Answering the Call: 
The Influence of Neuroimaging and 
Electrophysiological Evidence on 
Rehabilitation

Lara A Boyd, Eric D Vidoni, Janis J Daly

Functional recovery after brain damage or disease is dependent on the neuroplastic capability of the cortex and the nonaffected brain. Following cortical injury in the motor and sensory regions, the adjacent spared neural tissues and related areas undergo modifications that are required in order to drive more normal motor control. Current rehabilitation models seek to stimulate functional recovery by capitalizing on the inherent potential of the brain for positive reorganization after neurological injury or disease. This article discusses how neuroimaging and electrophysiological data can inform clinical practice; representative data from the modalities of functional magnetic resonance imaging, diffusion tensor imaging, magnetoencephalography, electroencephalography, and positron emission tomography are cited. Data from a variety of central nervous system disease and damage models are presented to illustrate how rehabilitation practices are beginning to be shaped and informed by neuroimaging and electrophysiological data.

LA Boyd, PT, PhD, is Assistant Professor and Canada Research Chair in Neurobiology of Motor Learning, School of Rehabilitation Sciences, University of British Columbia, T325-2211 Westbrook Mall, Vancouver, British Columbia, Canada V6T 2B5, and Adjunct Assistant Professor, Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center, Kansas City, Kan. Address all correspondence to Dr Boyd at: Laraboyd@interchange.ubc.ca.

ED Vidoni, PT, MSPT, is a graduate student and PhD candidate, Department of Physical Therapy and Rehabilitation Science, University of Kansas Medical Center.

JJ Daly, PT, MSPT, PhD, is Associate Professor, Department of Neurology, Case Western Reserve University School of Medicine; Director, Stroke Motor Control and Motor Learning Laboratory, Louis Stokes Cleveland Dept of Veterans Affairs Medical Center, Cleveland, Ohio.

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This PTJ special series provides an overview of the role of neuroimaging in rehabilitation.
Influence of Neuroimaging and Electrophysiological Evidence on Rehabilitation

Research conducted over the last decade has greatly increased the understanding of brain plasticity, that is, how neuronal circuits can be modified by experience or learning and in response to brain lesions.\textsuperscript{1-7} Neuroimaging and electrophysiological techniques that make it possible to study the function of the human brain in vivo may play a critical role in guiding the development of evidence-based rehabilitation interventions. People with neurological damage or disease consult physical therapists to assist in their recovery and restore their functional ability. Unfortunately, little is known about how the brain actually recovers from and compensates for neural damage. In the past, an incomplete understanding of the biological bases for recovery led to the use of intuitive and unsubstantiated rehabilitation methods.\textsuperscript{8-10}

Neuroimaging and electrophysiological techniques have the potential to reveal patterns of neural activation after brain damage and, perhaps more importantly, to identify the rehabilitation interventions that will stimulate the restoration of brain activation patterns. Underlying assumptions of research in which either neuroimaging or electrophysiology is used as a tool are that changes in motor behavior reflect alterations in neurophysiology and that studying such changes will lead to theoretical insights. Logically, these efforts ultimately will lead to the development of scientifically grounded rehabilitation approaches specifically targeted to enhance beneficial patterns of brain activity that can control the motor behavior that underlies restored function.

Our intent is to provide an overview of how data derived from neuroimaging currently are being used to inform rehabilitation interventions and what advances may be expected in the future. Emphasis is placed on how these findings may be used to alter clinical practice. Ideas are offered for optimizing rehabilitation interventions for people with brain damage. We highlight data that are beginning to demonstrate how best to facilitate motor learning after brain damage and disease, as this is a key component of neurorehabilitation.

Incorporating neuroimaging data, electrophysiological data, or both types of data when they are available offers several advantages in formulating and testing novel rehabilitation interventions. First, these data offer converging evidence concerning the relationship between regional brain damage and the involvement of various cortical regions in compensatory processes.\textsuperscript{11} Neuroimaging and electrophysiological data also offer methods by which progress toward the functional recovery of lost behaviors or skills may be tracked.\textsuperscript{12} Additionally, neuroimaging and electrophysiological data provide a means to quantify the dynamic reorganization of patterns of brain activation that is associated with particular interventions.

However, there are unique challenges to interpreting neuroimaging data. As mentioned in the article by Kimberley and Lewis in this Special Series, problems associated with altered hemodynamics and brain morphology complicate the interpretation of functional magnetic resonance imaging (fMRI) data. In addition, few studies have considered the issues of repeatability and reliability that occur with any imaging modality when populations with neurological damage are being studied. Head movement artifacts severely distort most imaging and electrophysiological data. Finally, restrictions on experimentally induced movement greatly limit the types of behavioral paradigms that are compatible with the imaging or electrophysiological environment. Although these difficulties are not insignificant, neuroimaging and electrophysiological methods are currently the only means by which brain function can be quantified during voluntary movements in humans.

Neuroplasticity: What Is It and Why Is It Important?

In the last decade, there has been increased interest in using a theory of neuroplasticity to explain why rehabilitation benefits people with central nervous system damage and to gauge the effectiveness of novel therapeutic treatments. Loosely defined, “neuroplasticity” refers to the ability of the brain to change in response to external stimuli, experience, or damage.\textsuperscript{13-15} Despite a large body of literature demonstrating neuroplasticity in animals,\textsuperscript{1,4,6,16,17} the molecular mechanisms and neurobiological bases for recovery after neurological injury in humans are still largely unknown. Until recently, the understanding of how people recover from neurological injury or disease was largely observational. Now, direct studies of neuroplasticity in humans are possible as a result of imaging and electrophysiological techniques.

Neuroplasticity encompasses a wide spectrum of phenomena and includes alterations in cortical properties, such as the strength of connections between synapses,\textsuperscript{18} adapted neuronal growth,\textsuperscript{1,2} changes in representational patterns within the cortex,\textsuperscript{6} and the recruitment of novel brain regions during task performance.\textsuperscript{19-22} The extent of neuroplastic change after brain damage is remarkable. It is this potential for beneficial recovery that underlies the motivation to develop more effective neurological rehabilitation methods. Importantly, it appears that positive or beneficial neuroplastic change is stimulated only by certain forms of behavioral interventions.\textsuperscript{6,16,17,23,24} Neuroimaging is one method by which rehabilitation sci-
Can Neuroimaging Data Be Used to Predict Recovery?

