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Review

Neuroimaging in aphasia treatment research: Quantifying brain lesions after stroke

Jenny Crinion [a,*], Audrey L. Holland [b], David A. Copland [c], Cynthia K. Thompson [d], Argye E. Hillis [e]

[a] University College London, Institute of Cognitive Neuroscience, London, UK
[b] University of Arizona, Department of Speech, Language and Hearing Sciences, Tucson, Arizona, USA
[c] The University of Queensland, Centre for Clinical Research & School of Health and Rehabilitation Sciences, Language Neuroscience Laboratory, Brisbane, Australia
[d] Northwestern University, Department of Communication Sciences and Disorders, and Neurology, Northwestern University, Evanston, IL, USA
[e] Johns Hopkins University School of Medicine, Department of Neurology, Baltimore, MD, USA

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ABSTRACT

New structural and functional neuroimaging methods continue to rapidly develop, offering promising tools for cognitive neuroscientists. In the last 20 years, advanced magnetic resonance imaging (MRI) techniques have provided invaluable insights into how language is represented and processed in the brain and how it can be disrupted by damage to, or dysfunction of, various parts of the brain. Current functional MRI (fMRI) approaches have also allowed researchers to purposefully investigate how individuals recover language after stroke. This paper presents recommendations for quantification of brain lesions derived from discussions among international researchers at the Neuroimaging in Aphasia Treatment Research Workshop held at Northwestern University (Evanston, Illinois, USA). Methods for detailing and characterizing the brain damage that can influence results of fMRI studies in chronic aphasic stroke patients are discussed. Moreover, we aimed to provide the reader with a set of general practical guidelines and references to facilitate choosing adequate structural imaging strategies that facilitate fMRI studies in aphasia treatment research.

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Introduction

Both functional imaging of healthy participants and lesion studies have shown that many brain areas beyond the classical Broca's and Wernicke's language areas are important for language comprehension and production (Awad et al., 2007; Dronkers et al., 2007; Fridriksson et al., 2007; Naeser et al., 1987; Wise et al., 2001). Therefore, a given language impairment can result from damage or dysfunction of several different brain regions (Bonilha and Fridriksson, 2009; Hillis et al., 2004; Newhart et al., 2007; Prabhakaran et al., 2007) due to the impact of the lesion not only on the function of the affected region but also on the many regions connected to it within the language network (Bonilha and Fridriksson, 2009). As such, determining not only the lesion site but also understanding the impact that the structural lesion can have on the function of other structurally intact brain areas is critical to our understanding of aphasia recovery. The present paper focuses on quantification of brain lesions in chronic stroke-induced

* Corresponding author at: Institute of Cognitive Neuroscience, University College London, 17 Queen Square, London WC1N 3AR, UK. Fax: +44 207 813 2835.
E-mail address: j.crinion@ucl.ac.uk (J. Crinion).

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aphasic individuals and conveys the consensus for minimum standards and ideals for characterizing the lesion (i.e., site and extent of infarcted tissue) that was reached during the Neuroimaging in Aphasia Treatment Research Workshop held at Northwestern University, a 2-day meeting devoted to discussions among international researchers. Understanding neuroplasticity of language networks requires a full assessment of brain damage in order to identify tissue that is available to support language recovery. Here we briefly discuss standards that were generally (if not universally) agreed upon, with regard to selection of stroke participants for language recovery studies, specification and measurement of lesion volume and location. We also discuss appropriate imaging methods for identification of lesion-related participant variables.

