Contents

Introduction

ROGER J. INGHAM

Organizing and finally assembling the chapters for this book has been one of life's more pleasurable education experiences for this editor. The impetus for the development of the book resides with the continuing far-sighted thinking of Dr. Sadanand Singh. He has been unflagging in helping the discipline of human communication sciences and disorders advance its knowledge base by publishing cutting-edge texts that help to define just what it is that our discipline can uniquely contribute to humanity—more specifically, just what that knowledge base can provide for our discipline's science and its quest for the alleviation of communication disorders. And that is precisely what this book aims to provide.

Our discipline often has appeared to struggle to define a distinctive body of knowledge that constitutes the discipline of human communication disorders (e.g., Bench, 1989; Ringel, Trachtman, & Prutting, 1984). It also is rather puzzling, however, that our researchers and clinicians would doubt that the discipline's search for the basis of human communication disorders and their alleviation constitutes a thoroughly identifiable discipline. Maybe it is because the boundaries of the discipline have always been permeable—but they are in ways that can be easily shown to have helped to enhance, rather than threaten, the discipline's existence. As argued some years ago (Ingham & Siegel, 1989; Siegel & Ingham, 1987), our field has thrived on its links to education, psychology, linguistics, and physiology. Indeed, from a historical perspective, the field of human communication disorders has always made some degree of commitment toward relating the principal disorders within the areas of speech, language, voice, and hearing to neurophysiology or neuroanatomy. The pioneers of our discipline, at least as it emerged in the United States—and especially in Iowa—obviously were very aware that the understanding and remediation of many disorders would rely on advances in neurology (Paden, 1970). Today, however, little doubt exists that the advances in neuroscience in recent years have started to permeate the boundaries of our discipline in a very substantial way—and that is reflected in the chapters of this book.

In the late 1980s, it became very obvious to many in the field that developments in computer science, neurology, and genetics would radically change the direction of research into the understanding and treatment of human communication disorders. It seemed inevitable that the methods and technologies that characterize our discipline were going to be profoundly influenced by developments taking place in each of these areas—and that if they did not have a positive influence, then our discipline's future would

be under threat. It obviously is hard to pinpoint precisely when a change occurs in the direction of thinking in any field of study. The Kuhnian notion (Kuhn, 1970) that large advances in science occur when a reigning paradigm within which that science is conducted is challenged by a new, incommensurate paradigm has been an appealing viewpoint. Viewed from the present, however, it is possible that Kuhn's conceptual framework may not have given due recognition to the dramatic impact that technological developments in other areas of science are likely to have on the direction of a discipline's research. Such development appears to have occurred with the emergence of imaging technologies that were able to track and map cerebral blood flow (see Posner & Raichle, 1994). Earlier brain imaging technologies, such as electromyography and even magnetic resonance imaging, obviously played an important part in research on neurologically related communication disorders before the late 1980s and paved the way for later developments. However, it was developments at Washington University School of Medicine in St. Louis, and especially two papers published by Petersen and colleagues from that institution in the late 1980s (Petersen, Fox, Posner, Mintun, & Raichle, 1989; Petersen, Fox, Posner, & Raichle, 1988), that propelled the growing integration of neuroscience and communication disorders. Of course, that growth was further fueled by the evolution of blood oxygenation level-dependent (BOLD) measurement using functional magnetic resonance imaging (fMRI) in the early 1990s, especially the development of event-related fMRI (see Buckner, 1998).

The rest is now history. The explosive growth in neuroimaging since the early 1990s is truly astounding. Just keeping abreast of this burst of knowledge requires considerable and constant attention to the major journal outlets, aided by the benefits of library search engines and Google. Some idea of the magnitude of that growth is captured in the following figure, constructed by Fox, Laird, and Lancaster (2005, p. 2), which documents the number of brain imaging papers published between 1988 and 2004.

Figure I–1 is of added interest because it also documents the gradual improvement in the number of these papers that provide data suitable for deriving meta-analyses across studies. Combinatory research has become increasingly necessary in order to establish the replicability of imaging findings with performance of different tasks, including speaking tasks. The work of Indefrey and Levelt (2004) has provided that capability for word production. Other meta-analysis techniques that take advantage of the levels of activation across studies have now started to appear, and some efforts have been made to apply these to imaging studies on developmental stuttering (Brown, Ingham, Ingham, Laird, & Fox, 2005). Undoubtedly, similar endeavors will soon emerge from the multiple imaging studies that are now being conducted on other communication disorders.

The chapters gathered in this book provide a kind of interim report on the contributions deriving from developments in neuroscience, particularly brain imaging, to the understanding and treatment of some of the principal communication disorders. The chapter authors were selected because they are actively engaged in programs of research that involve those disorders. But they also were asked to go beyond their own work, to offer readers a broad perspective. More

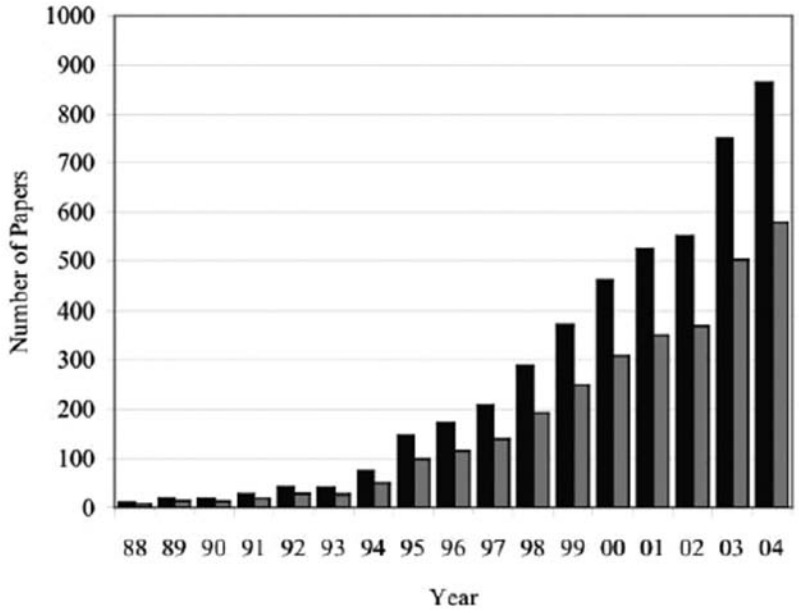

Figure I-1. Figure shows annual publication rates for all human brain mapping studies (*dark bars*) and for a subset suitable for quantitative meta-analysis (*light bars*) as reported by Fox, Laird and Lancaster (2005, p. 2). These data were derived from Medline searches. The criteria used to select the meta-analysis subset are described in the Fox, Laird and Lancaster (2005) paper.

specifically, they were asked to provide a chapter that covers the following general topics:

- Background on neurological research in the principal topic area
- Developments in brain research in that area that have been fostered by imaging technology
- Methodological issues that are important to that area
- A critical review of the current advances resulting from imaging research in that area
- A final section in which they derive their own conclusions and highlight promising future directions

Not all areas of brain imaging research in communication disorders have been embraced by the book's chapters. Regrettably, a chapter on brain imaging of children with language disorders is not included. Certainly, however, some encouraging signs indicate that research in this area is beginning to move forward (e.g., Plante, Holland, & Schmithorst, 2006), and future editions of this book will no doubt reflect these continuing developments. Undoubtedly, that also will be true for all of the topic areas embraced by this text.

