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Language Reorganization After Stroke: Insights from fMRI

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1. Introduction

As one of the most complex brain functions and a uniquely human mental faculty, language has a special status in brain sciences. Issues on language functioning have been investigated from various perspectives, including language acquisition in a developing brain, language dissolution in damaged brain, language processing in neurologically healthy adult speakers of one, two, or more languages, and so on. However, the neural substrates of language were not investigated in a great detail until the recent advancement of neuroimaging techniques. One reason for this situation is the fact that animal studies, which have considerably contributed to the growth of knowledge in other domains of brain sciences, are not an option when studying language. Until recently, most of our knowledge on the language-brain relationship came from lesion-deficit studies. Since naturally occurring focal cortical lesions, such as those found in stroke patients, rarely affect a single brain function and—in addition to cortically often run cortico-subcortically, it was difficult before the advancement of neuroimaging technologies to determine how the complex functionality of language relates with brain structures. Nevertheless, studying the neural underpinnings of language in patients with language disorders caused by illness or brain injury resulted in important observations and development of a theoretical framework in the 19th century (e.g., Broca, 1861) that led to a formulation of the fundamental research questions in this field that are still object of scientific inquiry. The lesion-deficit approach originated in the work of Broca, Wernicke, and Leichtheim in the 19th century, and was re-established and further developed by Geschwind, Galaburda, Goodglass, Kaplan, Kertesz and their students in the 20th century. This neurological or aphasiological model correlated language disorders and brain lesions, with the goal of explaining the effects of lesion on language performance and by extension the neural basis of language. In general, it mostly employed crude language concepts, such as speech production, comprehension, fluent vs. non-fluent speech, etc., without considering insights from linguistics. The situation dramatically changed with the development of generative grammar (Chomsky, 1957, and subsequent work) which postulates that language is a *mental organ* and that grammar is a theory of language, which is structured in a modular way and *somehow* instantiated in the brain (Chomsky, 1986). The generative paradigm turned out to be a productive theoretical approach in linguistics that has led to development of sophisticated theories, motivating a great deal of neuroimaging research on language.

Some basic ideas of the lesion-deficit approach have been questioned in light of new evidence from neuroimaging. For instance, the idea that there exist specific language-dedicated areas, such as Broca's area (Brodmann areas (BAs) 44, 45) and Wernicke's area (BA 22) that support language production and comprehension respectively, and that damage to either area, or to the white matter fibre tract that connects them—the arcuate fasciculus—, leads to specific aphasic syndromes (Ardilla, 2010) turned out to be at best an oversimplification (Hickok & Poeppel, 2004). The causal link between a lesion and specific behaviour, which has often been pointed out as the key feature of the model, appears to be misleading, because it is not possible to establish only on the bases of lesion whether the deficit is due to damage to a mechanism housed at the lesion site or due to damage to the connections passing through the site (Green & Price, 2001). Further complication of this issue is brought about by the facts that lesioned area may retain some functional capacity, that sometimes areas that are not close to the lesion site react to lesion by producing abnormal responses, and that "redundant" areas may take over the function that was previously supported by the lesioned area. In addition, this approach misses a difference between the areas that have a better blood supply and thus may be more resilient to damage, and other areas. It appears that we cannot specify all the areas supporting a specific task based on a lesion in the brain (Price, 2000; Green & Price, 2001). Regardless, lesion-deficit studies have enabled valuable insights into the brain-behavior relationship that secured this method a unique status in brain sciences. The basic framework has been modified over time to include methods, models, and formalities from other disciplines, such as experimental psychology, cognitive science, computational approaches (Chatterjee, 2005), and since recently it has been strongly affected by neuroimaging.

Functional neuroimaging techniques such as Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) have the capacity to fully specify areas supporting a specific task with a spatial resolution of 5-10 mm, revealing (relative) functional specializations of particular brain areas. The main contribution of functional neuroimaging to studying language is the insight that language is not a unified phenomenon and that in fact it is supported by many brain areas (Kutas et al., 2000; Price, 2010). A "single" language function, such as auditory comprehension, typically involves a complex of linguistic computations and representations that are carried out by cognitive subsystems supported by an extensive network of cortical brain areas and white matter pathways. For instance, the phonological subsystem supporting auditory comprehension activates certain temporal areas as well as the dorsal region of Brodmann area (BA) 44. The semantic level of auditory comprehension is also distributed; e.g., passive listening activates temporal region BA 22/42 bilaterally, while other semantic tasks may activate left BA 47, BA 45/46 and BA 44 (Friederici, 1998). The syntactic subsystem, which too contributes to auditory comprehension, is supported by Broca's area (BAs 44, 45), the angular gyrus (BA 39), the supramarginal gyrus (BA 40), the superior temporal gyrus (BA 22), involving also the white matter structures and deep grey matter structures, such as the basal ganglia (Kutas et al., 2000; Caplan et al., 2000). The auditory language comprehension network further depends on the functional connectivity between the areas, in particular the white matter pathways such as the inferior occipito-frontal fasciculus, the arcuate fasciculus, and the middle and inferior longitudinal fasciculi (Turken & Dronkers, 2011). Since auditory

sentence comprehension depends on memory and attention, the hippocampal, medial temporal, and frontal lobe structures that support memory, and the parietal lobe, which is implicated in attention, also contribute to language processing (Kutas et al., 2000).

