SUMMARY

In the recent years, the research on language processing have become increasingly focused on measuring brain activity by functional Magnetic Resonance Imaging (fMRI). Although the technology has become an indispensable research tool when constructing and testing theories on language function in neurologically intact brain, so far it has not been fully employed to answer the question of the utmost importance to patients with brain damage: How to recover the lost function? One goal of the present paper is to examine the potential of using fMRI in language recovery after stroke, with the focus on the idea that neuroimaging assessment of preservation of language function in these patients may be as useful as behavioral data on the loss of the function when designing individual language recovery treatments.

Key words: fMRI, stroke, aphasia, cerebral reorganization, neuroplasticity

INTRODUCTION

The history of neuroimaging is relatively short, going back only to the 1980s. Still, several efficient and highly sophisticated neuroimaging methods are available for human studies that any research on recovery of brain function needs to take into consideration. They include: functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single positron emission computerized tomography (SPECT), event-related potentials (ERP), electroencephalography (EEG), magnetoencephalography (MEG), and near-infrared spectroscopy (NIRS). In addition, there exist brain-imaging techniques that use radiolabeling, histological or optical imaging techniques, which are allowed in studies with animals. Unlike some other types of functions, recovery of language cannot be studied on animals. The same holds for other types of higher cognitive processing, such as consciousness, abstract reasoning, executive function, episodic or autobiographical memory, etc. Although the traditional clinical setting allows a direct observation of signs and symptoms in patients with brain damage, they cannot provide information on cerebral reorganization that takes place during recovery. Neuroimaging methods provide insights into structure and function of the brain areas implicated in a disorder or disease, which further helps to reveal the mechanisms of its deterioration as well as its recovery. fMRI best illustrates the rapid development of neuroimaging methods, given that it entered the scene exactly five years after the first PET studies were conducted (1). Yet, despite this method's popularity and its potential to complement lesion studies in important ways, like in evaluation of appropriateness and effectiveness of treatments (2), the impact of fMRI on studying mechanisms of language recovery after stroke has been underestimated so far. Perhaps this is not surprising, given the fact that fMRI still has not become a
“standard” in aphasic patients’ treatment or even in neurosurgery (3). The main focus of the present paper is on fMRI, not because of its popularity, but because it truly stands out among the current neuroimaging methods. It has become an indispensable tool in diagnosticians, and it has shown the potential to be equally useful in the field of recovery.

fMRI is a noninvasive, localizing technique that is widely used for detecting focal changes associated with brain activity (4-6). Its predecessors are MRI and PET. The former is a powerful structural imaging tool that has been developed on two elements: (i) magnetic resonance technology, and (ii) computerized tomography (CT) (7). Based on the differences in chemical compositions between the types of body tissue, MRI provides detailed anatomical grey and white matter scans with a high spatial resolution - below 1 mm³ (8). MRI scans are more informative than CT scans and are generally comparable to “fixed and sectioned anatomical material” (7). The information obtained by this method is useful when comparing structural differences in two types of population, or in the case of changes in gross brain structure. However, when it comes to recovery of function, the conventional structural CT and MRI scans do not show for instance whether a lesion has retained some functionality and hence their contribution to recovery studies is rather limited. Although fMRI is based on computerized tomography, it has other features that make it suitable for exploration of both structure and function.

Unlike structural neuroimaging methods, functional methods such as PET and fMRI are useful for studying brain functions. They measure brain activity indirectly, by measuring metabolic and vascular changes associated with neural activity, which is then related to motor, perceptual, or cognitive processes. PET was a predominant functional neuroimaging technique until the mid-1990s, when it began to be replaced by fMRI. This development was mostly due to the fact that PET requires injection of radioactive material, which limits the number of scans per subject in a session. In addition, acquisition of images in PET may be very slow, which makes its temporal resolution poor, and restricts the types of experimental designs in which it can be used. On the other hand, fMRI does not require use of injected radioactive material. It can be safely used in repeated scanning of a single subject within the same session. This means that fMRI allows making reliable conclusions on brain functions from single case studies, which is important given that recovery is a highly individual process.

