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Brain-Mapping Techniques for Evaluating Poststroke Recovery and Rehabilitation: A Review

James C. Eliassen, PhD,

Associate Director, Center for Imaging Research, and Assistant Professor, Department of Psychiatry and Neuroscience Graduate Program, University of Cincinnati Academic Health Center, Cincinnati, Ohio

Erin L. Boespflug, BS,

Graduate Student, Neuroscience Graduate Program, University of Cincinnati Academic Health Center, Cincinnati, Ohio

Martine Lamy, SB,

Graduate Student, Neuroscience Graduate Program, University of Cincinnati Academic Health Center, Cincinnati, Ohio

Jane Allendorfer, BS,

Graduate Student, Neuroscience Graduate Program, University of Cincinnati Academic Health Center, Cincinnati, Ohio

Wen-Jang Chu, PhD, and

Assistant Professor, Center for Imaging Research and Department of Psychiatry, University of Cincinnati Academic Health Center, Cincinnati, Ohio

Jerzy P. Szaflarski, MDPhD

Associate Director, Center for Imaging Research, and Associate Professor, Neuroscience Graduate Program, and Department of Neurology, University of Cincinnati Academic Health Center, Cincinnati, Ohio, and The Neuroscience

Abstract

Brain-mapping techniques have proven to be vital in understanding the molecular, cellular, and functional mechanisms of recovery after stroke. This article briefly summarizes the current molecular and functional concepts of stroke recovery and addresses how various neuroimaging techniques can be used to observe these changes. The authors provide an overview of various techniques including diffusion-tensor imaging (DTI), magnetic resonance spectroscopy (MRS), ligand-based positron emission tomography (PET), single-photon emission computed tomography (SPECT), regional cerebral blood flow (rCBF) and regional metabolic rate of glucose (rCMRglc) PET and SPECT, functional magnetic resonance imaging (fMRI), near infrared spectroscopy (NIRS), electroencephalography (EEG), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS). Discussion in the context of poststroke recovery research informs about the applications and limitations of the techniques in the area of rehabilitation research. The authors also provide suggestions on using these techniques in tandem to more thoroughly address the outstanding questions in the field.

Keywords

DTI; EEG; fMRI; MEG; NIRS; PET; poststroke recovery; rehabilitation; SPECT; stroke; TMS

Stroke affects over 780,000 people each year in the United States. Further, in 1999 more than 1,100,000 Americans reported negative impact of stroke on their daily lives including significant functional limitations.¹ Major efforts are underway to find better ways to improve the outcomes of stroke in the motor and cognitive arenas. Despite these efforts, many patients experience insufficient or only partial recovery; they are left with significant functional and/or cognitive deficits. Recent developments in neuroimaging have shed light on the reasons why some patients recover well while some do poorly. Although major progress in poststroke recovery research has been made with help from brain-mapping techniques, there are many obstacles that need to be addressed before we can develop better and more effective strategies that address the needs of stroke victims.

There is no consensus on the exact mechanisms involved in regaining the functions lost due to stroke. Major routes that have been implicated include changes at the molecular and cellular levels in the periinfarct and remote brain areas, involvement of the contralateral homologues via unmasking of the previously inhibited connections, and recruitment of other compensatory brain areas.²⁻¹² This review will focus on neuroimaging techniques that can be used to study these cellular and functional mechanisms of poststroke recovery.

In the healthy brain, mechanisms that inhibit axonal sprouting predominate. Inhibition of axonal sprouting is controlled by myelin-associated proteins, extracellular matrix proteins, and growth cone inhibitors. These growth-inhibiting factors continue to be expressed in traumatic brain injury but not in stroke. However, ischemic neuronal injury induces axonal sprouting.^{6, 10} In rodent models of stroke, ischemia initiates the formation of a glial scar directly adjacent to the damaged area in which numerous neurotrophic factors are expressed.^{2,4,13-15} Bordering this glial scar is a larger “growth-permissive zone” of the periinfarct cortex that expresses reduced levels of growth-inhibiting factors.^{4,5} In some human neuroimaging studies, increased signal in the periinfarct zone correlates with good functional recovery.¹⁶ According to experimental models of stroke, this improved recovery may be due to axonal sprouting.⁵

Variability in poststroke recovery has been suggested to be due, in part, to the influence of the directionality of axonal sprouting through activation of task-specific cortical areas. These experiences may help determine the destination of newly sprouting axons.^{2,3} For example, ischemic lesions in the adult rat cortex induce axonal sprouting that follows a specific biological time course; sprouting is “triggered” at 1–3 days after insult, “initiation and maintenance” of the sprouting response occurs between 7–14 days after insult, and at 28 days after stroke formation of new patterns of connections can be observed.^{4,5}

Most evidence indicates that functional recovery after stroke occurs primarily through reorganization of cortical activity in the vicinity of or connected to the infarct.⁴ Recent studies also suggest that recovery of motor function may involve alteration of intracortical wiring patterns. One potential role of these novel wiring patterns may be the recruitment of compensatory areas or areas of the brain that are not directly related to the damaged area. For example, Dancause et al. found evidence not only of axonal sprouting but also of the establishment of novel connections distant to the lesion and intracortical connections with the site of cortical injury.^{2,10} Further, Chen et al. have shown purine nucleoside inosine-stimulated projections from undamaged cortex into denervated regions of the mid-brain and spinal cord. This expansion coincides with improved behavioral performance.¹¹ The results of human neuroimaging studies mirror the results of animal studies suggesting the formation of new connections between the periinfarct cortex and the premotor, motor, and somatosensory cortical areas.¹⁷⁻²⁰ Further, in patients with subcortical stroke, the pattern of recovery first involves activation of both hemispheres of the cortex to sensory or motor stimulation of the affected limb, followed by reorganization and restriction of the activation pattern to the

infarcted hemisphere, contralateral to the affected limb.²¹ This reorganization is accompanied by increased activity in the supplementary motor areas of the damaged side.

Mechanisms of poststroke language recovery appear to be similar to the recovery after motor stroke; there is evidence of periinfarct zone and contralateral homologue contributions to language recovery. Saur et al. suggest that language reorganization after stroke occurs in three phases.⁹ First, there is reduced activation of remaining areas followed by upregulation of the entire language network, including contralesional homologues, and eventual “normalization of activation” or re-shifting of activation to the hemisphere affected by stroke. It is not clear if this finding is affected by the size of the lesion, because larger areas of damage were found to be associated with increased activation of the contralateral cortex. However, in some patients, improvement in language function after stroke relates to contralateral shift and not periinfarct zone recovery.²² Recent studies in younger patients who suffered peri- or prenatal stroke in the dominant left hemisphere show that recovery of language functions after stroke may result from transfer of these functions to the contralesional, healthy homologues.^{12,23} For example, Tillema et al. show that activation of anatomically identical areas in the unaffected hemisphere follows perinatal left middle cerebral artery stroke.¹² This mechanism may be specific to children; adults do not recover after stroke as well as children and are usually left with more deficits²⁴ despite reliable shifts of the language-related functional magnetic resonance imaging (fMRI) signal to the contralateral homologues.^{25,26} In the case of adults, the recovery of function may depend more on the periinfarct areas than in children.¹⁶ Further support for this age difference arises from functional neuroimaging studies showing that language in children becomes more left-hemispheric with age.^{27–29}

As this brief overview suggests, multiple mechanisms may exist for recovery of function after stroke. Evidence shows that recovery depends on the involvement of areas unaffected by stroke, either proximal to the damaged areas or in contralateral homologues. Among the many variables that influence recovery, the ones discussed here include the age at the time of the stroke, the size of the stroke, and the poststroke environment, including training or therapy.

Brain-mapping techniques have dual roles in tracking recovery after stroke. They provide information about the cellular and molecular processes arising naturally during stroke recovery and allow for the investigation of poststroke brain plasticity that may result from therapeutic interventions. Although functional changes are likely an expression of underlying cellular changes, here we define functional changes to be those that are observed either by manipulating behavior during brain mapping or by measuring regional brain metabolism if no task is being performed. The cellular and molecular mechanisms discussed previously – dendritic sprouting, axonal regrowth, and cell migration – would change the microscopic structure of brain tissue. Magnetic resonance spectroscopy (MRS), diffusion-tensor imaging (DTI), and ligand-based positron emission tomography (PET) or single-photon emission computed tomography (SPECT) techniques can provide insight into these cellular processes. DTI enables the visualization of white matter fiber tracts and the quantification of fiber tract integrity.³⁰ MRS allows for the detection and quantification of specific biochemicals in the brain, including a limited number of compounds with either a hydrogen (proton) or phosphorus spectroscopic signature. Finally, PET and SPECT offer the opportunity to investigate the binding of specific neurotransmitter-like ligands to cell surface proteins, such as the GABA receptor or the dopamine transporter.

Brain-mapping techniques that measure brain function during recovery and rehabilitation include regional cerebral blood flow (rCBF), regional metabolic rate of glucose (rCMRglc) PET or SPECT, fMRI, near infrared spectroscopy (NIRS), electroencephalography (EEG), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS). The word function, as used here, implies either the manipulation of a person’s behavior in order to

influence signal amplitude or the measurement of regional blood flow or metabolism in the absence of behavioral manipulations. In either case, the signal is assumed to relate to the ability of nearby neurons to process information, that is, to function. The way in which brain function is assessed depends upon the technique in question. For fMRI, function is assessed by measuring changes in blood flow that vary with the changing metabolic demands of neurons nearby. PET can measure not only blood flow but also oxygen and sugar metabolism directly. TMS can be used to determine the electrical excitability of brain tissue by measuring the muscular response to stimulation. EEG and MEG measure an electrical or magnetic signature of cortical pyramidal neuron excitation. NIRS senses the variation in intracranial absorption and reflectance of two specific near-infrared wavelengths of visible light, which are differentially absorbed by oxy- and deoxy-hemoglobin. Roughly speaking, fMRI, PET, and NIRS measure blood flow-related signals, whereas EEG and MEG record brain electrical activity and TMS directly induces brain electrical activity.

