Aphasia and aphasia recovery

Stephen M. Wilson[1] and Julius Fridriksson[2]

[1]Department of Hearing and Speech Sciences, Vanderbilt University Medical Center, Nashville, Tennessee, USA; [2]Department of Communication Sciences and Disorders, University of South Carolina, Columbia, South Carolina, USA

Address for correspondence: Stephen M. Wilson, Department of Hearing and Speech Sciences, Vanderbilt University Medical Center, 1215 21st Ave S, MCE 8310, Nashville, TN 37232. Phone: 615-936-5810. Fax: 615-936-6914. Email: stephen.m.wilson@vanderbilt.edu

Word count (Abstract/Text/References/Figure captions) = 5805.

Number of figures = 2

Acknowledgments: This work was supported in part by NIDCD (R01 DC013270 and P50 DC014664).

Abstract

Aphasia is an acquired impairment of language processing. In this chapter, we describe the nineteenth century foundations of the classical model of aphasia, and how it has been refined over time in response to increasingly sophisticated neuropsychological and neuroimaging studies. In most individuals with aphasia, language function recovers to some extent, suggesting that the language network is not immutable, but is capable of functional reorganization. We discuss predictors of aphasia recovery and brain changes that may be associated with successful recovery.

Nineteenth century foundations

Aphasia is an acquired impairment of the production and/or comprehension of language, due to brain injury. The most common etiology is stroke, but any kind of brain injury can cause aphasia, including neurodegeneration, tumors, resective surgery and traumatic brain injury.

Descriptions of aphasia in the medical literature date back to about 400 B.C, but the modern field of aphasia research began in 1861, when Paul Broca published a report of a patient with expressive aphasia and a lesion centered on the posterior left inferior frontal gyrus, the region now known as Broca's area (Broca, 1861). The details of the patient's speech impairment and cortical damage were complicated. However, what is important is that Broca proposed the idea that damage to a specific brain region would result in an expressive language deficit, because that region has a specific role in speech production. In 1861, Broca did not make anything of the fact that his patient's lesion was in the left hemisphere, but after observing several dozen cases of aphasia over the next few years, all associated with left hemisphere damage at autopsy, he famously declared "*nous parlons avec l'hémisphère gauche*" (we speak with the left hemisphere) (Broca, 1865).

Ten years later, Carl Wernicke, a young German neurologist, wrote a remarkable monograph on aphasia (Wernicke, 1874). Not only did Wernicke describe a different kind of aphasia—a receptive aphasia that we now call Wernicke's aphasia—but from his observations he derived an insightful model of language processing and the ways in which it can be disrupted by brain damage. Ludwig Lichtheim, a German neurologist, refined and expanded on Wernicke's model (Lichtheim, 1885), yielding the Wernicke-Lichtheim model (Figure 1A). The model describes input and output transformations: in language comprehension, auditory inputs ('a') map onto phonological representations in the posterior superior temporal gyrus ('A'), which are linked to

