Functionally Activated Brain Imaging (O-15 PET and fMRI) in the Study of Learning and Memory after Traumatic Brain Injury

Advances in functional imaging technology and cognitive neuropsychology have resulted in paradigms in which participants can perform cognitive tasks during functional image acquisition. We will discuss the application of two approaches (oxygen-15 positron emission tomography and functional magnetic resonance imaging) that have recently been used to examine components of learning and memory following traumatic brain injury (TBI). Activated functional brain imaging findings that we will discuss may suggest possible functional reallocation and reorganization of brain substrates involved in verbal learning and memory following brain injury. The findings also are clearly in line with other research that indicates a prominent role for the frontal lobes in learning and memory functioning, and support the concept of distributed neural networks for memory-related functions, cognitive load, and the potential for examining brain re-organization after injury. Key words: *functional magnetic resonance imaging (fMRI), memory, neuroimaging, positron emission tomography (PET), traumatic brain injury*

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WITHIN FUNCTIONAL BRAIN imaging, two major categorizations of imaging paradigms exist: "resting" and "activated." Resting paradigms examine images during static or nondynamic conditions. Several resting functional neuroimaging studies have been conducted following traumatic brain injury (TBI), most of which have demonstrated some degree of hypometabolism or hypoperfusion within various regions of the cortex, primarily within the frontal lobes. Such findings are not unique to TBI, however, and are, in fact, found in a variety of neurologic and psychiatric conditions. (See Ricker and Zafonte[1] for a review.) Activation studies that require participants to engage in some type of cognitive task, however, are likely to be far more sensitive to the functional effects of

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brain injury or disease than resting studies, as activation paradigms allow for the experimenter to manipulate cognitive demands during the imaging session.[2] In this presentation, we will discuss these types of neuroimaging paradigms, and how they have been applied in the examination of learning and memory following TBI.

"RESTING" VS. "ACTIVATION" STUDIES

In essence, "resting" brain imaging studies are those studies that occur when a patient is in a resting state (or at least not required to engage in any activity). Resting studies make no formal or systematic demands on the subject to perform a particular cognitive or motor task. The subject is typically positioned within the scanner and extraneous stimuli are controlled (e.g., through the use of earplugs or instructions to keep eyes closed). It must be noted, of course, that controlling random motor activity (e.g., occasional movement of extremities) is difficult, while controlling random cognitive activity (e.g., "talking" to oneself while in the scanner) during any type of scanning is virtually impossible.

Resting positron emission tomography (PET) and single photon emission tomography (SPECT) studies among individuals with TBI have consistently demonstrated (depending on the method and tracer utilized) either hypometabolism or decreased resting blood flow, most predominantly within the frontal cortex.[3–9] In most of these studies, the presumed physiologic deficits were generally in excess of what would have been predicted solely from lesions in structural scans such as computed tomography (CT) or magnetic resonance imaging (MRI). It must be noted, however, that the simple presence of findings of resting hypometabolism or decreased resting cerebral blood flow does not provide evidence of nonfunctional neural tissue. For example, in a sample of patients with Alzheimer's dementia, Duara and colleagues[10] demonstrated functional activation (i.e., increased blood flow) during cognitive testing in the same brain regions that, at rest, demonstrated significant hypometabolism.

Given that many nonspecific factors can affect resting scans, interpretation of the (at best) correlational relationship between a functional scan and performance on any given cognitive task must be made very cautiously, as the relationship is indirect. Furthermore, few studies have attempted to directly correlate findings to cognition. In those studies[7] that have, the findings from psychometric assessments were correlated with the results of functional imaging studies that were quite separated in time (sometimes up to months apart). With this time separation, truly valid conclusions cannot be drawn regarding the relationship between cognition and brain status. Functional activation studies, however, allow investigators to examine *in vivo* regional changes within the brain while actually engaged in cognitive or motor activities.