One of the most important potential uses for neuroimaging data is the prediction of recovery after brain damage. Multiple efforts are under way to determine whether this goal indeed may be achievable. For example, some investigators have attempted to predict final recovery from stroke on the basis of initial patterns of brain activation. However, work in this regard thus far has met with limited success, possibly because of the failure to understand the normal patterns of brain activation and what structures participate in learning new and relearning old movements. Magnifying these shortcomings is the difficulty of interpreting the significance of altered brain activation after damage.

The failure to predict final recovery from neurological injury or damage stems from the intricacy of normal brain function, the complexity of brain activation patterns, and the simplistic research designs and predictive models that are currently available. For example, multiple efforts have been made to determine who will recover from stroke. The pattern of brain activation associated with movement of the hemiparetic upper extremity (UE) after stroke clearly differs from that seen in control subjects and in patients moving their unaffected limb. During movement of the hemiparetic UE, people typically show various combinations of activation in the primary motor cortex (M1), the primary sensory cortex (S1), the premotor cortex, or the supplementary motor area in the undamaged, contralateral hemisphere. Because hemodynamic or blood flow changes mapped by fMRI are so widespread and variable in the brain after stroke, it is unclear what this altered pattern of activation signifies. For example, Feydy et al. using fMRI during a hand opening and closing task, reported that brain activation “refocused” or returned to a more normal pattern of contralateral activation in 8 of 10 subjects without M1 injury but persisted in an abnormal pattern in 3 of 4 subjects with M1 damage. Most interestingly, the shift, or lack thereof, in the pattern of brain activation to the unaffected contralateral (canonical) hemisphere was not related to functional recovery.

Two problems plague these data and those of other, similar studies of cortical function. First, behavioral outcomes too often are grossly characterized as good, moderate, or poor and are not assessed by use of functional measures with known reliability and validity. Second, there is a dearth of information regarding the response of cortical function to controlled interventions. These problems must be addressed carefully before data derived from neuroimaging can be used to predict the recovery of function and the response to treatment.

The goal of rehabilitation is to restore function; to accomplish this goal, it is possible that patterns of brain activation must be altered to allow changes in motor behavior. The relationship between brain function and behavior currently is not well understood. Typically, in people who are neurologically intact, the isolated movement of one UE is controlled by contralateral primary sensorimotor cortical activity. However, in people with UE hemiparesis caused by stroke, it is common for bilateral motor areas to be active during unimanual UE movements. This abnormal activation is seen commonly in fMRI examinations after stroke regardless
of lesion location. Activity in the undamaged, contralesional cortex could play an adaptive role in recovery from stroke or could be an epiphenomenon. Although much of the work examining recovery from stroke has considered which interventions, which type of patients, or both can change the magnitude of activity in the contralesional cortex, it is unclear whether normal patterns of brain function are a prerequisite for functional behavior.

One important aspect of recent work is the study of the relationship between motor function gains and changes in brain activation patterns that may control the restoration of function. In recent work, Dong et al. directly assessed the relationship between constraint-induce therapy and changing patterns of brain activity. In that study, 8 people who survived stroke that spared the hand motor representation in M1 completed 3 serial fMRI sessions concurrently with their participation in a 2-week program of constraint therapy (see Weinstein et al. for treatment details). A linear reduction over time was noted in the number of significantly active voxels (ie, the extent of regional brain activity) in M1 corresponding to the contralesional cortex, which was ipsilateral to the hand being moved. Furthermore, changes in voxel counts in ipsilateral M1 correlated with changes in functional measures (ie, Wolf Motor Function Test [WMFT] times, dexterity items subset). These data suggested that fMRI may be a useful tool for providing evidence for the link between changes in brain activation and the resulting gains in function associated with constraint-induced therapy.

With the goal of understanding comprehensively the relationship between changing patterns of brain activation and the structure of clinical interventions, numerous investigations currently are under way. In one such investigation, we are using fMRI to study people with moderate to poor hand function as they learn a novel motor task. Two hypotheses are motivating this research. First, we predict that patterns of brain activation are plastic and will be altered by motor skill acquisition. Second, we expect that for patterns of brain activation to change, task-specific training will be necessary; that is, simply increasing general arm use will not stimulate shifts in cortical activation. Our second hypothesis is based on past work that demonstrated the need for specificity of practice to stimulate cortical reorganization after an induced stroke in a nonhuman primate model. To characterize outcome, we calculated a ratio of brain activation (laterality index [LI]) that considers the magnitude and the extent of activity in M1 in association with sequential arm and hand movements, as demonstrated by fMRI.

Although preliminary at this time, data from a cohort of 9 subjects with chronic (>6 months) subcortical stroke support these hypotheses (Table). By random designation, 6 subjects received three 1-hour sessions of task-specific training using a joystick with the hemiparetic UE to complete a motor sequencing task; 3 other subjects who survived stroke underwent a program of increased general use of the hemiparetic UE. The increased use consisted of three 1-hour sessions during which emphasis was placed on using the hemiparetic arm to complete a series of tasks (eg, reach and retrieve objects or track a sinusoidal curve). The number of UE movements was controlled across the groups. Brain activity was monitored with fMRI at an initial practice session and at a delayed retention test that took place on a separate day following the 3 therapeutic sessions. Inclusion of a delayed retention test is critical, as data from this test reflect permanent changes in behavior associated with motor learning rather than temporary performance effects.