As mentioned earlier, an auditory neuroscience textbook cannot ever be more than an interim report on the current state of the almost explosive developments in the field that have a direct impact on

human communication disorders. Nevertheless, this book surely will serve as an important landmark in the literature. Each chapter presents not only an excellent overview of the state of knowledge but also some thoughtful ideas about the direction of future research. The elucidating commentaries provided by the authors are both absorbing and eye-opening for readers interested in this development in communication sciences and disorders. It has been a privilege to serve as editor for this book.

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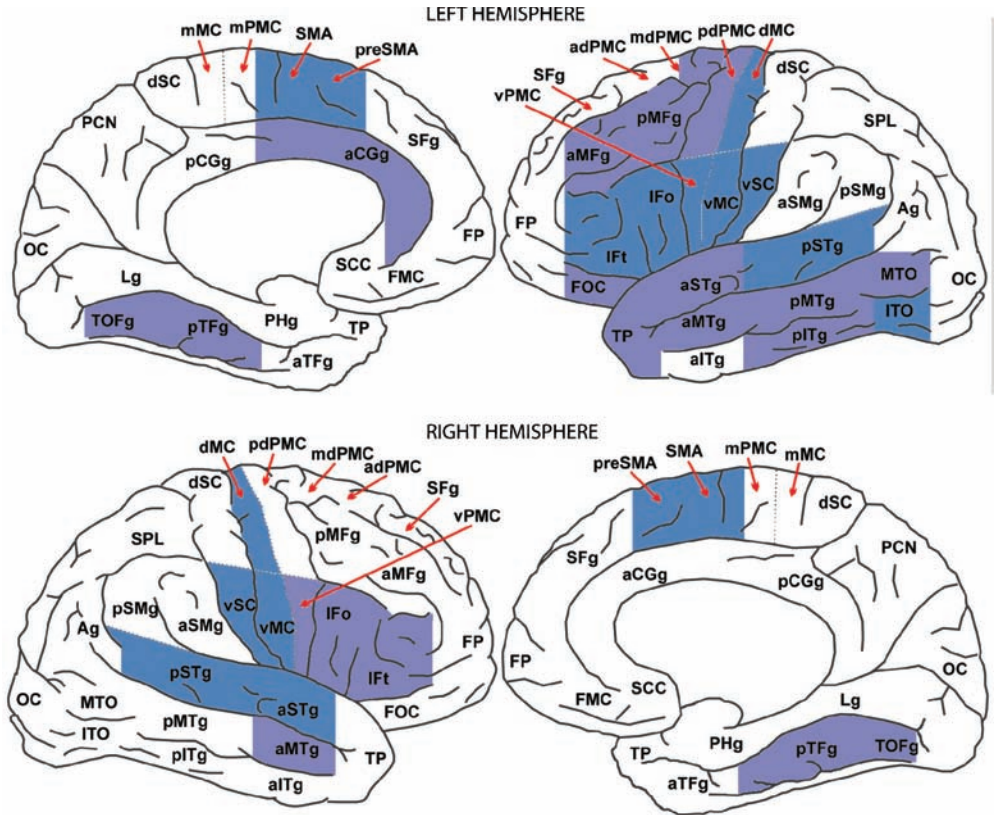

Plate 1. Schematic summary of regions of the cerebral cortex that are reliably active in neuroimaging studies of speech production. Areas in blue are active during monosyllable production (Ghosh, 2004; Guenther et al., 2006). Those in purple are recruited for word production and word generation tasks with a semantic component (based in part on Figure 3 from Indefrey & Levelt, 2004). aCGg, anterior cingulate gyrus; adPMC, anterior dorsal premotor cortex; Ag, angular gyrus; aITg, anterior inferior temporal gyrus; aMFg, anterior middle frontal gyrus; aMTg, anterior middle temporal gyrus; aSMg, anterior supramarginal gyrus; aSTg, anterior superior temporal gyrus; aTFg, anterior temporal fusiform gyrus; dMC, dorsal motor cortex; dSC, dorsal somatosensory cortex; FMC, frontal medial cortex; FOC, frontal orbital cortex (inferior frontal gyrus pars orbitalis); FP, frontal pole; iFo, inferior frontal gyrus pars opercularis; iFt, inferior frontal gyrus pars triangularis; ITO, inferior temporo-occipital junction; Lg, lingual gyrus; mdPMC, middle dorsal premotor cortex; mMC, medial motor cortex; mPMC, medial premotor cortex; MTO, middle temporo-occipital junction; OC, occipital cortex; pCG, posterior cingulate gyrus; PCN, precuneus; pdPMC, posterior dorsal premotor cortex; PHg, parahippocampal gyrus; pITg, posterior inferior temporal gyrus; pMFg, posterior middle frontal gyrus; pMTg, posterior middle temporal gyrus; preSMA, pre-supplementary motor area; pSMg, posterior supramarginal gyrus; pSTg, posterior superior temporal gyrus; pTFg, posterior temporal fusiform gyrus; SCC, subcallosal cortex; SFg, superior frontal gyrus; SMA, supplementary motor area; SPL, superior parietal lobule; TOFg, temporo-occipital fusiform gyrus; TP, temporal pole; vMC, ventral motor cortex; vPMC, ventral premotor cortex; vSC, ventral somatosensory cortex.