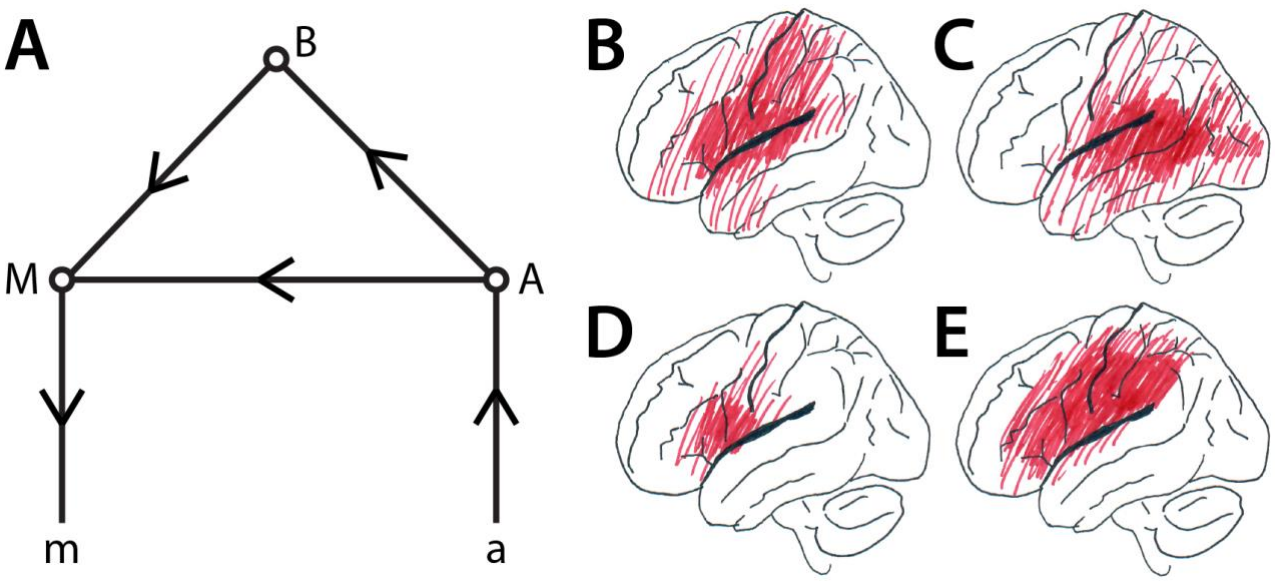

Figure 1

neurally distributed semantic representations ('B'), while in language production, these same semantic representations ('B') are linked to articulatory representations in Broca's area ('M'), which project to motor effectors ('m'). But critically, there is also a link between 'A' and 'M'. Wernicke motivated this link based on his observations that speech production was not intact in his patients with receptive deficits. While their speech was fluent (reflecting the preservation of 'M' and 'm'), it was garbled, with words and sounds mis-selected; today we would say *paraphasic*. Wernicke concluded that speech production must rely not only on the pathway from 'B' to 'M' to 'm', but must also depend on the phonological representations that he localized to the superior temporal gyrus ('A'). This architecture also raised the possibility that the pathway between 'A' and 'M' could be selectively disrupted, in which case language comprehension would be preserved (because 'a' to 'A' to 'B' is intact), while production would be fluent (because 'M' to 'm' is intact) yet paraphasic (because of the disconnection of the phonological representations in 'A'). Wernicke called this syndrome *conduction aphasia*. Similarly, disconnections of other pathways predict other patterns of deficits; for instance, disruption of the

pathway between ‘A’ and ‘B’ leads to *transcortical sensory aphasia* in which comprehension is impaired with relative sparing of repetition (because of the intact link between ‘A’ and ‘M’). From these examples, the predictive nature of the model can be readily appreciated.

Evolving understanding of the classic syndromes

In the 1960s, researchers at the Boston VA—Norman Geschwind, Harold Goodglass, Edith Kaplan, Frank Benton, and others—developed a sophisticated, multidisciplinary approach to aphasia, broadly based on the Wernicke-Lichtheim model. Geschwind’s (1965) work on disconnection syndromes put the model on a more modern anatomical footing, while Goodglass and Kaplan’s (1972) *Boston Diagnostic Aphasia Examination (BDAE)* provided a means for diagnosing major aphasic syndromes that are in most cases closely based on the syndromes proposed by Wernicke and Lichtheim. The BDAE remains widely used today.

In the 1970s and 1980s, research on the neuroanatomical basis of aphasia was transformed by the development of structural imaging (CT and MRI) and metabolic imaging with PET. Whereas previous generations of researchers had needed to wait potentially decades until autopsy to learn the neural correlates of observed language deficits, this information could now be obtained immediately. It became feasible to study groups of patients and identify general patterns, rather than relying on single cases and their idiosyncrasies. One of the most informative approaches was to create “lesion overlays” of patients sharing an aphasic syndrome or a particular kind of language deficit, so that the common neural substrates could be identified. Lesion overlays of classic aphasia syndromes proved to be at least broadly consistent with the Wernicke-Lichtheim model (Basso, Lecours, Moraschini, & Vanier, 1985; Kertesz, Lesk, & McCabe, 1977; Naeser & Hayward, 1978), with Broca’s and Wernicke’s aphasias associated with relatively anterior and

posterior lesion locations (Figure 1B,C), and transcortical aphasias sparing the perisylvian language network.

Yet there were some striking findings that challenged traditional concepts. Mohr (1976) showed that circumscribed damage to Broca's area (Figure 1D) did not suffice to cause persistent Broca's aphasia, which only followed from much larger lesions (Figure 1E). Basso and colleagues (1985) found that most patients' lesions were in accordance with the model, but there were a substantial minority with unexpected lesion localizations. In an elegant series of studies, Metter and colleagues showed that regardless of the particulars of structural damage, metabolic abnormalities in left temporo-parietal cortex were highly predictive of aphasia severity (Metter et al., 1989).

In the new millennium, "dual stream" models of language have been influential (Hickok & Poeppel, 2007; Wilson et al., 2011; Bornkessel-Schlesewsky & Schlesewsky, 2013). These models propose a ventral stream through the temporal lobes that maps auditory inputs onto meaning, and a dorsal stream that maps acoustic or phonological representations onto motor plans for speech production (Hickok & Poeppel, 2007), or may be involved in sequential processing more generally (Wilson et al., 2011; Bornkessel-Schlesewsky & Schlesewsky, 2013). In some respects, this ventral/dorsal dichotomy has supplanted the old posterior/anterior dichotomy of the Wernicke-Lichtheim model (Fridriksson et al., 2016, 2018). While the dual stream model has introduced some important novel concepts, such as the linguistic capacity of the right hemisphere ventral stream, and the idea that metalinguistic perceptual tasks depend on the dorsal stream, there is also considerable continuity with the classic model: the ventral stream corresponds essentially to the mapping between 'A' and 'B' in the Wernicke-Lichtheim model, while the dorsal stream corresponds to the link between 'A' and 'M'.