We are examining the patterns of change in function-related brain activity in M1 using region-of-interest analysis. Consistent with our hypotheses, fMRI data showed that task-specific training, rather than just increased use, stimulated refocusing of brain activation to the ipsilesional hemisphere (Fig. 1). Indeed, this pattern of altered brain activation was accompanied by motor learning, as indicated by faster response times for subjects in the task-specific training group at the retention test than at the initial practice session (Fig. 2). Most interesting thus far is our finding that subjects who showed the greatest change in the pattern of brain activation (as shown by a change in the LI) started with faster or more functional times on the WMFT (Fig. 3A). This relationship was found only between WMFT
times and the change in the pattern of brain activation; the initial LI did not predict WMFT times (Fig. 3B). Indeed, these data suggested that it is not the initial pattern of brain activation but rather the capability to change brain activation that predicts the recovery of function after stroke.

These data are helping to clarify earlier findings reporting a poor relationship between patterns of brain function and functional recovery after stroke. Other work has examined brain function and behavior at single time points.21,22,25,34,38,47 More relevant to rehabilitation scientists and clinicians is the capability for positive change in both behavior and patterns of brain function over time, as they relate to clinical interventions. Although preliminary, the data presented above illustrate ways in which neuroimaging studies may shape the design of clinical interventions. Through a better understanding of the response of the brain to skill acquisition, it is possible that in the future clinicians may be able to assess the potential for functional recovery early after stroke on the basis of changes in brain activity.

**Neural correlates of recovery after stroke in the lower extremity.** To date, few studies have examined the effect of rehabilitation interventions for the lower limb on brain function with fMRI techniques. We again note the complications inherent in study design methods mentioned in the article by Kimberley and Lewis in this Special Series. There are several additional challenges in designing experimental paradigms for the lower extremity. Dobkin48 demonstrated that behavioral gains associated with BWSTT (which emphasized skilled massed practice) were related to positive neuroplastic changes in motor cortical areas. Ultimately, data such as these may be used to determine how to optimize BWSTT parameters as well as to determine whether changes in the patterns of activation across the motor areas of the brain may be used to predict gains in walking ability after stroke.

**Magnetoencephalography (MEG)**

Multimodal integration of data from several brain imaging techniques permits a more coherent portrait of the brain following stroke and may provide a more meaningful index of the extent of plasticity phenomena underlying the recovery of sensori-
motor function. Functional magnetic resonance imaging provides fine spatial resolution (within millimeters) during motor task performance but is limited by temporal insensitivity (for definitions of temporal resolution and spatial resolution, see the article by Kimberley and Lewis in this Special Series).

In contrast, MEG provides high temporal resolution (within milliseconds) of signals from relatively restricted neuronal pools that are activated during cerebral processing; however, these data are limited by poor spatial precision. Owing to the factors outlined above, combined data derived from fMRI and MEG provide a more cogent representation of brain function in people with chronic stroke and quantify more completely the relationship between motor skill learning and dynamically shifting patterns of cortical activity. In addition, because MEG does not rely on hemodynamic signals (as fMRI does), it may be less affected by stroke. Because MEG directly measures electromagnetic signals from the brain, it is best able to reveal cortical function; however, it does not sensitively capture signals that originate from structures deeper in the brain, such as the basal ganglia or cingulate areas.

To illustrate the potential use of combined fMRI and MEG data to explain brain function after stroke, we recently completed a case study in which a study participant with upper-limb hemiparesis squeezed a prepressurized rubber tube to match a visually displayed force; all forces were normalized to the participant’s maximal voluntary grasp contraction. Two participants were studied: 1 with chronic stroke (>12 months after stroke) and 1 age-matched healthy control. Both participants performed the same motor task with fMRI and MEG monitoring on separate days. The participant who survived stroke used the hemiparetic hand for all responses; the control participant was matched for hand use. Consistent with our past fMRI work, when evaluated with MEG, the participant with chronic subcortical stroke (located in the posterior limb of the internal capsule) showed activation in both the ipsilesional and contralesional and the premotor cortex. In contrast, the control participant demonstrated a typical pattern of activation in M1 contralateral to the hand being used to respond, as indicated by fMRI (Figs. 4A and 4B).

For the control participant, multiple-dipole modeling of the forward-averaged data revealed a sequence of activation in primary and secondary visual areas, followed by activation in the midline supplementary motor area and M1 contralateral to the hand of movement. Activation curves demonstrated similar waveform morphologies for ipsilesional and contralesional M1 in the participant with subcortical stroke. However, activity in the contralesional cortex was delayed (Fig. 5; see delay in peak shown in yellow). Although these findings must be confirmed with more data, they do suggest that in the participant who survived stroke, contralesional activity did not play the lead role in motor control of the hemiparetic upper limb.

Although MEG offers a unique perspective on brain function, the data derived from this and other modalities are most useful when they corroborate other neuroimaging and clinical data. Future work with MEG should be directed at the evaluation of clinical interventions to assess whether therapeutic treatments normalize the timing of the onset of regional brain activation. However, as ongoing work suggests, MEG can be a valuable tool with which the impact of novel rehabilitation interven-
Diffusion Tensor Imaging (DTI)
An emerging technique that is based on magnetic resonance principles, DTI holds clinical and research promise. Diffusion tensor imaging can be used to monitor axonal bundles between regions in the central nervous system, making it a potentially useful tool. Particularly in white matter, water movement is not uniform in all directions (isotropic) but is dictated at least in part by nervous tissue structure (anisotropic). Water molecules are more likely to move, or diffuse, along the length of an axon rather than perpendicular to it.\(^5\) Using DTI, researchers can map structural characteristics, such as axonal tracts, by measuring the direction of diffusion of water molecules in each voxel. Through comparison with adjacent voxels, researchers and clinicians can build 3-dimensional schematics of likely white matter tract pathways.\(^5\) In contrast, magnetic resonance imaging cannot generate detailed maps of white matter. Further, DTI can be used to produce maps of the damaged brain without requiring people to move, a significant advantage in the evaluation of people with severe motor impairments. In sum, these issues render DTI a valuable, noninvasive tool with which to map both the normal brain and the damaged brain.\(^5\)