When studying language recovery, it is important to remember that not all the cases of language deficits require the same neuroimaging technique. The basic rule in applying neuroimaging techniques to research on cognitive functions and their recovery is to match the question of interest with the appropriate imaging method. In general, tomographic methods are used because of their high spatial resolution (i.e., they address the “Where in the brain...” questions), and the electromagneto-physiological methods because of their high temporal resolution (the “When...” questions). However, determining where in the brain activation has occurred is far from trivial, being associated with conceptual and technical difficulties. For example, we could use fMRI to investigate the activation of the inferior frontal gyrus in Broca’s aphasia, or activation of the superior temporal gyrus in Wernicke’s aphasia. However, since conduction aphasia is caused by damage to the arcuate fasciculus, i.e. the white matter tract that connects Broca’s and Wernicke’s areas (but see (9) for a different view), diffusion tensor imaging (DTI) can be used to map it and measure anatomical connectivity underlying brain activity. Thus, even though DTI is not a functional imaging technique, it could be useful in investigation of certain types of language deficits, in particular if combined with fMRI. Another technique that is potentially very useful in studying recovery of language function is transcranial magnetic stimulation (TMS) (10, 11). The technique allows the investigator to stimulate the cortex of the brain magnetically, inducing electrical discharge in the cortex and producing a certain type of behavior in a subject (2). Since TMS can temporarily disrupt a specific function by deactivating the brain region that is supporting it, it is a powerful tool for studying language deficits in the absence of any real lesion. If used together with other rehabilitative therapies, TMS may enhance recovery from brain injury. For these reasons, advanced neuroimaging techniques such as diffusion tensor imaging, perfusion imaging, voxel-based morphometry, etc. are becoming more present in lesion studies (12).

Whether the question of interest is related to diagnostics, monitoring of recovery, or investigation of the mechanisms of disorders, observing language in damaged brain requires noninvasive powerful neuroimaging tools. Studying language processing in damaged brain is probably best achieved with a methodology capable of capturing the complex nature and the multitude of simultaneous processes that create transient, intermediate linguistic representations that allow language to unfold in time. Not all neuroimaging techniques can separate these processes. As an illustration, techniques with low
temporal resolution, such as PET or blocked-design fMRI, are not capable of capturing these representations. On the other hand, fast-rate event-related fMRI with randomized trials can be used to study such processing (5). In summary, recovery of language function is not a passive process, which could benefit greatly from neuroimaging-guided rehabilitative practices. Among the currently available neuroimaging techniques, the most suitable candidate to capture and guide such recovery is fMRI. First, it does not require ionizing radiation or external contrast agents. Second, it has high spatial and relatively high temporal resolution, which enables mapping of physiological changes to cognitive processes. Third, it is becoming increasingly available in hospitals. In order to better understand the role fMRI should have in examining recovery of language function after stroke, few remarks on the mechanisms of stroke and aphasia are in order.

STROKE AND APHASIA

Stroke is a cover term for a group of heterogeneous pathophysiological causes of disrupted pattern of blood flow, which supplies blood to the brain and the spinal cord. This general characteristic applies to cerebrovascular diseases, too, but stroke differs from cerebrovascular diseases in having a sudden onset and in causing tissue damage. Thus, “a rupture of a large blood vessel that causes flooding of the brain with blood and occlusion of a tiny artery with softening in a small but strategic brain site both qualify as strokes” (13-17). Yet, it is possible to differentiate between two major types of stroke: ischemic and hemorrhagic strokes. In general, 80% of all strokes belong to the category of acute ischemic stroke. Ischemia occurs when the blood flow to the brain tissue is either disrupted due to an occlusion of one or more blood vessels, or is diminished due to low systemic perfusion pressure. Tissue injury caused by ischemia can be either temporary or permanent. If damage to brain is permanent, i.e., if it causes the death of brain tissue, an ischemic stroke qualifies as infarction. Unlike ischemia, hemorrhage in general is blood leakage into the brain and into extravascular spaces within the cranium.