Primary progressive aphasia

Primary progressive aphasia (PPA) is a clinical syndrome in which neurodegeneration of dominant hemisphere language regions leads to progressive language deficits, with relative sparing of other cognitive functions. In contrast to aphasia caused by stroke, its onset is insidious, and language deficits become progressively more severe over time. The study of PPA over the past few decades has contributed greatly to our understanding of the neural architecture of language. One reason for this is that different regions are damaged in PPA than in stroke. For instance, focal damage to the anterior temporal lobe is uncommon in stroke due to vascular anatomy, so the critical role of this region in lexical knowledge was largely unknown until the systematic investigation of semantic dementia in the 1990s (Hodges, Patterson, Oxbury, & Funnell, 1992).

Patients with progressive language deficits have been described for over a hundred years (e.g. Imura, 1943; Pick, 1892; Serieux, 1893), but the modern exploration of PPA began in the mid 1970s, when Elizabeth Warrington described three patients who presented with what she described as a selective impairment of semantic memory (Warrington, 1975). In each case, deficits emerged gradually and there was no discrete precipitating event like a stroke. The patients demonstrated severe lexical impairments in both production and comprehension. In fact, their deficits were not strictly linguistic: they also demonstrated loss of object knowledge. Meanwhile, their general cognitive function was well preserved, as were many language domains including syntax, phonology and speech production. A few years later, Marsel Mesulam described six patients with slowly progressive aphasia in the absence of generalized dementia (Mesulam, 1982). Imaging findings were generally consistent with left perisylvian atrophy. The selectivity of the language deficits was remarkable in both case series, and clearly demonstrated

that neurodegenerative processes can be focal in nature and have the potential to impact language areas of the brain.

In the next decade, pioneering research on PPA was carried out by Mesulam and his team, and many others including John Hodges, Karalyn Patterson and Julie Snowden. It became apparent that PPA patients could be classified into variants based on linguistic features, and that each variant was associated with distinct patterns of atrophy (Gorno-Tempini et al., 2004) and different underlying pathologies (Davies et al., 2005; Josephs et al., 2008). Maria Luisa Gorno-Tempini and colleagues defined three specific variants, which are now termed non-fluent/agrammatic variant PPA, semantic variant PPA, and logopenic variant PPA (Gorno-Tempini et al., 2004, 2011). The non-fluent/agrammatic variant PPA involves deficits in speech production and/or grammar and left-posterior fronto-insular atrophy. The semantic variant is defined by impaired naming as well as comprehension of single words in association with anterior temporal atrophy. Object knowledge is impaired except possibly at the earliest stages, and surface dyslexia (reading exception words as they are spelled) is almost invariably present. The patients described by Warrington (1975) would now be diagnosed with semantic variant PPA. The logopenic variant is characterized by impaired retrieval of single words and impaired repetition, with atrophy centered around the left temporo-parietal region. Phonemic paraphasias are also common. Most of the patients described by Mesulam (1982) would meet criteria for the logopenic variant.

Individual differences and multivariate perspectives

Much of our discussion so far has been framed about aphasic syndromes, which are helpful concepts for drawing generalizations and smoothing out the idiosyncrasies of individual cases. However, there are numerous different schemes by which patients can be classified (e.g. Botha et

al., 2015; Goodglass & Kaplan, 1972; Gorno-Tempini et al., 2011; Kertesz, 1982; Schuell, 1965), many patients are classified differently depending on which aphasia battery is used (Wertz, Deal, & Robinson, 1984), and there can be considerable variability among patients diagnosed with the same type of aphasia (Kertesz, 1982; Casilio, Rising, Beeson, Bunton, & Wilson, 2018). These considerations have led many researchers in the new millennium to approach individuals with aphasia not as undifferentiated members of groups, but as unique points in a multidimensional symptom space (Bates, Saygin, Moineau, Marangolo, & Pizzamiglio, 2005). In this view, syndromes would reflect regions of this space where patients tend to cluster.

An early example of this approach is a study by Elizabeth Bates and colleagues which investigated the neural correlates of fluency and auditory comprehension deficits, which were each quantified on a continuum (Bates et al., 2003). The authors' approach, which they dubbed *voxel-based lesion-symptom mapping*, involved making statistical inferences on the relationship between continuous behavioral measures, and damage to each voxel in the brain. A similar approach, *voxel-based morphometry*, was applied to study lexical access in neurodegenerative cohorts (Grossman et al., 2004)

This general approach can be applied to whole batteries of language measures at once, for instance a set of measures derived from quantitative linguistic analysis of connected speech samples (Wilson et al., 2010; Figure 2A-C). Brain damage can be quantified voxel by voxel, or linguistic deficits can be correlated with damage to specific regions (Caplan et al., 2007) or white matter tracts (Wilson et al., 2011; Figure 2D-H). Linguistic behavioral measures can be considered in relation to one another, such as a study by Myrna Schwartz and colleagues that identified an anterior temporal region as critical for lemma retrieval in speech production by