Pathology-specific changes can be detected with DTI. For example, after stroke, an increase in overall diffusivity has been detected, perhaps reflecting a progressive loss of restrictive cells and their membranes. This change is concomitant with a stroke-related loss of tissue volume.\(^5\) Interestingly, ischemia initially increases the anisotropic signal, presumably by pressing axons closer together.\(^5\) As time after stroke increases and cell death as a consequence of stroke occurs, the anisotropic signal decreases.\(^6\) Wallerian degeneration\(^5\) and, potentially, the severity of demyelinating disorder lesions also can be detected with DTI. The technique also shows promise for identifying diffuse axonal injury following traumatic brain injury (TBI).\(^5\) Furthermore, preliminary evidence suggests that recovery can be monitored with DTI as sequelae such as swelling subside.\(^5\)–\(^1\)

Finally, DTI appears to be a promising tool with which the recovery of function may be predicted. For example, DTI is capable of indicating the integrity of the corticospinal tract. In a study by Kunimatsu et al,\(^6\)
Figure 4.
(A) Location of the primary motor cortex source in a healthy control subject. (B) Location of the primary motor cortex sources in a subject with subcortical stroke. Anterior is toward the top of the source data (top panel); posterior is toward the bottom. Cortical activity is represented by the sinusoidal lines. Source localization is accomplished via coregistration of magnetoencephalography source data (top panel) and magnetic resonance imaging anatomic images (lower panel). Note that only unilateral cortical activity was evident in the cortex of the control subject (A). Activity was evident in both sensorimotor cortexes of the subject with right-sided stroke (B).

Figure 5.
Source waveforms for dipoles (areas of significant activation) in a subject with stroke. Red = dipole 1 from the hemisphere contralateral to the hemiparetic hand, which was used for task completion; yellow = dipole 2 from the undamaged, ipsilateral hemisphere. The timescale begins 500 milliseconds prior to movement onset and continues for another 500 milliseconds, for 1,000 milliseconds total. Peak activity in the undamaged, ipsilateral hemisphere was delayed relative to that in the contralateral hemisphere. These data suggest that the undamaged hemisphere did not play the lead role in stimulating motor output.
people with stroke in the corona radiata (descending white matter tracts in the brain) that spared the corticospinal tract recovered muscle strength (force-generating capacity) on the hemiparetic side, whereas those with damage to the corticospinal tract did not; no measure of functional recovery was offered.

To date, most rehabilitation-related research with DTI has not directly related interventions to brain maps but rather has simply indicated changes in brain organization as they relate to time after a lesion or has identified the relationship between the integrity of specific tracts and behavioral function. Overall, DTI is an extremely promising technique with which brain lesions may be characterized, recovery may be monitored, and the impact of rehabilitation strategies may be measured. At this point, however, rehabilitation-related research is just beginning to capitalize on this technique. More work is necessary before DTI can become an effective and well-characterized instrument in both research and clinical practice.

Electroencephalography (EEG)

Because the methodology and procedures associated with EEG are not covered in detail elsewhere in this Special Series, they are discussed here. Electroencephalography records the electrical signal generated at the scalp mainly by cortical pyramidal cell postsynaptic inhibitory and excitatory potentials. Recordings typically are obtained with an array of electrodes placed on the scalp in a standard configuration, and systems are available for simultaneous EEG recording from 1 to 124 channels. Signal amplitude is the difference in value between an electrode of interest (on the scalp) and a reference electrode. The EEG signal at any given scalp location, therefore, is a sum of thousands of synchronized potentials modified by the following factors: intervening tissues (eg, dura, skull, or scalp), the orientation of the generating cell array with respect to the recording electrode, and the conductive capabilities of the recording electrodes and the scalp-recording interface.

Advantages of EEG. The advantages of EEG signal measures include excellent temporal resolution of signals, a variety of signal characteristics that can be useful in different ways, accessibility in laboratories of rehabilitation scientists (in contrast to fMRI and MEG, which require expensive, special facilities), and relatively low cost (compared with the cost of fMRI). One major advantage of EEG is its temporal specificity; the EEG signal reflects cortical signal characteristics very close to the time of the event of interest. In contrast, the fMRI signal has an inherent delay (typically 4–10 seconds) between the onset of cortical activity and the observable change in voxel activation. Finally, EEG signals can be acquired for a wide variety of motor tasks, whereas fMRI and MEG are more restricted because of the need to hold the head still. The following signal characteristics and EEG measures have been used successfully for characterizing motor function and dysfunction or for measuring treatment responses: signal amplitude, signal latency (timing), percent desynchronization, frequency power analysis (spectral analysis), area of activation in terms of electrode location, source localization, and coherence. The definition and usefulness of each of these measures are described below.

Disadvantages of EEG. Because the recorded surface EEG signal is a sum of multiple potentials, the biggest disadvantage of this neuroimaging modality is poor source localization. In comparison, fMRI has excellent spatial resolution (millimeter precision) in determining the exact location of cortical activity. A second disadvantage of EEG is the intensive amount of time required for the analysis of signal characteristics, compared with the time required for clinical measures.

Figure 6.

Movement-related cortical potential (MRCP) and its components: the Bereitschafts potential (BP), the portion of the curve with a gently increasing negative value; the negative potential (NP), the portion of the curve with a steeply increasing negative value; and the positive potential (PP), the portion of the curve with an increasing positive potential. The onset of MRCP is indicated at the beginning of the BP. The MRCP amplitude is illustrated on the far right side as the difference between the baseline and the MRCP peak.
observational measures of motor behavior, such as the Fugl-Meyer Coordination Scale, provide immediate test results, whereas this is not possible for analysis of many EEG signal characteristics. A third disadvantage is that the equipment used to analyze EEG signals is somewhat costly, ranging from $20,000 to $60,000, depending on the sophistication and number of channels of the system. A fourth disadvantage is that the training needed to acquire and analyze EEG signals is time-consuming. Although these disadvantages are not trivial, it is possible for rehabilitation scientists to use EEG signal measures as a clinically based evaluative tool.