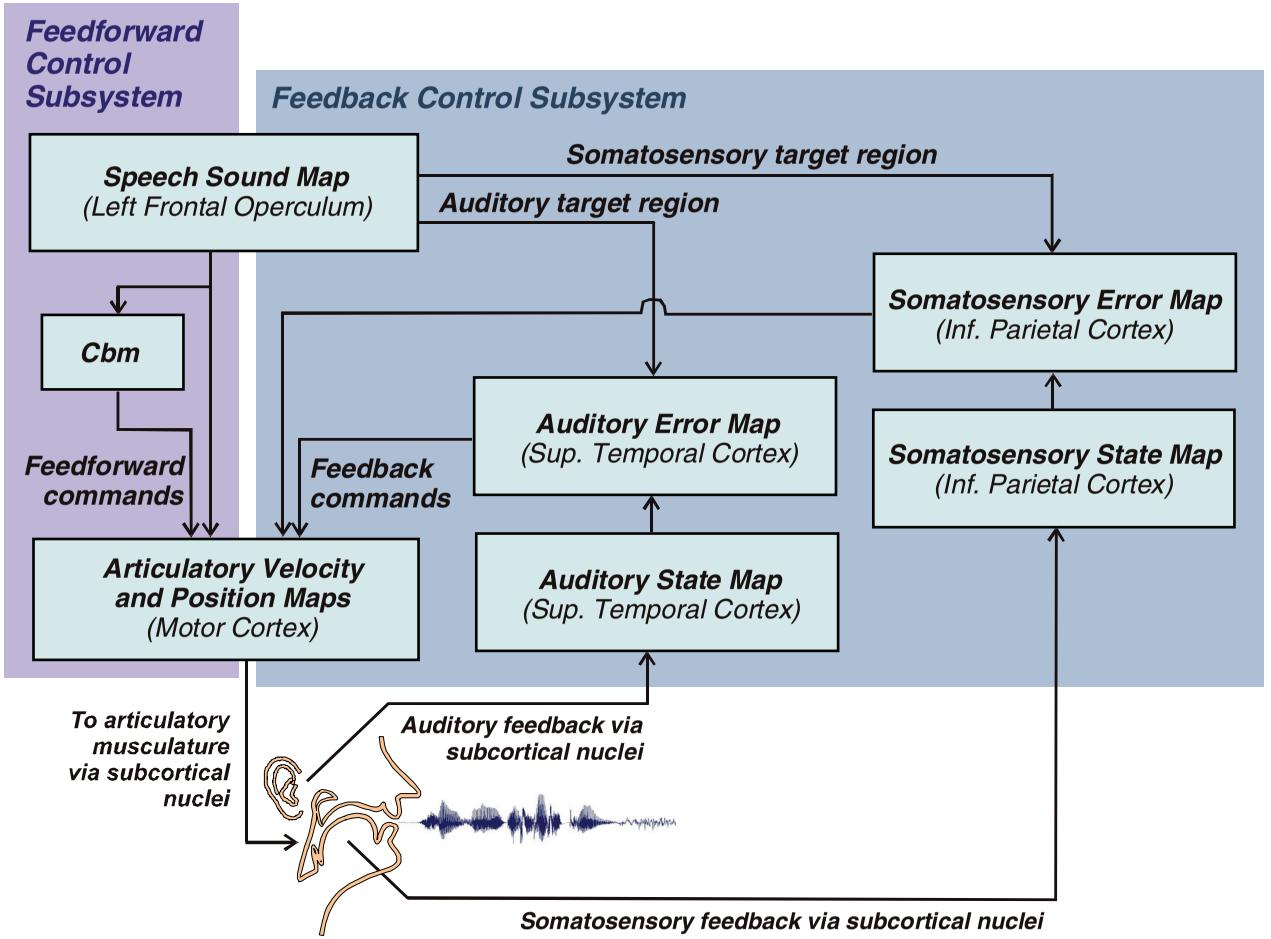

Plate 2. Schematic of the DIVA model of speech acquisition and production. See text for details. Cbm, cerebellum.

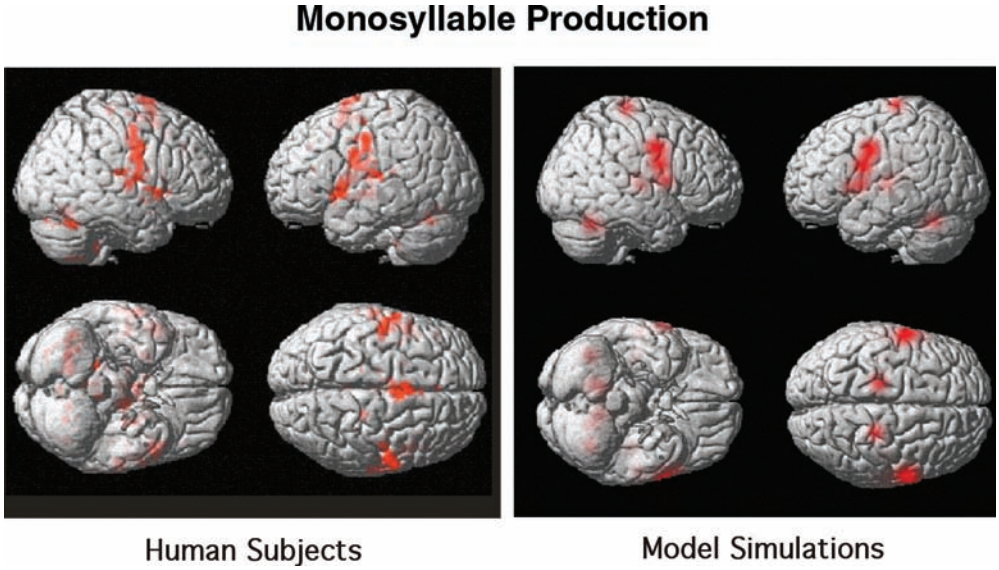

Plate 3. *Left:* fMRI activations measured in human subjects while they read single consonant-vowel (CV) syllables from a screen (10 subjects; random effects analysis, $p < .05$ corrected). *Right:* Simulated fMRI activations derived from the DIVA model's cell activities during single syllable production.