Participant variables: inclusion and exclusion criteria

Aphasia can be caused by a variety of lesion types, such as stroke, tumor, abscess, surgical resection of lesions or epileptic foci, head injury, and neurodegenerative disease, e.g., primary progressive aphasia. These etiologies have different consequences for recovery, and therefore should not be grouped together in studies of language recovery. For the purposes of this paper, we restrict our discussion to quantification of lesions in individuals who have suffered a stroke, the most common cause of aphasia. We note, however, that there are many different types of stroke: infarct from arterial occlusion, primary intracerebral hemorrhage, hemorrhagic infarct, subarachnoid hemorrhage, subdural hemorrhage, and venous infarct. These different types of stroke may differentially affect language, structure/function relationships, aphasia recovery and the neural mechanisms that support treatment-induced recovery. While this may be of interest, we suggest, at least in this early phase of aphasia research, limiting intra-studies to individuals with one type of lesion, e.g., ischemic stroke resulting from arterial occlusion (with or without subsequent hemorrhagic conversion). When the primary question is the effects of aphasia treatment in order to control for spontaneous recovery another consideration may be recruiting only those who are at least 6 months post onset of stroke. Studies of early recovery provide important information about how the brain recovers from stroke and aphasia. However, fMRI research has shown that activation patterns change over time as a function of natural recovery as well as in response to behavioral treatment (Saur et al., 2006, 2010). Overall, these studies emphasize the dynamic reorganization of brain function that occurs following stroke.

There is not yet evidence to suggest that aphasia treatment influences the progressive dynamics of brain reorganization during the early phases of recovery. Therefore studies targeting the early phases of spontaneous recovery may best use structural- and perfusion-weighted MRI to examine how structural damage or compromised cerebral perfusion influences early aphasia progression. Then after this initial natural history of recovery has been detailed fMRI may be more effective to characterize the neural changes associated with aphasia treatment outcome.

Functional imaging of acute stroke is also complicated by the fact that areas around the acute infarct may have compromised function due to low blood flow and may or may not proceed to infarct (see Fig. 1). These hypoperfused areas may contribute to patient deficits (Hillis, 2005) and may not show a BOLD effect in fMRI studies even in the presence of neural activation (Altamura et al., 2009; Prabhakaran et al., 2007) because of exhausted vascular reserve (inability to show a hemodynamic response to activation). This could create a lack of sensitivity to the BOLD response that is not related to hypoperfusion in the absolute sense, but rather to the fact that increased blood during the resting state changes the relative amplitude.

Even in chronic stroke, it is worth noting that there may be individual cases where chronic hypoperfusion could affect the BOLD response to activation (Murata et al., 2006; Prabhakaran et al., 2007; Thompson et al., 2010). To minimize null BOLD effects in group fMRI studies of chronic stroke aphasics it may be advisable to examine individual's hemodynamic response functions (HRF), rather than rely on the canonical HRF during statistical analysis of the fMRI data. In those in whom a poor BOLD signal is detected the individual's baseline cerebral ischemic condition could also be assessed, e.g., investigate if they also have significant hypoperfusion beyond the infarct as measured with computed tomography (CT) perfusion, MR dynamic contrast perfusion (PWI), or arterial spin labeling (ASL) MRI. Investigators could collect additional information about study participant's hemodynamic parameters by looking at stenosis of the internal carotid artery in the neck i.e., those with > 70% stenosis are most at risk for chronic, functionally significant hypoperfusion (typically measured with magnetic resonance angiogram (MRA) or CT angiogram (CTA) of the circle of Willis), or those with impaired vascular reactivity (as measured with vascular response to acetyzolamide or CO2 challenge or breath-holding[1]). However, the question remains