Usefulness of EEG in Describing the Cortical Control of Motor Function

Electroencephalography has been used for many years by neurologists as a diagnostic tool. In the last 20 years, there has been increased interest in studying EEG signal characteristics with respect to behavioral motor function in order to better understand the more sophisticated aspects of motor control. In such work, a command or event typically is required of a participant, who then must respond with a prescribed motor behavior. The cortical resting state is characterized by rhythmic or synchronous EEG activity; the term “desynchronization” is used to indicate a change from the synchronous, resting EEG potential as a result of task performance. The synchronous, baseline (resting) activity can result from a combination of contributing phenomena: pacemaker activity (pacemaker cells of the nucleus reticularis in the thalamus that fire in synchronous, rhythmic patterns when producing sleep spindles) and other rhythmic cellular networks (subcortical pacemaker or corticocortical networks). Thus, the relationship between EEG signal desynchronization and motor behavior is examined to determine the underlying cortical processes that support movement, learning, or both. Most notably for rehabilitation scientists, EEG signal desynchronization occurs while the brain prepares for and performs a motor task.

EEG Amplitude and Movement-Related Cortical Potentials

The movement-related cortical potential (MRCP) is a characteristic signal associated with voluntary motor performance that can be observed by averaging multiple movement trials of raw signals (30–50 trials). The MRCP has 3 characteristic components: Bereitschafts potential (BP), negative potential (NP), and positive potential (PP) (Fig. 6). The BP and the NP are associated with the planning of the movement, and the PP is associated with movement execution. To forestall confusion, it is important to note that planning stages entail an increasingly negative potential (BP and NP) that is conventionally shown in graphical terms to occur in the upward direction. The movement execution stage entails an increasingly positive potential (PP).
that is conventionally shown in graphical terms to occur in the downward direction (Fig. 6).

The amplitude of the MRCP has been successfully used as a measure for the differential characterization of cognitive effort levels during different types of motor tasks performed by healthy control subjects. For example, Fang et al.\textsuperscript{72} reported a higher MRCP amplitude for submaximal eccentric flexor muscle contractions than for concentric contractions (Fig. 7). The authors suggested that the higher amplitude of the EEG signal for eccentric contractions could indicate that a different or greater cognitive effort is required in the planning and execution of eccentric contractions. Fang and colleagues\textsuperscript{73} found that the same pattern of results occurred for maximal eccentric versus maximal concentric elbow flexor muscle contractions.

Electroencephalography amplitude measures also can successfully differentiate simple movements from complex movements. Characteristic differences have been noted that distinguish the EEG signals of simple thumb movements from those of praxis (tool-use) hand movements. These signal changes were noted during the time course of the higher amplitude of components of the MRCP.\textsuperscript{74} During cognitive planning (BP portion of the MRCP), the MRCP amplitude was higher for the complex movements than for the simple movements. Additionally, the distributions of higher-amplitude activity differed for the 2 types of tasks. That is, for the complex task, the distribution of higher-amplitude activity began in the left-hemisphere posterior parietal region; in contrast, cortical activity for the simple thumb movement was located more anteriorly and bilaterally in the sensorimotor region. The authors\textsuperscript{74} suggested that the activation of different areas supported the notion that early parietal cortical activity is essential for tool-use hand coordination but not for the control of simple movements. These results could prove useful to clinicians designing interventions for people with damage in the parietal region or parietal pathways. That is, if clinicians understand the need for parietal activation for tool use, they can set more realistic expectations for initial patient performance, target treatments more accurately, and formulate predictions regarding responses to therapeutic interventions.

Perceived effort level is another important variable that affects rehabilitation outcomes. The amplitude of early or later portions of the MRCP discriminated anticipated or actual force production, respectively, for an isometric index finger force production motor task.\textsuperscript{75} Specifically, the MRCP amplitude of the early planning phase was higher for a higher perceived force level, whereas the amplitude of the later movement-monitoring potential, or PP, was higher only when the actual force level was higher. These data illustrate the importance of accurately portraying the force needed for an exercise so that patients or clients do not expend unnecessarily elevated cortical effort during the planning phase for movement. Additionally, this research indicates that motor-impaired people, who may perceive a task as difficult or complex and who expend abnormally high cortical effort, may exhibit abnormally high fatigue or task failure or both.

Combined movements of the shoulder and elbow are difficult for people who have survived stroke and who have persistent motor deficits. The inherent difficulty of making movements of multiple joints after stroke also has been characterized by MRCP amplitude measures during functional reaching. Subjects in the chronic phase after stroke exhibited an abnormally elevated cognitive effort level in the sensorimotor and

\begin{figure}
\centering
\includegraphics[width=\textwidth]{abnormal_cognitive_effort}
\caption{Amplitude of the cortical signal or the cognitive effort level during a shoulder-elbow movement performed on a flat surface 14 cm in the northward direction away from the body (vertical axis). The cortical electrode locations are shown (C3 for the sensorimotor area and FZ for the frontal area) (horizontal axis). In both the sensorimotor and the frontal regions, there was an abnormally elevated cognitive effort level for the subjects with stroke relative to the control subjects ($P < .05$). (Reprinted with permission from Daly JJ, Fang Y, Perepezko EM, et al. Prolonged cognitive planning time, elevated cognitive effort, and relationship to coordination and motor control following stroke. \textit{IEEE Transactions on Neural Systems and Rehabilitation Engineering}. 2006;14: 168–171.)}
\end{figure}
frontal regions (ipsilesional hemisphere) during the planning stage (NP) for shoulder and elbow reaching movements76 (Fig. 8) and for a complex series of shoulder and elbow movements performed with the involved limb.73

Little information is available regarding the relationship between EEG measures of cortical dysfunction and shoulder motor impairment. Daly et al76 assessed the performance of a shoulder and elbow reaching movement component to investigate the relationship between cognitive effort level during that task and shoulder-elbow coordination assessed with the Fugl-Meyer Coordination Scale items for shoulder and elbow movements. In that study, Daly et al76 established that EEG measures did index motor impairment in that there was a significant association between shoulder-elbow coordination impairment and abnormally elevated prefrontal cognitive effort level (r = −.74, P = .02) (Fig. 9).