In contrast to resting functional imaging paradigms, activated functional imaging paradigms require participants to perform some type of cognitive or motor task. Such tasks are usually performed within a defined set of parameters, and usually some form of overt response is required in order to ensure that the task is measuring the desired variable (e.g., subjects must press a button when a particular stimulus is presented). Given the nature of the technology and the physiological events that are being measured—usually change in regional cerebral blood flow—activation studies have much shorter time windows than resting studies during which imaging data can be acquired (e.g., approximately 50 seconds during oxygen-15 PET imaging, as compared to 20 minutes in fluorodeoxyglucose PET). These briefer windows may make it easier for subjects to maintain a particular cognitive set or task, and may

make it less likely (but not impossible) that they will become distracted or bored during scanning. Finally, activation studies utilized allow researchers to perform subtraction analyses on data sets. The digital correlates of baseline cerebral blood flow and control tasks (e.g., simply having someone count or make a repetitive motor response) can literally be subtracted from the presumed activations that are related to one's dependent variable. Thus, the experimenter is able to make better inferences about the activations that are related to the cognitive process being studied.

Although activation studies have been conducted using PET and fMRI among non-neurologically impaired individuals and some neurologically impaired populations, virtually no studies have been made that use a functional neuroimaging activation approach to examine learning and memory functioning in individuals who have sustained severe TBI compared with healthy adults. Such studies, however, would allow for comparisons of brain activation patterns during learning and memory tasks between healthy adults and survivors of TBI who are experiencing "memory difficulties." Advances in functional imaging technology and physiological tracers allow for paradigms in which participants can perform cognitive tasks during functional image acquisition. We will discuss the application of two approaches (oxygen-15 positron emission tomography and functional magnetic resonance imaging) that have recently been used to examine aspects of memory following TBI.

Memory functioning (broadly defined) has been a dominant focus of both behavioral (i.e., neuropsychological) and neuroimaging studies in non-injured and injured individuals, and impairments in learning and memory functioning are certainly contributors to disability following TBI. Given this, the focus of the present article is on impairments and presumed brain reorganization in working and episodic memory after TBI.

LEARNING AND MEMORY FOLLOWING TRAUMATIC BRAIN INJURY

Problems with learning and memory are common following significant TBI.[11–12] The nature of memory complaints can vary, however, and certainly many subtypes of learning and memory impairment occur after TBI.[13–17] Although much of the clinical emphasis on learning and memory problems following TBI has characterized the nature of the problem as reflective of a retrieval deficit, growing evidence shows that many of the everyday memory deficits following TBI can be characterized as a problem in acquisition of new information.[13] Such findings are consistent with current thinking about the presence of working memory impairment after TBI, given that working memory is critical in the encoding of new information.[18]

Although impairments in both working and episodic memory are hallmark features of TBI, many of the classic standardized measures of learning and memory functioning have been designed to measure only limited aspects of the memory process. Studies that rely exclusively on neuropsychological test data, however, cannot provide any direct information regarding the underlying brain substrates that are involved in information processing. As a result, with the relatively recent development of memory assessment instruments derived from research in cognitive neuropsychology, investigators have been able to examine learning and memory functions following TBI in greater detail.

PATHOPHYSIOLOGY OF TBI AND IMPLICATIONS FOR MEMORY AND IMAGING

Many neuropathological mechanisms that result in cognitive impairment after brain injury have been proposed. However, they have evolved predominantly through experimental

animal models of TBI or through postmortem studies of humans who have sustained severe (and usually fatal) TBI. *In vivo* cerebral substrates have been described in human studies, but have usually involved individuals who sustained some form of focal cerebral injury or insult (e.g., focal ischemic infarct or tumor). In TBI, the neuropathology is usually multifocal—or more precisely, diffuse.[19,20] This, of course, makes specific neuroanatomical inferences difficult if not impossible. Acute CT scans may sometimes be read as normal, but many morphologic changes are not seen acutely by CT (e.g., atrophy and some types of white matter changes). In addition, early MRI scans may not reveal the extent of the neuropathology. For example, ventricular and cisternal changes are associated with TBI but are often delayed or are not seen in initial scans (see the review by Bigler in this issue). White matter changes are frequently noted on MRI, but the cortical metabolic correlates and distal effects of these changes often are not known. However, while structural imaging remains important for diagnosis and acute management of head trauma, CT and MR scans have shown little predictive utility. For example, structural imaging has correlated poorly with measures of injury severity, neuropsychological testing results, and patient outcome.