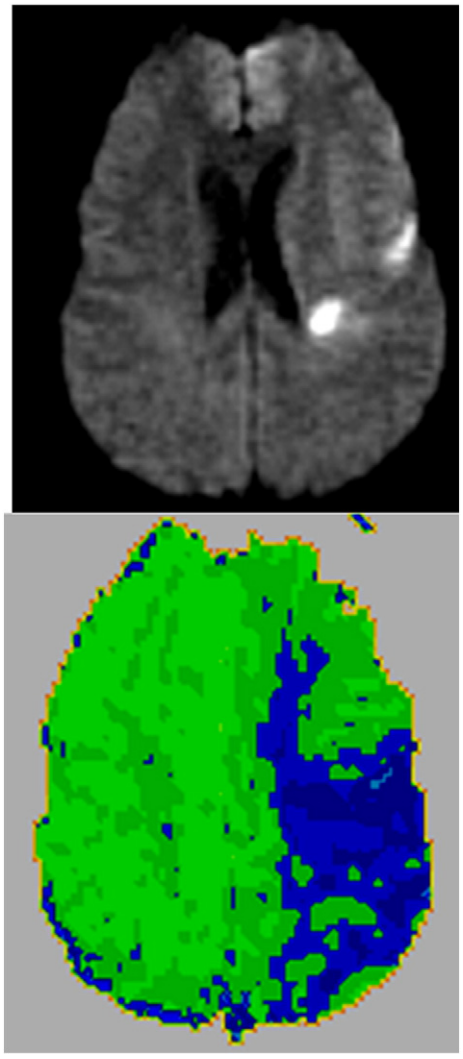

Fig. 1. A diffusion-weighted image (top panel) and dynamic contrast perfusion-weighted image (PWI; lower panel) illustrate in an acute ischemic stroke patient an area of hypoperfusion (blue on PWI) surrounding the area of densely ischemic tissue (bright white on DWI). This area of hypoperfusion is dysfunctional tissue that is at risk for progressing to infarct if blood flow cannot be restored quickly. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

[1] These challenges are not recommended for individuals with impaired vascular reserve purely for research purposes, however, because they could, at least theoretically, cause cerebral ischemia.

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whether or not blood flow is a good marker of neural activity in these patients.

Although the functional magnetic resonance imaging (fMRI) blood oxygen level dependent (BOLD) signal is increasingly used to examine the neural correlates of aphasia treatment, its reliability in areas of hypoperfusion is uncertain. At the same time, the BOLD response and its relationship to diaschisis is not well understood. Cerebral infarction can cause diaschisis, a reduction of blood flow and metabolism in areas of the cortex distant from the site of the lesion. Therefore, converging evidence from different imaging methods may help to assess the validity of the coupling between neural activity, blood flow, and the BOLD response. One could compare positron emission tomography (PET) to BOLD activation, or alternatively, one could use a modality that does not depend on blood flow, e.g., diffusion tensor imaging (DTI) or EEG, and then compare and contrast between modalities. For example, Fair and colleagues investigated the effect of chronic diaschisis as measured by resting PET on task-evoked BOLD responses during word-stem completion in a block design fMRI study in 3 patients, 6 months after a single left hemisphere stroke involving the inferior frontal gyrus and operculum. The BOLD responses were minimally affected in areas of chronic diaschisis. For the patients in this study, the mechanism underlying the BOLD signal, which includes a mismatch between neuronally driven increases in blood flow and a corresponding increase in oxygen use, appeared to be intact in areas of chronic diaschisis (Fair et al., 2009).

Currently, many fMRI studies of aphasia treatment exclude patients with hypoperfusion but perhaps this exclusionary criteria needs to be reconsidered. Rather, in cases with poor BOLD signal and chronic hypoperfusion researchers may choose to exclude the individuals from group fMRI studies and treat them as separate cases e.g., a case series approach. Alternatively, when a number of such rare cases are identified it may be appropriate to group them together and intra-study consider areas of hypoperfusion (as defined by stated threshold, using PWI or ASL) or impaired vascular reactivity as part of the lesion itself. For further and more in depth discussion of these approaches see Lesion identification section and the paper on 'Data Analysis' by Meinzer et al. in this issue.

Other lesion-related participant variables to consider for studies examining recovery from aphasic stroke will depend on the question(s) being investigated e.g., whether to include or exclude individuals on the basis of old lesions, bilateral lesions or multiple lesions. Clinical intuition based on extensive experience represents an important aspect of aphasia treatment and management. Therefore a sensible approach for aphasia research may be to distinguish those lesions with no known clinical correlates and clinically relevant lesions. Many old lesions, such as lacunar strokes or periventricular white matter changes, may or may not influence language or its recovery. Research with stroke individuals is particularly vulnerable to this problem. The imaging threshold for identifying old lesions will be quite variable, depending on which MR sequences are used, for example, fluid-attenuated inversion-recovery (FLAIR) is more sensitive to detecting white matter lesions than T1 MRI. Nevertheless, it is important to define inclusionary and exclusionary criteria with respect to these variables in order to compare results across studies and offer insights into variability across patients with similar lesions (Arnold et al., 2008; Basso et al., 1987). If the extent and location of brain damage relates to brain plasticity and functional outcomes with different aphasia treatment approaches, then it is possible that clinical researchers may rely, in part, on individual's structural neuroimaging data to design their fMRI studies and improve treatment outcomes.