For rehabilitation scientists, one main interest is identifying measures of cortical function that respond to interventions, demonstrating that improved cortical function drives more normal motor control. In a pilot study of 3 people who had survived stroke and who had persistent upper-limb motor deficits (>12 months), Daly et al76 investigated this possibility using EEG amplitude measures. In response to intensive motor learning, the people with chronic stroke showed a significant improvement in cognitive effort, as indicated by EEG measures during shoulder and elbow reaching movements (Fig. 10).76

**EEG Latencies and Movement-Related Cortical Potentials**

Some researchers have studied the cognitive planning time required for motor tasks by using a measure of the latency (time) required for cognitive planning prior to movement or electromyographic signal onset. Cognitive planning time can be defined as the duration of time from MRCP onset to electromyographic signal onset. Fang and colleagues...
found that in healthy adults, greater cortical planning time was required for eccentric than for concentric muscle contractions for both sub-maximal\textsuperscript{72} and maximal\textsuperscript{73} elbow flexor muscle contractions. They used a measure termed a “motor map” to simultaneously illustrate measures of both the EEG latency and the EEG amplitude (see above) for eccentric and concentric muscle contractions (Fig. 11).\textsuperscript{75} This EEG map is useful for illustrating multiple measures (in this case, amplitude, timing, and general distribution of cortical activity).

Functionally useful movements are performed in a timely manner. Many people with motor impairments have difficulty initiating movements at the desired time, and the potential contribution of the central nervous system has not been well described. Researchers\textsuperscript{76} found that people with chronic stroke and with persistent motor deficits exhibited an abnormally prolonged cognitive planning time (EEG-derived MRCP measure) in the sensorimotor (2,734±1,205 milliseconds for people with chronic stroke and 1,466±779 milliseconds for control subjects; \(P=.03\)) and frontal regions during shoulder and elbow reaching movements (Fig. 12).\textsuperscript{76}

Researchers have used EEG latency measures to study the relationship between delayed central nervous system function and the capability to maintain a desired movement trajectory. Daly et al\textsuperscript{76} investigated the relationship between cognitive planning time and the accuracy of shoulder and elbow movement trajectory maintenance. Movement trajectory maintenance was defined as the deviation of the actual pathway from the desired pathway, which was a 14-cm path that required shoulder flexion and elbow extension on a horizontal surface. Path deviation was measured at 60 Hz. There was a

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**Figure 11.**
Group average of topographical maps of cortical potential showing spatial and temporal distributions of electrical activity at the cortical surface for concentric (upper panel) and eccentric (lower panel) elbow flexor muscle maximal voluntary contractions. The maps show the following: the preparation was longer and started earlier for eccentric than for concentric muscle contractions; the negative potential was greater (darker blue) during eccentric than during concentric muscle contractions, especially during late preparation and execution periods in the frontal and parietal lobes; and the activation area was larger for eccentric than for concentric muscle contractions. EMG=electromyographic signal, NP=negative potential. (Reprinted by permission of Elsevier from Fang Y, Siemionow V, Sahgal V, et al. Distinct brain activation patterns for human maximal voluntary eccentric and concentric muscle actions. Brain Res. 2004; 1023:200–212.)
moderately high and significant association between abnormally prolonged motor and prefrontal region (ipsilesional hemisphere) motor planning time and movement trajectory maintenance ($r/H_{11005}.50$, $P/H_{11005}.048$; $r/H_{11005}.52$, $P/H_{11005}.050$, respectively).

For people with motor deficits arising from cortical infarcts, it is critical to develop interventions that restore the brain function that is necessary to drive normal motor control. In order to be successful in this endeavor, it is important to develop cortical function measures that can indicate gains in response to treatment. In a small pilot study, Daly et al. demonstrated that this is possible by showing that a measure of cortical planning time could indicate gains that resulted from intensive motor learning.

Cortical Function During Motor Behavior and Spectral Analysis

Many researchers have used frequency power analysis (spectral analysis) of EEG signals to characterize cortical function during normal motor behavior on the basis of the amplitude of the signal within a specific frequency band of the EEG signal. Two frequency bands of interest for motor tasks are the alpha band (8 to 12 Hz) and the beta band (13 to 24 Hz). Examination of specific frequencies within these bands also can be valuable. For example, the mu wave represents the characteristically enhanced signal desynchronization observed within the alpha band prior to movement onset, during the planning phase. In contrast, the beta rhythm is observed during the execution of movement.

For control subjects who are healthy, EEG spectral analysis was useful in differentiating right from left limb movements or limb dominance. Neuper and Pfurtscheller showed that the cortical control of dominant right foot movements could be differentiated from that of nondominant left foot movements by the amplitude of the beta response (ie, higher amplitude for nondominant foot movements). Similarly, a higher beta amplitude was shown for movement of the nondominant hand than for movement of the dominant hand. Electroencephalography spectral analysis also was used to characterize distinct topographical locations for 2 separate frequency bands, showing differences between the mu wave signal and the beta band signal. The mu wave exhibited a widespread distribution of cortical activity during limb segment movements, but the beta band showed a discrete area of cortical activity concentrated along the midline closest to the representational area of the moving body segment (eg, the foot). Unfortunately, the mu rhythm during the planning phase cannot differentiate successfully among finger, wrist, and arm movements.

Alpha and beta band analysis also can differentiate handedness successfully. For right-handed people, a greater amplitude in the alpha band signal was evident in the contralateral hemisphere for dominant hand movements than for nondominant hand movements. Complicating matters was the finding that for left-handed people, equal alpha band activity was noted for both right hand and left hand movements. Furthermore, in the right-handed people (versus the left-handed people), greater contrast was exhibited in the left hemisphere for left index finger or right index finger movements.