The human brain makes only 2% of body weight, yet 20% of the body’s oxygen supply is consumed in metabolic processes of nervous tissue (14). In order to receive that much oxygen, which is transported to the brain by the vascular system, the nervous system requires constant circulation. Different parts of the brain can be damaged due to a failure of specific components of the cerebrovascular system. Stroke or cerebrovascular incident (i.e. a “brain attack”) is sudden loss of circulation to an area of the brain, causing loss of function performed by that brain area. With a toll of 10% of all deaths worldwide in 1999 (15), stroke is still the third leading cause of death in most countries (13, 15) and the leading cause of disability in the USA (16). One of the factors most likely to cause death or long-term damage in stroke patients is cerebral edema, i.e. swelling of the brain due to the rapid influx of water during the first week following the incident (17). The outcome of the incident depends on whether or how fast swelling will subside. Furthermore, depending on whether they affect primary cortex (e.g. motor, sensory), association cortex (e.g. visual, auditory) or cortex involved in higher cortical functioning, strokes cause anatomic, physiological, and functional changes (18), resulting in different impairments. Of those who survive it, stroke leaves 20 – 25% of patients initially aphasic (19), affecting also to a certain extent the motor function in this population. After rehabilitation, only 31% of patients achieve normal neurological functioning (16), which indicates the need for better treatments.

Language functioning is affected differently by damage to different parts of the brain. These different types of language deficits are referred to by the term “aphasia”. Typically, aphasia affects more than one language modality (e.g., speech, comprehension, reading, writing, etc.), and is characterized by a sudden onset. Given that the language function is disrupted while other cognitive functions are typically spared, aphasia has a tremendous impact on the quality of life of aphasic persons: it compromises their most personal relationships as well as social relationships, affecting the way these individuals function in society. Since most of the persons who suffer from aphasia are unable to return to work due to language and language-related deficits, they often become an economic burden to society. Recovery of function after stroke is therefore a public health issue (15), and any promise of improvement of the quality of life in aphasic population deserves consideration.

Research on language recovery after stroke has not yet paid much attention to the question of how the differences in stroke mechanisms may affect language deficits and the associated recovery processes. Part of the reason for this neglect is that until recently appropriate methods that could have enabled such sophisticated research were lacking. Still, even though the recent advancement of neuroimaging methods has enabled such research, the question of how different stroke mechanisms shape the patterns of language deficits has not been embraced by researchers. Since lesions traditionally associated with aphasia tend to be large, implicating multiple brain areas, it is crucial to add neuroimaging
methods to the current practices in language rehabilitation, because they can help in disentangling the reorganizational issues. Furthermore, lesions caused by a stroke often run subcortically. Although the differences in grey and white matter responses to ischemia have been recognized, together with the fact that even minor white matter strokes often cause extensive neurological damage (15), not much is known about the effects of lesioned subcortical structures on language functioning and its recovery in such cases. Functional neuroimaging can help us to understand better which structures within the distinct areas affected by a stroke contribute to the impaired function in a particular case. This is an important issue, because spontaneous reorganization due to recovery is often marked by atypical patterns of language processing. Knowing these patterns and understanding why and when they occur is crucial in designing successful treatments for aphasic patients.