However, language is even more complex than what postulating the basic linguistic levels such as phonetics/phonology, morphology, syntax, semantics and discourse typically entails. Evidence from aphasia suggests that, for instance, certain aspects of syntax may be impaired with other syntactic aspects being spared in the same patient, which indicates that analyses of language at a much finer level of granularity are needed. In order to investigate language in the brain at a finer level, researchers used a variety of methodologies to study components of the linguistic levels, such as processing of syntactic movement of sentential elements, and storage and manipulation of traces left behind the moved elements (e.g., Grodzinsky, 2000; Fiebach et al., 2001, 2002). Activation in the left inferior frontal gyrus, for example, was reported for both a specific syntactic operation that moves elements in a sentence, *syntactic movement* (Grodzinsky, 2000; Ben-Shachar et al., 2003, 2004), and for an aspect of working memory (WM) that has been claimed to support exclusively syntactic processing, *syntactic WM* (Fiebach et al., 2001). Intra- and inter-sentential processes are so intricate that it may not be possible for neuroimaging or as a matter of fact any other current method in the brain sciences to fully capture their temporal and spatial dynamics at the level of analysis they require, allowing reliable conclusions on the principles of cerebral organization of language (Poeppel & Embick, 2005; Pulvermüller, 2010). Thus, methodological refinements that will better align research on the neural basis of language with the developments in theoretical linguistics are much needed.

Following the realization that language is more distributed in the brain than previously thought and that there may not be one-to-one mappings between specific brain areas and language tasks (e.g., speech production, comprehension), the focus has recently shifted from the search for highly specialized "language areas" to efforts to capture the spatial and temporal dynamics of language as a distributed function. An example of model that is anchored in this view, which incorporates insights from lesion-deficit studies, neuroimaging, and electrophysiological studies, is the dual-stream model of speech production and comprehension (Hickok & Poeppel, 2000, 2007). According to this model, language is functionally realized via two broad *streams of processing*, the dorsal and ventral streams. Namely, cortical speech processing begins with a spectrotemporal analysis supported by auditory cortices in both hemispheres. Thus computed information moves to the phonological network in the middle to posterior portion of the superior temporal sulcus, where there is a slight left hemisphere (LH) bias for processing involving phonological processes and representations. From this point, information moves via the dorsal stream, which is strongly left-lateralized and supports auditory-motor integration in speech processing, and the ventral stream, which is bilateral with a slight LH bias and supports auditory comprehension. In other words, the dorsal stream maps phonological representations onto articulatory motor representations, and the ventral stream maps them onto lexical conceptual representations. The dorsal stream in its posterior part involves a portion of the Sylvian fissure at the parietal-temporal boundary, supporting the sensory-motor interface; its anterior portion in the frontal lobe includes Broca's area and its vicinity,

while its more dorsal premotor component "corresponds to the portions of the articulatory network" (Hickok & Poeppel, 2007, p. 395). The ventral stream in its posterior portion (posterior middle and inferior portions of the temporal lobes) supports linking of phonological and semantic information (the lexical interface), while its more anterior areas support the combinatorial network.

In addition to capturing the differences in the respective functional anatomies of the two processing streams, the dual-stream model also aligns research on language with the recent developments in cognitive neuroscience that seek to establish a broader understanding of *what* and *where* of the processes in the brain. For instance, according to recent research on vision, audition, and the visuomotor system, sensory-motor integration and spatial stimuli processing are carried by a dorsal stream, while stimuli perception and recognition are carried by the ventral stream (Saur et al., 2008). To put it differently, the two processing streams support different types of computations in the brain regardless of the domain, including language. What is in particular interesting about this model is not only its distributed and dynamic nature, but also its ability to incorporate *interface* components of language functioning. This is an important feature that brings the model closer to the theories on human cognitive architecture that postulate existence of *integrative* and *interface* modules (e.g., Jackendoff, 1997, 2002), providing the neural basis to cognitive interface modules. More importantly for our purposes, the two pathways for language postulated by the dual stream model capture language processing in neurologically intact brain—at least in tasks prototypical for each of the streams (Saur et al., 2008) and account for aphasic syndromes (Hickok & Poeppel, 2004).

In order to further illustrate the role of fMRI in language research, with a particular regard to language reorganization after stroke, we will next address the concept of explanatorily significant progress in cognitive neuroscience, against which contribution of fMRI to post-stroke aphasia research will be discussed. Then, we will focus on issues such as aphasia, patterns of aphasic deficits, and the brain's potential to adapt to lesions causing aphasia. We will conclude the chapter discussing some methodological challenges in using fMRI to study post-stroke aphasia and questions for future research.

1.1. Neuroimaging: Towards *explanatorily significant progress*?

The impact of neuroimaging on language studies and its contribution to our understanding of the language-brain relationship has recently been challenged in light of the findings indicating that in addition to supporting a particular language function, a single brain area may be activated in tasks that are not language related (Hickok & Poeppel, 2005; Fedorenko & Kanwisher, 2009; Pulvermüller, 2010). Hickok and Poeppel (2005) argue that, despite the large number of published neuroimaging studies that address various aspects of the question of how language is instantiated in the brain, the progress has not been *explanatorily significant*. For instance, neuroimaging reveals that Broca's area, which was traditionally defined as a "classical language area", supports various tasks related to memory, music (e.g., Maess et al., 2001; Patel, 2003), calculation, object manipulation (Binkofski et al., 2004), motor imagery (Binkofski et al., 2000), perception of meaningful but not meaningless sequences of hand and mouth actions (Fadiga et al., 2006a, Fadiga et al., 2006b), time

perception, rhythmic perception, processing of complex geometric patterns (Fink et al., 2006), prediction of sequential patterns, and so on.