Lesion identification

Precise lesion identification in subjects with structural brain damage is essential for understanding lesion-deficit mappings in the human brain. The accuracy of the functional imaging data will be dependent on how well the lesion is identified and subsequently measured. High-resolution and high-definition imaging methods are likely to detect brain regions where anatomical damage is subtle or invisible to the eye. Most functional imaging studies will require at least a high-resolution T1 image, e.g., high-resolution three-dimensional (3D) magnetization-prepared rapid acquisition with gradient echo (MPRAGE). This will improve not only the normalization of the functional images for each patient in a group fMRI study, but also will enable the description of each patient's functional activation patterns in the context of their own structural damage e.g., superimpose their functional activations onto their own structural images to identify the ipsi-and contra-lesional activation. Brain regions activated during specific language tasks can then be compared to the lesion locations associated with impairment of the task of interest. The convergence of findings obtained from both lesion-deficit and functional neuroimaging approaches can offer strong support for hypotheses regarding brain–behavior relations and treatment effects.

The lesion-based approaches to the study of brain–behavior relations for language have focused primarily on the status of gray matter (i.e., the cortical and subcortical tissue), yet stroke rarely affects just the gray matter. It can damage white matter tracts, and other sequences such as T2* and FLAIR are better than T1 in visualizing white matter changes. There are mixed views regarding how to handle signal changes in the white matter, clinically best seen on FLAIR imaging (see Fig. 2). White matter changes are common among people with diabetes and hypertension (people most at risk for stroke), and their significance is controversial. We suggest that in chronic aphasic stroke patients, non-specific white matter changes in isolation should not be identified as part of the stroke lesion unless they are the density of cerebrospinal fluid.

Where researchers are specifically investigating if white matter tracts have been damaged by the stroke, diffusion tensor imaging (DTI) to detect reduced white matter fractional anisotropy may be the most sensitive approach currently available Martino et al. (2008). An interesting application of DTI has been the study of Wallerian degeneration of clinically relevant white matter pathways, such as the corticospinal tract and the corpus callosum, following an ischemic stroke. The term Wallerian degeneration usually refers to the secondary degeneration of white matter fibers distant from the primary lesion, from 2 months to many years after stroke (Werring et al., 2000; Yu et al., 2009). How these secondary white matter diffusion changes impact on brain function and the BOLD response as measured with fMRI is currently a matter of intense investigation. In the area of aphasia, much of the focus of DTI has been on identifying white matter tracts that connect various nodes within language networks, such as components of "Broca's area" or "Wernicke's area" e.g., (Catani and Mesulam, 2008) and lesions within these tracts in aphasic individuals that relate to the language impairment. An alternative approach uses DTI to highlight that aphasia treatments can alter both function and structure of the brain areas that survived the stroke with corresponding positive behavioral outcomes. Schlaug et al. (2009) examined the density of white matter fibers in the right hemisphere in six participants with chronic, non-fluent aphasia before and after receiving melodic intonation aphasia treatment. They found that the density of the white matter tracts in the right hemisphere had increased among the participants upon completion of the treatment. The use of DTI in lesion analysis is still in the early stages but holds great promise to help advance our understanding of brain–behavior relationships as a means to evaluate the status of language networks, rather than simply considering the integrity of brain regions in isolation.