It is puzzling that after more than 20 years since the initial neuroimaging studies on language, functional neuroimaging has shaped the theories on the brain-language relationships in neurologically intact population, while its impact on the theories on recovery of language function has remained rather modest. This is partly due to the challenges related to the use of fMRI in studying language recovery after stroke. On the one hand, general challenges are related to the difficulties such as combining insights from fMRI with information obtained from other techniques, then methodological issues like patient motion, artifacts, low contrast-to-noise ratio, or more complex ones like the problem of reverse inferencing (20), or the fact that group averaging, which is typical for the method, can be misleading (3). On the other hand, there is a set of specific challenges that characterize the use of fMRI in recovery of language function. The main concern in this respect is related to the fact that recovery processes are primarily individual, while neuroimaging methods typically seek activations of neuronal systems that are common to all subjects, treating intersubject variability as noise (3, 21). Thus, instead of looking for averaging across a group of patients, fMRI should be used to elucidate the specifics of spontaneous or intervention-based recovery in individual cases, addressing at the individual level issues such as cerebral reorganization, recruitment of remote areas, and increased activity in lesioned areas (22). These issues are addressed in the next section.

FUNCTIONAL RECOVERY FOLLOWING STROKE

Focal brain damage caused by stroke and recovery from it cause a change in large-scale networks that support specific functions (e.g., language). Since no two lesions are ever the same, these changes require that lesion-behavioral deficit studies focus on individual cases. One problem with lesion-deficit associations that follows from this observation is that sometimes similar lesions result in different behavioral deficits, and sometimes different lesions result in similar deficits. Insights from neuroimaging can help in explaining these phenomena. For example, neuroimaging provides evidence that in some instances a damaged area may retain some functionality; alternatively, different neuronal systems may take over the function of the damaged area. fMRI can measure and determine atypical or abnormal activation (e.g., underactivation or overactivation at the lesion site), and it can also noninvasively monitor functional changes within a wider network that supports language function, revealing spontaneous redistribution of function to another area. In other words, it can capture the reorganization processes at work. Thus, fMRI may provide a window into the organizational flexibility of the human brain, regardless of whether the reorganization is caused by a pharmacological, surgical, or behavioral intervention, informing thereby research on neuroplasticity (18).

Namely, even though functions of brain areas are in principle localizable, the localization is not fixed. For example, language is typically localized in the left cerebral hemisphere. However, due to neuroplasticity, if a child suffers injury to the left hemisphere areas that support language, the homologous areas in the right hemisphere will typically take over the function. Similarly, the adult human brain also retains plastic potential (23). For example, functional recovery from aphasia is often associated with the activation of the homologous areas of the contralateral hemisphere (usually in the right hemisphere), regardless of the type of aphasia and thus regardless of the exact location of lesion. This process represents the brain's adaptation to the lesion and it begins within days post onset, taking sometimes weeks, months, or in some individuals even years to complete. In other cases, the ipsilateral hemisphere recruits remote areas that are not typically activated by the function. Interestingly, the lesion site may retain some functionality, which emerges once edema has reduced and circulation has been reestablished in the lesioned area (24). fMRI can show which areas are engaged by specific tasks, indicating how cognitive reorganization is associated to the neuronal reorganization. Note that cognitive reorganization assumes the neuronal reorganization; it is functional reorganization that takes place when a patient develops a new cognitive strategy for impaired function. Thus, by showing whether particular tissue is viable and what areas have taken over the function, fMRI can inform us on
the type of cerebral reorganization that enables the cognitive reorganization. This information is useful in predicting which functions might recover and which might be lost - an insight that is critical when devising rehabilitation therapies.

One important distinction between neuropsychological assessment and neuroimaging assessment is that the former is focused on functional impairment, while the latter focuses on the preservation of function in damaged brain (25). Thus, in order to take advantage of the preservation of function, it is necessary to turn to the subtle mechanisms of cerebral reorganization that elude structural and behavioral assessments. As discussed above, most researchers agree that these mechanisms involve spontaneous recovery, recruitment of remote areas, extension of specialized areas, and increased activity in spared areas (22). In addition, reorganization operates on the principles such as redundancy and degeneracy (25). For example, redundancy is at work when intact areas that are inactive in neurologically healthy subjects compensate for a function of the damaged area in a stroke patient. Thus, redundancy applies only to the way the systems function. On the other hand, degeneracy means that several brain regions can support the same cognitive task and hence it applies to structure-function relationships (21).