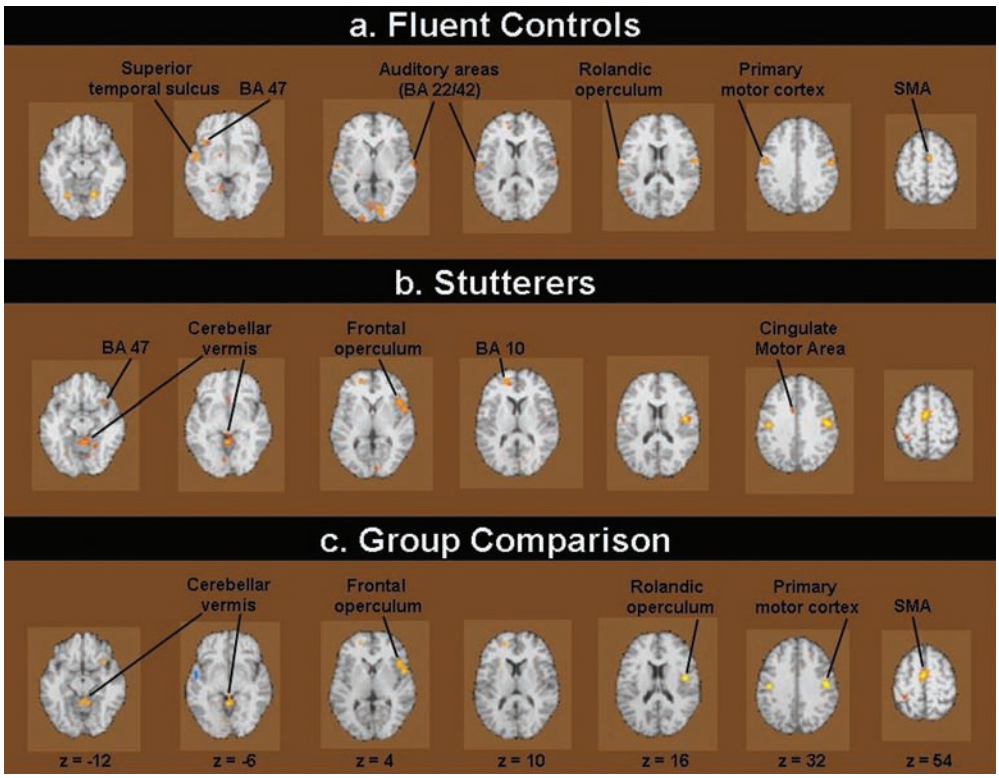

Plate 4. Axial slices (at seven different Z levels) demonstrating foci (in orange) of major activation likelihood estimates (ALEs) from meta-analyses for fluent control subjects and stuttering speakers across eight brain imaging studies on stuttering (Braun et al., 1997; De Nil et al., 2000 and 2003; Fox et al., 1996 and 2000; Ingham et al., 2004; Neumann et al., 2003; Preibisch et al., 2003). *Panel a*: Major ALE foci for the fluent control subjects. Principal sites of activation are labeled on only one side of the brain. *Panel b*: Major ALE foci for the stuttering subjects. The labels highlight activations seen uniquely in the stuttering group. *Panel c*: Group comparison of the ALE foci from the two groups. For this panel only, orange indicates that activations are more numerous in stutterers than in control subjects, and blue indicates they are more numerous in control subjects than in stutterers (in the latter, activations are seen only for the superior temporal sulcus). Labels highlight the vocal-motor areas shown by the meta-analysis to have large cross-laboratory concordance. The bilateral auditory areas, present in controls but absent in stutterers, are below threshold in the group comparison. The Talairach Z coordinates for the slices are shown at the bottom of the figure. The same set of seven slices is shown in all three panels. The left side of a slice is the left side of the brain. The threshold for all analyses is $P < .05$. BA, Brodmann's area (see Chapter One); SMA, supplementary motor area.

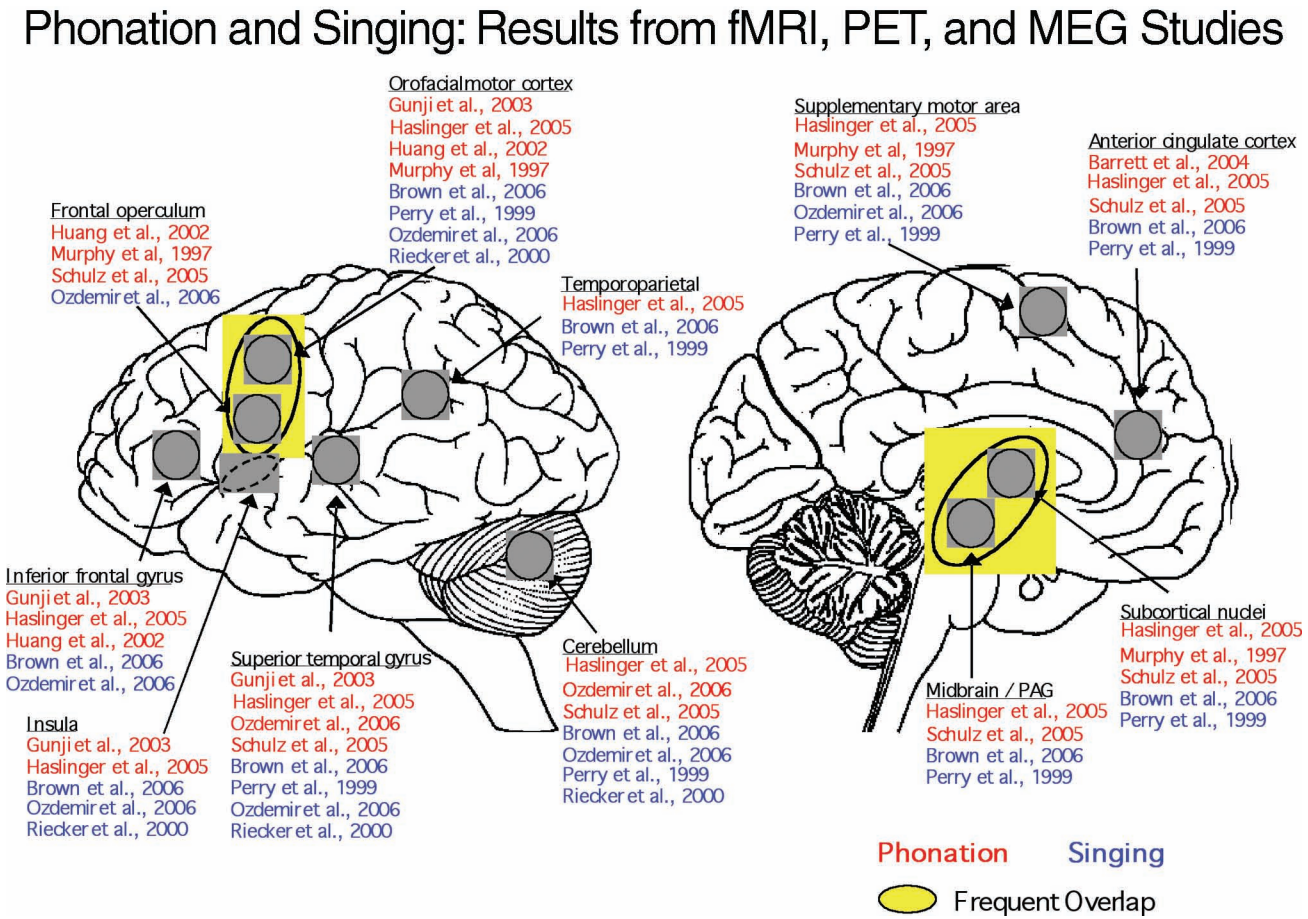

Plate 5. A schematic diagram of the regions of the brain found active during phonation for speech and during singing. The studies of phonation are listed in red, and those of singing are listed in blue. Two sets of regions often are combined into one large region of activity in some studies: the orofacial motor cortex and the frontal operculum, and the subcortical nuclei and the periaqueductal gray (PAG).