The specific research question dictates the experimenter's choice of technique. Brain condition can be examined at one or more points during rehabilitation or recovery; three basic approaches exist. The first approach involves assessing the severity of brain injury at the outset of the experiment as a predictor of recovery or rehabilitation success. For example, TMS resting motor threshold at 24 hours following a stroke has been shown to predict the degree of recovery, with normal resting thresholds predicting good outcome and abnormal thresholds predicting poor outcome.³¹ The second approach assesses brain function at study termination to define attributes associated with better or worse outcomes, that is, markers of recovery.¹⁹ In the third approach, by combining before and after measurements, one can identify longitudinal changes that track recovery.^{29,32} The study of stroke rehabilitation is relatively new, having suffered from the longstanding view that lost functions were not recoverable. The field is rapidly evolving, but there are few standardized approaches to the use of brain-mapping methods. This article is intended to illustrate ways in which several widely used brain-mapping techniques may aid stroke rehabilitation research.

Details of Cellular and Molecular Techniques

DTI

DTI allows for the visualization of white matter fibers and the quantification of white matter tract integrity. In essence, this technique estimates the directional structure of white matter fiber tracts, that is, the restriction to free diffusion of water in all directions (Figure 1). This relatively new MRI technique can be used to investigate poststroke brain plasticity by assessing structural changes in white matter fiber tracts following stroke and the relationship of these changes to functional recovery. The premise of this technique is based on the fact that, in an unobstructed sphere, water diffuses equally in all directions or isotropically. DTI quantifies the difference in directionality of the diffusion experienced by water molecules with respect to the white matter fiber tracts or the degree of diffusion anisotropy. Water molecules diffuse more freely along white matter fiber tracts and through the nerve cell axons than orthogonal to the tracts, where neuron and glial cell walls obstruct passage (high diffusion anisotropy; Figure 1A).^{30,33,34} The tensor theory is used in DTI to characterize the molecular diffusion of water in white matter. A tensor is a mathematical construct describing the three-dimensional properties of an ellipsoid (Figure 1B). In DTI, diffusion measurements are taken in multiple directions, and tensor decomposition is used to calculate the diffusivities that are parallel and orthogonal to the white matter fibers. These diffusivity measures are expressed using various indices such as the mean diffusivity, also referred to as trace, apparent diffusion coefficient (ADC), or trace apparent diffusion coefficient (trADC). trADC reflects average level of water diffusion in all directions in a voxel; fractional anisotropy (FA) reflects the directionality of water diffusion or the degree of anisotropy in a voxel.^{33,35,36} In white matter, diffusion anisotropy is high (high FA values); but in gray matter and cerebrospinal fluid (CSF),

diffusivity is similar in all directions and diffusion anisotropy is low (low FA values). A reduction of a previously high fractional anisotropy reflects a decline in white matter tract integrity.³⁷

Following stroke, focal reductions in white matter tract integrity result in FA value asymmetries between the two hemispheres^{38–44} and in reduced FA values in patients compared to matched regions in control subjects.^{45–48} Observations of poststroke reductions in diffusion anisotropy are used to investigate axonal damage and its ability to predict functional recovery. DTI studies performed at multiple times following stroke report retrograde and/or anterograde degeneration within the corticospinal tract, as indicated by the progressive decrease in FA.^{38,42,44,47} Reductions in FA are negatively correlated with reductions in neurological deficits and improved motor functions.^{38,42,47} Furthermore, reduced FA values in the affected hemisphere (compared to the unaffected hemisphere) within 2–4 weeks of stroke onset are associated with poor motor recovery 3 months post stroke, indicating that the degree of FA reduction may be predictive of motor function outcome.^{38,41,44,45,49}

Thalamic hypometabolism and cortico-spinal tract integrity also are associated with poststroke motor recovery.⁵⁰ Herve et al. performed DTI at 1 week and 6 months following stroke to investigate changes in thalamic metabolism associated with infarcts of the middle cerebral artery.⁵¹ They report increased mean diffusivity in the ipsilateral thalamus located away from the infarct site but no corresponding change in FA, which may be due to a lack of fiber bundles oriented in parallel within the thalamus. These authors also note a trend toward reduction in ipsilateral thalamic volume,⁵¹ consistent with previous investigations reporting progressive atrophy of the ipsilateral thalamus.^{52,53} However, future studies are necessary to elucidate the role that poststroke alterations in thalamic diffusivity have in relation to motor recovery.

A handful of studies have also used DTI to study poststroke aphasia, which occurs in about 20%–50% of stroke patients.^{54,55} A case study by Selnes et al. reports no impairments in language repetition or comprehension in a patient with a left arcuate fasciculus lesion as determined by DTI 2 years following stroke.⁵⁶ However, in a larger study of 27 patients who had suffered from left hemisphere stroke, Breier et al. finds that lower FA values in the superior longitudinal and arcuate fasciculi of the left hemisphere correlate with decreased ability to repeat spoken language and that lower FA values in the left arcuate fasciculus also correlate with deficits in comprehension.⁵⁷ Given the high prevalence of language dysfunction that occurs following stroke, the relationship between DTI measures and poststroke aphasia warrants further investigation.

In addition to quantifying the architectural integrity of white matter tracts and other brain tissues, DTI tractography allows for the visualization of the directionality of different fiber systems in two dimensions by using a color convention such as red, green, and blue to represent fibers crossing from left to right, anterior to posterior, and inferior to superior, respectively,⁵⁸ as well as the three-dimensional reconstruction of white matter tracts (see refs. ³⁵ and ⁵⁷ for review). Researchers use DTI tractography to investigate different types of fiber tract damage resulting from stroke and how different types of damage can affect or predict functional recovery. Cho et al. performed DTI within 7–30 days following stroke and used DTI tractography to categorize corticospinal tract (CST) damage into four types: (A) CST is preserved around the infarct and originates from the primary motor cortex; (B) CST is preserved around the infarct but does not originate from the primary motor cortex; (C) CST is interrupted at the infarct, losing its cortical connections; and (D) extended CST degeneration such that the CST does not reach the site of infarct.^{59,60} Motor function was tested 6 months after stroke, and patients with type D damage exhibited the least amount of recovery, whereas those with type A damage recovered the most. These results are consistent with previous findings that patients with disrupted white matter tracts, in which the CST fibers descending from the motor

cortex to the site of infarct are undetectable or the CST does not reach the infarct site, have worse clinical prognosis than patients with white matter tracts that are displaced but otherwise preserved.^{40,61,62}

Similar to the studies investigating FA reductions in poststroke white matter tract degeneration and increased mean diffusivity in the thalamus after stroke, DTI tractography at multiple time points provides insight into the evolution of structural changes during recovery. Jang et al. show that at 3 weeks post stroke, the affected regions of the internal capsule and corona radiata have lower FA and higher ADC values compared to controls, and the corticospinal tract descending from primary motor cortex in the affected hemisphere is either disrupted or faint. At 5 months post stroke, motor function is markedly improved, and there are no significant differences in FA or ADC values compared to controls.⁶³ In addition, corticospinal tract fibers descending from primary motor cortex are observed on the affected side (at the more stringent threshold), demonstrating the capacity of the CST to recover from damage.⁶³

Although DTI is a relatively new technique, it can make important contributions to poststroke recovery research by providing quantitative information regarding structural integrity. The application of DTI tractography in the localization of stroke lesions relative to motor, sensory, and cognitive pathways and in the assessment of axonal degeneration allows for more accurate prognosis of long-term recovery and/or disability. In combination with other techniques (e.g., fMRI), DTI can provide a clearer understanding of how tissue integrity allows for functional recovery. Complementary use of DTI and other brain-mapping techniques in future studies will further our understanding of the role of fiber tract integrity in poststroke recovery and allow for advancements in providing targeted and more effective stroke therapies.

Limitations of DTI

As with any MRI technique, the use of DTI is limited to individuals who do not have ferrous metal objects in their bodies. Presence of even non-ferrous metal objects in the head, such as a titanium aneurism clip, would interfere with the DTI signal and exclude a person from this type of imaging. The DTI signal is also susceptible to distortion due to head movement. The quality of the DTI image is therefore dependent on the ability of an individual to keep his or her head as motionless as possible during image acquisition. This ability varies with each individual and is limited by his or her tolerance for discomfort and immobility. There is also the issue of improving the signal-to-noise ratio to obtain more precise measures of anisotropy and more accurately track white matter fibers. Unfortunately, methods for improving the signal-to-noise ratio lengthen the image acquisition time providing an increased opportunity for head movement and discomfort. DTI tractography is only as accurate as permitted by image resolution and the algorithms for calculating fiber orientation, and fiber orientation may be heterogeneous inside a single voxel at low resolution. Because of these technical limitations, there is ongoing development of methods to account for head movement, efficiently improve signal-to-noise ratio, and refine fiber tracking algorithms to better resolve fiber orientation heterogeneity. Despite its limitations, DTI has very relevant applications in the area of stroke recovery and rehabilitation, allowing for noninvasive investigations of brain tissue integrity and white matter fiber tract structure following stroke.

MRS

MRS is a noninvasive imaging technique that allows for measurements of specific brain metabolites. In stroke research, MRS can be used to investigate biochemical changes in the brain during acute, subacute, and chronic stages, as well as to measure potential markers of recovery. [¹H]-MRS and [³¹P]-MRS are commonly used in human research. [³¹P]-MRS is able to measure high-energy phosphates in living tissue, for example, phosphocreatine (PCr), phosphomonoesters (PME; e.g., phosphocoline), phosphodiesteres (PDE; e.g.,

glycerophosphocholine), inorganic phosphate (Pi), and ATP. [³¹P]-MRS is also able to measure intracellular pH using the pH-dependent Pi chemical shift. These high-energy phosphates can be used as indicators of altered bioenergetics associated with stroke or poststroke recovery. [¹H]-MRS is able to measure a variety of marker compounds that can indicate loss or damage to a specific cell type. These marker compounds include N-acetyl aspartate (NAA), lactate (Lac), choline (Cho), creatine and phosphocreatine (Cr/PCr), myo-inositol (mI), and amino acids such as glutamate (Glu) and glutamine (Gln) and the neurotransmitter -amino butyric acid (GABA). [¹H]-MRS is most commonly used in stroke research, largely due to its clinical availability and increased sensitivity over [³¹P]-MRS. [³¹P]-MRS also presents some additional technical challenges over [¹H]-MRS.