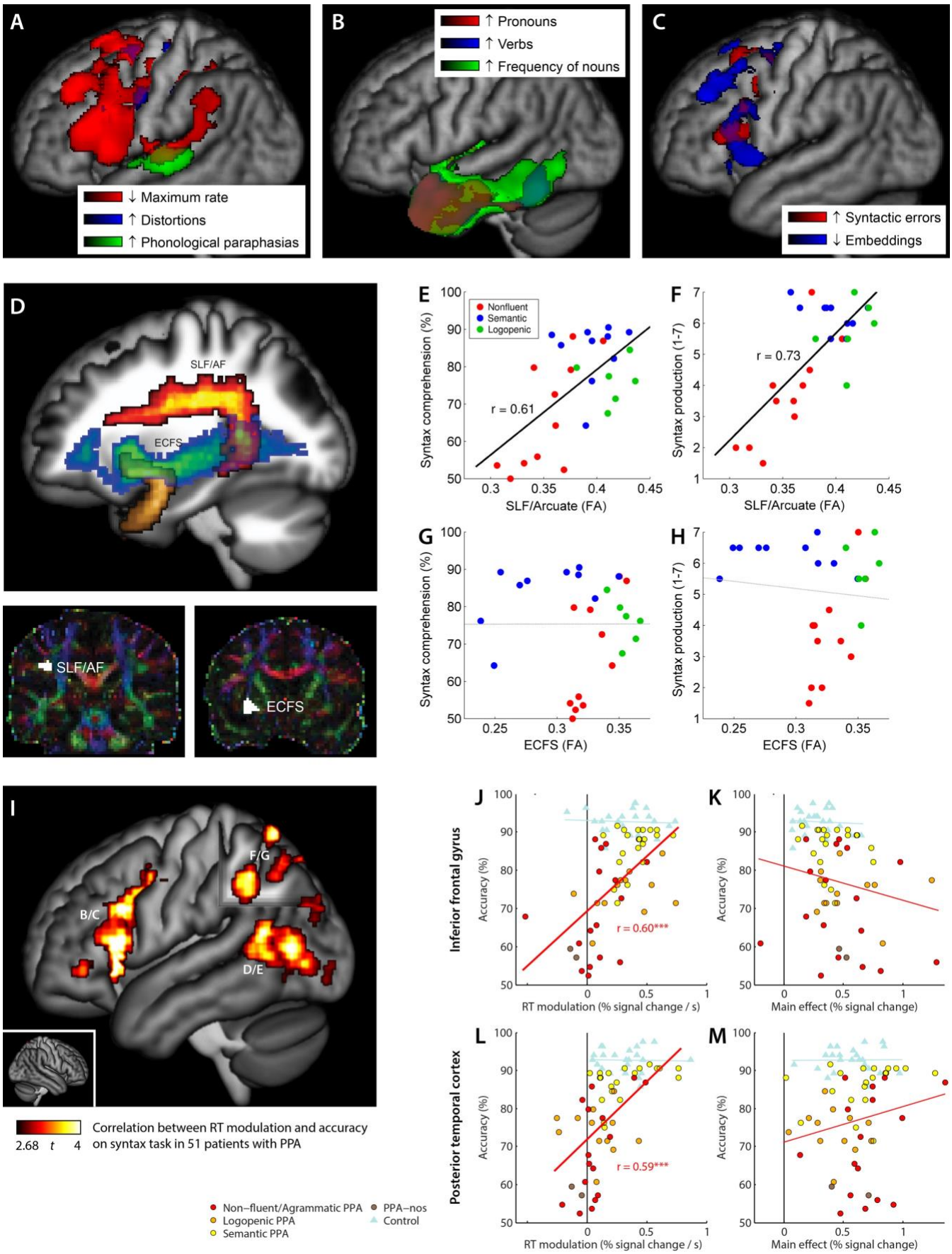
A
↓ Maximum rate
↑ Distortions
↑ Phonological paraphasias
B
↑ Pronouns
↑ Verbs
↑ Frequency of nouns
C
↑ Syntactic errors
↓ Embeddings
D
SLF/AF
ECFS
SLF/AF
ECFS
E
Nonfluent
Semantic
Logopenic
r = 0.61
Syntax comprehension (%)
SLF/Arcuate (FA)
F
r = 0.73
Syntax production (1-7)
SLF/Arcuate (FA)
G
Syntax comprehension (%)
ECFS (FA)
H
Syntax production (1-7)
ECFS (FA)
I
F/G
B/C
D/E
2.68 t 4
Correlation between RT modulation and accuracy on syntax task in 51 patients with PPA
J
Inferior frontal gyrus
Accuracy (%)
r = 0.60***
RT modulation (% signal change / s)
K
Accuracy (%)
Main effect (% signal change)
L
Posterior temporal cortex
Accuracy (%)
r = 0.59***
RT modulation (% signal change / s)
M
Accuracy (%)
Main effect (% signal change)
Non–fluent/Agrammatic PPA
Logopenic PPA
Semantic PPA
PPA–nos
Control

Figure 2

semantic function itself by covarying out scores on the Pyramids and Palm Trees test of semantic association (Schwartz et al., 2009).