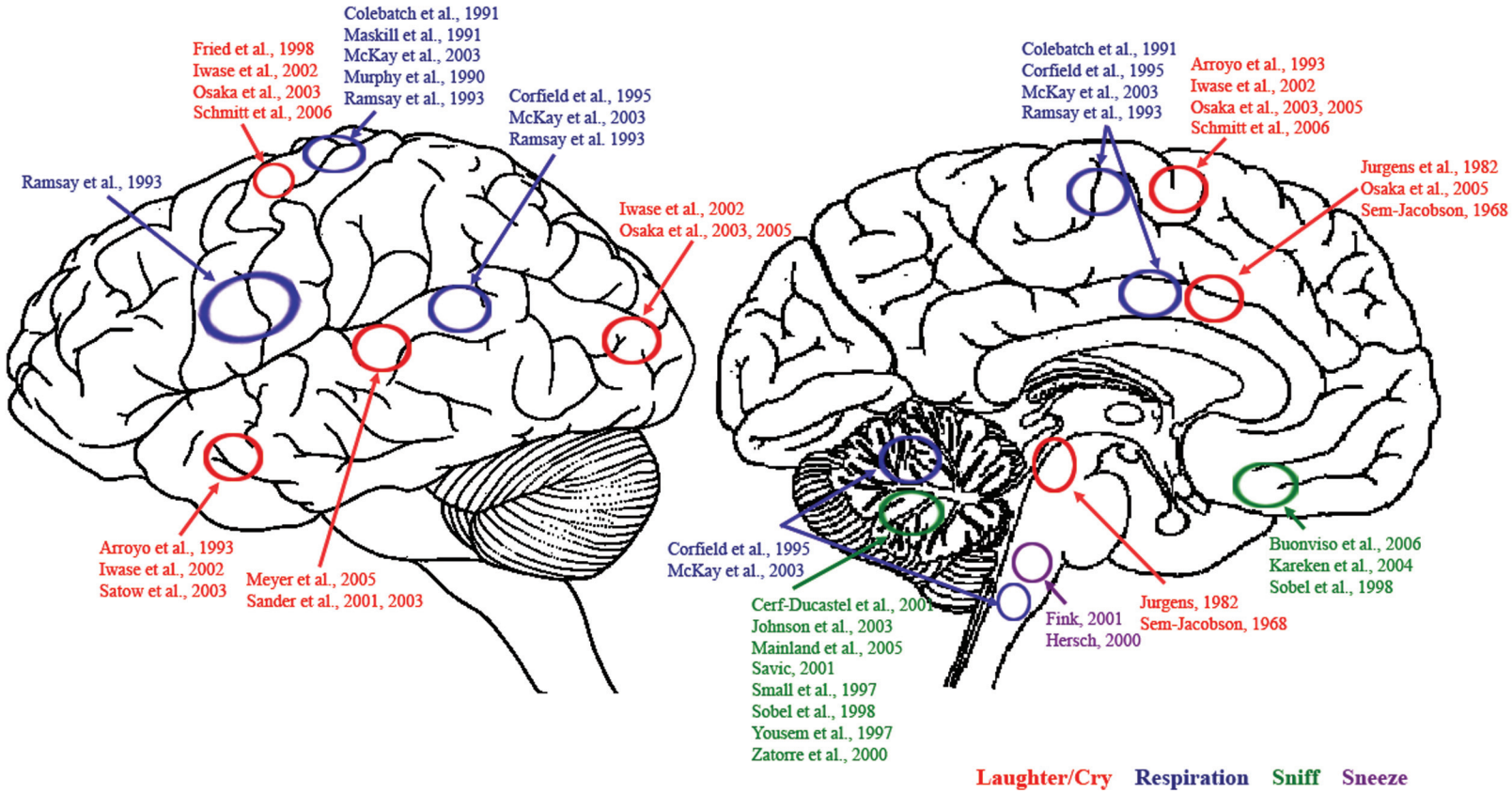

Plate 6. A schematic diagram of the regions of the brain found active during voluntary and automatic or reflexive upper airway behaviors, including laughter and cry, respiration, sniff, and sneeze. The reported results include those from neuroimaging studies in humans, clinical reports of brain lesion locations in patients with disruption of these behaviors, and some results of studies in mammals, for which no human data on cortical involvement are available.

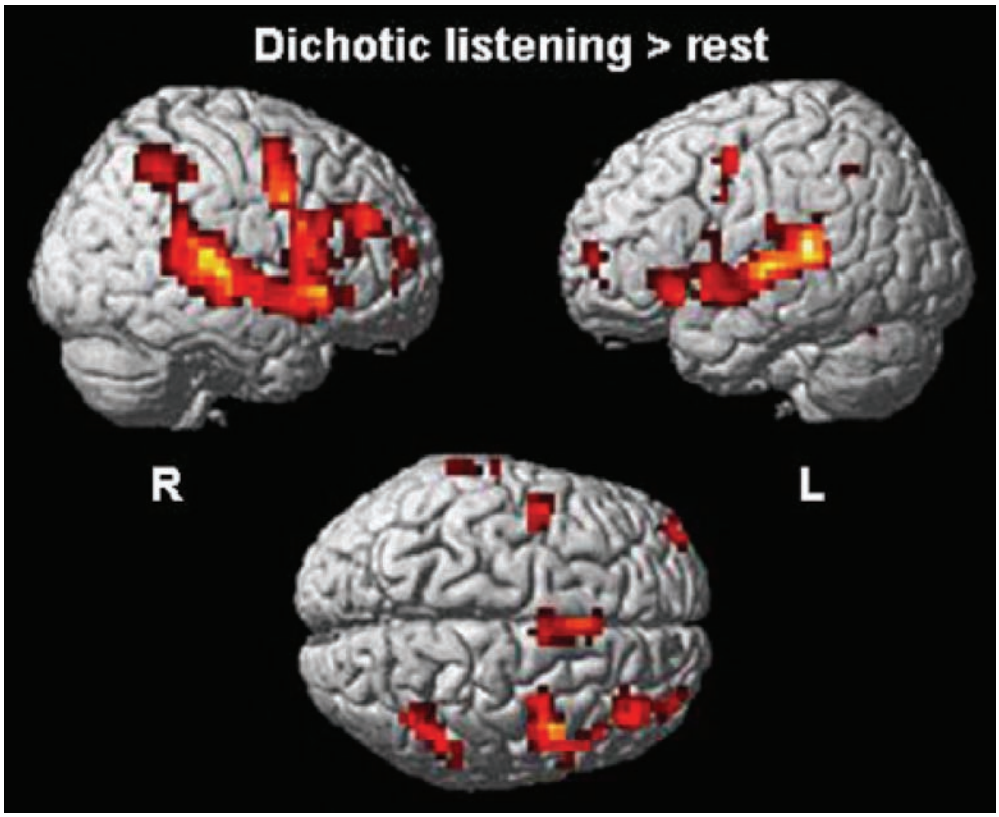

Plate 7. Cortical areas in which activation is greater during dichotic processing. Reprinted with permission from Jancke et al. (2003).

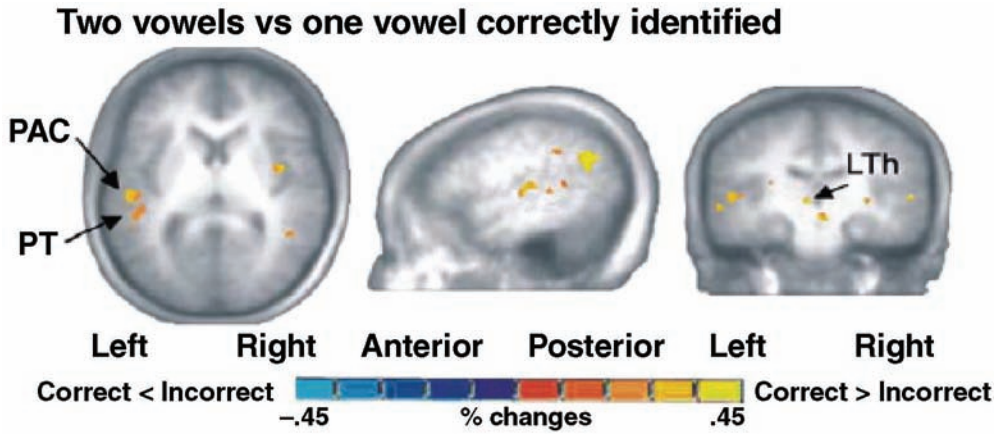

Plate 8. Differences in average activation between trials in which one or two vowels were correctly identified. LTh, left thalamus; PAC, primary auditory cortex, PT, planum temporale. Reprinted with permission from Alain et al. (2005).

production deficits who were given syntactic mapping treatment to improve sentence production, and brain activation maps were obtained before and after therapy with fMRI using a block paradigm silent sentence production task. Treatment effects for one patient generalized to non-treatment tasks, with increased activation of Broca's area after therapy. Treatment of the second patient did not generalize to non-treatment tasks, and little change, except for less diffuse activity, occurred in the activation maps after treatment.

