316. doi:10.1016/j.cortex.2010.09.004

Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behavioural Neurology*, *12*, 191–200. doi:10.1155/2000/421719

Rorden, C., Karnath, H.-O., & Bonilha, L. (2007). Improving lesion-symptom mapping. *Journal of Cognitive Neuroscience*, *19*, 1081–1088. doi:10.1162/jocn.2007.19.7.1081

Sapolsky, D., Bakkour, A., Negreira, A., Nalipinski, P., Weintraub, S., Mesulam, M. M., … Dickerson, B. C. (2010). Cortical neuroanatomic correlates of symptom severity in primary progressive aphasia. *Neurology*, *75*, 358–366.

Saur, D., & Hartwigsen, G. (2012). Neurobiology of language recovery after stroke: Lessons from neuroimaging studies. *Archives of Physical Medicine and Rehabilitation*, *93*, S15–S25. doi:10.1016/j.apmr.2011.03.036

Saur, D., Ronneberger, O., Kümmerer, D., Mader, I., Weiller, C., & Klöppel, S. (2010). Early functional magnetic resonance imaging activations predict language outcome after stroke. *Brain*, *133*, 1252–1264. doi:10.1093/brain/awq021

Saygin, A. P., Dick, F., Wilson, S. M., Dronkers, N. F., & Bates, E. (2003). Neural resources for processing language and environmental sounds: Evidence from aphasia. *Brain*, *126*, 928–945. doi:10.1093/brain/awg082

Seghier, M. L., Patel, E., Prejawa, S., Ramsden, S., Selmer, A., Lim, L., … Price, C. J. (2016). The PLORAS Database: A data repository for predicting language outcome and recovery after stroke. *NeuroImage*, *124*(Part B), 1208–1212. doi:10.1016/j.neuroimage.2015.03.083

Seghier, M. L., Ramlackhansingh, A., Crinion, J., Leff, A. P., & Price, C. J. (2008). Lesion identification using unified segmentation-normalisation models and fuzzy clustering. *NeuroImage*, *41*, 1253–1266. doi:10.1016/j.neuroimage.2008.03.028

Specht, K., Zahn, R., Willmes, K., Weis, S., Holtel, C., Krause, B. J., … Huber, W. (2009). Joint independent component analysis of structural and functional images reveals complex patterns of functional reorganisation in stroke aphasia. *NeuroImage*, *47*, 2057–2063. doi:10.1016/j.neuroimage.2009.06.011

Teichmann, M., Rosso, C., Martini, J.-B., Bloch, I., Brugieres, P., Duffau, H., … Bachoud-Levi, A.-C. (2015). A cortical-subcortical syntax pathway linking Broca's area and the striatum. *Human Brain Mapping*, *36*, 2270–2283. doi:10.1002/hbm.22769

Thothathiri, M., Kimberg, D. Y., & Schwartz, M. F. (2012). The neural basis of reversible sentence comprehension: Evidence from voxel-based lesion symptom mapping in aphasia. *Journal of Cognitive Neuroscience*, *24*, 212–222. doi:10.1162/jocn_a_00118

Tsapkini, K., Frangakis, C. E., & Hillis, A. E. (2011). The function of the left anterior temporal pole: Evidence from acute stroke and infarct volume. *Brain*, *134*, 3094–3105. doi:10.1093/brain/awr050

Tyler, L. K., Marslen-Wilson, W. D., & Stamatakis, E. A. (2005). Differentiating lexical form, meaning, and structure in the neural language system. *Proceedings of the National Academy of Sciences*, *102*, 8375–8380. doi:10.1073/pnas.0408213102

Warren, J. E., Crinion, J. T., Lambon Ralph, M. A., & Wise, R. J. S. (2009). Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. *Brain*, *132*, 3428–3442. doi:10.1093/brain/awp270

Wernicke, C. (1874). *Der Aphasische Symptomencomplex*. Breslau: Cohn and Weigert.