The same basic idea can be extended to functional imaging studies, where language measures in individuals with aphasia can be correlated with functional activation across the brain (Crinion & Price, 2005; Fridriksson, Baker, & Moser, 2009; Griffis, Nenert, Allendorfer, & Szaflarski, 2017; Wilson et al., 2016). For instance, Wilson et al. (2016) showed that in a large cohort of patients with PPA, individuals with spared syntactic processing recruited a left-lateralized fronto-temporal-parietal network, whereas those with syntactic processing deficits did not (Figure 2I-M).

In the last few years, researchers have begun to apply multivariate approaches such as factor analysis and machine learning methods to unraveling the complex relationships between patterns of brain damage and profiles of language deficits. Multivariate analyses of language deficits have shown that panels of linguistic variables can be reduced to smaller numbers of underlying explanatory factors (Butler, Lambon Ralph, & Woollams, 2014; Mirman et al., 2015; Casilio et al., 2018). For instance, Casilio and colleagues showed that 79% of the variance in a set of 27 connected speech measures could be explained with reference to just four underlying factors, which they labeled paraphasia, logopenia, agrammatism and motor speech. The explanatory factors can then be associated with patterns of brain damage. For example, Mirman et al. (2015) showed that speech recognition and speech production factors were associated with damage to adjacent regions in the superior temporal gyrus and supramarginal gyrus respectively.

Taken together, these kinds of studies have resulted in a fundamental shift in how we think about language and the brain. Traditionally, researchers thought in terms of associations between brain regions and aphasic syndromes. Nowadays, we think in terms of interacting brain

networks, and the roles they play in specific language domains and processes (Fedorenko & Thompson-Schill, 2014).

Historical perspectives on aphasia recovery

Most research on aphasia has focused on its nature, primarily in relation to specific language and speech impairments, and the links between impairment and lesion location. Far less research has been devoted to understanding recovery from aphasia. Nevertheless, aphasia treatment was addressed by some of the early pioneers of aphasiology. Paul Broca speculated as to whether the right hemisphere could be trained to take on language function in aphasic patients with left hemisphere damage (Broca, 1865). His premise was that even though the left hemisphere was dominant for language, the right hemisphere may have the potential to learn language much like a child initially learns language. Broca actually administered aphasia therapy to at least one patient who, based on Broca's report, showed improvements in vocabulary and reading. Although Broca did not describe his approach to improve vocabulary, the reading remediation focused on initially relearning the letters of the alphabet. Then, the training moved to putting letters together to form syllables and, finally, to form whole words. However, the transfer to whole words did not proceed as Broca had expected, as the patient relied more on whole word recognition rather than letter-by-letter reading. Interestingly, Broca suggested that one of the main reasons why aphasic patients did not relearn language at a faster rate was because they also tended to have cognitive problems that impaired the learning process. This is one of the earliest accounts of aphasia therapy and demonstrates that even 150 years ago, it was recognized that aphasic patients could potentially benefit from therapy.

The era of modern aphasia therapy is typically thought to start with work by Hildred Schuell, a speech-language pathologist at the Minneapolis VA Hospital, who primarily treated

soldiers who were aphasic as a result of gunshot wounds suffered during World War II. Schuell's approach was based on engaging the impaired language system using controlled and often repeated auditory stimuli, and a hierarchy of treatment steps, many of which are still in use today in clinical aphasia therapy. The premise of the approach was to enable retrieval of words that, in Schuell's opinion, had not been lost as a result of the brain damage but, rather, were preserved but could not be easily accessed. Schuell's approach improves lexical access while also promoting encouragement and confidence to transfer what has been gained in treatment to real life communication. Today, many different aphasia treatment approaches are used in clinical practice and the focus varies from impairment-based approaches that directly target speech and language improvement to more functional approaches that emphasize successful communication with relatively less emphasis on lessening the severity of the language impairment.

Predicting recovery from aphasia

Most patients with stroke-induced aphasia experience some improvements in speech and language processing in the weeks and months following onset, regardless of whether or not they receive aphasia therapy (Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995). This is typically referred to as 'spontaneous recovery' and its extent can vary widely across patients. The bulk of spontaneous aphasia recovery occurs within the first three months after stroke onset (Enderby & Petheram, 2002; Pedersen et al., 1995) and most patients are considered to be stable with regard to aphasia severity at six to twelve months post stroke. Although it can be difficult to predict if, and how much, individual patients will recover, some general guidelines exist. One of the strongest predictors of poor outcome is larger lesion size (Kertesz, 1988). This makes sense, since patients with more extensive cortical damage have less residual brain tissue that can assume whatever language functions were lost as a result of the stroke. Naturally, the patients

with the largest lesions also tend to have the most extensive language impairment, which is probably why overall aphasia severity predicts long term recovery (Kertesz, 1988; Kertesz, Harlock, & Coates, 1979). Lesion location is also important for spontaneous aphasia recovery. Patients with relatively greater damage to perisylvian regions experience less recovery compared to patients with similar lesion size but less perisylvian involvement, and damage to temporal lobe language areas is more likely to result in lasting language deficits than damage to frontal lobe language areas (Metter et al., 1989; Mohr et al., 1976).