MRS can measure pathophysiological processes consequent to a stroke or other brain damage. These processes include a failure of energy metabolism, edema, and breakdown of neuronal membranes. In ischemic stroke, a reduction of oxygen availability to brain tissue triggers a failure of energy metabolism (decreased PCr levels in [³¹P]-MRS), failure of ATP-dependent pumps followed by lactate surge (increased Lac levels in [¹H]-MRS), and acidosis (decreased Pi chemical shift vs. PCr in [³¹P]-MRS) in the affected tissue. These processes induce a cascade of events including a decrease in intracellular calcium concentration, free radical formation, membrane breakdown, and, ultimately, cell death. Spectroscopic techniques including [¹H]-MRS and [³¹P]-MRS are able to detect this failure of energy metabolism as well as its direct (acidosis and increases in lactate levels) and indirect (membrane breakdown and demyelination) effects, particularly during the acute stages following a stroke. These techniques are valuable tools to investigate the metabolic changes induced by rehabilitation in poststroke recovery.

[¹H]-MRS—N-acetyl aspartate (NAA) is predominantly found in the axons and nerve processes in the human brain.⁶⁴ The exact function of NAA remains unknown, but it is thought to be a marker of neuronal integrity. Specifically, NAA levels may provide markers for energy storage or indicate mitochondrial function.^{65,66} Decreased NAA levels usually indicate neuronal loss or damage to neuronal mitochondria. Longitudinal studies of stroke in humans demonstrate an initial decline in NAA in the affected area followed by a continuing fall of NAA during the first week after stroke onset.^{67–69} This work suggests ongoing ischemia even at 1 week after stroke onset,⁶⁹ which may be important for the timing of therapeutic interventions. Therefore, NAA may become a valuable biomarker for correlating poststroke recovery with neuronal viability in the ischemic penumbra.

Creatine (Cr) and phosphocreatine (PCr) have overlapping spectra when measured by [¹H]-MRS and therefore are usually indicated as a total creatine (Cr+PCr). Total creatine acts as an energy buffer and phosphate transport system in both neurons and glial cells in the brain. Because Cr/PCr cannot be easily distinguished using [¹H]-MRS, this technique is rarely used to study phosphocreatine metabolism directly and is instead used as a marker of energy availability. However, the use of higher field MRI scanners (≥ 3 T), and the development of advanced software such as LCMoDel,⁷⁰ may provide an avenue to individually quantify total creatine using [¹H]-MRS. Today, [³¹P]-MRS techniques are more commonly used to study phosphocreatine and its relationship to energy metabolism.⁷¹ It has been suggested that the complete absence of total creatine measured by [¹H]-MRS indicates necrotic tissue, although findings of reduced total creatine levels are difficult to interpret.⁷² Reductions in total creatine have been found following infarction and continue to decline up to 10 days following stroke onset.⁶⁹ Changes in the total creatine peak may be due to changes in the equilibrium of the creatine kinase metabolic reaction or a change in cell population. Specifically, glial cells have been shown to have higher levels of creatine than neurons.⁷³ Therefore, changes in total creatine may reflect a change in the proportion of neurons and glia in a particular region (e.g., formation of a glial scar). Finally, total creatine has been shown to be greater in gray matter as

compared to white matter.⁷⁴ Thus, for clinical applications such as stroke recovery, it is important that the tissue content is determined in order to properly correct the metabolite ratios.

Choline (Cho) has been proposed as a marker of cell membrane integrity. In healthy brain tissue, the choline peak is thought to reflect the levels of two compounds involved in membrane synthesis and degradation: glycerophosphocholine and phosphocholine.⁷⁵ Changes in the choline peak have been noted after brain infarction,^{67–69} although the direction of these changes is inconsistent. Increases in the choline peak are thought to be reflective of the breakdown of cell membranes. For example, demyelination is associated with an increase in choline-containing metabolites. The neurobiology behind the decreases in choline metabolites remains unclear.⁷⁶

Although lactate (Lac) is not normally detected in the brain, it is an excellent indicator of metabolic status. Lactate concentration rises in a tissue when it is produced at a rate that exceeds the tissue's ability to degrade it or remove it from the blood stream. A rise in brain lactate following cerebral ischemia has been noted in several studies and continues to persist weeks or even months after a stroke.^{67–69} Elevated lactate levels are found in regions adjacent to infarcted areas and even in the contralateral hemisphere of patients with very large infarcts.⁷⁷

Neurotransmitters such as gamma-aminobutyric acid (GABA), glutamate (Glu), and its substrate glutamine (Gln) play an important role in the pathophysiology of stroke and stroke recovery. These amino acids are excellent targets for study with [¹H]-MRS due to their role in neurotransmission (both excitatory and inhibitory), metabolism, and excitotoxicity. However, their concentration of GABA is low in the human brain, and the considerable overlap of Glu and Gln signals have made the measurement of GABA and GLU in stroke patients difficult with current [¹H]-MRS methods. The measurement of Glu and GABA is possible with advanced MRS methods such as spectral editing, multiple-quantum filter methods, and the echo time (TE averaged method).^{78,79} Because these advanced MRS methods require a great degree of technical expertise, most neurotransmitter research in stroke to date has been limited to animal or cell models. New MRS techniques have been developed to better detect these low concentration metabolites,^{78,79} which may open further avenues for research into the role of these neurotransmitters in poststroke recovery.

[¹H]-MRS can be used as a predictor of clinical outcome—One of the best measures of clinical outcome from stroke is the volume of the infarct, as determined by T2-weighted MR imaging.⁸⁰ However, it has been found that the combination of NAA concentration and infarct volume is a better predictor of poor poststroke outcome than either NAA concentration or infarct volume alone.⁸¹ Preliminary evidence suggests that the best clinical recovery is seen in patients with relatively normal NAA, Cr/PCr, and Cho peaks.⁸²

Stroke is frequently associated with various comorbidities, including depression. Although, it affects 16%–72% of stroke survivors,⁸³ the etiology of poststroke depression is poorly understood. [¹H]-MRS can and has been used to study this comorbidity of stroke. [¹H]-MRS studies suggest that early onset (within 10 days) poststroke depression is associated with increased glutamate levels in the frontal lobes.⁸⁴ This may reflect abnormalities in glutamatergic transmission during the early poststroke period and have implications in the development of new therapeutic interventions. [¹H]-MRS has also been used to study diaschisis, a common occurrence after infarction that results in brain dysfunction from interregional disconnection. Diaschisis is commonly defined as reduced regional brain functioning due to deafferentation or interruption of normal inputs to a region not directly affected by the stroke. The resolution of diaschisis is an important component of recovery from stroke.⁸⁵ The presence of diaschisis is associated with increased Cr/NAA ratio and reduced

rCBF, which may serve as useful markers for assessing the benefit of therapeutic interventions.
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[¹H]-MRS in stroke rehabilitation—Little work has been done to directly measure the effects of rehabilitation and therapeutic interventions on metabolic changes during stroke recovery. However, the available [¹H]-MRS studies have demonstrated that metabolite concentrations can be used as a marker of future clinical outcomes, as well as an indicator of cerebral reorganization and recovery. For example, it has been shown that Cr/NAA ratio is increased in the ipsilateral hemisphere 6 weeks after stroke.⁸⁷ At 1 year after stroke, there is an increase in rCBF and Cho/Cr ratio in the contralateral hemisphere and a reduction of the previously elevated Cr/NAA ratio in the ipsilateral hemisphere.⁸⁷ Although it is unclear how these findings directly relate to degree of recovery, they provide insight into how neurochemistry in infarcted regions changes over time. These findings may be used as markers of cerebral reorganization and neural plasticity, though further study must be done to better characterize the relationship between changes in these compounds and changes in cell membrane, synaptic integrity, and, ultimately, functional recovery.

[³¹P]-MRS in stroke research—As illustrated in Figure 2, [³¹P]-MRS is well suited for investigations of key players in energy metabolism that may change as a function of stroke and poststroke recovery including ATP, phosphocreatine (PCr), and inorganic phosphate (Pi). PCr has been recognized as an important buffer to maintain stable levels of ATP in the brain and other tissues. Because the synthesis of PCr in the mitochondria is very sensitive to the supply of blood to the tissue, reduced PCr/ATP ratios (due to depleted PCr and unchanged ATP levels) can be used as an indicator of ischemic severity. Additionally, decreased ATP/Pi and increased PCr/Pi ratios have been proposed as markers for the severity of cerebral damage and may be useful indices of clinical outcomes.^{88–91} In general, it has been found that subacute and chronic infarcted regions show a dramatic reduction in overall levels of phosphorous metabolites.⁷⁶

In addition to the ability to measure bioenergetic molecules, [³¹P]-MRS can also be used to study phospholipids. Commonly studied phospholipids present in neuronal and glial membranes include the phosphodiester (PDE) and phosphomonoester (PME). Changes in phosphodiester and phosphomonoester ratios may be an index of phospholipid turnover or metabolism.⁹² Finally, [³¹P]-MRS investigations have demonstrated that acidosis is present in infarcted regions in the subacute stage, whereas alkalosis is present at a more chronic stage.⁷⁶ Persistent alkalosis is a common finding in chronic stroke⁹³ and is thought to result from damage to pH regulatory systems^{94,95} or proliferation of phagocytes in the infarcted region.⁹⁶ Further research is needed to characterize the effects of stroke on pH levels and the implications of poststroke acidosis/alkalosis for stroke recovery and rehabilitation.

