Functional Reintegration of Prefrontal Neural Networks for Enhancing Recovery After Brain Injury

Anthony J.-W. Chen, MD; Gary M. Abrams, MD; Mark D’Esposito, MD

Functions of the prefrontal cortex (PFC) are fundamental to learning and rehabilitation after brain injuries, but the PFC is particularly vulnerable to trauma. We propose approaches to cognitive training that are hypothesized to specifically enhance PFC function. We present a theoretical framework that generates hypotheses regarding the effects of training on the functional integration of processes across distributed networks of brain regions. Specific outcome measurements that may be used to test these hypotheses in clinical trials are proposed. This neural network-level approach may guide cognitive rehabilitation and facilitate development of adjunctive biologic treatments to enhance the effects of training. Key words: brain injuries, cranioencebral trauma, frontal lobe, learning, magnetic resonance imaging, neuronal plasticity, prefrontal cortex, recovery of function, rehabilitation

GOAL-DIRECTED BEHAVIOR, at the core of what we consider human, depends critically on the function of the frontal lobes and, specifically, the prefrontal cortex (PFC). The PFC is multimodal in nature, with extensive connectivity to almost all other brain regions, and is thus likely a critical node in a network of brain regions that subserve important cognitive and emotional functions.1-3 Perhaps the most fundamental PFC function is the guidance of learning, consistent with a critical role in recovery and rehabilitation after brain injuries.

The integrity of the PFC and its associated networks must be considered in the prognosis for recovery from any brain injury. The PFC is particularly vulnerable to traumatic brain injuries (TBI) and the most common cognitive-behavioral sequelae of TBI are referable to such injuries.4,5 Trauma may cause focal cortical lesions or subcortical axonal injuries that disconnect frontal networks; in either case, it may lead to deficits in motivation, attention, working memory, and goal planning, deficits that interfere with rehabilitation. Restoration of PFC function is thus a crucial goal for enhancing recovery from brain injuries.
PFC cognitive deficits have been particularly challenging to rehabilitate. A clear theoretical framework based on neural mechanisms underlying PFC function may assist in the development of more effective therapies. Cognitive rehabilitation treatments, including clinical trials, rarely consider these neural mechanisms. An additional emphasis on the neural mechanisms that mediate PFC functions may result in treatment prescriptions that differ from more traditional behavioral therapy. This approach would combine a detailed understanding of a patient's brain lesions and neural dysfunction and then incorporate observations from cognitive neuroscience to result in specific treatment prescriptions. This approach may also offer new biologic targets for treatment development.

To provide information that reflects neural mechanisms of functional recovery, outcomes must measure changes at the level of regional brain networks. Functional imaging techniques, such as functional magnetic resonance imaging (fMRI), provide methods to measure changes in function over the whole brain, and are thus well-suited to analyses of interregional networks. Functional imaging studies of cognitive processing in patients with neurologic injury such as TBI show that this measurement approach is feasible, although this approach is just beginning to be applied to understanding neural changes with rehabilitation. Functional imaging may be able to provide data necessary for guiding cognitive rehabilitation when used in the context of a theoretical model that generates testable hypotheses regarding the key intermediate pathways of treatment effects.

A UNIFYING THEORETICAL FRAMEWORK: FUNCTIONAL INTEGRATION IN PFC NETWORKS

A theoretical framework for rehabilitation of any cognitive function should be founded on current concepts regarding neural mechanisms underlying the cognitive processes being targeted. Brain-behavior relationships can be organized along 2 conceptual domains: functional specialization—the idea that functional modules exist within the brain, that is, areas of the cerebral cortex that are specialized for a specific cognitive process, and functional integration—the idea that a cognitive process can be an emergent property of interactions among a network of brain regions, which suggests that a brain region can play a different role across many functions.

Based on the observations of patients with frontal lesions, the types of specific cognitive processes that have been attributed to the PFC have been referred to in the clinical neuropsychological literature as "executive" functions. This label encompasses a diverse collection of processes, including divided and sustained attention, working memory, flexibility of thought, set-shifting, motor sequencing, planning, and the regulation of goal-directed behavior. Neural models of PFC function, based on physiologic studies in animals and humans, emphasize its role in the executive control of mental processes whose primary operative sites are localized elsewhere in the brain. From an evolutionary perspective, control is a natural extension of the motor system from which the PFC evolved, and as the “highest” level of the motor system this control might be expected to extend far beyond the regulation of body movements. In fact, executive control can be viewed to encompass higher level influences over sensory input, internal states (both emotion and cognition), and motor output. By exerting influence over these domains, humans have evolved increasingly more sophisticated control over interactions with both the natural world and each other. This control permits the goal-directed override of primitive and inflexible reactions to environmental stimuli, what Mesulam refers to as the "default mode." These underlying functions of the PFC may be mediated by modulatory interactions between the PFC and other brain regions in dynamic functional networks.