A variety of other approaches are available that provide insight regarding brain function, and additional lesion measures are rapidly developing. These include CT perfusion, MR spectroscopy, SPECT, and positron emission tomography (PET) and may also contribute additional information when available. For example, gradient echo or

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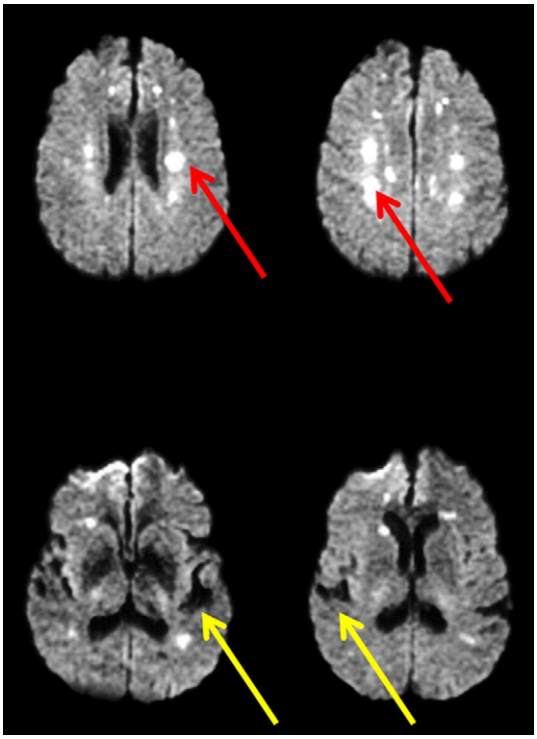

Fig. 2. DWI sequences are ideal for distinguishing white matter hyperintensities from old stroke. White matter hyperintensities appear white (red arrows), whereas old strokes appear black (the density of cerebrospinal fluid; yellow arrows) on DWI sequences. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

susceptibility-weighted images are very sensitive to old and new microhemorrhages that might influence overall recovery after stroke, while MR spectroscopy or PET can identify hypometabolic regions that contribute to the deficits. All of these different neuroimaging techniques might improve the description of the patient's anatomical brain damage and its impact on their functional activation patterns in fMRI studies.

As mentioned earlier, when patients with chronic hypoperfusion are studied, MRA (or CTA), vascular reactivity measures, or perfusion imaging is particularly useful. In such cases, areas of hypoperfusion (as defined by a stated threshold, using PWI or ASL) or impaired vascular reactivity would also be considered as part of the lesion itself. For example, a 4 s delay in time to peak (TTP) arrival of contrast compared to the homologous region in the normal hemisphere on dynamic contrast PWI is often considered dysfunctional tissue and might be included as part of the lesion (DeLeon et al., 2007). ASL provides a more absolute measure of regional cerebral flow (rCBF) than TTP, but rCBF can also be calculated from dynamic contrast PWI using arterial input function. However, to date ASL is more technically challenging than dynamic contrast PWI. As such, in many cases it can be lower resolution, with less brain coverage (fewer slices, unless using continuous ASL), and take longer in the scanner (requiring greater patient cooperation). Nevertheless, ASL has the distinct advantage that it does not require intravenous contrast. For an example see a recent study (Thompson et al., 2010) that used ASL with a modified PICORE/Q2TIPS sequence (Luh et al., 1999) to examine hypoperfused tissue in six individuals with chronic stroke-induced aphasia. These combined approaches hold considerable potential to provide a more comprehensive understanding of brain fMRI activity during language-processing tasks.

Lesion site

One of the most important predictors for aphasia outcome is lesion site, although other factors such as lesion size, age, handedness, education, co-morbidity, and motivation may influence recovery patterns (see Rapp et al., this issue, for discussion). Brain damage following stroke is typically distributed in a complicated fashion, limited by the vascular anatomy rather than functional anatomy, affecting the structure and function of neighboring and distantly connected regions (Thomalla et al., 2004; Young et al., 2000). Each of these regions may have different degrees of structural damage and functional impairment (Rorden et al., 2007; Young and Scannell, 2000). There are presently many ways of identifying the site of a lesion, including using anatomical landmarks such as specific gyri, or identifying approximate locations on an atlas of Brodmann's areas, identifying the coordinates in a single brain e.g., Talairach space or average population based MNI Space (Mazziotta et al., 2001; Mori et al., 2008), specifying regions of interest (Mori et al., 2008), or identifying affected voxels on a given atlas to which the patient's scans are registered. These methods provide convenient and automated means for macroanatomical labelling of multi-subject functional imaging data and do not require significant neuroanatomical experience. However, all methods have strengths and weaknesses and all are limited by individual variability of brain size and shape and variability of the sulci and gyri especially in higher order cortices, such as those involved in language processing. Therefore, any macroanatomical atlas based on a single brain such as the Talairach brain may often provide inaccurate information about functional localisation (Fischl et al., 2008).