Degeneracy can support recovery in several ways. First, damage affects only one of the degenerate systems supporting a particular function: even though the specific neuronal system affected by the lesion cannot support the function any more, the rest of the degenerate systems are now engaged in producing the same output. In such a case, fMRI shows activation of only unaffected areas activated by the same task (that is, all the areas minus the lesioned area). Second, if one degenerate neuronal system is typically activated in healthy population, and other systems are latent, then damage to the predominant system would lead to activation of the latent systems. In this scenario, fMRI would show activations of the areas that took over the function during recovery, although these areas are not typically activated in neurologically intact individuals. As an example, expressive and receptive aphasia characterized by damage to the left inferior frontal gyrus (LIFG) (Bas 44 and 45) and superior temporal gyrus (LSTG) (BA 22) respectively are often associated with activations in the right hemisphere homologues of Broca's and Wernicke's areas (18). Finally, yet another pattern of cortical compensation of functionality within a set of equally functional neuronal systems for a specific task would simply exclude the damaged system, leaving the reorganization processes to rely on an intact system.

In summary, degeneracy supports reorganization by allowing a function to be taken over by a neuronal system that is capable of supporting it. However, the picture is further complicated by the fact that as complexes of functional components, higher cognitive functions are typically supported by multiple brain areas.

As pointed out above, behavioral and structural methods cannot inform us on the mechanisms of reorganization following stroke: they lack the ability to image plastic reorganization. It is precisely this ability that makes fMRI a preferable method for investigation of recovery of function in stroke patients. However, a cautionary note is in order. Like other techniques that evaluate cerebral function based on hemodynamic measurements, fMRI is “at a physiological distance from the actual neuronal event. These methods assume that neuronal firing and blood flow increments or decrements are tightly coupled. In most cases, this holds true in the normal brain... but may not always be true in pathological states” (2,5). In cases of large cerebral infarctions, techniques based on relative blood flow measurement are also faced with a problem of how to determine a cerebral blood flow baseline in a hemodynamically unstable tissue. Other potential problems include the assumption that larger areas of activations represent stronger evidence for brain activity, which may be misleading, in particular when it comes to activation of small subcortical structures (8). With these caveats in mind, the relationship between lesions caused by stroke and the subsequent language dysfunction is best interpreted in the context of the capacity of fMRI to capture the correlations between structural and functional abnormalities.

CONCLUSION:
WHY WE SHOULD COMBINE fMRI WITH LESION STUDIES

Despite its importance as a neuroimaging assessment tool, fMRI is hardly the only method that is relevant for recovery of function after stroke. For instance, lesion, drug, and electrophysiological studies remain critical in studying functional recovery. As a matter of fact, lesion studies nicely complement neuroimaging studies on recovery of language function and may increase the interpretative power of fMRI findings. For example, if an area shows activation due to a specific cognitive task, all we know is that there exists a structure-function correlation. However, damage to that particular area may lead to disruption of the function, indicating that the area is necessary for that specific task. If combined, these two findings constitute...
pretty strong evidence that the area in question indeed supports that particular function. Yet, regardless of their power to provide causal evidence for a function, lesion studies have become widely neglected since the advancement of neuroimaging techniques. In a recent paper, Chaterjee (12) has discussed the issue of overwhelming presence of fMRI studies in current cognitive neuroscience research, pointing out that an extreme view according to which fMRI is “the ultimate method” of research is surprisingly widespread, even though the view is misleading. (The decision on what methods to use depends on the questions that need to be answered.) This seems to be due to the appeal of fMRI images and perhaps even more because of the false impression that complex cognitive processes can be localized at specific bits of brain (26).

What is puzzling about lesion-deficit studies is this sudden change in their status. Ever since Broca’s (27) discovery that damage to the third frontal convolution of the left hemisphere is associated with speech loss, human lesion studies have been a valuable source of evidence on the necessity of a specific brain area for a particular function. However, unlike studies involving animals that induce lesions for experimental reasons, human lesion studies are limited to cases with pathological lesions, such as those caused by a stroke. Since natural lesions often involve multiple brain areas, or cut across the white-matter pathways, thereby impairing functions of distant brain areas, it is often difficult to interpret them.