Importantly, these executive control processes are attributed to the lateral PFC, whereas medial portions of the PFC, such
as the anterior cingulate (ACC) and the orbitofrontal cortex, are considered to be functionally separable. The ACC may be particularly involved in processes that underlie evaluation of conflict.\textsuperscript{17} This may be a basis for functions, such as error detection, in which a performed action must be compared with an expectation of the correct action and other functions of self-evaluation. The orbitofrontal cortex may be particularly involved in processes that underlie emotional regulation, including motivation, and valuation of reward information.\textsuperscript{18} Each PFC functional subdivision likely subserves different computational functions, contributing to cognitive control, although these functional subdivisions have extensive reciprocal connections with each other and appear to work together in a dynamic way to regulate other regions of the brain.

In summary, the PFC plays a central role in the integration of neuronal activity distributed over multiple brain regions to facilitate processes that are relevant to the context.\textsuperscript{3,19,20} Thus, goal-directed behavior emerges from an integrated network of brain regions. Any analysis of plasticity in PFC function after brain injury should consider this integrative function of the PFC, including the relationships between the PFC and functionally interconnected regions. These are not well accounted for with traditional measures of PFC activity. We therefore propose a simplified approach for assessing changes in the function of the PFC and associated networks, and apply this model to the analysis of rehabilitation treatments. This approach includes the measure of (1) PFC activity, including levels of activity and connectivity between PFC subdivisions, reflective of the integration of processing within PFC networks; (2) PFC-to-posterior connectivity, reflective of the integration of PFC, and posterior processing; and (3) modulation of posterior cortical activity, reflective of the influence of the PFC on posterior activity. The output of these neural changes will be reflected in behavioral changes. We further discuss these measurements in sections “Potential Neural Mechanisms of Recovery of Function After Training” and “Hypothesis Testing.”

This model may be applied to an example. In the healthy brain (see Fig 1a), information from the external environment drives activity within posterior sensory regions from the “bottom-up” via mechanisms of early sensory perception. To guide subsequent processing for task or goal relevance, PFC networks modulate posterior activity in a “top-down” fashion (e.g., guided by internal states such as knowledge from previous experience, expectations, and goals).\textsuperscript{3} This top-down influence upmodulates relevant posterior networks relative to nonrelevant networks, resulting in an integration of the relevant networks, which may actually be distributed across brain regions, to achieve a coherent output.\textsuperscript{21,22} For example, when a person is looking at a crowd of people, the visual scene presented to the retina may include a myriad of angles, shapes, people, and objects. However, if the person is a police officer looking for an armed robber escaping through the crowd, some mechanism of downmodulating processing of irrelevant visual information while upmodulating task-relevant information is necessary for an efficient and effective search.

When PFC networks are injured (either by direct injury of the nodes of the network or by damage to the pathways that connect them), the changes may be understood as a loss of functional integration (see Fig 1b). In contrast to the example above, a person with PFC injury may be left with visual processing that is driven by bottom-up stimuli, with poor ability to selectively upmodulate networks that process the relevant information in preference to the many distractors in the environment. Similarly, she may have difficulty selectively attending to other important information, keeping task-relevant information in memory, or prioritizing her activities to achieve important goals. She is left with disorganized behavior, mirrored by neural activity that is not organized by top-down guidance. This is exactly what is observed in patients with frontal injuries.\textsuperscript{23,24}

www.headtraumarehab.com
Figure 1. A 3-component model for evaluating changes in functional integration is illustrated by showing how the flow of information in sensory processing is guided by prefrontal function. (A) In the healthy brain, information from the external world enters the brain from the "bottom-up" through sensory perception. Relevant information (symbolized by an up arrow) is surrounded by irrelevant distraction information (symbolized by ambidirectional arrows) with little intrinsic differentiation. Later sensory processing is modulated by the PFC based on task or goal relevance so that information is differentially processed (symbolized by a large green up arrow for relevant information, and by smaller down arrows for irrelevant information). (B) When the PFC is injured, we propose that there is a loss of functional integration. That is, there is a loss of organization and integration within PFC networks. Weakened anterior-posterior functional connectivity may result from structural disconnection such as axonal injury or subcortical lesions, or other failures of communication. The end result is a loss of top-down modulation of posterior activity, so that posterior processing is poorly modulated for task relevance.
TRAINING INTERVENTIONS: TARGETING PFC NETWORKS