While cytoarchitectonic probabilistic maps currently offer the most precise tool for the localization of brain functions as obtained from functional imaging studies, such maps do not cover the whole cortical surface and intrinsic variability in functional anatomy will also be observed because the anatomical 'landmarks' e.g., sulcal and gyral borders in structural MRI scans do not necessarily correspond to functionally relevant cytoarchitectural structure (Amunts et al., 2007; Eickhoff et al., 2005, 2007). For example, the striking variations in the sulcal landmarks of Heschl's gyrus demonstrate that anatomic variability poses a serious obstacle for functional localisation based on macroanatomical labelling methods (Leonard et al., 1998). Nevertheless, currently, there is no evidence that any one of these structural labeling approaches is more valid than any other. Regardless of which method is selected, it is important that investigators specify clearly how they determined the site of lesions.

Lesion volume

Although reporting the 3-D volume of a lesion would seem to be straightforward, it can vary considerably depending on the threshold of the lesion detection approach, type of MR sequence used as discussed above, and method of quantification. Stroke-induced lesions can affect both cortical and subcortical tissue. Therefore, lesion volume measurements need to include both. The challenge to investigators is that they must report how they define the borders of both cortical and subcortical lesions. As noted in the previous section, where indicated researchers also should consider as part of the "lesion" areas of tissue dysfunction, which can be addressed using a measure of hemodynamic function (e.g., regional cerebral blood flow (rCBF), blood volume, time to peak arrival of contrast agent). The "lesion" can then be defined either as a binary structural/function lesion or as continuous structural/functional lesion e.g., rCBF, white matter integrity-fractional anisotropy, or gray matter tissue density. Usually, the gold-standard method for lesion identification and volume measurement rests on the manual definition of abnormal brain tissue by a trained professional e.g., (Bates et al., 2003). The volume is measured manually by extrapolating where normal brain would be present from the patient's non-lesioned hemisphere or from an age-appropriate normal atlas. To determine the precise location and extent of damage, the lesion is demarcated on every slice and a lesion volume can then be generated, e.g., using the region of interest facility in Analyze software (Mayo Biomedical Imaging Resource, Mayo Clinic).

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This approach is laborious, operator-dependent (Ashton et al., 2003; Filippi et al., 1995), and time-consuming.

Alternatively, several semi-automated and fully automated procedures for lesion identification and volume measurements have been proposed. Automated methods nearly always have higher inter-rater and intra-rater reliability, but may fail to identify imaging artifacts that are appreciated by the human eye, which can lead to lower validity if not checked. They can be divided in two categories according to the nature of the MRI images used to identify the lesion: (i) multi-channel or multi-spectral methods that operate on several weighted MRI images, including T1, T2, PD, and FLAIR images, with or without contrast agents e.g., (Kabir et al., 2007); and (ii) mono-channel or mono-spectral methods that use only one contrast MRI image (e.g. T1 image) (Stamatakis and Tyler, 2005; Wilke et al., 2003). In functional MRI studies each participant usually has only one anatomical image (usually a T1 image). In this case, each image provides a continuous measure of brain composition in many thousands of voxels across the whole brain. These signal values can be converted into an estimate of gray, white, CSF and lesion density at every brain voxel e.g., (Seghier et al., 2008). Using such a continuous measure of gray matter density can circumvent user-based errors introduced by the binary classification of whether an area appears damaged or not. If volume is measured with an automated method the investigator must specify the lesion detection thresholds used, e.g., 10 contiguous voxels with a tissue density value more than 2 s.d. below normal.