[³¹P]-MRS in stroke recovery and rehabilitation—Although we are not aware of any published reports of poststroke rehabilitation research utilizing [³¹P]-MRS, this technique has demonstrated promise for the study of the brain's resting-state metabolism. [³¹P]-MRS allows for the assessment of membrane breakdown, demyelination processes, and intracellular energy metabolism and may prove to be a sensitive marker of recovery and plasticity in the brain. For example, we suspect that poststroke recovery relies on the return of neuronal activity, a process that depends on efficient ATP synthesis and availability. The ATP/ADP ratio may be an indicator of the normalization of neuronal function in the affected brain regions, such as the ischemic penumbra. Although ADP levels cannot be directly measured by [³¹P]-MRS techniques, they can be determined by using a combination of [³¹P]/[¹H]-MRS. Future studies combining these two techniques would allow for further characterization of recovery processes following stroke. These markers could prove useful in assessing the effects of rehabilitation on brain metabolism and vice versa.

Limitations of MRS in Stroke Recovery

Although MRS techniques show great promise in clarifying the neurochemical changes that occur with stroke and stroke recovery, technical limitations affect its widespread applicability. One particular challenge with MRS research as it is applied to stroke is that baseline neurochemistry, especially as it relates to healthy aging, is not fully understood. Furthermore, acquisition and analysis of MRS data require considerable technical expertise and equipment. For example, the use of higher field MRI systems (≥ 3 Tesla) is required for more accurate metabolite quantification. In addition, although whole-brain MRS measurements can be acquired (e.g., 2D CSI [^1H]-MRS), many MRS studies to date utilize a region of interest (ROI) approach for data collection and/or analysis. This ROI approach requires technicians with good knowledge of neuroanatomy for proper ROI placement and limits data collection to regions hypothesized to have been directly affected by stroke (e.g., the penumbra) or regions thought to be involved in poststroke recovery (e.g., downstream cortical areas). This ROI approach limits generalizability of results to a larger population and is unable to examine changes in other regions of the brain. Voxel-wise approaches (such as those used in fMRI techniques) that can examine whole-brain chemistry will greatly aid in the advancement of this field. Nevertheless, MRS remains a sensitive measure of neurochemistry *in vivo* and should continue to provide valuable information on how neurochemistry in the brain changes with stroke recovery and rehabilitation.

Ligand-based PET and SPECT

Conducting PET and SPECT imaging studies using radioactively labeled neurotransmitters or transporter ligands allows the examination of the density and regional distribution of specific cell surface proteins in the brain. Information on receptor and transporter distribution or density can indicate the signaling viability of nerve cells in a given brain region. Thus, ligand-based nuclear medicine techniques enable quantitative description of cellular neurotransmitter systems. Currently, ligand-based nuclear medicine techniques are not in widespread use in rehabilitation research but appear to have a niche for examining acute stroke. For example, a search of PubMed for “(PET OR SPECT) AND (binding OR ligand) AND brain AND stroke” yields 119 citations as of February 2008. Adding “AND (rehabilitation OR recovery)” decreases that number to four, all PET studies, of which two used rCBR or rCMRglc (discussed below), one examined [^{18}F]-fluoromisonidazole binding to “hypoxic but viable tissue,”⁹⁷ and one reviewed human and cat literature on, among other things, flumazenil, “a marker of neuronal integrity” that binds the GABA receptor.⁹⁸ Although this simplistic search approach suggests that few researchers use ligand-based PET or SPECT to examine stroke recovery or rehabilitation, there is a substantial body of stroke research. Arguably, these techniques will contribute to stroke rehabilitation research as interest increases in the cellular processes these ligands characterize. Therefore, we will discuss the questions these techniques could address.

A wide variety of PET and SPECT ligands are available to the research community. Even though diagnostic and treatment monitoring procedures are the primary clinical uses, a significant number of ligands have been developed to bind structures of interest in the brain (cf., ref. ⁹⁹). PET ligands are most commonly labeled with ^{18}F or ^{11}C depending upon the chemical makeup of the molecule to be labeled, whereas SPECT ligands are often labeled with ^{123}I or ^{99}Tc . All major neurotransmitter systems can be examined with one or more ligands. The gamma-aminobutyric acid (GABA) receptor, which has been useful in studies of epilepsy and stroke, has been labeled with ^{123}I -iomazenil or ^{18}F -flumazenil and used to visualize stroke extent.^{100, 101} Moreover, evidence exists that the prognosis of aphasia recovery is related to the density of GABA receptor binding in language areas.¹⁰² Both dopamine D1 and D2 receptors can be visualized with PET and SPECT.⁹⁹ The D2 form selectively binds ^{11}C -raclopride,¹⁰³ ^{18}F -fallypride,¹⁰⁴ and ^{123}I -iodobenzamide.¹⁰⁵ The serotonin (5HT)-2A receptor selectively binds ^{18}F -altenserin, ^{18}F -setoperone, or ^{123}I -2-

ketanserin, while PET ligands exist for the 5HT-1A receptor.⁹⁹ PET and SPECT ligands also exist for the dopamine and serotonin transporters. For the 5HT transporter, these include ¹²³I-ADAM,¹⁰⁶ ¹¹C-MADAM,¹⁰⁷ and ¹¹C-DASB.¹⁰⁸ For the dopamine transporter, examples include ⁹⁹Tc-TRODAT,¹⁰⁹ ¹²³I-βCIT,¹¹⁰ and ¹⁸F-FPCIT.^{111,112} Ligands also exist for a variety of other receptors, including nicotinic and muscarinic acetylcholine receptors, adenosine receptors, opioid receptors, and many others.⁹⁹ Dopamine function, being important to movement coordination in the striatum, could be affected by stroke, and dopamine imaging might provide a measure of improvements with rehabilitation. GABA has been suggested as a marker of neuronal integrity as it may be neuron-specific.¹¹³ Ligand-based imaging is likely to become more widespread in rehabilitation research, because it indicates the functionality of brain tissue with respect to specific neurotransmitter systems. In addition to GABA and potentially dopamine, other ligands may inform stroke research, although the role of other neurotransmitter systems in recovery is not yet clear.

Details of Functional Techniques

The next section discusses the brain-mapping techniques that measure function through their dependence upon, influence over (e.g., TMS), or assumed relationship to behavior (resting state metabolic measures). PET, fMRI, NIRS, MEG, and EEG all assess changes in brain function by determining changes in signal amplitude that result from experimenter-directed manipulations of behavior or resting state metabolism. TMS, by contrast, affects behavioral output directly by stimulating brain tissue with a rapidly fluctuating magnetic field that induces electrical activity in the underlying neurons. Approaches that depend on behavioral manipulation usually compare relative signal changes between a control and an active condition, whereas metabolic measures can indicate absolute levels of function in a particular condition.

PET and SPECT

In addition to their uses for detecting neurotransmitters, PET and SPECT also can be used to measure neurophysiological processes that relate to metabolism. These include regional cerebral blood flow (rCBF), regional metabolic rate of glucose (rCMRglc), and regional metabolic rate of oxygen (rCMRO₂). Two methods for measuring cerebrovascular stress reactivity also exist, CO₂ inhalation or acetazolamide (Diamox) challenge. These challenge methods increase CO₂ partial pressure globally leading to widespread vasodilation and can be used to distinguish continued ischemia in the penumbra from diaschisis or to determine whether tissue can respond to increased metabolic demand.^{87,114} Cerebral perfusion can be examined indirectly with the lipophilic SPECT radiopharmaceuticals ¹²³I-IMP, ^{99m}Tc-HMPAO, and ^{99m}Tc-ECD,¹¹⁵ which cross the blood-brain barrier and diffuse into healthy brain tissue at a rate proportional to regional blood flow.⁸⁷

The various SPECT and PET tracers interact with the brain differently but share the principles of radioactive decay as their detection method. Some tracers accumulate in the brain over time, and others pass through the brain only briefly. For instance, a widely used PET radiopharmaceutical is the radioactive sugar analogue 2-deoxy-2-¹⁸F-D-glucose (FDG), which assesses rCMRglc. Active cells in the body (e.g., neurons) take up FDG, but it is only partially enzymatically digested and accumulates within active cells over time. The more active the cell, the more FDG it accumulates over time (Figure 3). ¹⁸F is radioactive and decays into oxygen with a half-life of 109 minutes. The decaying fluorine atom emits a positron (antimatter electron) that, upon collision with real matter, releases two gamma rays that are detected by the PET “camera.” In an analogous manner, rCBF changes can be assessed using oxygen-15 labeled water or inhaled oxygen with PET or ¹³³Xe inhalation and SPECT. ¹⁵O has a short half-life of 2 minutes, restricting its use to medical centers with an on-site cyclotron. ¹³³Xe has a much longer half-life of 5 days, but it has rapid clearance from the brain. Once injected

or inhaled, these radiotracers enter the blood and travel in greater quantity to active brain regions. The radioactive decay events are then detected in greater number coming from active brain regions.