The theoretical framework we described above has implications for the design, implementation, and testing of training interventions used in rehabilitation. If we accept that PFC networks are an important target for rehabilitation after brain injury, how can the function of such networks be effectively enhanced? We discuss principles of training that may be valuable for enhancing PFC function.

Training tasks should challenge patients to engage “top-down” modulatory processes mediated by the PFC

Functional MRI studies aimed at investigating normal brain-behavioral relationships can provide guidance for the type of tasks that can engage PFC networks. For example, tasks that involve working memory (eg, the maintenance of information over a short period of time), selective processing of competing information based on task relevance, and performance of dual tasks all preferentially activate lateral PFC networks. In contrast, medial PFC systems may be engaged with tasks requiring monitoring of conflict and error correction. Each of these tasks shares the requirement to recruit top-down control processes for successful performance. During the performance of these tasks, it is the processing demands, and not the specific contents of stimuli per se, that activate PFC networks. For example, the PFC is engaged during working memory tasks, regardless of the type of information that must be remembered (eg, words vs objects, auditory, visual, or olfactory). Thus, an additional general principle is that training of specific top-down control processes, and not content, is important in the design of training tasks that aim to target the PFC.

In addition to process-specific training, a goal-oriented approach should be included

Such an approach focuses on improving PFC function in the context of achieving particular goals. The content of the goals, and thus the content of the tasks, may be individualized. Neural subprocesses involved in goal management may be trained regardless of the specific content. For example, in one goal-management program formalized for research purposes (GMT), patients are asked to go through 5 main steps. First, they are asked to stop and explicitly outline the goals of their actions. Patients are guided in generating personally relevant goals, which may include achieving everyday tasks such as planning a meal or making a doctor’s appointment. Subsequent management of goal-generated tasks would require steps that would further engage PFC networks. These steps include generation of subgoals and listing of associated tasks; learning and recalling goals and subgoals; and executing the goal-oriented tasks. These steps may require processes including sustaining attention, holding information in working memory, and self-evaluation of performance through comparing the intended outcomes with actual outcomes. All of these processes engage subdivisions of the PFC.

Training tasks should adaptively challenge the patient

Even tasks that engage PFC control processes may become less challenging with practice, and thus less effective at encouraging learning. As a patient’s proficiency with a PFC function improves, tasks may be adjusted in such a manner that demands for PFC processes are increased. This is more specific than simply increasing the “difficulty” of the task, as parameters that are adjusted should quantitatively vary the level of engagement of specific PFC processes and not simply vary the level of general arousal or motivational processes. For example, to progressively increase working memory demands, stimulus load (the number of items to remember), or the length of the delay period (during which patients need to remember the items) can be increased in training tasks. Olesen and colleagues recently showed that an adaptive training program can increase working
memory capacity as measured behaviorally with an accompanied increase in PFC network activity as measured by fMRI.32

Training material should cross sensory modalities

PFC is multimodal association cortex, serving to integrate information from all modalities. Thus, the processes subserved by PFC networks may involve any sensory modality. This is illustrated in functional imaging studies of working memory processes that reveal similar activation of PFC networks whether visual, auditory, or even olfactory content is used.29,33 Thus, training across multiple modalities may maximize engagement of these underlying PFC networks.