Thus, both lesion-deficit studies and neuroimaging have strengths and weaknesses. Since these strengths and weaknesses are complementary, it is important to obtain insights into the recovery processes from both methods. Providing complementary evidence is critical for making treatment decisions, where the sooner the treatment is initiated, the better the outcome. In terms of weaknesses, lesion studies have traditionally been used to probe function, even though their real strength is in providing information on the brain structure (12). On the other hand, pathological lesions are typically complex, rarely conforming to a single neuroanatomical system, and patient profile usually contains more than one functional deficit (21, 25). This makes it difficult to confidently interpret the relationship between the functional deficit and the brain area supporting a particular function (25), which in turn makes it difficult to predict recovery. In addition, lesion studies cannot tell us whether the deficit is due to a loss of neuronal support for function (i.e., because of the lesion itself) or whether it is due to dysfunction of a larger network within which the area functions as a component (i.e., undamaged areas become unresponsive). Another problem related to lesion studies is that their attempts to abstract away from the structural data of a homogenous group of patients disregard the issue of how often the lesion to a specific area occurs without causing a particular deficit, or how often the deficit arises in the absence of lesion to that particular area (e.g., there is evidence on Broca’s aphasia without damage to Broca’s area). All these problems call for another method.

On the other hand, when it comes to studying brain’s functionality, fMRI is typically used with neurologically intact population. Most of the time experiments are conducted with psychology undergraduate students, which makes these studies only partially relevant for investigation of function recovery. This is mainly due to the fact that the effects of age or individual premorbid experiences on functional reorganization in the brain are far from clear at the moment. Ideally, neuroimaging studies with neurologically intact population would inform us on what areas normally participate in a specific function, lesion studies would reveal what areas are necessary for that function, while neuroimaging of recovery would provide information on the reorganization processes implicated in its recovery. Thus, investigating recovery of function in stroke patients requires insights from both lesion-deficit studies and neuroimaging of reorganization, regardless of whether it is spontaneous, drug induced or behaviorally triggered reorganization.

In summary, because fMRI is a noninvasive and powerful localization technique, it should complement lesion-deficit studies in order to provide insights on brain organization and functional changes that take place in the course of recovery. The future will certainly bring new and more powerful techniques that will advance the study of functional recovery and cerebral reorganization. For now, in order to guide rehabilitation, neuroimaging would need to refocus on imaging brain reorganization. At the same time, lesion-deficit approach would need to consider that improvement of rehabilitation practices for language recovery in stroke patients depends on combining lesion studies with new assessment methods and innovative neuroimaging techniques that allow on-line visualization of brain structure and its functionality.
REFERENCES


fMRI U OPORAVKU JEZIČKE FUNKCIJE NAKON MOŽDANOG UDARA
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SAŽETAK
Od nedavno je proučavanje jezika počelo da se sve više usmerava na merenje aktivnosti mozga pomoću imidžinga funkcionalnom magnetnom rezonanci (fMRI). Iako ova tehnologija postaje nezamenjivo istraživačko sredstvo u konstruisanju i testiranju neurokognitivnih teorija, ona još uvek nije sasvim iskorištena kada se radi o pitanju koje najviše zanima bolesnike sa oštećenjima mozga: Kako povratiti izgubljenu funkciju? Jedan od ciljeva ovog rada bio je da istraži potencijal fMRI u oporavku jezičke funkcije nakon moždanog udara, sa fokusom na ideju da fMRI omogućava procenu do koje mere je očuvana neka funkcija kod ovih bolesnika, što za dizajniranje individualnih tretmana može biti jednako važno kao i bihevioralne procene o gubitku funkcije.

Kljucne reči: fMRI, moždani udar, afazija, reorganizacija, neuroplastičnost