The lesion volume can then be measured using statistical analyses on a voxel-by-voxel basis ultimately providing brain maps indicating regions of significant tissue damage. Methods such as voxel-based morphometry that look at correlations between gray and white matter density in relation to behavioral factors (Ashburner, 2009) may be useful here to measure the lesion volume. With this approach the structural MRI scans are typically evaluated relative to a cohort of healthy brains. Statistical analyses on a voxel-by-voxel basis ultimately provide brain maps indicating regions of significant gray or white matter loss corresponding to the lesion location and volume. Analysis of an individual over time is also possible and can reveal subtle volumetric changes that would be difficult to identify otherwise (Good et al., 2001; Gorno-Tempini et al., 2004).

Ultimately, images can be produced that demonstrate lesion overlap in large patient cohorts, providing a powerful means to determine which cortical regions are likely to be essential for specific language processes. The 3-D images not only enable researchers to examine common and unique regions of brain damage across individuals, but also allow examination of the damaged regions for a cohort relative to their language behavior and functional brain responses (e.g., BOLD signal in fMRI). Schofield and colleagues adopted this approach to compare brain structure and function in two subgroups of 21 stroke subjects with either moderate or severe chronic speech comprehension impairment (Schofield et al., 2012). Both groups had damage to the supratemporal plane; however, the severely aphasic group suffered greater damage to two unimodal auditory areas: primary auditory cortex and the planum temporale. The effects of this damage were investigated using fMRI while subjects listened to speech and speech-like sounds. Pronounced changes in functional connectivity were found in both groups in undamaged parts of the auditory hierarchy. Compared to controls, moderate aphasics had significantly stronger feedback connections from planum temporale to primary auditory cortex bilaterally, while in severe aphasics this connection was significantly weaker in the undamaged right hemisphere. This result highlights that structural damage following stroke can have remote, bilateral functional effects in the task-related brain network that predicts language behavior and possibly aphasia treatment outcome. Understanding the lesion location and extent was key not only to understanding the severity of the aphasia but also the individual's functional connectivity. Given this, it is possible that the beneficial effects of aphasia treatment may be expressed at the network level of functional connectivity of the remaining language system, rather than in any given region, be it in the left or right hemisphere.

Another approach is voxel-based lesion-symptom mapping (VLSM) a method and software for analyzing relationships between behavioral deficits in neurological populations and lesion sites associated with those deficits (Bates et al., 2003). The major difference and advantage of VLSM over previous lesion-mapping methods is that it allows researchers to examine such data without stipulating behavioral cutoffs (e.g., impaired vs. spared performance), or identifying lesion sites of interests (e.g., parietal patients vs. inferior frontal patients). Instead VLSM calculates the statistical relationship between performance on a given task (such as naming or reading) and the status of a given brain voxel (damaged or healthy) across the whole brain. Patients are divided into two groups according to whether they do or do not have a lesion affecting a specific voxel. Behavioral scores are then compared for these two groups, yielding a *t*-statistic for that voxel. The procedure is then repeated several times for each voxel included in the analysis. Individuals with multiple strokes do not need to be excluded when using VLSM because it does not take into account how the effect of damage to one voxel depends on the effect of damage to other voxels. Rather, it looks for the most significant correlations between behavior and damage, irrespective of damage to other brain regions. VLSM maps can then be generated that show brain areas that are statistically related to a task of interest, can predict individual aphasic's performance on fMRI tasks and may in turn be a biomarker for treatment outcome.

For example, Geva and colleagues used VLSM to determine the relation between inner and overt speech investigated previously using functional imaging (Geva et al., 2011). They showed that the neural correlates of inner speech abilities were affected by lesions to the left pars opercularis in the inferior frontal gyrus and to the white matter adjacent to the left supramarginal gyrus, over and above overt speech production and working memory. Their VLSM result suggests that inner speech cannot be assumed to be simply overt speech without a motor component and that the use of overt speech as a fMRI task to understand inner speech and vice versa might result in misleading conclusions, both in imaging studies of aphasia treatment and clinical practice. Combining differences in brain structure and function might explain this.