OVERVIEW OF FUNCTIONAL IMAGING IN TBI

One way to overcome some of the limitations of structural neuroimaging is through the use of functional neuroimaging. Functional neuroimaging studies have as their primary advantage the capacity to provide an index of brain physiology, usually in reference to some previously defined anatomic region of interest. PET has been used as a research tool since the 1970s, but its application to TBI is only more recently being investigated (see review by Bergsneider and colleagues in this issue). By selecting appropriate radiolabeled compounds, PET has the capability of demonstrating specific biochemical or physiologic processes involved in cerebral metabolism. The PET image represents the spatial distribution of radioisotopes administered to the individual. Resolution and anatomic detail limitations do exist, but such limitations can be somewhat attenuated by superimposing or digitally warping the PET image on to a static image (i.e., standardized MRI for group data, or actual MRI images for individual participants). Historically, PET studies have used tracers such as [18F]-fluorodeoxyglucose (FDG) for the identification of resting (i.e., non-activated) regional brain metabolism. Activated studies of motor or cognitive activity can be accomplished through the use of tracers such as oxygen-15 (O-15) dissolved in water.

SPECT has been used as an alternative approach to PET, with its primary application being the gross localization of regional cerebral blood flow. SPECT imaging is based on the idea that chronic regional changes in rCBF can be indirectly gauged via externally placed gamma cameras, which detect the regional accumulations of tracer flow (or, in some applications, receptor-binding isotopes). The advent of multiple-headed scanners has improved resolution (although not to the point or PET or fMRI). Several sources of potential measurement error remain in SPECT technology, however. Unlike PET, most applications of SPECT imaging require that regional counts be normalized to an area that is presumably free of injury (which may be difficult to ascertain in diffuse injury such as TBI). Color SPECT images can be visually impressive, but reliable and valid interpretation is really only accomplished through quantitative pixel counting.[21] SPECT has been shown to have improved correlation with neuropsychologic testing when compared with structural

imaging following severe head injury, but caution must be applied in interpretation as control subjects have also been shown to have "abnormalities" on SPECT imaging.[22] These criticisms are not unique to SPECT, however, as all forms of functional (and for that matter, structural) brain imaging are subject to artifact and limitations that may confound interpretation. Substance use or the presence of emotional disorders can also impact upon the interpretation of results. Both PET and SPECT have been shown to be of use in research studies following brain injury, but there is no particular PET or SPECT profile that is clinically reliable or diagnostic for the presence of brain injury secondary to head trauma.[1,23]

OVERVIEW OF FUNCTIONAL ACTIVATION: MEASURES OF rCBF

In the case of monitoring regional cerebral blood flow, PET and fMRI measure the distribution of organic compounds that are linked to brain activity. For example, change in blood flow in fMRI is determined by relative deoxyhemoglobin/hemoglobin concentrations, and in PET, change in blood flow is determined by measuring the degradation of the radioactive isotope oxygen-15. Thus, an increase in deoxyhemoglobin (as occurs in fMRI), or an increase in the number of annihilated oxygen isotopes (as occurs in O-15 PET), allows for inferences regarding the relationship between brain structure and behavior. However, a measurement of rCBF does not delineate the mechanisms of cerebral activity and, due to limitations in temporal resolution, it provides virtually no information regarding the exact timing between brain activity and behavior. In other words, researchers measure the systemic fluctuation in blood flow that is associated with neural activation and not neural firing itself. Thus, the neurotransmitter systems responsible for activation, as well as the timing and arrangements of cell firing, remain undetectable with these neuroimaging techniques.

It should also be noted, that a measurement of rCBF is not equivalent to a measurement of cerebral metabolism, which is typically discussed in reference to cerebral glucose utilization. Although in healthy individuals resting blood flow has been highly correlated with cerebral metabolism, the stability of this relationship is much less clear following TBI. In fact, discordance between CBF and metabolism, or decoupling, has been observed in both the acute phases of TBI,[24] as well as during more long-term follow up. (See Bergsneider et al, this issue).