Metabolically based techniques define brain activity irrespective of cognitive manipulations that might engage or disengage particular brain regions. Because of tissue damage, brain regions within or near a stroke, as well as distant to it, exhibit reduced metabolism. The stroke region exhibits reduced signal due to cell death, while nearby regions, like the penumbra, may exhibit reduced metabolism for other reasons. Acutely, the penumbra can suffer from ischemia, albeit less severe than the region of the stroke. In the longer term, the penumbra may exhibit reduced metabolism due to the loss of cellular inputs from the stroke region. Distant cortical sites may also exhibit metabolic decreases due to a reduction in inputs from the stroke region (i.e., diaschisis). For instance, cortical hypometabolism resulting from thalamic stroke appears in PET images but resolves with behavioral recovery.^{116,117} Contralateral hemisphere oxygen metabolism in regions homologous to the stroke can be reduced, possibly as a result of degeneration of inputs from the damaged hemisphere.¹¹⁸ In addition, the degree of reduced cortical perfusion, in one case due to striatal or capsular strokes, correlates with aphasia severity.¹¹⁹ In a 6-month longitudinal study of natural aphasia recovery, the authors initially observed widespread depression of rCMRglc with ¹⁸FDG PET in both cortical hemispheres up to 2 weeks after stroke. After 6 months, this metabolic reduction reversed significantly, suggesting that metabolic increases correlate with aphasia recovery.¹²⁰

In addition to measuring basal metabolic function, which has a presumptive relationship to brain function, rehabilitation paradigms often use neuroimaging to relate brain activity changes to therapeutic success. Rehabilitation studies using rCBF, rCMRglc, or rCMRO₂ take generally similar approaches. An experimenter administers the tracer to a patient and allows that patient to perform a motor or language task. For rCBF or rCMRO₂, the task would be performed concurrently or immediately following tracer administration. Successive tracer administrations can be performed while the experimenter systematically varies the behavioral task (i.e., alternating blocks of rest and active movement). For rCMRglc, there is less of a time constraint. The behavioral paradigm may take several minutes and then images can be taken of the accumulated FDG throughout the brain. Following a washout period, this cycle can be repeated. With blood flow and oxygen metabolism measures, repetitions can be greater in number and much quicker. In a rehabilitation paradigm, the question of interest would be whether the patterns of rCBF, rCMRglc, or rCMRO₂ in the brain change systematically as a function of treatment. Early studies provided some evidence that therapy was correlated with behavioral improvement and a corresponding metabolic recovery.^{121,122} Current approaches actively manipulate behavior during scan acquisition. Researchers can relate activation changes to specific behavioral improvements. This approach has enabled the demonstration of homologous nondominant hemisphere participation in language rehabilitation,¹²³ bilateral sensory and motor cortex reorganization following specialized arm movement training but not a control rehabilitation paradigm,¹²⁴ and the effect of constraint-induced movement therapy in chronic stroke patients.¹²⁵ The number of PET and SPECT imaging studies of the effects of rehabilitation have increased enough in recent years to warrant review of therapeutic findings, which also include fMRI research.¹²⁶

Limitations of PET and SPECT

PET and SPECT both have advantages in that the degree of radioactivity of the injected sample often can be precisely measured and quantified allowing for a precisely defined rate of glucose metabolism, blood flow, or oxygen consumption to be determined. Quantifying the rate may involve arterial blood sampling, which elevates the invasiveness of the technique. On the other hand, these techniques involve low doses of radiation and may include vascular catheterization.

Both PET and SPECT are limited in their temporal resolution by the sensitivity of the radiation detectors. For PET, the acquisition time may be as little as 40 seconds with some rCBF techniques, while SPECT and rCMRglc take longer because of the need to accumulate tracer before imaging takes place. ^{15}O paradigms require an on-site cyclotron owing to the 2-minute half-life of this isotope. ^{18}F , ^{99}Tc , and ^{123}I all have longer half-lives allowing for more flexibility in the image acquisition timing. In general, however, PET and SPECT techniques have very low temporal resolution and have medium spatial resolution on the order of 5–10 mm.

Functional MRI

MRI is based on the absorption and emission of radio waves by tissues placed into the magnetic field of the MRI scanner. When materials are placed in a magnetic field, protons in the material line up with the field like tops spinning in a gravitational field. Once the protons line up with the magnetic field, they are able to absorb radio waves. Like a playground swing where one pushes at the rate the swing oscillates, protons in a magnetic field only absorb radio waves at their resonant frequency, which depends upon the magnetic field strength (63 MHz for a 1.5 Tesla MRI, 172 MHz for a 4 Tesla MRI). Because the predominant sources of protons in the human body are water and fat, MRI mainly measures how water and fat protons behave in different tissues.

The tissue of interest for fMRI is blood. It was discovered in the early 1990s that water in blood behaves differently, from an MRI standpoint, near oxygenated compared to de-oxygenated hemoglobin.¹²⁷ fMRI developed from the combination of this technique and the adaptation of suitable mathematics.¹²⁸ fMRI is now a widely used brain-mapping technique. The fMRI signal measures something akin to rCBF. A change in blood oxygenation leads to a change in blood oxygenation level dependent (BOLD) signal. Regional cerebral blood flow, blood volume, and oxygen extraction rate all affect the BOLD signal,¹²⁹ so the BOLD signal is not a pure measure. Although increased blood flow increases the BOLD response, the fMRI signal is not absolutely quantifiable in the same sense that SPECT and PET measures may be. fMRI is quantifiable only in a relative sense (e.g., percent signal change), which indicates the degree of difference between an active and a resting state. For instance, brain activation during right-hand finger tapping must be calculated relative to a comparison behavior like rest or left-hand finger tapping. Early fMRI studies used extended blocks of time for active and resting periods (~30 seconds) for comparison.¹²⁸

Experimenters using fMRI must create behavioral paradigms that activate particular brain regions, for example, motor cortex or language areas. In the simpler paradigms, activation is measured by comparing the MRI signal obtained while a patient is resting with the signal during movement or language production, mathematically subtracting one set of images from the other. More recent fMRI paradigms can identify brain activation in response to brief cognitive, perceptual, or motor events lasting a few seconds or less. Such events can include conditions as minimal as tapping a finger once, twice, or three times.¹³⁰ The adaptation single-trial averaging and related techniques, similar to the approach for event-related potentials, and the relatively high temporal resolution of fMRI have allowed event-related designs to flourish in the past decade.¹³¹ Also, in human studies, the spatial resolution with fMRI is much better than with PET or SPECT, with images of a typical resolution of 3 mm and often less.¹³² A BOLD image of the whole brain can be obtained in about 3 seconds, although the actual time will vary inversely with resolution and coverage. Because of the relative speed of image acquisition, behavioral paradigms for fMRI experiments can be more versatile than simple active-resting block paradigms. Event-related fMRI paradigms are increasingly common for imaging studies where successive behavioral events may differ from one another. For instance, a researcher studying language wants to know the difference in brain activation between

deciding if a letter string is a real word or a pseudo-word. A block design would require the researcher to present blocks of real words and blocks of pseudo-words together. Because a subject recognizes which block is taking place as soon as the first word is presented, decision-making does not require verbal processing throughout the block. An event-related design can randomize the presentation order, thus requiring participants to read each letter string before deciding.

Language and movement representations change with recovery and rehabilitation therapy. Natural recovery studies are prevalent using both nuclear medicine and fMRI techniques. Because fMRI is noninvasive, multiple rounds of data acquisition can take place within a session and multiple sessions can take place over the course of therapy. For these reasons, we focus here on multisession therapy studies. Differences in fMRI measures before and after therapy indicate the location and degree of change with time with a greater degree of spatial precision than other brain-mapping techniques (Figure 4). Over that last decade, rehabilitative strategies have been increasingly studied with fMRI. Initial individual patient case studies were followed by larger group studies. In a block design study of metacarpal-phalangeal flexion-extension movements, one study reports that after constraint-based therapy there was increased activation in the ipsilesional premotor area, secondary somatosensory cortex, and bilateral superior posterior cerebellum, where changes correlated with improved grip strength.¹³³ Activation in the undamaged hemisphere has also been reported to result from constraint-induced motor therapy.^{20,134} Aphasia therapy also induces changes in fMRI brain activation. The high temporal resolution of fMRI allows investigation of brain activation timing. For example, the time to peak fMRI activation in aphasic subjects decreased following therapy, which is consistent with a reduction in verbal processing time.¹³⁵ Only more recently have randomized controlled clinical trials been conducted on larger numbers of patients in a head-to-head comparison of exercise versus arm training.¹³⁶

Limitations of fMRI

fMRI research requires careful behavioral paradigm design. Even apparently similar motor or language tasks may activate appreciably different brain regions. Consider this purely hypothetical example. In a rehabilitation protocol, dorsolateral prefrontal cortex (PFC) is engaged by performance of an arm-movement tracking task during therapy and its engagement changes during rehabilitation. If researchers use a finger-tapping task to assess brain activation with fMRI, and finger-tapping does not activate dorsolateral PFC, one cannot tell how therapy may have altered dorsolateral PFC function. This example exposes one confounding aspect of neuroimaging. One cannot assume that all the brain regions that participate in behavioral improvements will be identified by fMRI unless the fMRI task is exactly the same as the therapy, in which case, the generalizability of training effects could be questioned. This contrived example illustrates the possibility that therapy may engage brain regions whose roles in recovery may not be understood, and the effects of therapy could be missed by poor task design. Also, fMRI and any other behavioral activating paradigm cannot distinguish between excitatory and inhibitory activity because both generate metabolic increases that are met with increased blood flow. Research with fMRI, therefore, requires consideration of what brain regions might be recruited to restore function and what their roles could be in the rehabilitation process.

Despite potential task design dilemmas, fMRI represents a reasonable method for examining brain activation, especially because it is noninvasive. Unfortunately, reasonably large costs also are associated with the enterprise as a whole, including significant image-processing demands, information storage needs, and data management commitments. Like PET and SPECT, image processing is complex, but fMRI data sets also can be larger; each patient represents 500 or more megabytes per visit. fMRI activation is not quantifiable in metabolic

terms, only in relative terms of signal intensity change. MRI scanners are loud, and the enclosed space can make some patients uncomfortable. Because completely motionless subjects provide the best images, limb movement and vocalization paradigms may degrade image quality, and patients' tolerance for discomfort and immobility also affects the caliber of activation.