New Techniques Applied to Aphasia

PWI and DWI

Another imaging method with great potential to add to the current understanding of the recovery process in aphasia is the utility of perfusion-weighted and diffusion-weighted magnetic resonance imaging (MRI), specifically in uncovering the tissue death versus recovery and behavioral implications of that process. In brief, *perfusion-weighted imaging* (PWI) is a protocol used with MRI in which image intensity is indicative of protons perfusing brain tissue (marked either by injection of MR contrast or by use of arterial spin labeling) and gives information about areas of reversible ischemia in which hypoperfusion is observed (Srinivasan, Goyal, Al Azri, & Lum, 2006). In *diffusion-weighted imaging* (DWI), the MR sequence is sensitive to the diffusion of water molecules and, because areas of ischemia have restricted water diffusion, the intensity of ischemic tissue is greater than that of intact tissue (Srinivasan et al.). Its use in acute stroke is valuable because the diffusion-restricted tissue can be seen within 30 minutes of the onset of stroke. Additionally, PWI is correlated with the severity of neurological deficit and the severity of aphasia (Fridriksson, 2002). PWI can be compared with DWI giving the diffusion-perfusion mismatch and is used to provide information about tissue that is no longer receiving oxygen (ischemic tissue), as opposed to tissue that is still receiving oxygen but unable to function (the "ischemic penumbra"), allowing salvage with reperfusion methods.

Hillis and colleagues have used these measures to attempt to elucidate the network of brain regions associated with reading (2005), articulation (2004b) writing of verbs (2003), and naming (2006), and to determine the benefit of reperfusion in specific area(s), as indicated by improved performance. The basic assumption underlying this work is that the region of hypoperfusion is associated with impairment of a specific language function consequent to the stroke on the first day, and that reperfusion of the region results in recovery of the specific language function. All of the studies have employed similar methodology: PWI and DWI data were gathered and language testing was conducted at both 1 day and 3 to 5 days after stroke. This paradigm allowed the investigators to determine the diffusion-perfusion mismatch within 24 hours of the event, test language function at that point, and then observe recovery of specific language functions with reperfusion of specific brain regions. Areas of hypoperfusion are defined by TTP maps indicating a greater than 2.5- to 4.5-second delay in arrival of contrast in the specific region of the impaired hemisphere relative to the homologous region in the intact hemisphere.

A recent issue of debate has been the potential role of the left fusiform gyrus in visual word processing. Several studies have demonstrated activation in this region during reading tasks (Cohen & Dehaene, 2004; Cohen et al. 2002, 2004), and this region has been implicated in patients with pure alexia (Cohen et al., 2004; Henry et al., 2005). By contrast, other studies have provided contrasting evidence including the fact that isolated lesions to this region do not consistently result in deficits in word form processing (Price & Devlin, 2003). Hillis et al. (2005) found that acute damage to the visual word form area (VWFA)—the left middle fusiform gyrus—is not associated with impairment of written word comprehension or written lexical decision. Equal proportions of patients who had damage to this region and of those who had no infarct had difficulty with written word comprehension. Instead, damage to this region was associated with impaired oral naming. Hillis and colleagues suggested that left VWFA may be involved during reading but that the role also can be assumed by the right VWFA.

In another study, Hillis and colleagues used PWI and DWI techniques to examine two patients who presented with impaired written verb naming and found hypoperfusion in the region of the posterior IFG and the precentral gyrus, with reversal of symptoms on reperfusion (Hillis, Wityk, Barker, & Caramazza, 2003). In an attempt to resolve the longstanding debate regarding the role of insula on apraxia of speech (see Chapter Four), Hillis et al. (2004b) also examined 80 patients within one day of their stroke. A strong association between apraxia of speech and Broca's area was observed in patients with insular damage as well as in those without insular damage, suggesting that the left posterior IFG is vital to the planning of speech articulation.

More recently, Hillis et al. (2006) examined the cortical regions that were involved in the the process of naming in 87 patients with stroke. Regression analyses resulted in models of improved naming that strongly suggested the *necessity* of BA 37 (posterior and inferior temporal and fusiform gyrus, accounting for 71% of the variance) for naming performance (both oral and written naming). The specificity of this region to naming was highlighted by the fact that it was clearly not involved in the improvement of single word auditory comprehension (which was clearly governed by BA 22, accounting for 81% of the variance). Hillis et al. concluded that a network of left hemisphere regions that include posterior and inferior temporal and fusiform gyrus and Wernicke's and Broca's areas are involved in naming, and that presumably each of these regions contributes differently to the underlying mechanisms of lexical retrieval.

Another study by Hillis and colleagues (2004a) explored the extent of cortical hypoperfusion associated with lesions limited to subcortical structures (specifically to the left caudate nucleus, with or without damage to the putamen, globus pallidus, and nearby white matter) and its correlation with verbal fluency in aphasia. All 24 subjects in this study exhibited hypoperfusion of at least one of the cortical regions of interest in the left perisylvian region; an interesting but not surprising finding (as in the work of Metter and colleagues) was that the area of cortical hypoperfusion was correlated with aphasia classification (based on the Boston classification system)—that is, patients with anomic aphasia had hypoperfusion in either the superior or inferior temporal gyrus, those with Broca's had

hypoperfusion in left IFG, those with Wernicke's had hypoperfusion in the left superior temporal gyrus, and those with the global type had hypoperfusion of all left hemisphere perisylvian regions of interest. Again, clinical improvement with lessening of aphasic symptoms was observed with reperfusion of the cortical areas; therefore, the investigators argue that this improvement is evidence against the idea that the hypoperfusion of cortical regions is due to diaschisis.

The methodology of the foregoing studies represents a unique and groundbreaking approach to investigating the complex language network because the underlying pathologic process is in the acute phase and therefore brain reorganization has yet to take place (i.e., it is doubtful that another brain region has taken over the function of an infarcted area). As Hillis argues (2006), identifying regions of infarct and regions of low blood flow at the onset of brain damage (i.e., within a day after the stroke) allows the identification of brain mechanisms operative before reorganization, rehabilitation, or recovery.