The present discussion will focus on approaches that capitalize on changes in hemodynamic response (namely changes in regional cerebral blood flow, or in levels of blood oxygenation). It should be noted that additional approaches have been used in TBI (e.g., electroencephalogram and quantitative electroencephalogram reviewed by Wallace and colleagues in this issue), and other approaches that await empirical validation in TBI (e.g., optical imaging approaches such as near-infrared spectroscopy, and event-related procedures such as magnetoencephalography).

Functional imaging by means of [O-15]-water PET has certain constraints that at present limit the paradigms that can be used. First, the task window during which an activity can be reliably scanned is somewhat short. A corollary problem also is associated with the time window for scanning: the activity needs to continue essentially for the duration of the scan in order to assure that the change in blood flow has been sampled sufficiently. Such temporal constraints limit what tests and time frames can be employed.

Using O-15 water activation, Fletcher and colleagues[25] demonstrated different functional neuroanatomical substrates for encoding and retrieval among neurologically intact

individuals. These substrates were generally consistent with previous psychometric (and even some animal) investigations, but a greater role of the frontal lobes in learning was indicated. In addition, these investigators also found lateralized activation differences. Activation was greater in the left frontal lobe during encoding, but greater in the right frontal lobe during retrieval. These findings are comparable to those of published investigations in non-impaired participants using O-15 PET[26] and functional magnetic resonance imaging.[27,28] Comparable studies in persons with TBI are needed, however.

OVERVIEW OF FUNCTIONAL MAGNETIC RESONANCE IMAGING

Functional magnetic resonance imaging (fMRI) involves the rapid acquisition of a series of MRI scans that are subsequently analyzed for changes over time. In current use, the most common dependent variable that is measured in fMRI is that of oxygenated blood within the context of changes in regional cerebral blood flow (rCBF). Oxygenated blood is magnetically different from deoxygenated blood (or, to be technically correct, hemoglobin is magnetically different from deoxyhemoglobin), and thus it is reasonable to expect it to be represented differently on MRI scans. It has been known for quite some time (using tracers such as Xenon-133 and Oxygen15 in PET) that changes in regional brain activity result in changes in rCBF. In other words, increased activity in a particular brain region should result in increased blood flow to that region. Because the blood that is flowing to a brain region is freshly oxygenated, it would be expected to be of greater signal intensity in a brain region that is experiencing increased flow. Basically, baseline activation is measured, and then is digitally subtracted from subsequent context-dependent activations. In the context of an appropriate experimental design, it is logical to infer that a particular activity is related to changes in blood flow in a given region.

It should be noted that fMRI maintains several potentials advantageous to 15-O PET imaging. For example, in a research setting, fMRI allows for a longer window of measurement that provides researchers with greater latitude in developing activation methodologies. Additionally, because of the widespread clinical use of MR, fMRI has greater potential availability and is significantly less expensive (the cost of PET is typically two to three times greater). In addition, within the context of rehabilitation and outcomes research, the use of fMRI is often preferred because it does not require the administration of an isotope, which allows for repeat measures (federal regulations exist regarding the frequency of radioisotope/pharmaceutical administration).

STATE OF THE LITERATURE/ CURRENT STUDIES

In spite of the fact that cognitive activation studies have appeared throughout the literature since the early 1980s (with PET) and early 1990s (with fMRI), a surprising paucity of such research is found that has examined individuals who have sustained TBI. In fact, we know of only three such studies (one using PET, two using fMRI) in this population.

PET data

A recent study by Ricker and colleagues[29] suggests that the cerebral mechanisms involved during episodic or long-term memory performance in TBI subjects is significantly different from that observed in healthy subjects. Behaviorally, the TBI subjects were more impaired relative to controls on recall than recognition. In fact, behaviorally the TBI patients performed at normal levels during a recognition task. Using oxygen-15-water

PET in a cognitive activation paradigm, we have demonstrated that there are robust differences between five TBI subjects and four healthy controls on tasks of free recall (power = .99, alpha = .01), cued recall (power = .96, alpha = .01), and recognition (power = .86, alpha = .01).