When a single area is associated with a variety of tasks, it is important to understand whether the activation of that area during a specific task reflects that the area in question is necessary for the task or whether it perhaps reflects strategies used to optimize performance on the task (Price, 2000). In case of Broca's area, growing number of neuroimaging studies report activation in this area, without providing a principal explanation of how it contributes to the functionality across domains. Several proposals have been put forth to explain the rich functionality of Broca's area. For example, it has been proposed that it supports: (a) selection of information from competing sources (Thompson-Schill, 2005), (b) a broader cognitive control function (Novick et al., 2005, 2010), (c) language specific linearization of hierarchical language dependencies (Grewe et al., 2005), (d) processing of hierarchical dependencies like those found in language and musical syntax (Opitz & Friederici, 2007), to mention a few.

Despite the current lack of consensus on the role of Broca's area in a variety of tasks involving cognition, perception, and action, the fact is that evidence from neuroimaging has enabled insights about the involvement of this area in various types of processing, helping to reveal some widely accepted misconceptions on this intriguing brain area. As an example, building on some earlier CT findings, structural MRI has established that the brain area that Pierre Paul Broca pointed out as probably responsible for the speech loss in his historic patients Leborne and Lelong in the 1860s does not actually coincide with what we call today "Broca's area" (Dronkers et al., 2007). Together with structural and other functional neuroimaging methods as well as with new observer-independent methods of cytoarchitectonic analysis (Amunts et al, 1999, 2003), fMRI has created a new picture of this area. Further, functional MRI and PET evidence supports the view that damage to Broca's area is neither sufficient nor necessary to induce Broca's aphasia and that, in contrast to the previously held belief on the existence of functionally highly-specialized language areas, there may be no brain areas that are dedicated *exclusively* to specific language functions.

When it comes to the fact that an impressive amount of data on a specific brain area does not necessarily translate into explanatorily significant progress, Broca's area is not an exception. A large body of evidence indicates that the extrastriate body area (EBA) and the fusiform body area (FBA) also support variety of tasks (Downing & Peelen, *in press*). There is currently little understanding of their roles in these tasks, and in particular their roles in across-domains information binding remains unclear. Downing & Peelen (*in press*) have proposed that the body areas in the occipitotemporal cortex (OTC) do not actually support processing of the body itself (as a category), but rather its shape and posture (that is, its features), forming a perceptual network that supports processing in other cortical systems. Further examples of relative functional specialization of brain areas and distribution of function pertain to the case of action and action words. For instance, verbs *lick*, *pick*, and *kick* activate not only the brain areas that are typically engaged in processing of words and concepts; they also activate the areas that support realization of actions to which these words refer. In a recent fMRI study Hauk and colleagues (2004) have shown that tongue

movements were associated with the activation of the premotor areas posterior to the inferior frontal area typically activated by face-related words, and overlapping activations in the motor cortex were found for arm-related words and finger movements, and for leg-related words and foot movements. In another fMRI study, Orlov and colleagues (2010) found consistent segregated activations within the OTC for five different visually presented categories of body parts, such as the upper face, lower face, upper limbs, trunk, and the lower limbs. More importantly, the OTC was a site where the visual information converged with the information on these categories from the motor domain. What is interesting about these findings is not only the triple dissociation in the neural support of the mentioned cases of verb category (Hauk et al., 2004), or the evidence on which particular area of OTC supports which body-part category (Orlov et al., 2010), but rather the insight on how the cortical language and action systems in the former case, and vision and the motor system in the latter case, contribute to the human conceptual combinatorics. It appears that regardless of the domain (e.g., words vs. actions, visual perception vs. movement) certain features of an object are selected, combined, and arranged into configurations that can be accessed by mechanisms supported by different brain areas. Furthermore, activations in the OTC have also been reported in congenitally blind participants in tasks involving tactile stimuli, Braille reading, and imagery of object shapes when canonical sounds of these objects were presented (Mahon et al., 2009).

Another interesting finding comes from Chen and Zeki's (2011) fMRI study in which, adopting Kant's distinction between inherited concepts, such as time and space, and acquired ones, such as artifacts, the authors investigated whether different brain mechanisms support processing of inherited (e.g., faces) versus acquired concepts (e.g., chairs). In addition to the evidence for an "overlapping and segregated system for object representation" (p. 9) in the ventral visual cortex, they also found a fronto-parietal activation associated with violation of the inherited concepts that was not found when deformed artifacts were presented. Based on these findings, they conclude that the distinction between the two categories is neurally supported and that there may exist a hard-wired preference for processing of certain features of objects. Taking these findings into account, one could wonder whether features associated with body shape and posture could also be hard-wired in some sense. Bodies and faces provide important cues on identity of others (Peelen & Downing, 2007). Given that meaning in humans is highly systemic, it is possible that selection and extraction of such specific cues from the visual stimuli is neurally specified to the OTC areas. Thus, the body areas in OTC may form a part of an *interface* which, by extracting information on specific features of stimuli, enables the conceptual network to select, combine, and arrange these features into interpretable configurations. An important step towards explanatorily significant progress in this research area will be to explain how the perceptual network interfaces with a distributed conceptual network.

We can conclude that, although a principled explanation of brain areas with rich functionality, such as Broca's area and OTC, is currently lacking, the accumulating knowledge about these areas is valuable in itself as it continues to clarify issues on the brain-behaviour relationship. It has led to a revision of the traditional conceptualization of an intriguing area, such as Broca's, as well as to appreciation of the complex nature of functional segregations within OTC. Research on both brain areas also exemplifies how

methodological advancements in neuroimaging have contributed to the growth of knowledge on brain's functionality.

Debates among researchers who study the neural correlates of language go beyond the functionality of Broca's area and the question of existence of brain areas supporting exclusively language vs. possibly having multiple relative specializations (e.g., Fedorenko and Kanwisher, 2009; Grodzinsky, 2010; Pulvermüller, 2010), and extend to issues such as neuroplasticity in developing and injured brains, brain's potential for language reorganization after injury, and the role of hemispheric specialization in such processes. Studying these issues holds a key to better understanding of not only language in the brain, but also human cognitive architecture more generally.