Wilke, M., de Haan, B., Juenger, H., & Karnath, H.-O. (2011). Manual, semi-automated, and automated delineation of chronic brain lesions: A comparison of methods. *NeuroImage*, *56*, 2038–2046. doi:10.1016/j.neuroimage.2011.04.014

Wilson, S. M., DeMarco, A. T., Henry, M. L., Gesierich, B., Babiak, M., Mandelli, M. L., … Gorno-Tempini, M. L. (2014). What role does the anterior temporal lobe play in sentence-level processing? Neural correlates of syntactic processing in semantic variant primary progressive aphasia. *Journal of Cognitive Neuroscience*, *26*, 970–985. doi:10.1162/jocn_a_00550

Wilson, S. M., Galantucci, S., Tartaglia, M. C., & Gorno-Tempini, M. L. (2012). The neural basis of syntactic deficits in primary progressive aphasia. *Brain and Language*, *122*, 190–198. doi:10.1016/j.bandl.2012.04.005

Wilson, S. M., Galantucci, S., Tartaglia, M. C., Rising, K., Patterson, D. K., Henry, M. L., … Gorno-Tempini, M. L. (2011). Syntactic

processing depends on dorsal language tracts. *Neuron*, *72*, 397–403. doi:10.1016/j.neuron.2011.09.014

Wilson, S. M., Henry, M. L., Besbris, M., Ogar, J. M., Dronkers, N. F., Jarrold, W., … Gorno-Tempini, M. L. (2010). Connected speech production in three variants of primary progressive aphasia. *Brain*, *133*, 2069–2088. doi:10.1093/brain/awq129

Wilson, S. M., Lam, D., Babiak, M. C., Perry, D. W., Shih, T., Hess, C. P., … Chang, E. F. (2015). Transient aphasias after left hemisphere resective surgery. *Journal of Neurosurgery*, *123*, 581–593. doi:10.3171/2015.4.JNS141962

Wilson, S. M., Ogar, J. M., Laluz, V., Growdon, M., Jang, J., Glenn, S., … Gorno-Tempini, M. L. (2009). Automated MRI-based classification of primary progressive aphasia variants. *NeuroImage*, *47*, 1558–1567. doi:10.1016/j.neuroimage.2009.05.085

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. doi:10.1162/089892904322984535

Xing, S., Lacey, E. H., Skipper-Kallal, L. M., Jiang, X., Harris-Love, M. L., Zeng, J., & Turkeltaub, P. E. (2016). Right hemisphere grey matter structure and language outcomes in chronic left hemisphere stroke. *Brain*, *139*, 227–241. doi:10.1093/brain/awv323

Yourganov, G., Smith, K. G., Fridriksson, J., & Rorden, C. (2015). Predicting aphasia type from brain damage measured with structural MRI. *Cortex*, *73*, 203–215. doi:10.1016/j.cortex.2015.09.005

Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: Significantly improved efficiency and reliability. *NeuroImage*, *31*, 1116–1128. doi:10.1016/j.neuroimage.2006.01.015

Zhang, Y., Kimberg, D. Y., Coslett, H. B., Schwartz, M. F., & Wang, Z. (2014). Multivariate lesion-symptom mapping using support vector regression. *Human Brain Mapping*, *35*, 5861–5876. doi:10.1002/hbm.22590

Appendix 1: Software resources

The program most commonly used to manually delineate lesions is **mricron** (Rorden & Brett, 2000; http://people.cas.sc.edu/rorden/mricron/index.html). Another excellent program that can be used for lesion delineation is **ITK-SNAP** (Yushkevich et al., 2006; http://www.itksnap.org).

Intersubject normalisation is most often performed with **SPM** (Friston, Ashburner, Kiebel, Nichols, & Penny, 2007; http://www.fil.ion.ucl.ac.uk/spm) using either the unified segmentation (Ashburner & Friston, 2005) or DARTEL (Ashburner, 2007) algorithms. Another good choice is **ANTS** (Avants, Epstein, Grossman, & Gee, 2008; http://stnava.github.io/ANTs).

VLSM and VBM can be carried out with the author's MATLAB toolbox **vlsm** (Bates et al., 2003; http://langneurosci.mc.vanderbilt.edu/resources.html), with **NPM** (Rorden, Karnath, & Bonilha, 2007; included with mricron), or with any mainstream neuroimaging analysis package, such as **SPM** (Friston et al., 2007; http://www.fil.ion.ucl.ac.uk/spm). The **Statistical Non-Parametric Mapping (SnPM)** toolbox (Nichols & Holmes, 2002; http://warwick.ac.uk/snpm) is recommended for use with SPM.