NIRS

Similar to PET and fMRI, NIRS measures blood flow changes. NIRS is sensitive to the differential absorption of near-infrared light (650–950 nm) by oxy-hemoglobin (HbO₂) and deoxy-hemoglobin (HbR).¹³⁷ Near-infrared wavelengths are only weakly attenuated by the scalp and skull and can penetrate several centimeters into the cranium.¹³⁸ NIRS uses an interdigitated array of near-infrared sources and detectors placed on the scalp allowing a resolution roughly equivalent to the source-detector separation, typically 3 cm or less.¹³⁸ As the concentrations of HbO₂ and HbR fluctuate during cognitive activity, the detector signals also fluctuate. NIRS is noninvasive and portable and does not require the expense of an imaging system such as MRI. NIRS systems also can be implemented as wearable devices potentially allowing brain activity monitoring under completely ecological conditions.¹³⁹ The behavioral paradigms and uses are similar to those for fMRI. In addition to HbO₂ and HbR, the combined signals produce total Hb, which is an estimate of regional cerebral blood volume.¹³⁸ Also, the fast response to neuronal activation can be obtained with related techniques such as event-related optical signals, which derive from the near-infrared light-scattering properties of active neurons.¹⁴⁰

The attraction to NIRS derives from its ability to monitor moving patients. Both gait and hand movement studies have been conducted with ataxic patients in rehabilitation. Generally these findings agree with other imaging findings. For example, NIRS activation level in prefrontal cortex oscillates between the acceleration and steady phases of gait in healthy subjects but remains sustained throughout both phases for ataxic patients.¹⁴¹ In hand movement and gait studies, early poststroke activation is bilateral¹⁴² but reverts to unilateral or asymmetrical activation with recovery.^{143,144}

NIRS limitations

NIRS ability to ascribe signal changes to brain functions depends upon the ability to map the infrared signal to the appropriate underlying tissue. NIRS itself provides no anatomical information but, like EEG and MEG, must use scalp anatomy to estimate where in the brain the signals arise. The spatial resolution is typically coarse, at 3 cm or more, but may improve with technical advancements, whereas the temporal resolution can be quite high. Like with fMRI, inhibitory and excitatory activity cannot be discriminated. The obvious advantage of NIRS is that ambulatory and proximal limb movement studies can be conducted in natural living environments.

MEG and EEG

MEG and EEG techniques work in a completely different manner than the image or blood-flow-based brain-mapping methods already discussed in this article. Active neurons generate small electrical currents across their cell membranes, specifically along the dendrites, as they process incoming signals from other neurons. These small electrical currents generate fluctuating electrical voltages that are detectable by means of surface electrodes placed on the scalp (EEG). These fluctuating electrical signals also generate small magnetic field oscillations at right angles to the current flux, which can be detected by the magnetometers that are part of an MEG array. MEG and EEG detect signals that arise predominantly from the dendritic fields of cortical pyramidal neurons. EEG and MEG detect this signal from a large area on the order of several square centimeters. Although largely similar in what kind of information they detect, MEG and EEG differ in several important ways. With EEG, the tissue between the scalp

electrode and the cortex attenuates the strength of the signal and the signal strength decreases with the square of the distance between them. On the other hand, tissues do not attenuate the MEG signal, but the magnetic fluctuations drop off as the cube of the distance between source to detector increases. Additionally, EEG picks up stronger signals from electrical sources that point straight out of the scalp, such as the tops of cortical gyri. MEG picks up stronger signals from sources oriented parallel to the scalp, that is, sulcal walls. Because tissues do not affect the MEG signal, MEG typically enables better signal source localization than EEG.

As with fMRI, EEG and MEG techniques may use an event-based approach to identify the characteristics of brain activity in response to specific behaviors, evoked or event-related potentials (EPs/ERPs), and event-related magnetic fields (ERFs). The presence of EPs in response to upper limb sensory stimulation¹⁴⁵ and the magnitude of ERPs in response to spoken words¹⁴⁶ can predict the quality of language recovery. As observed with other techniques, a higher degree of asymmetry in ERPs when compared to standard EEG signals such as coherence or delta-wave amplitude also appear to provide information about recovery and rehabilitation. For example, researchers have observed that the degree of signal synchrony was greater between medial and lateral motor areas in stroke patients than in healthy subjects but reduced with recovery.¹⁴⁷ In another study, the degree of reduction in delta-wave signals from perilesional brain tissue correlated with the amount of language recovery following rehabilitation.¹⁴⁸ In addition, by co-registering the electrode or magnetometer positions to the head, complex source localization calculations can be used to estimate where in the brain particular signals arise. Using this technique, a study has shown that an asymmetric localization of the magnetic sources responsive to contralateral median nerve stimulation is associated with better recovery than a symmetric localization in the two hemispheres.¹⁴⁹

EEG and MEG limitations

As with NIRS, no anatomical information is collected by EEG and MEG. There are template brain spaces available to approximate where signals arise in the brain based on the electrode or magnetometer position. Acquisition of an anatomical MRI scan can allow for individualized assessment of source localization. MEG offers somewhat better localization than EEG because the intervening tissue does not attenuate magnetic fields, although this better localization comes at a significant price differential. Advanced EEG systems may cost a few to tens of thousands of dollars, whereas MEG systems cost in the millions.

TMS and EMG

TMS influences ongoing brain and muscle activity by stimulating weak electrical currents in brain tissue through electromagnetic induction. These electrical currents can disrupt mental processes like visual perception¹⁵⁰ or stimulate muscle contraction. TMS is delivered through a small paddle placed near the scalp. Inside this paddle is a coil of copper wire wound around a figure-of-eight or doughnut-shaped ring to form an inductive loop. Electric current is passed quickly through the wire coils by discharging a capacitor to produce a strong but transient magnetic field. The rapid fluctuation of this magnetic field induces weak electrical potentials in the underlying brain tissue. These electrical potentials are strong enough to depolarize neurons and affect normal electrical processes in nearby brain tissue. Based on the ability of TMS to produce muscle responses, TMS must cause action potentials directly or indirectly in descending corticospinal motor neurons.¹⁵¹ The effects of TMS can be measured by recording electromyograms (EMG) in arm, hand, or finger muscles or by measuring changes in behaviors like reaction time or response accuracy. TMS is delivered typically in one of three ways: as a single pulse, as a paired pulse, or as a rapidly repeating train of stimulation. There has been recent interest in determining whether TMS itself can be used as a therapeutic intervention. This article does not consider that aspect of TMS but only its use in brain mapping to understand changes in cortical electrophysiology.

TMS techniques can be used to measure several aspects of cortical electrophysiology. For single-pulse TMS over motor cortex, these measures include the size (EMG amplitude) and timing of muscle contractions, called motor-evoked potentials (MEPs). Some studies have demonstrated that arm or hand muscle MEP amplitudes measured soon after a stroke can predict the degree of behavioral recovery weeks to months later.^{152–156} Moreover, MEP amplitudes increase as a result of therapeutic behavioral training.¹⁵⁷ For paired pulse TMS, the presence of a conditioning pre-pulse at, for example, 80% of a muscle's MEP threshold followed by an above-threshold stimulus can affect MEP amplitude to the second pulse. A 3- to 5-ms delay reduces MEP amplitude (intra-cortical inhibition; ICI), whereas a 10- to 15-ms delay increases MEP amplitude (intra-cortical facilitation; ICF).¹⁵⁶ Some work suggests that stroke alters intra-cortical excitability (ICI and ICF),¹⁵⁶ and successful recovery is associated with normalization of these measures.¹⁵⁸ Repetitive TMS (rTMS) can be used to determine whether a particular region participates in a recovered function by assessing whether focal stimulation there alters behavior. In one study of aphasia, it was demonstrated that some stroke patients use the right inferior frontal gyrus homologue of Broca's area to process language. Repetitive TMS over this site disturbed performance of a linguistic task in these patients.^{159,160} Determining the scalp area from which one obtains an MEP in a particular muscle produces a two-dimensional activation map for that muscle. Several studies have used this approach to show the effects of natural recovery and rehabilitation. In a study of chronic stroke patients, increases in map size and displacement of the map correlated with better functional recovery.¹⁶¹ Constraint-based therapies all appear to increase map size for limb muscles in correlation with improved behavioral function.^{17,18,162,163}

Limitations of TMS

Although specific limitations affect the interpretations of TMS, it must be noted that this is one of few and certainly most widely used techniques to directly stimulate the brain. Used as a mapping technique, TMS provides only two-dimensional maps of the brain surface. Used only for MEP magnitude measurements at a single point, no map is produced. Like NIRS and EEG/MEG, no anatomical information can be collected with this technique. Localization of the stimulation site must be approximated from scalp landmarks or can be estimated by collecting an anatomical MRI image and placing suitable MRI-visible landmarks, such as Vitamin E capsules, during stimulation. The difficulty in interpreting TMS results arises, for the most part, from the variety of measurements that can be made and how individual investigators interpret these measurements.

Summary and Discussion

According to the National Stroke Association, there are almost 5 million stroke survivors in the United States.¹⁶⁴ Approximately 780,000 people each year experience a new or recurrent stroke, of which approximately 600,000 are first attacks.¹ Our current understanding of how the brain repairs itself after a stroke needs to keep pace with the increasing need for treatment of stroke in the chronic recovery stage. Brain-mapping techniques provide an important set of tools for the study of how brain function changes after a stroke. However, the neurophysiological mechanisms that support natural recovery and rehabilitation of function are poorly understood. Because the view that therapeutic interventions can restore lost abilities has recently regained acceptance, the mechanisms by which therapy enables functional recovery necessitate further study. Researchers, therefore, need a clear understanding of what brain-mapping tools exist and how they can be used to investigate stroke recovery and rehabilitation. In this review, we have tried to provide a summary of what brain-mapping techniques exist, what they measure, how they have been or may be used in stroke research, and their limitations.