2. fMRI of post-stroke aphasia

Establishing potential for long-term recovery of language in post-stroke patients requires information on which neuroanatomical areas are damaged by a stroke, what the extent of damage is (Naeser & Palumbo, 1994), and with which areas is the remaining functionality associated (Price, 2000). Having this information as early as possible allows patients with poor prediction of recovery to sooner enroll in non-verbal treatment programs that may improve their communication abilities, and patients with good prediction of recovery to early begin intensive behavioral or stimulation interventions specifically designed to optimize their recovery of language.

While structural neuroimaging can provide important insights on changes in the brain structures after a stroke, functional neuroimaging is essential in deriving predictions on recovery based on the remaining functionality. As a matter of fact, one critical aspect of the progress in language-brain research enabled by neuroimaging methods pertains to the insights on neuroplasticity and the brain's ability to reorganize the function after injury. Neuroplasticity—or brain plasticity—is a term that refers to the brain's ability to adapt to change, be it environmental pressure, learning experience, or brain damage (Johansson, 2011). The ability of damaged brain to recover language depends on the type of damage, lesion site and size. Individual brain dynamics and factors such as intensity of speech therapy, involvement in social interaction and verbal communication outside the speech therapy setting, concomitant diagnoses such as depression as well as age, sex, and so on also affect one person's potential for recovery, leading to different individual results in recovery of stroke patients with similar lesions. These factors add up to such a large variability in recovery that a recent follow up study with first-ever stroke patients up to 90 days after stroke onset "failed to identify any prognostic factors" (Johansson, 2011, p. 152.).

A classic example of the brain differently adapting to different types of lesion is represented by low-grade gliomas vs. stroke. In the former case, the functionality is typically taken over by the surrounding areas (Desmurget et al., 2007), while in the latter case activations have been reported in both perilesional and contralesional areas. fMRI evidence also shows that smaller stroke lesions are typically associated with activations of perilesional areas, while larger stroke lesions induce activation of the homologue areas in the opposite hemisphere (Cao et al, 1999). Aligned with these findings are insights that a better language recovery is associated with the activations in the original network (Karbe et al., 1998). Functional

language reorganization after stroke — and in particular the role of the right hemisphere (RH) in it — has been debated in the literature for several decades. Curiously, until recently the patterns of language recovery after stroke were typically studied in chronic aphasia (Cramer & Riley, 2008), where in fact reorganization has already taken place. In order to understand better the post-stroke reorganization of language processes, we need to study acute and subacute aphasia, focusing on the remaining functionality of the lesioned area(s) and new functionality of areas not typically recruited by a certain language task. Before we review the dynamics of language reorganization and recovery from aphasia, few remarks on aphasic language are in order.

2.1. Becoming a structure: Patterns of aphasic language

Aphasia is a language disorder caused by brain damage due to a stroke, traumatic brain injury, tumour, atrophy and other neurological conditions. Patterns of language deficits differ across various types of aphasia, depending mostly on the size and location of brain lesion. While there are numerous classifications of aphasias, all aphasic types can be roughly divided into non-fluent (such as Broca's aphasia, transcortical motor or global aphasia) and fluent aphasias (e.g., Wernicke's aphasia, anomic and transcortical sensory aphasia). Regardless of the type of aphasia or language of aphasic person, all aphasic speech is characterized by errors in use of grammar. As a general principle, more complex elements of a language paradigm are more vulnerable, while more frequent elements are more resistant to impairment (Paradis, 2001; Ulatowska et al., 2001). One way in which complexity may affect aphasic language abilities is reflected in these patients' efforts to simplify their speech output by choosing short, simple sentences, as found in non-fluent, agrammatic speakers, or by choosing random substitutions of items within a paradigm, as found in fluent, paragrammatic aphasic speakers. Further, agrammatic Broca's aphasics typically perform better on tasks involving nouns than on tasks involving verbs, which are grammatically more complex than nouns. In fact, verb deficit is among the main defining features of this type of aphasia: only a small number of verbs is typically found in spontaneous speech of these patients regardless of language. They typically omit auxiliaries (such as *is, will*), and either omit or substitute inflectional affixes (such as *–ed* in *walked*) (Miceli, Silveri, Villa & Caramazza, 1984; Menn & Obler, 1990; Hagiwara, 1995, Friedmann & Grodzinsky, 1997; Bastiaanse & Thompson, 2003; Burchert et al., 2005; Druks & Carroll, 2005; Diouny, 2007; Bastiaanse, 2008). It has been claimed that paragrammatic speakers, on the other hand, exhibit the opposite pattern, performing better on tasks involving verbs than those with nouns, and making semantic errors and circumlocutions in production of critical forms (Druks, 2002).

Another often reported feature of Broca's aphasia is a specific pattern of sentence comprehension: these patients comprehend sentences such as (1)-(3) above chance, while their comprehension of noncanonical sentences, such as (4)-(6), is at chance (Caramazza & Zurif, 1976; Hickok et al., 1993; Mauner et al., 1993; Grodzinsky et al., 1999, Grodzinsky, 2000).

Canonical sentences:

1. The girl kissed the boy (active),
2. The girl that kissed the boy is tall (subject-relative),
3. It was the girl that kissed the boy (subject cleft).

Non-canonical sentences:

1. The boy was kissed by the girl (passive),
2. The boy that the girl kissed is shy (relative),
3. It was the boy that the girl kissed (cleft).