POTENTIAL NEURAL MECHANISMS OF RECOVERY OF FUNCTION AFTER TRAINING

Rehabilitation of PFC dysfunction through training may be considered a process of guiding mechanisms of plasticity for the “reintegration” of functional PFC networks. That is, mechanisms of plasticity following brain injuries include the possibilities of reorganization of available network components, or the generation of new network components. Mechanisms of plasticity at the cellular level that may support reorganization or regeneration include alterations in metabolism, synaptogenesis, and synaptic pruning, including growth of new long-distance projections, and perhaps neurogenesis (reviewed in reference 34). These cellular changes do not fully describe the process of functional recovery, as the same changes could, if unguided, lead to tumor growth, for example. Ultimately, for these neuronal changes to affect neurologic function, they must be translated into changes in the functioning of networks of neurons. It is suggested that effective training guides these neuronal changes to achieve functionally integrated networks and coherent behavioral output. Although there are as yet few studies of these mechanisms of plasticity in the PFC, there is much evidence to support this principle in motor and sensory cortex.35-38

As an example, when diffuse axonal injury disconnects cortical regions in the anterior-posterior networks illustrated in Figure 1b, rehabilitation treatments may guide the cellular mechanisms above to enhance the functional reintegration of networks. At least 3 different levels of change may support reintegration of network function. First, integration of residual intact PFC regions with relevant posterior regions may be supported by synaptic reorganization and synaptogenesis. Second, within each PFC subdivision, network circuitry is likely analogous to a diffusely organized, parallel distributed network. With respect to functional recovery, this suggests the possibility of some redundancy in the circuitry, such that residual intact areas may be able to reorganize to take over function previously supported through other networked neurons. Training would, in essence, help in making damaged, poorly integrated collections of neurons into more efficient, better integrated functional networks for the performance of relevant tasks. Third, reorganization across the PFC subdivisions is possible. Given the extensive connectivity between the triad of PFC subdivisions (ie, lateral, medial, orbital), when one region is damaged, it is possible that other regions in this highly interconnected network may also reorganize, interacting with the residual neurons of the damaged region to provide the deficient function via a newly integrated functional network.

HYPOTHESIS TESTING

To determine whether particular training prescriptions enhance the function of PFC networks, treatment trials must be matched with the appropriate behavioral and network-level physiologic measurements. We propose a novel combination of fMRI measurements that should provide sufficient information to test hypotheses regarding network-level mediators of treatment effects. This discussion will be limited to hypothesis-driven
Table 1. Hypothesized changes in fMRI measurements of functional integration*

<table>
<thead>
<tr>
<th>PFC activity</th>
<th>Anterior-posterior connectivity</th>
<th>Modulation of posterior activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated frontal injury</td>
<td>Extent of activity: ↑↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Dispersion: ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intra-PFC connectivity: ↓</td>
<td></td>
</tr>
<tr>
<td>Attention and working</td>
<td>Extent of activity: ↑↓</td>
<td>↑</td>
</tr>
<tr>
<td>memory process</td>
<td>Dispersion: ↓</td>
<td></td>
</tr>
<tr>
<td>training</td>
<td>Intra-PFC connectivity: ↑</td>
<td></td>
</tr>
<tr>
<td>Goal management training</td>
<td>Extent of activity: ↑↓</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Dispersion: ↓</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intra-PFC connectivity: ↑</td>
<td></td>
</tr>
<tr>
<td>Training with repetitive</td>
<td>Extent of activity: ↓</td>
<td>↓ on trained content</td>
</tr>
<tr>
<td>stimuli</td>
<td>Dispersion: ↓</td>
<td>No change on nontrained tasks</td>
</tr>
<tr>
<td>(&quot;automatization&quot;)</td>
<td>Intra-PFC connectivity: ↓</td>
<td></td>
</tr>
</tbody>
</table>

*FMRl indicates functional magnetic resonance imaging; PFC, prefrontal cortex.

Measurements and is not meant to be a comprehensive introduction to functional brain imaging (see references 39 and 40). Predicted findings discussed next are summarized in Table 1.

**Hypothesis #1: Treatments that effectively target PFC networks result in changes in the integrative functions of the PFC, whereas other treatments do not.** As stated above, a central function of the PFC is the functional integration of task-relevant neural networks. Guided by the conceptual model presented above, the following 3 questions comprising this hypothesis may be addressed with specific measurements.

1. **Is functional integration within PFC networks changed by the intervention?**
   This question is best addressed with outcome measurements that are made possible with functional brain imaging such as fMRI. Prior functional imaging studies of TBI have primarily relied on univariate analyses to gauge differences in the level or extent of brain activity, leading to results that are limited to stating that PFC activity has increased or decreased. PFC activity has been found to both increase or decrease with injury, training, and perhaps fatigue, making it difficult to fully interpret these changes alone. For example, increases in activity have been described as representing compensation, recruitment, or maladaptive responses, while decreases in activity have been described as representing neural efficiency, automatization, or failure of recruitment. Thus, univariate measurements of activity provide only a starting point for understanding plasticity in PFC networks. Measurements that are more reflective of the integrative functions of PFC networks would be valuable.