The Use of TMS in Aphasia

Transcranial magnetic stimulation (TMS) is a noninvasive imaging technique that allows for focal stimulation of cortical areas in humans with 1-mm accuracy if the image-guided robotic TMS system is used (see Fox et al., 2006; Lancaster et al., 2004). TMS has various applications: (1) it can be used to create a temporary "virtual" lesion in unimpaired subjects; (2) it also can be used to produce an evoked response such as a motor evoked potential from motor cortex; (3) it can be used in combination with PET to map connectivity; and (4) it has been used recently to treat neurologically based illnesses such as depression (George et al., 1995). The use of TMS for a given purpose depends on the frequency and amplitude of stimulation in a given cortical region. Recently, TMS has been used to promote a deeper understanding of aphasia through brain maps and examination of recovery patterns in aphasia. A detailed review of the growing literature on TMS and speech production and perception, not addressed in this chapter, is provided by Devlin and Watkins (2006); here, a brief overview of structural language, in relation to the neural substrates of aphasia, is offered.

Essentially much of the work stimulating BA 44 in normal subjects suggests that syntactic processing (grammatical structures) is linked to this area, as found in Broca'a aphasia (e.g., Shapiro & Caramazza, 2003). Of interest, TMS to this area facilitated reaction times (RTs) for syntactic decisions, but semantic decision reaction times were unaffected. It is critical, however, to map the complete network because lesions of this area alone do not produce aphasia. Shapiro and colleagues (2001) found that 1-Hz stimulation of dorsolateral prefrontal cortex disrupted verb but not noun processing (slowed reaction times for verbs).

Specific to aphasia, recent work in TMS has provided some preliminary support for the role of the right hemisphere in the pathogenesis of the disorder. For example, TMS of the right temporal-parietal junction disrupts the reading of words in patients with aphasia but not in control subjects (Coslett & Monsul, 1994). More recently, the right IFG has been the focus of study in aphasia. Winhuisen and colleagues (2005) used task-related PET to determine the hemisphere

of stimulation. In their study, all 11 aphasia subjects showed left IFG activation when stimulated with TMS and increased RT (or increased errors) to verb-picture matching or word generation tasks. Of note, 5 of the patients had greater PET activation on the right than on the left, and TMS stimulation on the right resulted in increased RTs.

Recovery from aphasia recently has been studied using this modality. Meister and colleagues (2006) used TMS connectivity patterns to examine recovery in aphasia. In this study, 12 participants with aphasia received TMS of the right- or left-hand motor cortex during phonation. Age-matched control subjects also were tested. All subjects were required to "read or phonate syllables" after a cue. A control condition was employed in which subjects saw a letter string and read silently. TMS was initiated 600 ms before the onset of the cue to read, 150 ms after the onset of reading, and 800 ms after reading stopped. The excitability of the hand area on the right or left was the dependent measure, and hand excitability was assessed by recording the motor evoked potential (MEP) from motor cortex stimulation of left or right cortex. Results showed that the nondominant MEP was more easily elicited during reading out loud than during phonation, which did not increase excitability of motor cortex. The results are interpreted as evidence of connectivity between motor and language areas in aphasia and a role of the right hemisphere in recovery, because right hemisphere excitability was greater in the patients with aphasia than in control subjects. It must be cautioned, however, that connectivity cannot be assessed using this methodology; rather, TMS of a given region during PET and examination of the activity in areas remote from TMS stimulation can provide an index of connectivity. Of interest, these data support growing evidence for a role of the right hemisphere in recovery from aphasia (see Table 5–2). Finally, a small number of recent studies, primarily from Naeser's group in Boston, have used TMS as a treatment for naming impairment in aphasia (Naeser et al., 2005a, 2005b). These investigators stimulated right inferior parietal cortex with the rationale that this area is critical to recovery from aphasia and reported that in a few patients, naming ability was improved with rostral stimulation, compared with caudal or posterior stimulation.

Conclusions

Has imaging advanced the science in aphasiology? The evidence answers both yes and no. Essentially, imaging data in aphasia have replicated what was known from lesion studies and intuition. The neuroscience of the aphasia knowledge base, however, has expanded exponentially over the past two decades, with a particular emphasis on an underlying network of regions that appear to be essential for the comprehension and production of language. Imaging technology has allowed investigators to examine resting-state metabolic brain changes associated with aphasia and functional brain activation during language tasks in persons who have sustained damage to one or more of the regions involved in the "normal" language neural network.

As noted, the growing body of literature in this area has validated many of the classic studies reported centuries ago but also has indicated the extent of the interconnections between brain regions

and helped to elucidate the effects on regions, ipsilateral and contralateral to a stroke, that are not lesioned but are nonetheless functionally impaired. Moreover, the use of imaging to explore the neural changes associated with recovery from stroke and treatment of aphasia provide new insights into this communication disorder. One of the important contributions of the recent imaging work is the reevaluation of the role of right hemisphere in the process of recovery of language. Moreover, data obtained from the studies reviewed in this chapter suggest that recovery of language in aphasia is not a random process; rather, the process seems to be predictable to a certain extent, and the neural mechanisms underlying aphasia will ultimately govern the nature and extent of behavioral improvements. Certainly, clinicians engaged in treating patients with aphasia have a lot to be encouraged about in terms of plasticity of the adult brain. The unambiguous finding across all the studies is that changes in language performance that are measured through behavioral assessments are associated with functional changes in the neural architecture. Also, the accumulated data are sufficient to provide some guidance to practitioners and clinicians in devising better language treatment programs that capitalize on the presumed functional architecture of the brain and its potential for systematic change.

This information has led to advances in treatments, both behavioral and organic (e.g., reperfusion of viable areas critical to recovery), that have the potential for reducing the devastating and debilitating symptoms of aphasia. At this point, however, the studies being conducted are so diverse that the variability within the database results in a situation in which any unified view of aphasia is impossible to ascertain. This variability emerges from differences across studies in imaging technique and methodology, task selection, subject selection criteria and demographics, and varying theoretical constructs driving different studies. Thus, even with the availability of meta-analytic techniques, the variability across studies obscures clear conclusion about the neuroscience of aphasia. What is needed is a multicenter approach with similar methods (behavioral and imaging) to derive a better understanding of aphasia. Accordingly, this chapter concludes with cautions needed in interpretation of the data to date and some recommendations for future studies.

Cautions

One of the difficult issues facing neuroimaging research in aphasia pertains some to some of the basic assumptions underlying the causality of specific language deficits subsequent to brain damage. Indeed, several reviews have raised concerns regarding the inability of neuroimaging to make any concrete predictions regarding the necessity for and sufficiency of a particular neural region during a specific language task (Poldrack, 2000; Price & Friston, 1999, 2002a, 2002b; Price, Mummery, Moore, Frakowiak, & Friston, 1999). That is, the fact that a region is active during a task does not clearly indicate that it is responsible in the processing for the task. This is the same issue (but in reverse) put forth by Jackson (1874) when he noted that because a lesion disrupts a function does not mean that the function is stored in that region. Moreover, the PET data reviewed earlier (from Metter and colleagues), clearly show that structural

lesions cannot clearly explain aphasic behaviors, even in a noncausal manner. Accordingly, Poldrack and Price and their colleagues have stressed the importance of exploring the following issues as they relate to specific regions within a cognitive network:

- *Necessity*. Understanding whether or not a region is necessary would require manipulation of the causal factor (i.e., the brain region), and in neuroimaging, researchers can manipulate only the task and then observe what that manipulation does to the activation of the region, except perhaps with the use of TMS to produce a virtual lesion of a given cortical area. Aphasia certainly is a condition in which researchers can come close to manipulating the causal factor, in that a specific region that can be defined is manipulated (by the lesion itself); however, many complicating factors exist in this population, as described later on, and functional lesions are not well understood, yet clearly are related to the pathogenesis of aphasia.
- *Sufficiency*. To understand the sufficiency of region to a task, the entire network of regions involved in the task must be known, and this is not yet possible with neuroimaging alone. However, with the use of electrophysiological measures (e.g., ERP) and manipulative stimuli such as TMS, some of the components of these networks are beginning to be uncovered.
- *Degeneracy*. Added to this is the notion from Price and Crinion (2005) of degeneracy of a brain region. That is, because language can recover after an aphasia-producing stroke, more than one network of brain regions that can subsume language functions must be present. This complicates the picture uniquely in this population and makes critical the difference between normal and disordered brain functioning. Again, the use of TMS, along with continued investigations into changes in perfusion early on in recovery, may delineate the importance of each region within a network in performing differing language tasks.

Interpretation of the fMRI data appears to be critically dependent on the tasks tested in the scanner. For instance, tasks that require verbal output such as word repetition (Heiss et al., 1997, 1999; Karbe et al., 1998) indicate that good language recovery depends ultimately on the extent of left hemisphere activation. By contrast, for tasks that require auditory comprehension, activation of right hemisphere regions is not unsurprising (Leff et al., 2002; Musso et al., 1999). Indeed, Sharp et al. (2004) have shown that activation in the right fusiform regions correlates with accuracy on a semantic decision task in patients with aphasia, as well as in normal control subjects. One way to help isolate neural patterns of activation specific to recovery of language is to make theoretically motivated predictions regarding brain activation patterns associated with task specific comparisons. For instance, if the goal is to identify neural regions underlying semantic processing and the experimental task is a semantic judgment task (e.g., triplet judgment task), then a control task would need to be one that does not involve semantic processing (e.g., font size judgment). Very often, researchers

design comparisons that are either too "tight" (e.g., semantic judgment versus phonological judgments) or too "loose" (e.g., semantic judgment versus visual fixations), both of which are troublesome because they detract from obtaining interpretable data.

To understand the nature of studies of language recovery in aphasia, it is vital to recognize that affected persons demonstrate great variability in expression of their symptoms. Moreover, the great intrasubject variability found in any person with aphasia increases the challenge in studying the neural underpinning of this disorder. These sources of subject variability are amplified in neuroimaging when they are combined with the variability across participants with respect to treatment effects as well as areas of activation. A related issue is that when patients are unable to perform a specific task in the scanner, either no consistent activation occurs or, inversely, more activation occurs in the undamaged neural regions. Therefore, it is important to ensure that participants can perform the specific experimental task within the scanner with reasonable accuracy in order to obtain reliable activation patterns, and to develop a methodology that allows for examination of error responses compared with correct ones. This requirement does pose problems for neuroimaging studies examining recovery subsequent to a specific language treatment. Typically, pre-treatment performance mandates that the patient show difficulty with the specific behavior that is being changed in treatment and examined during neuroimaging. Researchers will have to devise clever paradigms to evaluate the neural substrates of treatment effects so that changes in activation as a function of the degree of improvement on the trained behavior are interpretable.

Another fundamental methodological issue critical to interpreting fMRI results in patients with aphasia is the recent observation that the nature of the hemodynamic (BOLD) response is altered if not delayed in these persons (Peck et al., 2004; Pineiro et al., 2002). Certainly, this parameter must be taken into account in designing block or event-related designs and during data analysis of this population. Moreover, unlike PET, fMRI studies cannot readily examine speech production, limiting their utility in a full understanding of a disorder that crosses both comprehension and production of language.

Recommendations

One recommendation relates to the documenting of relevant information in imaging studies of aphasia to garner the possibility of building a consistent database of studies that may be compared. Early on, Brookshire (1983) urged researchers to provide relevant subject descriptions of aphasia participants so that characterization of those subjects could be gleaned from the studies. This allowed for other researchers to directly compare their subjects and make inferences and draw conclusions about a larger population, as well as to replicate studies. This demographic information included such details as age, handedness, and time after onset of stroke and helped to provide an indication of the "state" of the aphasia in the participants. As has been evident in the literature reviewed in this chapter, subject characteristics play as important a role in imaging research as they did in the behavioral

studies with which Brookshire was concerned. The obvious example is the acute versus chronic stages of aphasia recovery and its possible influence on the shift of activation from left to right dominance. In most cases, age at stroke and time after onset of stroke was reported in the studies reviewed here; however, the severity of aphasia often was not reported. As noted earlier, one potential pitfall of functional imaging in aphasia is the inability of subjects to perform the tasks required in the scanner, which certainly becomes more of a concern with more severely aphasic participants. Additionally, the extent of hypoperfusion is related to severity of the disorder, and more severely affected patients tend to show greater right-sided asymmetries. These facts emphasize the importance of reporting severity details, particularly in group studies, where inclusion or exclusion of more severely impaired patients could skew the data.

Gender of participants also may be important to include, in view of the different findings on imaging studies in normal males and females (e.g., Bell, Willson, Wilman, Dave, & Silverston, 2006; Cahill, 2006). In fact, Cahill claims that the effects of gender can no longer be considered negligible and must be further investigated in normal and disordered populations in order for the science to progress. In brief, significant differences have been found in brain morphology, neurotransmitter levels, and laterality, as well as in the BOLD signal in males and in females during cognitive tasks (i.e., males tended to have higher intensity activations and larger numbers of active voxels), and these findings appear to be task dependent (i.e., BOLD differences were evident for working memory tasks, but not for a spatial attention task). A surprising finding is that often the behavioral responses may or may not reflect significant differences when the brain structure or function measures do. Although the sample sizes in studies with participants who have aphasia generally are too small to make comparisons based on gender, future studies may benefit from reporting the gender of their subjects.

Other variables that may be important for reporting would be (1) handedness, in light of the differing findings regarding laterality in left-handed subjects, and (2) languages spoken, in light of the building evidence about differing language representations and corresponding neural substrates in bilingual and multilingual participants. Of course, in group studies, the more homogeneous the group, the better, but for small group and single case reports, more subject description is necessary and currently is missing in many of the studies reported here.

Finally, and perhaps of greatest importance, researchers are urged to include the coordinates for the regions reported in their studies using a standard system (e.g., Talaraich). At present, these coordinates are the only standardized maps of regions of the brain that will allow for comparison of a region of interest across studies. Currently, regions of interest are reported in narrative terms (e.g., right IFG), occasionally accompanied by designations of Brodmann's areas, but do little to provide an exacting representation of activity patterns between neural regions. Although these notations for regions are roughly agreed upon, they do not allow for more sophisticated cross-study comparisons or replications. Fox, Laird, and Lancaster (2005) strongly encourage the inclusion of these normalized coordinates so that a meta-analysis may be conducted that allows direct