Stroke type matters, as patients with ischemic stroke experience less early recovery compared to those with aphasia as a result of hemorrhagic stroke (Holland, Greenhouse, Fromm, & Swindell, 1989). In the acute stage, the sequela of hemorrhagic stroke are more complicated than in ischemic stroke and hemorrhagic patients tend to be sicker than their counterparts with ischemic stroke as indicated by higher mortality rates and longer discharge times from the hospital. However, as long as the hemorrhagic patient survives, they can expect to experience greater return in function compared to patients with ischemic stroke.

Even though the bulk of aphasia recovery occurs within the first year after stroke, aphasia severity can sometimes be quite dynamic in the chronic phase. In a longitudinal study, Audrey Holland and colleagues followed individuals with chronic aphasia who were tested twice, at least one year apart (Holland, Fromm, Forbes, & MacWhinney, 2017). They found that over half of their participants experienced improvements in overall aphasia severity that were greater than the standard error of measurement, whereas approximately a quarter of the participants were stable, and the remaining participants declined. The mean time post-stroke among the participants was 5.5 years, which suggests that individuals can experience considerable aphasia recovery, even several years after stroke.

Brain changes associated with aphasia recovery

What are the neural substrates that underlie recovery from aphasia? This question has been addressed in many functional imaging studies. It is clear that the mechanisms of recovery are different at different stages of recovery. In the acute post-stroke period, reperfusion of the ischemic penumbra appears to be a major determinant of the rapid improvements that are often seen acutely (Hillis et al., 2002). In the early subacute period (the first few weeks after stroke), there is fairly compelling evidence that right frontal regions play a compensatory role (Winhuisen et al., 2005; Saur et al., 2006), which is more likely to reflect recruitment of domain general cognitive resources than language reorganization (Geranmayeh, Brownsett, & Wise, 2014). However, the recruitment of these regions decreases over time (Winhuisen et al., 2007), with left lateralization returning over time (Heiss & Thiel, 2006; Saur et al., 2006).

Language outcome has been shown to be associated with the extent to which typical left frontal and temporal language regions can be activated by language processing (Griffis et al., 2017). Fridriksson (2010) found a strong association between anomia treatment success and increased cortical activation (as measured using fMRI) in the left hemisphere. Specifically, patients who fared well in treatment also experienced a significant increase in left hemisphere activation, suggesting that recovery from anomia in chronic stroke may be mediated by the left hemisphere. In a follow-up study, Fridriksson and colleagues related change in functional activity in perilesional cortex to change in correct naming (Fridriksson, Richardson, Fillmore, & Cai, 2012). To address the relationship between change in brain activation and improvement in naming, activation was compared between two baseline and two post-treatment fMRI runs in perilesional cortex. A regression analysis revealed that activation change in the perilesional frontal lobe was a predictor of correct naming improvement. Treatment-related change in the

production of semantic paraphasias was most robustly predicted by activation change in the temporal lobe, while change in phonemic paraphasias was predicted by activation change involving both the left temporal and parietal lobes. These findings suggested that changes in activation in perilesional regions are associated with treated recovery from anomia.

Other researchers have argued that the right hemisphere plays a major role in aphasia recovery. For example, Weiller et al. (1995) reported that right hemisphere homotopic areas were activated for language processing in a group of patients who had largely recovered from Wernicke's aphasia. However, it is possible that a group selected for excellent recovery from Wernicke's aphasia may represent a rather exceptional group of individuals. In a larger and more representative group, Crinion and Price (2005) showed that recruitment of right posterior temporal cortex for narrative comprehension was associated with preserved comprehension in post-stroke aphasia. However, this was not interpreted as a finding of reorganization per se, because narrative comprehension depends on both temporal lobes in neurologically normal individuals too.

Whereas localized changes in brain activity may be important for aphasia recovery, it seems plausible that changes in functional network connectivity also plays a role. In fact, it could be the case that changes in connectivity are the primary driver of aphasia recovery. In a recent well-powered study, Siegel et al. (2018) found that reemergence of network modularity, a measure comparing the density of connectivity within networks to the density of connectivity between networks, at three months and one year post-stroke was associated with aphasia recovery in stroke patients.

Conclusion

The study of aphasia has provided some groundbreaking findings in regard to the neuroanatomical organization of language. Much of this work has relied on lesion-symptom associations to infer which regions of the brain are crucial for, not just associated with, the execution of given speech or language tasks. Although the technologies and methodologies used in these studies have evolved enormously, especially in the last three decades, the basic premise of the studies has not changed: if a given cortical region or network supports a specific function, then damage to that region should cause an impairment in that same function. The influence of aphasia studies on the neuropsychological understanding of language is perhaps most evident in the current zeitgeist of dual stream models that have become mainstream in the field. Although much of the work on aphasia has focused on understanding normal brain-behavior relationships, a parallel focus has centered on the clinical manifestations of speech and language impairment to inform clinical practice. Ideally, the study of aphasia will proceed with a united focus where basic science informs clinical research, and vice versa.