Ricker and colleagues[29] found that left frontal lobe rCBF changes in TBI subjects were reduced during free retrieval when compared to controls, but rCBF increases were noted in more posterior brain regions in TBI subjects during both free and cued recall. Such changes may be a function of a different level of processing (e.g., use of a phonological strategy rather than a more executive-organizational strategy[30]). The change in allocation of neural resources during tasks with greater cognitive load may suggest greater frontal lobe involvement that may be a function of greater effort.[31] In other words, the individuals with TBI must exert greater cognitive effort in order to perform the task. Greater increases in posterior rCBF may represent less cognitive demand and/or an increased dependence on a different level of processing.

Mean regional rCBF changes in the cerebellum were observed during free recall in the control group but not in the TBI sample. This finding is quite interesting, but its significance is not clear. Certainly a growing body of literature is supporting theories that pertain to the role of the cerebellum in human cognition,[32] but the results also may be explained from a more purely neuroanatomic perspective. Established connections are found between the cerebellum and frontal association cortex.[33,34] It is quite possible for injury in a cerebral hemisphere to affect the contralateral cerebellar hemisphere (a phenomenon known as crossed cerebellar diaschisis[35]) that results in lower—or at least unmeasurable—activations in individuals with brain injury.

Of additional note is the finding that during recognition tasks, both TBI and controls performed at comparable behavioral levels (*and* within normal limits). However, the TBI group still demonstrated increase change in regional cerebral blood flow relative to the controls. Although this finding is from an episodic (rather than working) memory paradigm, the idea is supported that TBI subjects must exert more cognitive effort than controls to attain the same level of overt behavior.

fMRI studies of working memory after TBI

The first neuroimaging activation study that investigated working memory (WM) in individuals with TBI[36] examined only individuals with a very recent history of mild head injury (i.e., within one month after sustaining injury). As in the Ricker et al[29] PET study reviewed here earlier, the mild TBI subjects patients in that study did not demonstrate behavioral impairment on a verbal WM task; however, they did show right-lateralized activation, displaying a right lateralized increase in activation (particularly right prefrontal and right parietal) in response to increased verbal WM load.

We recently employed fMRI to study functional cerebral activity after TBI.[37] To our knowledge, our study is the first fMRI data set collected to date in moderate and severe TBI patients. We compared nine moderate and severe TBI subjects to seven healthy controls on a modified version of the Paced Auditory Serial Addition Test, a test of working memory and speed of information processing. Structural MRI scans (read by a neuroradiologist who was blind to group membership) suggested that one of TBI patients had a left frontal contusion, one patient had a right frontal contusion, one had bifrontal contusions, and the remaining six had diffuse injury.

The results of fMRI scanning demonstrate that, relative to healthy controls, persons

with moderate or severe TBI demonstrate increased blood flow and more widespread dispersion of cortical activation during working memory tasks. While we found that the same general cerebral regions were activated between TBI and healthy controls on fMRI (e.g., frontal, temporal and parietal activation), we also noted: (1) the TBI subjects showed more right hemisphere activation relative to controls, and (2) activation was more diffusely represented (i.e., more dispersed) in the TBI subjects relative to controls. Random effects analyses demonstrated significant activation in the middle frontal gyrus, and superior and middle temporal gyri in both TBI patients and controls. Interestingly, however, the TBI group displayed greater activations in the right hemisphere, while healthy controls displayed greater left hemisphere activation in these same regions (see Figure 1).

In addition to the random effects analyses, group differences in laterality of activation were also assessed by means of a laterality index (Left − Right/Left + Right × 100). TBI subjects displayed activation that was significantly more lateralized to the right hemisphere compared to healthy controls ($t = -2.041$, $p = .031$). The difference in means between the groups represents a large effect size ($d = .96$). More specifically, five of the six subjects with right lateralized activation (i.e., negative laterality index scores) were from the TBI group, while five of seven subjects with left lateralized activation were healthy controls. In order to determine whether the overall cerebral laterality effect was specific to particular regions of the brain, laterality indices were created to examine activation in each cerebral lobe separately (using the same basic formula: L − R/L + R × 100). Each lobe of the brain tended to display the same trend, though only the laterality index for the frontal lobe reached statistical significance ($t = -1.866$, $p = .042$).