Apart from these general features, patterns of impairment of aphasic speech production and comprehension differ in structurally different languages in ways that reflect specific features of particular languages. Better understanding of cross-linguistic differences in patterns of aphasic language is important for development of theories capable of accounting for data across languages as well as for designing treatments usable in languages that are less studied than English. For instance, omission of articles (*a, an, the*) is typical for English speaking aphasics, whereas this is not an option in languages that do not have articles, such as Croatian. Similarly, in highly inflected languages such as Slavic, bound morphemes (e.g. *–ed* in *walked*) cannot be omitted, because that would result in nonwords; instead, bound morphemes are substituted. Since languages such as English allow omission of bound morphemes, patterns of aphasic deficit in English-speaking aphasics differ from patterns of aphasic speakers of languages structurally different from English.

Cross-linguistic differences in aphasic patterns are found not only at the word level, but also at the sentence-level. As an example, Ardila (2001) found that the comprehension strategies in Spanish speaking Broca's aphasics differed from the patterns found in English speaking Broca's aphasics. The reported differences in the patterns of aphasic performance reflect structural differences between the two languages, with English-speaking aphasics relying on word-order strategies, and Spanish-speaking aphasics relying on morphosyntactic markers with high cue validity in this language. Similarly, Kljajevic and Murasugi (2010) have shown that, unlike English speaking Broca's aphasics, whose strategy was based on word order, Croatian aphasic speakers relied on case cueing as a strategy in comprehension of wh-structures when their comprehension was compromised. Case cueing as a strategy in Croatian is language-specific: Croatian has a free word order and marks semantic roles of elements in a sentence by morphological cases. In contrast, English has a strict word order and these roles are assigned to a word's position in a sentence. Thus, highly inflectional languages appear to support strategies that are not available in languages without rich morphology. More importantly for our purposes is that when different strategies are used in a particular task, the areas activated by the task may differ in patients with a lesion in the same brain area. This complicates interpretation of findings and prediction of recovery, making it difficult to understand whether such activations reflect language processes or compensation strategies (Sidtis, 2007). Differences in cognitive strategies used in a particular task represent a difficulty of the same order in fMRI research as individual anatomical and functional variability among aphasic patients (Zahn et al., 2006).

In addition to cross-linguistic variability in patterns of aphasia, individual differences in reacting to lesion, differences in speed of recovery, intensity and length of speech therapy, the degree of social involvement and communication outside speech therapy and so on also affect patterns of recovery in aphasic patients. Thus, it is important to study aphasia not only across structurally different languages, but also individually, taking into account individual differences in patients' potential for recovery and strategies enabled by the

structural peculiarities of a particular language. In both cases, fMRI is an indispensible tool of investigation, neuroimaging assessment and neuroimaging-guided rehabilitation.

2.2. Grammatical category as the main organizing principle of language in the brain?

It has often been claimed that one hallmark of aphasic language is a double dissociation between verb and noun production in non-fluent vs. fluent aphasia, with a better production of verbs than nouns in fluent, and better production of nouns than verbs in non-fluent aphasia. The dissociation is interpreted as evidence of two different mechanisms supporting the two grammatical categories, with the left frontal lobe supporting verb production and the left temporal lobe supporting production of nouns. However, neuroimaging evidence on the neural substrates of verbs and nouns is heterogeneous (Perani et al, 1999; Tyler et al., 2001; Shapiro et al, 2006; Arévalo et al., 2007; Luzzatti et al., 2006), and even suggests that BAs 45 and 9 may support encoding of grammatical properties of words, regardless of the grammatical category. One could object that the heterogeneity of neuroimaging evidence may be due to the fact that verb processing is not a monolithic task, reflecting different aspects of verb processing. More direct evidence on a network of areas supporting verb category comes from research by Luzzatti and colleagues (2006): verb deficit in their aphasic participants was associated with the posterior temporo-parietal, fronto-temporal perisylvian, insular and basal ganglia lesions in the left hemisphere.

Luzzati et al.'s (2006) finding is consistent with the evidence that shows that an aphasia syndrome can have different localizations (Ardilla, 2010) as well as with the growing cross-linguistic evidence obtained in a variety of tasks that indicate that fluent aphasic speakers, too, have difficulty with verbs. Namely, fluent aphasic patients produce fewer verbs in spontaneous speech than neurologically intact speakers (Bastiaanse et al., 1996; Edwards, 2002; Kim & Leach, 2004) and exhibit problems with verb retrieval (Bastiaanse & Jonkers, 1998; Kambanaros, 2008), access to argument structure and thematic representation of verbs (Russo et al., 1998), finite verb inflection (Varlakosta et al., 2006), and time reference through verb forms (Kljajevic & Bastiaanse, 2011). Thus, verb deficit is present in aphasia regardless of whether the lesion causing the disorder is located in the anterior vs. posterior cortical areas, or whether it runs cortically or cortico-subcortically.

These findings indicate the need to focus on analysis of features, instead of grammatical categories as such, and the importance of considering findings from both lesion-deficit studies and functional MR imaging. Combining the two methods is crucial when studying aphasia, because each method has unique strengths and weaknesses. As pointed out in section 1, lesion-deficit studies may contribute information on which area is necessary for a specific function. However, they cannot tell us whether a deficit is caused by lesion to that specific site or to a network to which the area belongs (Price, 2000; Turken & Dronkers, 2011). Naturally occurring lesions are typically large, rarely affecting a single area, and complex in the sense that they affect more than one function. On the other hand, fMRI provides information on the remaining functionality of the injured tissue, involvement of other brain areas "taking over" the function, and the reorganization processes at work. However, due to the correlational nature of fMRI evidence, combining this method with lesion-deficit studies leads to strong evidence that a specific brain area supports a particular function.