References

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

Bates, E., Saygin, A. P., Moineau, S., Marangolo, P., & Pizzamiglio, L. (2005). Analyzing aphasia data in a multidimensional symptom space. *Brain and Language*, *92,* 106–116.

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.

Bornkessel-Schlesewsky, I., & Schlesewsky, M. (2013). Reconciling time, space and function: A new dorsal-ventral stream model of sentence comprehension. *Brain and Language, 125,* 60–76.

Botha, H., Duffy, J., Whitwell, J., Strand, E., Machulda, M., Schwarz, C., … Lowe, V. (2015). Classification and clinicoradiologic features of primary progressive aphasia (PPA) and apraxia of speech. *Cortex, 69,* 220–236.

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

Broca, P. (1865). Sur le siège de la faculté du langage articulé. *Bulletins de La Société D'anthropologie de Paris, 6*(1), 377–393.

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

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.

Casilio, M., Rising, K., Beeson, P. M., Bunton, K., Wilson, S. M. (2018). Auditory-perceptual rating of connected speech in aphasia. Manuscript: University of Arizona and Vanderbilt University Medical Center.

Crinion, J., & Price, C. (2005). Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. *Brain, 128,* 2858–2871.

Davies, R., Hodges, J., Kril, J., Patterson, K., Halliday, G., & Xuereb, J. (2005). The pathological basis of semantic dementia. *Brain, 128,* 1984–1995.

Enderby, P., & Petheram, B. (2002). Has aphasia therapy been swallowed up? *Clinical Rehabilitation, 16,* 604–608.

Fedorenko, E., & Thompson-Schill, S. L. (2014). Reworking the language network. *Trends in Cognitive Sciences, 18,* 120–126.

Fridriksson, J. (2010). Preservation and modulation of specific left hemisphere regions is vital for treated recovery from anomia in stroke. *Journal of Neuroscience, 30,* 11558–11564.

Fridriksson, J., Baker, J. M., & Moser, D. (2009). Cortical mapping of naming errors in aphasia. *Human Brain Mapping, 30,* 2487–2498.

Fridriksson, J., den Ouden, D.-B., Hillis, A., Hickok, G., Rorden, C., Basilakos, A., … Bonilha, L. (2018). Anatomy of aphasia revisited. *Brain, 141,* 848–862.

Fridriksson, J., Richardson, J. D., Fillmore, P., & Cai, B. (2012). Left hemisphere plasticity and aphasia recovery. *NeuroImage, 60,* 854–863.

Fridriksson, J., Yourganov, G., Bonilha, L., Basilakos, A., Den Ouden, D.-B., & Rorden, C. (2016). Revealing the dual streams of speech processing. *Proceedings of the National Academy of Sciences of the United States of America, 113,* 15108–15113.

Geranmayeh, F., Brownsett, S. L. E., & Wise, R. J. S. (2014). Task-induced brain activity in aphasic stroke patients: What is driving recovery? *Brain, 137,* 2632–2648.

Geschwind, N. (1965). Disconnexion syndromes in animals and man. *Brain, 88,* 237–294.

Goodglass, H., & Kaplan, E. (1972). *Boston Diagnostic Aphasia Examination*. Philadelphia: Lea & Febiger.

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

Gorno-Tempini, M. L., Hillis, A., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S., … Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology, 76,* 1006–1014.

Griffis, J. C., Nenert, R., Allendorfer, J. B., & Szaflarski, J. P. (2017). Linking left hemispheric tissue preservation to fMRI language task activation in chronic stroke patients. *Cortex, 96,* 1–18.

Grossman, M., McMillan, C., Moore, P., Ding, L., Glosser, G., Work, M., & Gee, J. (2004). What's in a name: Voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. *Brain, 127,* 628–649.

Heiss, W.-D., & Thiel, A. (2006). A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain and Language, 98,* 118–123.

Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nature Reviews Neuroscience, 8,* 393–402.

Hillis, A. E., Wityk, R. J., Barker, P. B., Beauchamp, N. J., Gailloud, P., Murphy, K., … Metter, E. J. (2002). Subcortical aphasia and neglect in acute stroke: The role of cortical hypoperfusion. *Brain, 125,* 1094–1104.

Hodges, J., Patterson, L., Oxbury, S., & Funnell, E. (1992). Semantic dementia: Progressive fluent aphasia with temporal lobe atrophy. *Brain, 115,* 1783–1806.

Holland, A., Fromm, D., Forbes, M., & MacWhinney, B. (2017). Long-term recovery in stroke accompanied by aphasia: A reconsideration. *Aphasiology, 31,* 152–165.

Holland, A. L., Greenhouse, J. B., Fromm, D., & Swindell, C. S. (1989). Predictors of language restitution following stroke: A multivariate analysis. *Journal of Speech and Hearing Research, 32,* 232–238.

Imura, T. (1943). Aphasia: Characteristics symptoms in Japanese. *Psychiatra et Neurologia Japonica, 47,* 196–218.

Josephs, K., Whitwell, J., Duffy, J., Vanvoorst, W., Strand, E., Hu, W., … Petersen, R. (2008). Progressive aphasia secondary to Alzheimer disease vs FTLD pathology. *Neurology, 70,* 25–34.