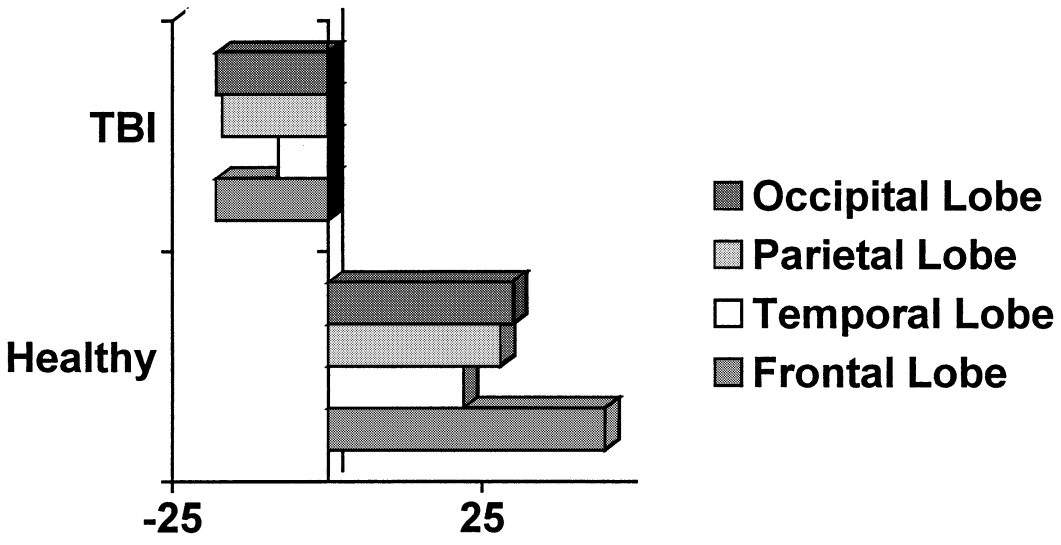

Fig 1. Laterality indices for fMRI data

(*Note:* Positive numbers indicate greater lateralization to the left hemisphere, and negative numbers indicate greater lateralization to the right).

For the purposes of computing the dispersion of activations, activation outside the middle frontal and temporal gyri was considered diffuse or "dispersed." These regions were chosen because they were consistently activated in the healthy control group. Based upon the diffusion index, TBI subjects were found to display significantly more widely dispersed activations than did the healthy controls ($t = 1.969$, $p = .035$). This difference represents a large effect size ($d = 1.00$). More specifically, six of the nine subjects with more diffuse activation (i.e., positive diffusion index scores) were from the TBI group, while three of four subjects with less diffuse activation were controls. Thus, we know that after moderate and severe TBI, behavioral impairment is found in working memory, and this is reflected in altered cerebral activation. That is, TBI subjects showed increased right compared to left hemisphere activation on this verbally based task, and TBI subjects also needed additional cerebral resources to perform the task. What is not known, however, is where within working memory the deficiency is occurring.

Conclusions from PET and fMRI research findings

Taken together, the limited functional neuroimaging literature in TBI suggests that at the cerebral level, individuals with TBI process information less efficiently than controls. This finding has been demonstrated not only in working memory, but also in a simple episodic memory paradigm. Although many unknowns remain—such as the specific mechanisms in working memory that initiate activation and the degree to which task difficulty interacts with the various components of working or episodic memory—these findings support the hypothesis that individuals with TBI engage in greater "cognitive effort" even to attain the same level of cognitive performance as controls. We also hypothesize that there is the need not only for more effort but for greater numbers (i.e., more dispersed)—and differently lateralized—cerebral resources.