Relating Brain and Behavior Through the Use of EEG-Derived Measures of Coherence

Coherence is the term used to identify a measure of the relationship between 2 EEG signals acquired from 2 different recording electrodes; the comparison is based on power (amplitude squared) frequency values. “Cross-spectral analysis” is the tech-
nical term for the procedure used to calculate coherence. A measure of coherence between EEG signals or between an EEG signal and an electromyographic signal can be used to compare signal synchrony between cortical areas or between a cortical area and electromyographic signal characteristics. Coherence has been used for more than 40 years to compare corticocortical signals in a number of conditions, such as epilepsy, abnormal human development, and sleep disturbances. Coherence is measured on a scale ranging from 0.0 to 1.0. Two signals are identical or completely coherent if the coherence value is 1.0.

Wheaton et al successfully used EEG coherence measures to study the relationship between parietal and premotor cortical regions during the preparation and execution of praxis (tool-use) hand movements. They found that during movement planning, beta band coherence was greatest between the premotor area and the hand motor area. The supplementary motor area had greater coherence with the motor and parietal areas than with the premotor area. However, there was no increase in coherence above the baseline for the motor and parietal regions. These findings provided evidence for potential networks between brain regions for praxis hand movements and suggested that parietal-frontal networks may be important in preparatory cortical processing for praxis hand tasks.

In an attempt to explain the cortical function underlying recovered hand motion after stroke, Gerloff et al used a measure of EEG coherence. They found that corticocortical coherence was decreased in the stroke hemisphere and increased in the nonstroke hemisphere. These authors used multiple imaging measures, including EEG frequency power analysis and EEG coherence indexes, to reach the conclusion that motor recovery was based on enhanced activation in both the ipsilesional hemisphere and the contralesional hemisphere. Furthermore, these data implied that enhanced cortical activity in the contralesional hemisphere may “facilitate control of recovered motor function by operating at a higher-order processing level, similar to but not identical with the extended network concerned with complex movements in healthy adults.”

We can clarify that these authors used EEG frequency power analysis and EEG coherence indexes to reach the conclusion that enhanced activation was associated with recovery. Interpretation of these EEG measures should not be confused with the fMRI measure of volume of activation, for which evidence has shown that a reduced volume of activation is associated with recovery. In fact, a reduced volume of activation (fMRI measure) could exist simultaneously in the presence of enhanced electrical amplitude (EEG measures) or enhanced coherence (EEG).

It is clear that the data derived from EEG may be used to inform clinical practice and aid in the design and evaluation of new clinical interventions. Because EEG is an older technology, the body of literature in this field is both rich and robust; however, only recently have rehabilitation scientists begun to exploit EEG to examine brain function associated with therapeutic interventions. As interest in understanding neuroplastic change associated with behavioral interventions and rehabilitation approaches continues to grow, it is likely that the use of EEG as an investigational and clinical tool will increase concurrently. Because EEG is a relatively affordable technology (compared with fMRI or MEG), it is possible that it could be used in the clinical environment to determine capability for neuroplastic change and to document progress toward recovery. It is possible that mapping changing brain function in association with clinical interventions will become routine as physical therapists increase their understanding of the neuroplastic underpinnings of functional recovery.

**Neuroimaging and Parkinson Disease (PD): Dynamic Cortical Networks**

The basal ganglia and prefrontal cortex form a network that is essential for planning movements and cognitive tasks associated with motor learning. Damage to the basal ganglia, in particular, disrupts the capacity for mastering skills, even when the motor output requirements are quite minimal. In PD, degeneration of the basal ganglia as a result of the loss of striatal dopamine causes a striking array of behavioral motor and cognitive deficits. People with PD have a broad spectrum of disabilities, including problems with motor planning, motor skill learning, and implicit or habit learning. For PD, the importance of developing evidenced-based interventions is underscored by animal models of the disease, which demonstrated that functional disabilities can be ameliorated on a long-term basis only through specific types of rehabilitation training. One of the primary difficulties for physical therapists who treat people with PD is the variability of function among people. In addition, because the course of this disease is not well characterized or uniform among people, it is difficult to predict changes in behavioral ability. Some people with PD appear to maintain old motor skills, whereas others do not. Data derived from positron emission tomography (PET) have shed some light on this problem.

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Typically, nuclei within the basal ganglia (the caudate nucleus and the putamen) in concert with the prefrontal cortex, participate in the learning and selection of movements. To identify whether this network was interrupted or spared by PD, Dagher et al. used $H_2^{15}O$ PET to map brain activation in people with PD and control subjects who were healthy. An overview of the technical aspects and advantages and disadvantages of PET is presented in the article by Kimberley and Lewis in this Special Series and will not be repeated here.

In a study of Dagher et al., H$_2^{15}$O was used as a labeling marker for water to enable the study of blood flow to various regions of the brain during task performance in people with PD. The study participants were asked to perform the Tower of London task, a cognitive-motor task that requires participants to plan movements in advance (or forward-plan) in an attempt to rearrange a tower of balls. In members of both the PD group and the control group, overlapping areas of the prefrontal cortex were active. However, only members of the control group showed activation of the caudate nucleus of the basal ganglia. In contrast, members of the PD group showed activation of an entirely different region of the brain, the hippocampus. This finding was not evident in the control group; members of the control group showed suppression of the hippocampus. Most interesting, there were no differences in the behavioral abilities of members of the 2 groups as they completed the Tower of London task.

What do these data indicate about the potential for rehabilitation and daily functioning for people with PD? It is important to note that despite equivalent cognitive performance and motor performance in members of the PD and control groups in the study of Dagher et al., people with PD used an entirely different cortical network. This shift in the brain activation pattern demonstrates the remarkable degree of residual neuroplastic ability for people with PD. However, this compensatory pattern also may indicate a less efficient use of regional brain activation for planning and motor problem solving. The hippocampus is essential for factual memory and explicit planning and typically is not involved in tasks that require motor planning, such as the Tower of London task. If the hippocampus is used for planning, as demonstrated by Dagher et al., then it may not be available for other operations.

These findings are even more interesting in light of earlier work by the same group. In a similar study with the same task, Owen et al. discovered that a separate group of people with PD showed minimal basal ganglia activity without compensatory hippocampal activation. In that work, members of the PD group performed more poorly than members of the control group. Disease severity explains the differences between these 2 studies. When severity is moderate (Hoehn-Yahr Scale score of 2 or 3), a compensatory network may be activated in people with PD, and behavioral function is stabilized. In contrast, as PD progresses (Hoehn-Yahr Scale score of 3 or 4), it appears that this compensatory strategy fails both at the brain level and at the behavioral level.