Stroke rehabilitation research could benefit from a unifying theoretical framework. Frameworks have been proposed for quantifying the process of recovery^{156,165} or for distinguishing whether metabolic impairments arise from diaschisis or ischemia.^{87,114} In what follows, we describe some existing concepts that might be useful in further shaping the theoretical backdrop of stroke rehabilitation research. Such a framework, we hope, will help in explaining how patterns of injury and recovery relate to one another. Why, for instance, does engagement ipsilateral to the stroke cortex lead to worse recovery in some cases but not others? There appear to be some similarities between stroke recovery patterns and models of behavioral interference that are useful to describe. Kinsbourne and Hicks describe the concept of functional cerebral distance.¹⁶⁶ When two tasks share processing resources or when they interfere with one another, they are close in functional cerebral distance. Tasks that are easily performed simultaneously are far apart in functional cerebral distance. In one conceptualization, close functional cerebral distance arises from significant anatomical interconnection between regions.¹⁶⁷ Interconnected regions may process similar kinds of information.¹⁶⁸ Thus, engagement of a region by one task may interfere with simultaneous engagement of a functionally close region by a similar task.¹⁶⁷

This concept might be loosely adapted to explain why certain regions are recruited to restore lost abilities during recovery and rehabilitation. For instance, if motor cortex was partially damaged from stroke, remaining motor cortex is close in functional cerebral distance and might be expected to support recovery processes. As stroke volume increases or encompasses larger areas, residual motor cortex may be insufficient to take on lost functions. In this case, more distant regions would be predicted to participate in the recovery process, for example, ipsilateral premotor or supplementary motor area or contralateral motor cortex. As strokes become larger or damage an area more completely, regions with greater functional distance are recruited to support recovery processes. What we lack in this conceptualization is a way to determine functional distance or, alternatively, to determine the order in which regions will be recruited (i.e., which regions come first, second, etc.).

To give a specific example, functional distance might be measured by quantifying diaschisis.¹⁶⁹ By comparison with a quantitative PET¹⁷⁰ or SPECT template of rCMRglc or rCBF, it might be possible to determine for an individual stroke patient how much diaschisis is present in different brain regions. For brain regions outside the penumbra, areas with greater diaschisis could be defined as being functionally closer than areas with less. Then researchers could assess whether the amount of diaschisis correlates with the amount of brain activity after recovery or rehabilitation.

Brain mapping will play an integral role in defining the neurophysiology of stroke rehabilitation and recovery. The techniques described here can be used to assess how the brain responds actively or passively to behavioral and physiological challenges. Given the limitations of each technique and the complexity of many of the issues concerning rehabilitation, the most thorough approaches may require the use of one or more of these methods at the same time. For instance, because TMS does not acquire anatomical data, it may be best used in combination with structural and functional MRI. Because fMRI provides no quantification of blood flow, an additional NIRS session or PET scan could provide substantial information about the absolute level of blood flow or metabolic activity. Because EEG and MEG source localization depends upon several stages of assumptions, an fMRI scan could help limit the solutions to source localization (e.g., combined EEG and fMRI). The demand for information about stroke rehabilitation will undoubtedly be driven by patient demand in the coming decade. The accurate utilization and understanding of brain-mapping techniques will play a key role in the quality of information that clinicians and clinical researchers can provide to patients.

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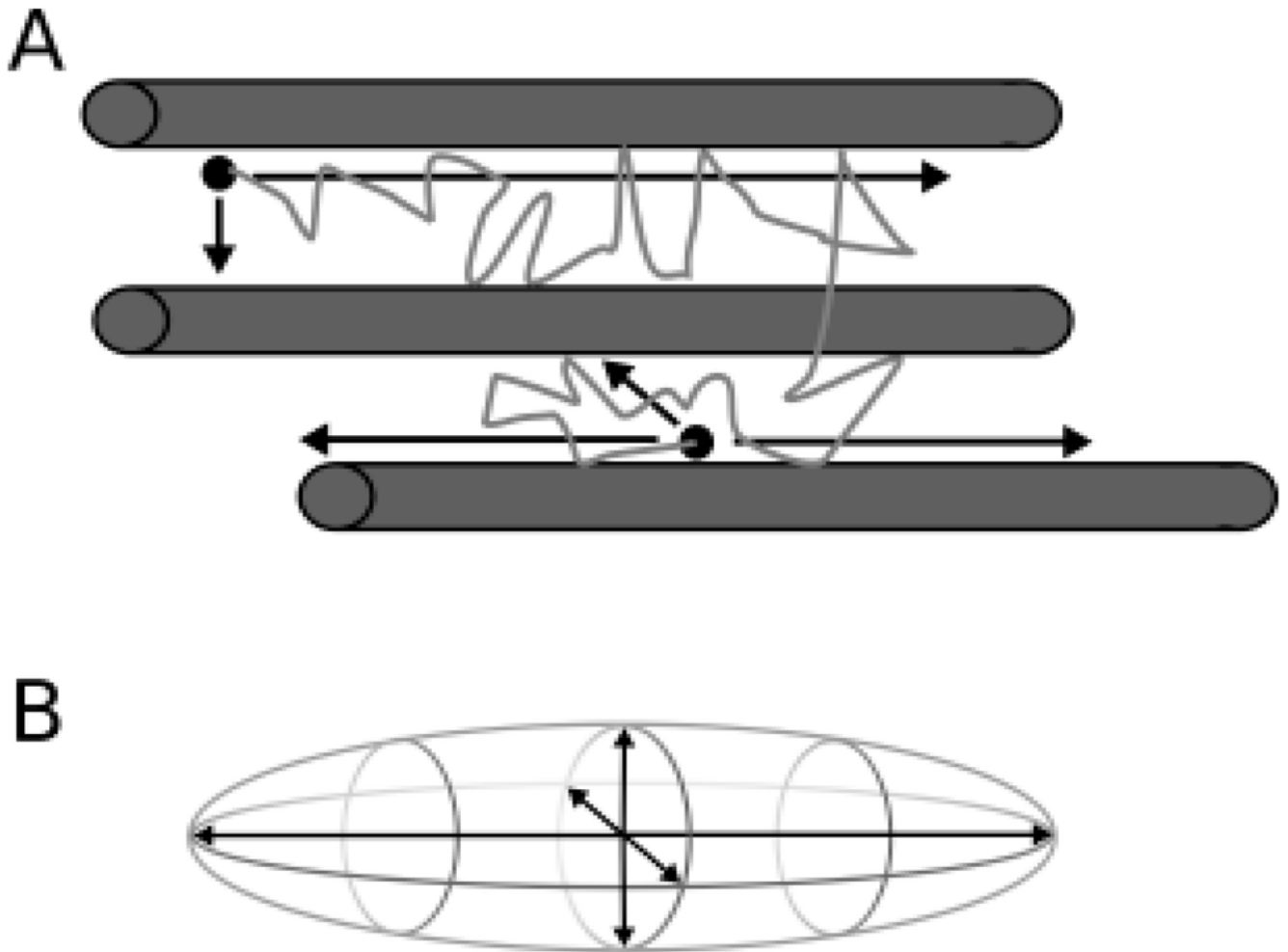


Figure 1. Depiction of water molecule movement. (A) Water molecule (black dots) diffuse more freely along white matter tracts (gray cylinders) than across them, where passage is less restricted, as represented by the black arrows and path of the water molecule. (B) Diffusion of water molecules can be quantified using the three-dimensional properties of an ellipsoid.

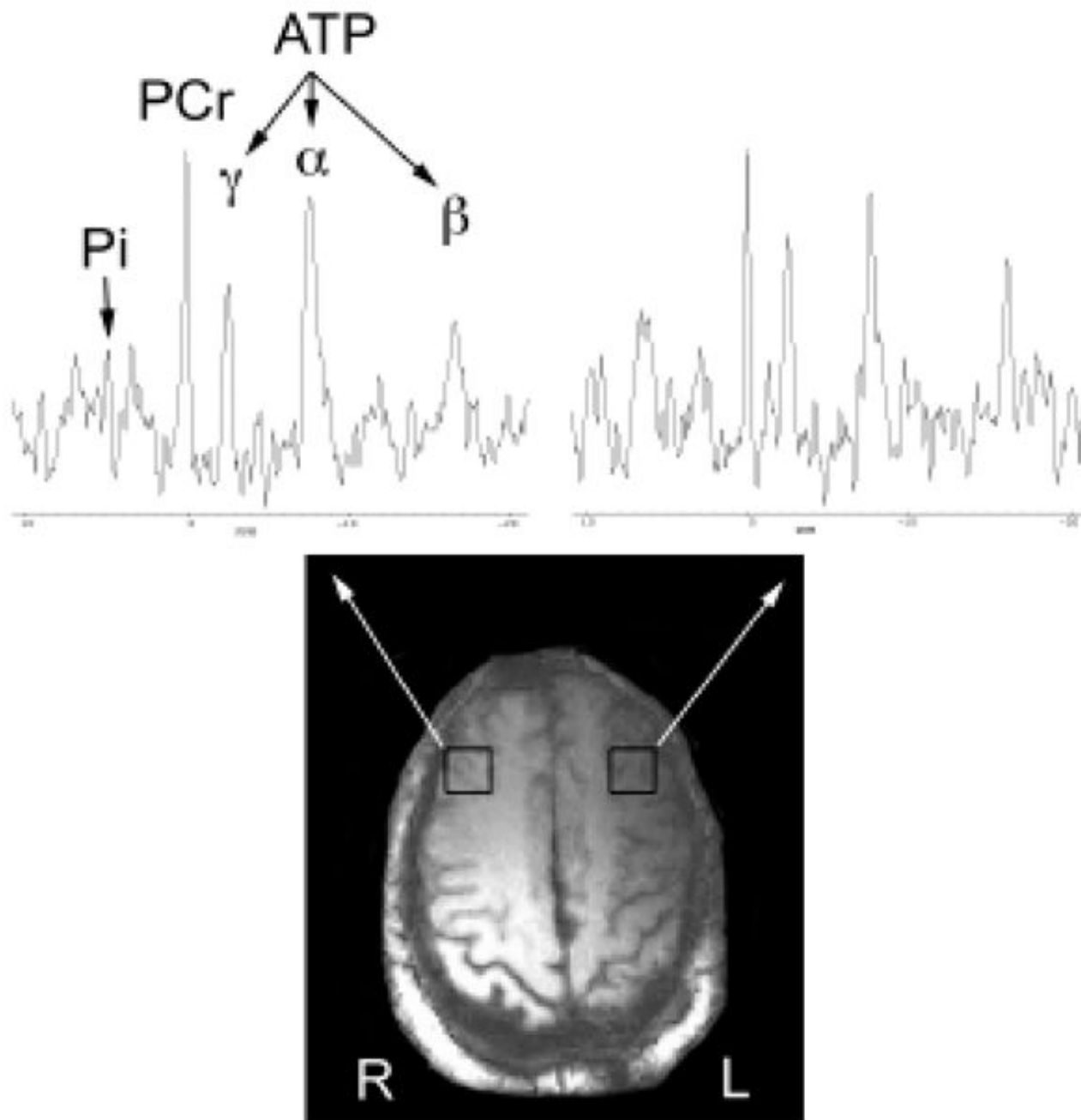


Figure 2. Phosphorous spectra from two brain locations. Representative ^{31}P -MRS spectra from a patient with a left internal capsule stroke. The single voxel (voxel size 13.8 cc) ^{31}P -MRS spectra are selected from the voxels indicated by the white boxes. Major ^{31}P -MRS metabolites such as inorganic phosphate (Pi), phosphocreatine (PCr), and adenosine triphosphates (γ -, α -, and β -ATP) are labeled. Reductions in gamma- and beta-ATP levels are evident in the spectrum from the left hemisphere.