Conceptually, when the injured brain is rehabilitated with the training described above, PFC networks would be hypothesized to be re-integrated. That is, after brain injury, more widespread activation occurs when a more diffuse, but poorly integrated PFC network is recruited to perform a function. With effective rehabilitation, activity within PFC networks should be better integrated during task performance, resulting in a less-diffuse pattern of activity (see Table 1). These conceptual hypotheses may be better addressed by a combination of quantitative fMRI measurements.
of the dispersion of activity (eg, the spread of task-related activation in a specified brain region) and the level of functional connectivity within PFC networks.

Introducing measurements of functional connectivity allows an additional and novel step forward in testing these hypotheses in rehabilitation studies. Functional MRI methods for measuring connectivity between brain regions are actively being developed. In general, multivariate statistical methods make use of the temporal characteristics of activity in separate brain regions to make inferences regarding the functional relationships of these brain regions. We hypothesize that increased functional integration of PFC networks should be reflected in measurements showing increased task-relevant connectivity between functional subdivisions of the PFC after injury.

2. Is functional integration between PFC and posterior regions changed by intervention? Conceptually, the strength of connectivity between the PFC and posterior regions reflects how effectively PFC controls processing in posterior regions. For example, during a visual working memory task, PFC should be more strongly connected to task-relevant visual cortex when there are no distractors than when a distraction is present. This prediction was supported in a recent fMRI experiment performed in our laboratory.

The effects of rehabilitation interventions on PFC networks can be addressed with fMRI by measuring changes in functional connectivity between anterior and posterior brain regions before and after training. We hypothesize that effective PFC rehabilitation training would result in increases in task-relevant functional connectivity between anterior and posterior regions. In contrast, training that does not emphasize PFC processes, such as memorizing simple motor sequences, would not result in such increases in connectivity. In fact, repetitive training with the same motor sequence may actually decrease the connectivity between PFC and motor cortex as the task becomes more automatic.

3. Is there a change in task-relevant top-down modulation of posterior brain areas? The overall effectiveness of PFC function can be considered in the context of how well the PFC can modulate other brain processes, such as those in sensory and motor cortices. The level of modulation of posterior neural processing may be quantified using an index of top-down modulation. To derive such an index, one must compare the level of activity in a posterior content-specific brain region when processing of information by that region is relevant to the task versus when it is not. For example, in 2 conditions when individuals are presented with matched visual information, activity in a scene-selective visual cortex area is upmodulated when individuals need to pay attention to scenes to achieve a task, and downmodulated when they need to ignore scenes. Several lines of evidence suggest that the PFC is the source of this top-down signal. For example, individuals with reduced PFC function, from injury or from "normal" aging, are less able to modulate sensory processing to selectively attend to task-relevant materials.

We hypothesize that measurements of top-down modulation would increase with effective rehabilitation therapy that targets PFC processes. This may be contrasted with training regimens that do not emphasize top-down control mechanisms, such as an associative memory training regime involving purely memorization of lists of items.

Hypothesis #2: Functional reintegration of PFC networks is an important mechanistic pathway by which rehabilitation training enhances frontal
executive function. We hypothesize that training that effectively improves indices of neural markers of functional integration in PFC networks will result in improvements on clinical measures of frontal executive function. For example, improved clinical performance on tasks requiring working memory would be correlated with neurophysiologic measurements of top-down modulation and anterior-posterior connectivity. Similarly, improved functional performance on goal management tasks would be correlated with improved connectivity within the PFC, as well as increases in measures of PFC-posterior connectivity and top-down modulation. This hypothesis may be tested by utilizing these measurements in the context of rehabilitation trials.