In this example, neuroimaging data provided a cogent explanation for why 2 groups of people with PD behaved differently. It is clear that behavioral measures of disease severity were unable to adequately distinguish between people who could plan and those who could not; both studies enrolled people with a Hoehn-Yahr Scale score of 3. The distinction that can be made by considering neuroimaging data is important, as it allows clinicians to determine who can continue to learn by using forward planning and who cannot. These data are extremely valuable to clinicians who are formulating rehabilitation interventions, as they indicate what level of recovery or maintenance of function may be accomplished by people with PD.

Recovery From TBI: What Can Be Learned From Neuroimaging?

Functional neuroimaging methods, such as PET and fMRI, are being used to reveal and monitor the cerebral consequences of plasticity associated with TBI. In addition, data derived from neuroimaging tools can aid in evaluation of the effectiveness of different rehabilitation interventions. To date, the majority of this work has investigated cognitive rehabilitation. Functional neuroimaging after TBI has shown reliable differences in brain activity in several regions of the frontal cortex consistently involved in regulating behavioral function after TBI. Like the work in stroke rehabilitation, these studies most often have examined single time points and largely have not considered specific rehabilitation interventions for TBI.

Using fMRI, Kim et al. examined the effect of short-term constraint-induced therapy on the patterns of activation in motor cortical areas. In that work, the authors used a mixed sample of participants with brain injury and participants who survived stroke, each with lesions in the motor cortical areas and associated white matter. All showed behavioral
recovery. Brain scans were obtained while participants made a fist or sequentially opposed their finger and thumb using the hemiparetic arm. Scanning took place 2 weeks before a 2-week therapy trial and after the therapy trial. Neuroplastic change was evident in the motor network but was not uniform across participants. Most participants demonstrated new activation in the contralateral premotor cortex after therapy. However, some participants showed increased activation in the ipsilateral supplementary motor area and motor cortex. Although it is difficult to draw broad conclusions from these data, it does appear that neuroimaging reveals that the capability for neuroplastic change is preserved after TBI. It also appears that the pattern of change associated with this intervention is patient dependent. This neuroimaging work supports other findings that have suggested that the behavioral improvements associated with constraint-induced therapy are related to neurophysiological changes at the cortical level.

A larger body of literature suggests that electrophysiology can be used to predict outcomes following TBI. Cortical evoked potentials indicated by EEG appear to offer a prognostic measure for an otherwise unresponsive, comatose patient. In addition, speech evoked potentials measured by EEG both appear to correlate with the stage of functional recovery after TBI. These findings have been supported by similar studies demonstrating that evoked potentials are predictive of long-term recovery in pediatric patients. Up to this point in this article, we have considered mostly pathologies that result in well-defined, albeit sometimes large, regions of injury. Traumatic brain injury often causes the additional problem of widespread, diffuse neuronal injury. Such damage likely results in a broad and unpredictable spectrum of deficits. This problem presents greater difficulties in the use of neuroimaging and electrophysiological techniques to categorize people with TBI.

Other Central Nervous System Diseases: Can Neuroimaging Inform Practice?
Recent work has considered the relationships among rehabilitation, recovery, and brain function in other diseases of the central nervous system. In these trials, cortical reorganization has been examined largely with fMRI to determine the potential for recovery in people with multiple sclerosis (MS) and Alzheimer disease (AD). Data from a recent study in which fMRI was used to map brain function in order to examine the response of people with MS to motor training suggested that this population is not able to optimize the recruitment of motor cortical areas with task practice. In that study, people with MS failed to demonstrate task-related reductions in the levels of activation in M1, S1, or the parietal lobe of the contralateral hemisphere. This finding of reduced neuroplastic change in association with skilled task performance may reflect a specific form of plasticity that is unique to people with MS. It is possible that MS induces a transsynaptic degeneration that affects brain regions that appear unaffected. This may be due to the fact that MS is a white matter disease. It is possible that the plasticity indexed by neuroimaging is demonstrating functional reorganization of the gray matter above MS-induced white matter lesions; to date, there is no evidence of white matter plasticity. The net result may be an inability to recruit the cortical areas in a normal fashion. Despite the fact that the body of literature regarding the use of neuroimaging to examine rehabilitation for people with MS is very small, these data suggest that a limited ability to stimulate training-dependent neuroplastic change may hamper recovery. Additional trials are needed to determine whether this is indeed the case.

AD
The use of neuroimaging to examine rehabilitation for people with AD is limited, just as it is for people with MS. Maintenance of the ability to perform tasks of daily life has been demonstrated via robust examples of preservation of the implicit memory system in people with AD. Intract implicit memory has been confirmed with fMRI, showing that both behavior and brain activation for this subset of memory may be modified in people with AD. For example, Lustig and Buckner used fMRI to demonstrate that people with early-stage dementia can continue to activate the prefrontal cortex normally. Although these data are promising, no clinical trials have yet investigated how this preserved function may be harnessed to benefit people with AD through a therapeutic intervention.

Conclusion
Recent advances in the understanding of how the brain reorganizes itself in response to behavioral training and rehabilitation interventions have stimulated novel investigations with neuroimaging and electrophysiological techniques that permit examination of the dynamic evolution of brain activity. This new ability to relate neuroplastic brain changes to rehabilitation interventions permits a more cogent examination of the relationship between brain function and therapeutic interventions. Increasingly, investigators are taking advantage of the potential of neuro-
imaging, electrophysiology, or both to discern which treatments best stimulate positive neuroplastic change in combination with behavioral recovery. In the future, it is likely that these advances will both accelerate and stimulate a greater understanding of the relationship between brain function and therapeutic interventions. This research ultimately should help to advance clinical practice and provide rehabilitation scientists with a more accurate view of how interventions shape patterns of brain activity and lead to the restoration of behavioral function.

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