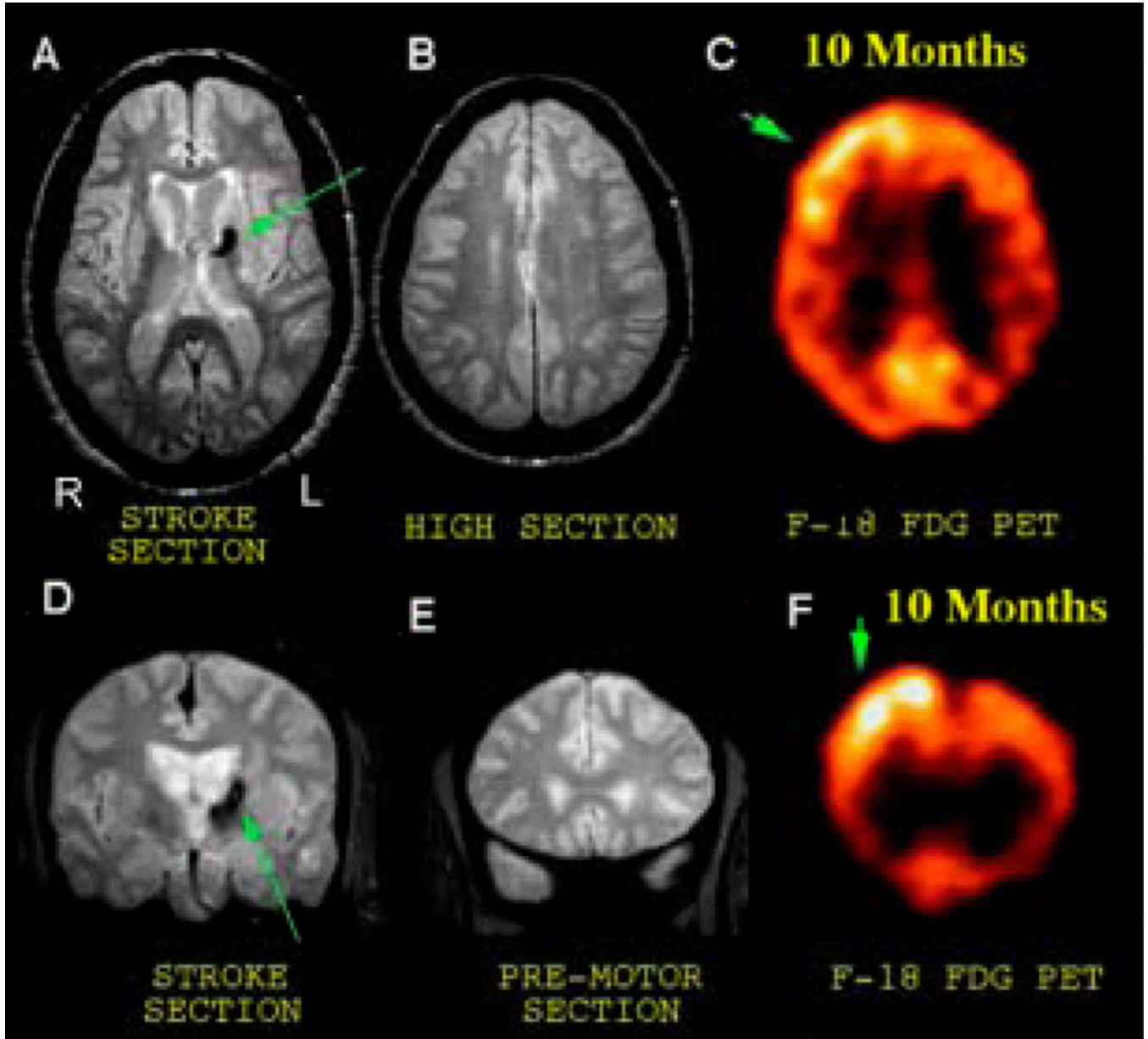


Figure 3.

Effects of stroke on FDG PET. Anatomical MRI and [^{18}F]-FDG PET in a patient with left internal capsule infarction. Panels A and D show the stroke location (arrows) in axial and coronal slices, respectively. Although the premotor region (shown in B and E) appears structurally normal, the [^{18}F]-FDG images (C and F) show a region of hypermetabolism in the premotor cortex of the contralesional hemisphere. [^{18}F]-FDG images were acquired 10 months after infarct. All images are in radiological convention, as labeled in panel A, with the left side of the brain on the right side of each image.

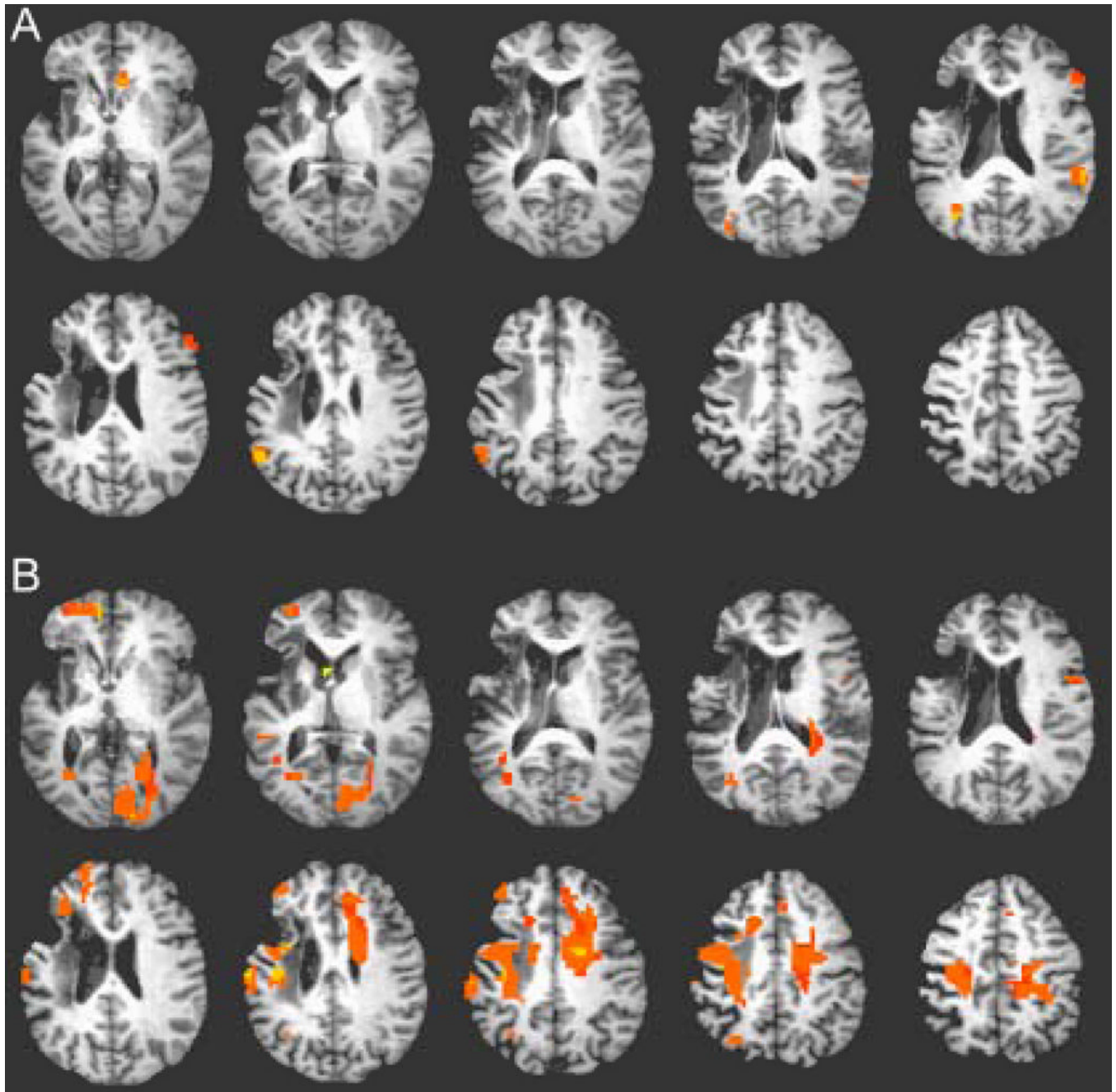


Figure 4. Representative fMRI activation map. Changes in fMRI brain activation during wrist flexion/extension following 8 weeks of electrical stimulation with a neuroprosthetic device. Subject is a 52 year-old woman, 4 years after left hemisphere infarct. (A) Pretherapy scan with right (affected) wrist flexion/extension. (B) Posttherapy scan with right wrist flexion/extension showing increases in brain activation in bilateral motor regions. Posttherapy scan was conducted 13 weeks after the pretherapy scan. $p < .01$; $n = 25$ voxels. All images are in neurological convention with the left side of the brain on the right side of each image.