Reliability and other considerations

Whatever methods the investigators choose to use to identify and characterize the lesion volume, site or other characteristics, intra-rater and inter-rater reliability must be reported. At least for lesion characterization purposes, MR scanner-to-scanner variability may not be a significant problem as long as magnet strength and sequences used are consistent, but these should be clearly specified. At least MR scanner-to-scanner variability is very small compared to the variability across individual brains.

For functional imaging studies of aphasia treatment, structural/functional lesions should ideally be defined by imaging at the same time or closely matched, e.g., within 2 weeks before the onset of treatment and again directly following the end of treatment. Important structural as well as functional changes might occur over time, e.g., changes in gray matter density in response to relearning (Boyke et al., 2008; Driemeyer et al., 2008; Kloppel et al., 2010). In addition, when structural imaging measures (e.g., changes in gray matter density) are to be used as an outcome measure of aphasia therapy pre- and post-therapy imaging, protocols must be identical.

Caveats and future directions

Whereas the previous paragraphs depict a relatively consistent and homogenous picture, several caveats should be kept in mind.

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First, the discussion of methods above assumes in general that the structure of the chronic lesioned brain is a fixed entity, often neglecting that stroke damage to the cortex and/or subcortical structures may continue to change over time, resulting in not only tissue loss in the core lesioned area but also Wallerian degeneration resulting in structural (Thomalla et al., 2004) and functional changes in remote brain regions. However, acquired language impairment is not always associated with obvious focal damage. For example, in cerebellar diachisis, left frontal lesions result in functional changes and tissue loss in right cerebellar regions (Shih et al., 2006). These secondary lesion effects may not be visible by eye, but can be detected using automated methods that detect gray and white matter volumetric changes in high-resolution images and the cumulative effects of these structural changes may potentially impact language recovery. Second, whereas most work in the field focuses on studying the effects of treatment and language recovery on the BOLD response, some reports indicate that learning new skills in healthy subjects can result in increases in gray matter density (Draganski and May, 2008; Draganski et al., 2004; Mechelli et al., 2004). Similarly, language treatments in aphasic patients that improve performance may be expected to correlate with not only changes in the BOLD response, but also plasticity in gray matter density in the structurally intact cortices involved in the recovery process. Third, one caveat of many previous investigations has been the focus on short-term improvements in performance. More experiments are required to assess the effects of aphasia treatment on both structural and functional brain plasticity, their interaction with specific language learning and the extent to which improvements are retained in the long term. Finally, it should be kept in mind that the effects of treatment on language recovery in acute and chronic aphasic stroke cannot be assumed to be the same. The mechanisms underlying recovery at different stages after stroke are very likely to differ not only in their effects on cortical structure and function, but also the neural networks that subserve language processing and behavioral consequences. Clearly more work is needed in this area.

Summary

Detailed lesion characterization can contribute to the understanding of not only the structural mechanisms underlying aphasia, but also when combined with fMRI studies the structural and functional plasticity supporting language recovery. As such, every functional neuroimaging study of aphasia treatment should begin by adequately characterizing the lesions of the study participants. The results may critically depend on features of the lesion, such as location and volume. At present, there are no gold standards for characterizing lesions, but there are many methods that can be applied to provide sufficient information to use for evaluating changes in functional activation that occur as a result of treatment. There are few studies comparing both reliability and validity of different approaches to lesion localization or quantification. However, the accumulation and analysis of data to which various methods are consistently applied by the same or different investigators will allow more definitive guidelines to emerge in the future.

Data from fMRI studies will need to be integrated with those from high-resolution structural MRI to advance our understanding of which individuals with aphasia are likely to recover after stroke and enhance our ability to predict which treatment approach may best benefit them. Despite limitations, including the scarcity of detailed anatomical data especially in population studies of aphasic stroke patients, work that has been already accomplished raises the exciting hypothesis that currently available noninvasive neuroimaging techniques, combining structural and functional MRI, could offer early biomarkers to recovery and help develop targeted treatment programs.

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