2.3. fMRI of language deficits

One example of language deficits that occur in all types of aphasia is naming deficit. This deficit is typically tested in a naming task, where a patient is required to name visually presented objects or pictures of objects. While imaging overt speech is crucial for assessment of speech recovery in aphasic individuals, important insights on language recovery processes were obtained in fMRI studies that used the silent paradigm (Davies et al., 2006; Harnish et al., 2008). One problem related to using covert speech is that it prevents monitoring of task performance (Peck et al., 2004). In contrast, imaging overt speech allows analysis of accuracy and reaction times, which are important indicators of treatment effects in aphasia (Thompson & van Ouden, 2008). However, unlike silent paradigm, neuroimaging of overt aphasic speech is associated with challenges. Some of them are artifacts due to speaking and head movement and artifacts caused by jaw and tongue movements during articulation. Hearing and speech recording may also be difficult in such experiments, because of the scanner noise. In addition, non-fluent aphasic patients' speech may be difficult to transcribe, because it is typically hesitant, effortful, and characterized by many false starts. It is precisely the hesitant nature of aphasic speech and differences in timing of response output that make the block design a preferred choice over the event related design when assessing overt aphasic speech (Martin et al., 2005). The main advantage of using the block design is the possibility of collecting data during the silent period, which is enabled by the hemodynamic response delay. Using the block design during blood oxygenation level-dependent (BOLD) fMRI relies on "the temporal dynamics of the hemodynamic response delay where increased blood flow remains 4 or 8 seconds after the response", allowing data collection after the task and "during the silent period of no speech, minimizing motion artifact from overt speech" (Martin et al., 2005, p. 195).

The main assumption when choosing this method is that the hemodynamic response in aphasia patients is similar to that in controls. However, it has been pointed out in the literature that stroke affects blood flow, thereby affecting performance on cognitive tasks, even in patients whose infarcts were not in the cortex (Pineiro et al., 2002). Bonakdarpur and colleagues (2007) studied differences in a hemodynamic response function (HRF) in 5 post-stroke aphasic patients and 4 healthy individuals, focusing on Broca's area and the posterior perisylvian network (including Wernicke's area, the angular and supramarginal gyri), and RH homologues of these regions, plus the occipital area as a control area. The main finding of their study is a delay in time to peak in the left perisylvian area in 3 aphasic patients (up to 20 seconds after stimulus) that were not found in their left visual cortex, or in the same areas in the control subjects. This is an important finding, because "many fMRI studies with stroke patients use a canonical HRF for data analysis, peaking at about 6 seconds following a cognitive event", which makes it possible that these studies actually missed or underestimated activations (Thompson & den Ouden, 2008, p. 476). However, Peck and colleagues (2004) report decrease in TTP of the hemodynamic response in right auditory cortex, homologue of Broca's area, motor cortex and pre-suplementary motor area associated with improved performance on overt word generation tasks after a treatment of 3 aphasic patients. This indicates that TTP data contain valuable information on patients' response to treatment, because changes in TTP reflect changes in the amount of time that a patient spends on a task from presentation of stimulus to verbal response. Thus, fMRI can

be used to evaluate speed of processing in perilesional areas and other areas of the brain that take over the function of injured area(s) (Peck et al., 2004). Additional challenges are fMRI signal variability in general (Bandettini, 2009) and possibly insufficient signal to noise ratio for BOLD signal detection in damaged areas in aphasic patients in particular (e.g., Bonakdarpour et al., 2007).

Since naming difficulties occur in all types of aphasia, they are in the focus of rehabilitation as well as neuroimaging research on recovery of language in aphasic patients. Other types of aphasic deficits have also been investigated by fMRI. In a recent study, Thompson et al. (2010) studied brain correlates of verb argument structure processing in aphasic patients and healthy elderly people. Verb processing critically depends on verb's argument structure. Aphasic patients, in particular non-fluent aphasics, have difficulty producing verbs with more complex argument structure. In an fMRI study with event-related design Thompson et al. (2010) have shown that aphasic patients exhibited the right hemispheric preference in processing verb argument structure while recruiting the spared tissue in the posterior language network. The activated brain areas were the same as those in the non-brain damaged control subjects; that is, argument structure processing typically activates bilateral posterior perisylvian region in healthy young and elderly subjects. Thus, activations in the RH in aphasic patients reflect recruitment of the spared tissue in this network.

Recently, Saur and colleagues (2006) have shown that the patterns of reorganization differ at distinct phases of language post-stroke recovery. They studied sentence comprehension in aphasic patients at three different time points: acute, subacute and chronic phase. The main finding of their study is that the acute phase is associated with little perilesional activation, the subacute phase is associated with activation of the right hemisphere homologous areas, while in the chronic phase a re-shifting of function to the left hemisphere language areas is associated with further language improvement. According to this model, activation of the right hemisphere areas in a chronic aphasic patient would indicate poor recovery. Saur et al.'s model of temporal dynamics of post-stroke language recovery opens some important questions: For instance, Why progress in language recovery after stroke seems to require changes in lateralization? Does this hold for both small and large lesions? Will the same pattern emerge when patients are tested on a different task?

Another recent functional MR imaging study focused on the brain's potential to reorganize syntax in post-stroke patients (Tyler et al., 2010). Syntax is believed to be strongly left-lateralized and the study set out to investigate the RH's capacity to take over syntactic processing following damage to the LH. The main finding of the study is that lesion in left BA 47/45 impaired syntax and resulted in decreased activity, while increased activation in the homologous RH areas did not result in better syntactic performance in their aphasic participants. Their findings indicate that the brain cannot reorganize syntax after injury to left BA 45/47 and that the capacity of RH to take over function critically depends on the type of language function. This is an important finding that sheds new light on the debate on the role of the non-dominant hemisphere in language recovery in damaged brain.