Kertesz, A. (1982). *Western Aphasia Battery*. London: Grune and Stratton.

Kertesz, A. (1988). What do we learn from recovery from aphasia? *Advances in Neurology, 47,* 277–292.

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

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

Lichtheim, L. (1885). On aphasia. *Brain, 7,* 433–484.

Mesulam, M. (1982). Slowly progressive aphasia without generalized dementia. *Annals of Neurology, 11,* 592–598.

Metter, E. J., Kempler, D., Jackson, C., Hanson, W. R., Mazziotta, J. C., & Phelps, M. E. (1989). Cerebral glucose metabolism in Wernicke's, Broca's, and conduction aphasia. *Archives of Neurology, 46,* 27–34.

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.

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

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

Pedersen, P., Jorgensen, H., Nakayama, H., Raaschou, H., & Olsen, T. (1995). Aphasia in acute stroke: Incidence, determinants and recovery. *Annals of Neurology, 38,* 659–666.

Pick, A. (1892). Ueber die Beziehungen der senile Hirnatrophie zur Aphasie. *Prager Medicinische Wochenschrift, 17,* 165–167.

Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain, 129,* 1371–1384.

Schuell, H. (1965). *Differential Diagnosis of Aphasia with the Minnesota Test: Administrative manual for the Minnesota test for differential diagnosis of aphasia* (Vol 1). University of Minnesota Press.

Schwartz, M. F., Kimberg, D. Y., Walker, G. M., Faseyitan, O., Brecher, A., Dell, G. S., & Coslett, H. B. (2009). Anterior temporal involvement in semantic word retrieval: Voxel-based lesion-symptom mapping evidence from aphasia. *Brain, 132,* 3411–3427.

Serieux, P. (1893). Sur un cas de surdite verbale pure. *Revue de Médecine, 13,* 733–750.

Siegel, J. S., Seitzman, B. A., Ramsey, L. E., Ortega, M., Gordon, E. M., Dosenbach, N. U. F., … Corbetta, M. (2018). Re-emergence of modular brain networks in stroke recovery. *Cortex, 101,* 44–59.

Warrington, E. (1975). The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology, 27,* 635–657.

Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Müller, S., Bier, D., … Diener, H. C. (1995). Recovery from Wernicke's aphasia: A positron emission tomographic study. *Annals of Neurology, 37,* 723–732.

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

Wertz, R., Deal, J., & Robinson, A. (1984). Classifying the aphasias: A comparison of the Boston Diagnostic Aphasia Examination and the Western Aphasia Battery. In *Clinical Aphasiology* (pp. 40–47). BBK Publishers.

Wilson, S. M., Demarco, A. T., Henry, M. L., Gesierich, B., Babiak, M., Miller, B. L., & Gorno-Tempini, M. L. (2016). Variable disruption of a syntactic processing network in primary progressive aphasia. *Brain, 139,* 2994–3006.

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.

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.

Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W. F., & Heiss, W. D. (2005). Role of the contralateral inferior frontal gyrus in recovery of language function in poststroke aphasia: a combined repetitive transcranial magnetic stimulation and positron emission tomography study. *Stroke, 36,* 1759–1763.

Winhuisen, L., Thiel, A., Schumacher, B., Kessler, J., Rudolf, J., Haupt, W. F., & Heiss, W. D. (2007). The right inferior frontal gyrus and poststroke aphasia: a follow-up investigation. *Stroke, 38,* 1286–1292.

Figure captions

Figure 1 (A) The Wernicke-Lichtheim model (Lichtheim, 1885). (B) Lesion overlay of 14 patients with Broca's aphasia (Kertesz et al., 1977). Intensity of shading indicates number of patients with lesions. (C) Lesion overlay of 13 patients with Wernicke's aphasia (Kertesz et al., 1977). (D) Lesion overlay of 13 patients with infarction restricted to Broca's area (Mohr, 1976). (E) Lesion overlay of 10 patients with persistent Broca's aphasia (Mohr, 1976).

Figure 2 Neural correlates of language deficits in individuals. Voxel-based morphometry revealed distinct regions where atrophy was predictive of speech (A), lexical (B) or syntactic (C) deficits (Wilson et al., 2010). Arrows denote increases or decreases in the prevelance of the phenomena listed. Dorsal and ventral language tracts were identified with diffusion tensor imaging (D). SLF/AF = Superior Longitudinal Fasciculus/Arcuate Fasciculus; ECFS = Extreme Capsule Fiber System. Degeneration of dorsal tracts was associated with deficits in syntactic comprehension (E) and production (F), while degeneration of ventral tracts had no effects on syntactic comprehension (G) or production (H) (Wilson et al., 2011). Functional imaging identified brain regions where recruitment for syntactic processing was predictive of success in syntactic processing in PPA (I). In the inferior frontal gyrus (J, K) and posterior temporal cortex (L, M), BOLD modulation by syntactic complexity was predictive of accuracy (J, L), but the non-specific recruitment for the task was not (K, M) (Wilson et al., 2016).