Hypothesis #3: Training that effectively targets PFC networks, resulting in improved functional integration, will be more likely to result in transfer of behavioral improvements to untrained, ecologically relevant tasks. Failure of transfer has been a limitation of many training approaches, but explanations for such treatment failures are lacking. Why do the effects of training frontal executive functions not transfer? The first consideration is the nature of the training tasks, as addressed in section, "A Unifying Theoretical Framework: Functional Integration in PFC Networks." To extend this further, it would be worthwhile investigating the neural mechanisms that mediate transfer of functions. We hypothesize that an important intermediate pathway for behavioral transfer effects to new, real-world contexts is the functional integration of PFC networks. We hypothesize that if PFC networks are a substrate for transfer, then training that effectively improves indices of functional integration in PFC networks will be more likely to improve behavioral performance on untrained tasks, including, in particular, tasks that require similar top-down control processes, applied to new situations that were not specifically trained. This contrasts in a subtle way with training to improve performance of specific tasks (e.g., preparing a peanut butter sandwich in the rehabilitation center kitchen), rather than the processes that help a person plan and cook meals. A patient may be able to learn this specific task well enough to return home and prepare this same meal, but not be able to apply the same processes of idea generation, planning, and prioritizing necessary to prepare a different meal when the peanut butter runs out. Even greater challenges requiring flexibility in control processes are presented in many workplaces.

Testing this hypothesis requires that neural and behavioral measurements, such as neuropsychological measures of executive function and functional task performance, are made in the same clinical trials so that the contribution of neural changes to behavioral changes may be analyzed.

CANDIDATE PATIENTS FOR PFC TRAINING APPROACHES

These training approaches would be best tested in a subset of patients with TBI who have mild-to-moderate executive dysfunction. Optimally, candidates would have preservation of some PFC function. Clinically, this may correspond to Rancho Los Amigos Outcomes VI–VIII. In particular, patients likely need to have the motivation to participate and some residual ability for goal-directed behavior. Anatomically, the ideal candidates would be patients with residual viable PFC cortex, with potential for reorganization of functional connections. That is, there must be available nodes and potential for connections in order for the networks within the PFC to reorganize. Thus, patients with mild-moderate frontal contusions or multifocal axonal injury would probably be prime candidates for training therapies. As lateralization of PFC function is not as strict as in other brain areas, patients with even severe unilateral damage may indeed be candidates as well. Unilateral damage may be compensated for through recruitment and reorganization of analogous contralateral PFC networks. Patients who have severe bilateral damage or total transection of subfrontal axonal pathways would likely be poor

www.headtraumarehab.com
rehabilitation candidates. In accord with severe disconnection syndromes, patients with significant thalamic lesions (especially bilateral) may also be poor candidates. These anatomical considerations translate, functionally, to exclude patients who suffer from a severe lack of initiation and motivation, such as in akinetic mutism.

CONCLUSION AND FUTURE DIRECTIONS

In summary, we hypothesize that after effective rehabilitation training aimed at enhancing PFC function, activity within the PFC should become better integrated, and there should be evidence of increased anterior-posterior functional connectivity. As further evidence of improved functional integration, there should be increased task-relevant modulation of posterior brain activity. Baseline PFC activity based on univariate analyses of fMRI data may or may not be increased. In contrast, training with repetitive stimuli, allowing “automatization,” would result in diminished PFC activity, reduced integration of PFC function, decreased anterior-posterior functional connectivity, and diminished task-relevant modulation of posterior brain activity. To further test how these neural network-level changes relate to performance on neuropsychological tests and performance in real-world activities, neurophysiologic, neuropsychologic, and functional performance measurements must be obtained together in clinical trials.

Combining a theoretical framework that incorporates an understanding of functional neural integration with neurophysiologic outcome measures may provide a powerful approach for improving training for patients with brain injuries. It is clear, however, that cognitive training alone may not be enough to overcome many of the deficits experienced by patients with brain injuries. A better understanding of plasticity in PFC networks may provide new targets for rehabilitation therapies. In particular, learning-related changes in PFC networks may be modified by pharma psychotherapies, more direct extrinsic targeting of PFC networks with methods such as transcranial magnetic stimulation, and adjunctive biologic modifiers of plasticity such as physical exercise, stem cells, and growth factors. Evaluation of treatments may be guided by our theoretical model of functional neural reintegration, providing mechanistic and clinically relevant outcome data to guide improvements in therapy. Ultimately, these forms of therapy should be considered adjuncts, while properly designed training regimens guide healing in the injured brain and provide the basis of all rehabilitation therapies. These approaches should be integrated into comprehensive programs for the neurologic rehabilitation of individuals with brain injury.

REFERENCES


42. Ricker JH, Hillary FG, DeLuca J. Functionally activated brain imaging (O-15 PET and MRI) in the study

www.headtraumarehab.com