Hemispheric differences in specialization for language were first observed in the 1850s, when Broca and his contemporaries reported that LH damage was associated with aphasia

more often than RH damage. This insight led to the conclusion that the LH is dominant or specialized for language (Josse & Tzourio-Mazoyer, 2004). Neuroimaging obviously opened new possibilities for investigation of hemispheric specialization for language—an issue of high importance for work with patients who suffered unilateral brain lesions. Functional neuroimaging methods including fMRI have recorded activations across different brain areas in both hemispheres associated with a variety of language tasks in patients ranging from mild to severe aphasia and at different temporal post-stroke points (acute, subacute, chronic), resulting in controversial evidence. Future research needs to address in more detail the role of contralesional areas in language recovery, in particular in acute and subacute phases, in studies with large number of patients and including variety of language tasks.

2.3.1. Imaging the bilingual post-stroke brain

With at least 50% of the world's population being bilingual (Weeks, 2010) and stroke as one of leading causes of disability worldwide, the issue of how brain damage affects patterns of aphasia in those who speak more than one language receives increasing attention among researchers. The term "bilingual aphasia" currently refers to aphasic speakers who were fluent in two languages (or dialects) before they had a stroke. Since bilingual aphasics do not necessarily exhibit the same type and extent of language deficit in both languages, researchers now agree that these patients should be assessed in both languages (Fabro, 2001). However, they do not agree on the question of in which language the patient should receive speech therapy (Abutalebi et al., 2009). Another hotly debated issue related to this topic is the cortical organization of two languages in a bilingual brain: Are different languages supported by different brain areas? Or are they supported by the same brain areas, sharing processing resources?

The neural basis of bilingual aphasia and its recovery patterns are still largely unknown (Paradis, 1987), which is not surprising given that it is not clear whether two languages of a healthy bilingual speaker are supported by the same or different brain areas. Research so far indicates that the most common patterns of recovery in bilingual aphasia are: (a) parallel recovery in both languages, (b) selective recovery, in which one language recovers over time while the other does not, and (c) successive recovery, in which both languages recover, with one of them improving before the other (Paradis, 1985). Variations within these patterns have also been observed, such as so-called alternating recovery (in which recovery of language A is followed by recovery of language B, which is associated with the loss of language A), alternating antagonistic recovery (in which alternations between spared A-lost B vs. lost A-spared B happen day after day), mixing of the two languages in speech production, etc. (Green, 2001). The variability in recovery patterns is so great that bilingual aphasia represents one point of research where progress was remarkably limited: "No correlation has been found between pattern of recovery and neurological, etiological, experiential or linguistic parameters: not site, size or origin of lesion, type or severity of aphasia, type of bilingualism, language structure type or factors related to acquisition or habitual use" (Paradis (1995, p. 211), cited in Green & Price (2001, p. 191)). Obviously, much more work needs to be done in this area in order to establish how the brain accommodates more than one language and how it mediates bilingual recovery.

Investigation of neural correlates of treatment by using functional neuroimaging is an important new perspective in research on bilingual aphasia. Functional neuroimaging is critical in this type of research, because it can provide information on functional reorganization in the brain that is not available through other methods (Meinzer et al., 2007; Green, 2008). For instance, in a longitudinal single case study, Abutalebi and colleagues (2009) used fMRI and dynamic causal modelling to investigate recovery of language in a Spanish-Italian bilingual aphasic speaker. They designed a treatment for naming deficit in their patient, JRC, who suffered from global aphasia, with anomia affecting equally both languages. Testing was done before a picture naming-based speech therapy, specifically designed to improve JRC's naming abilities, after the specific speech therapy, which took 6 weeks, and after the global speech therapy, which was administered over 4 months. The patient chose to rehabilitate his second language, Italian. The authors report improvement in picture naming, increased activations in the brain areas supporting naming as well as in the areas supporting language control processes, but no generalization of improvement to the language that was not treated—Spanish. Following the initial better L1 than L2 pattern, a reverse patter of better L2 than L1 due to speech therapy in L2 was observed, which was associated with worsening of performance on naming tasks in L1. Similarly, while in early post-stroke phase activations associated with performance in L1 and L2 were similar in location and extension, the specific speech in L2 was associated with language reorganization only on tasks in L2, which JRC fully recovered. Interestingly, the activation pattern reflecting behavioural improvement was similar to the language activation pattern in healthy bilinguals, with the left inferior frontal gyrus and the left fusiform gyrus supporting picture naming. Their findings on the role of control processes in recovery of language open the question of how to best manipulate these processes in neuroimaging-guided treatment of language disorders in bilingual speakers. Theoretically, the findings are relevant for the debate on whether treatment in one language inhibits overall recovery of both languages.

2.3.2. Imaging the impact of language training on post-stroke brain

After a stroke, spontaneous language recovery takes places during the first 6 to 12 months. It has been pointed out in the literature that it is difficult to disentangle whether changes in language behaviour result from the healing processes (diaschisis) or neuronal reorganization (Pulvermüller et al., 2005; Hillis, 2006). fMRI is an important research tool not only in investigation of spontaneous language recovery, but also in treatment-induced recovery (Crosson et al., 2010). For instance, it can map changes in brain functionality following a treatment to assess its effectiveness (Menzer et al., 2011). However, even though the field of rehabilitation neuroscience is growing, current understanding of how therapy affects language recovery is still limited (Cherney & Small, 2006), regardless of the importance of treatment effectiveness assessments in the acute and subacute post-stroke phases (Cramer & Riley, 2008). Research so far has shown that longitudinal fMRI of aphasic language is an effective tool for detection of changes in activation patterns (Saur et al., 2006) and activation magnitude (Meltzer et al., 2009) over time.

For instance, Vitali and colleagues (2007) used event-related fMRI design in a single-case study of two severe, chronic aphasic patients. They studied picture-naming performance

before and after a phonological cueing training, and found improvement in naming of the trained sets of items, which did not generalize to the untrained materials. The neuroimaging findings from this study confirm that both types of processes are associated with improvement of the naming function: activations of the perilesional areas indicating restitution of function in the original network, and activations of the contralateral homologue areas, indicating compensation strategies at work. More importantly, the study indicates that improvement of function is possible even in chronic patients. One can hope that neuroimaging-guided rehabilitation practices represent a transition to a new paradigm of language rehabilitation that will become increasingly available in hospitals.

An important aspect of the use of fMRI in treatment-induced recovery of aphasia pertains to combining this method with transcranial magnetic and electrical stimulation to guide rehabilitation and enhance recovery (Devlin & Watkins, 2007; Naeser et al., 2005). As an electrical organ, the brain is susceptible to modification of function via electromagnetic stimulation. Studies using repetitive TMS and transcranial Direct Current Stimulation (tDCS) in combination with fMRI and EEG have shown that targeting specific brain areas may improve naming abilities not only in aphasic but also in patients with Alzheimer's dementia (AD). For instance, repetitive TMS can increase or decrease cortical excitability, inducing inhibition at frequencies ≤1 Hz or facilitation at ≥ 5 Hz. Cotelli et al. (2006) found that administering an rTMS intervention during which both the left and right dorsolateral prefrontal cortex was stimulated in 15 patients diagnosed with mild to moderate AD significantly improved these patients' ability to name actions. In another study, Cotelli et al. (2008) have shown that rTMS improved naming of actions and objects in 24 patients in the advanced stage of AD. Interventions such as rTMS are warranted in patients with AD, because evidence suggests some functional deficits in AD are associated with damage to specific brain areas (Horasty et al., 1999). For instance, Apostolova and colleagues (2008) have shown that language function in AD patients correlated with gray matter atrophy in specific brain areas, and that, overall, language performance of AD patients critically depended on the integrity of the perisylvian cortical regions. Further, it has been shown that although cortical atrophy is relatively widespread in early AD and affects both hemispheres, the LH regions seem to be affected earlier and more severely than the RH areas, with the latter areas taking about two years to reach the level of atrophy of the LH areas, establishing atrophic symmetry (Toga & Thompson, 2003).

Evidence on improvement of naming due to stimulation is even more robust in aphasic patients (e.g., Naeser et al., 2005; Martin et al., 2009), where lesions are focal, and treatment is intended to encourage *recovery* of function instead of enhancement of *compensation*, as in AD patients. TMS nicely complements fMRI because it can be used to test the hypotheses on the retained functionality of the lesioned area or newly acquired functionality of activated areas not typically involved in a specific language function. Such treatments are often based on the assumption that brain areas that assume functionality of the damaged areas may be temporarily disrupted by stimulation, which then forces the original areas to take over the function. A treatment of aphasia that is based on this principle is known as *constraint induced aphasia therapy* (Pulvermüller et al., 2001).

The above examples from naming tasks show that improvement of language performance is possible even in chronic aphasic and AD patients. The role of fMRI is likely to grow with

further developments of research in this area, improvement of stimulation methods and their increasing contribution to rehabilitation practices.

3. Challenges and limitations

The main goal of this chapter was to discuss the increasing role of fMRI in current research on language in post-stroke brain. While fMRI has become an essential tool for research on brain's functionality, some challenges make it difficult to justify the overwhelming enthusiasm of the research community regarding this method. Several influential publications reviewed challenges in conducting functional MR imaging in general (e.g., Utall, 2001; Devlin & Poldrack, 2007; Bandettini, 2009, among others) and in research on language in particular (e.g., Sidtis, 2006). Among the problems associated with the use of fMRI to study language are: processes at the macroscopic level that fMRI records may not reflect the processes at microscopic level, lack of consensus among researchers on localization practices, differences in practices in dealing with individual neuroanatomical variability, the fMRI signal variability, the correlational nature of fMRI evidence and its interpretation with regard to cognitive processes, and limited temporal resolution (Utall, 2001; Devlin & Poldrack, 2007; Bandettini, 2009). In addition, there are some challenges specific to using fMRI in research with post-stroke patients, such as artifacts due to production of overt speech, individual variability in functional recovery and use of cognitive strategies, small number of aphasic participants in studies, and the issue of choosing an appropriate method of analysis (e.g., choosing specific ROIs may leave out some areas that may turn out to be important). Furthermore, lesions typically have different extent and lack of an overlap of lesions may lead to missing activations in perilesional areas (Zahn et al., 2006). Neural substrates of language recovery after stroke and functional reorganization involve networks supported by connections that enable interactions among regions. Thus, more research is needed on how disruption of white matter pathways affects recovery of function and how they contribute to initiation of functionality in areas previously not implicated in the function at question (Turken & Dronkers, 2011).

4. Conclusion

In conclusion, the impact of neuroimaging on studying language has been profound. Methods such as fMRI have shown that the traditional concept that language is "located" in specific brain areas such as Broca's and Wernicke's is oversimplified and that the brain supports language processing via complex, sophisticated networks. The growing number of fMRI studies on language in neurologically intact and injured brains has enabled arriving at neurally relevant linguistic generalizations and deepened our understanding of possible principles of the neural organization of language, post-lesional neuroplasticity and recovery processes, revealing also that some previously widely held assumptions do not hold. Still, some specific questions on where in the brain certain linguistic representations are formed, where in the brain specific linguistic computations take place, how the non-dominant hemisphere supports recovery of language in injured brain, or how bilingual brain recovers language functionality—will probably have to wait for answers for some time.

5. Acknowledgement

6. References

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