The present PET and fMRI findings are consistent with previous studies of healthy adults that demonstrate prefrontal and parietal activations during working and episodic memory tasks.[38–41] These findings also suggest that individuals with TBI are still able to frequently invoke activity in many of the same regions as controls. Of note was the general comparability of both behavioral performance and brain activation during recognition tasks in both control and TBI groups. This is not necessarily surprising for a number of reasons. First, psychometric studies have established that verbal recognition memory performance is relatively robust, even following severe brain injury.[13–17,42] Second, recognition tasks represent very simple and passive paradigms, and thus may require less extensive neuronal processing (i.e., less cognitive effort) than recall tasks. Thus, recognition is a relatively low-load cognitive condition that should not require a large allocation of cognitive or neural resources.

Several methodological issues and potential shortcomings must be considered in the current functional neuroimaging literature. First, these studies all have small sample sizes, which limit statistical analyses and the conclusions. The tasks that have been used are more similar to those encountered in the clinical assessment of brain injury, but they may not be of sufficient complexity to allow a more detailed functional "dissection" of learning and memory substrates (as might be defined from a cognitive neuroscience perspective). The construct of "memory" is multifaceted, however, and the use of other stimuli and paradigms (e.g., memory for visually presented information, paired associate learning, interference tasks, etc.) may yield very different results. Likewise, learning and memory impairment is not the only deficit

encountered following brain injury. Patients with TBI can present with a host of executive control and other cognitive impairments that are associated with altered activity in other brain regions.

The few samples of TBI survivors that have been studied using functional activation paradigms may not be representative of those encountered in many clinical settings. Functional activation studies can only be reliably performed with very cooperative participants who are able to tolerate a physically constraining environment (i.e., without head movement or other extraneous motion), while simultaneously engaging in complex cognitive tasks. Different patterns of brain activation are likely to occur during various stages of recovery, and thus future studies could examine how the reallocation of neural resources changes over the course of recovery following TBI.

IMPLICATIONS OF FUNCTIONAL IMAGING STUDIES FOR THEORIES OF BRAIN REORGANIZATION

The present PET and fMRI findings may suggest possible functional reallocation of brain substrates involved in verbal memory following brain injury. Two lines of overlapping explanation are found: One is that there has been reorganization; the other is that greater effort is required of the injured brain.

Recovery of function after brain injury is often assumed, at least in part, to be the result of some form of reorganization in the brain.[43,44] Neural plasticity is thought to underlie at least some of the changes that occur from the process of neurorehabilitation,[45,46] but to date little empirical evidence has been available in humans of the substrates of this plasticity. Individuals who sustain TBI often demonstrate some degree of recovery. It is very difficult to determine, however, if the improvement is simply the result of natural spontaneous recovery, or if it is due in whole or in part to intervention (e.g., cognitive rehabilitation). The concept of neural "plasticity" is often invoked as the explanation for any improvement seen in function. Used by itself, however, the concept has little explanatory power. For example, improved behavioral function may simply be the result of learning "tricks" in compensating for deficits.[44] In addition, the fact that changes occur at a molecular or cellular level is not evidence, in and of itself, of actual functional improvement.[43] Thus, in order to infer that an intervention has had a beneficial impact both functionally and neurally, one must utilize procedures that allow for the integrative analysis of both behavior and physiology. Functional neuroimaging during the performance of cognitive tasks is one approach that would permit investigators to further determine what techniques truly impact upon the cerebral substrates of learning and memory.

Some investigations have utilized fMRI in assessment motor recovery. For example, Miyai and colleagues[47] have recently presented fMRI findings obtained during the rehabilitation phase of 12 patients who sustained hemiparetic strokes. The results indicated that patients who demonstrated improved use of the affected limb also had new or enhanced activation detected by fMRI in the supplementary motor area, the contralateral sensorimotor cortex, or the ipsilateral parietal cortex. By contrast, patients without significant recovery demonstrated lower relative fMRI activations. The findings suggest that successful brain reorganization during recovery after stroke involves multiple cortical areas, and that lack of activation might predict a poor recovery. We hypothesize that the same cerebral reorganization occurs with cognitive interventions.

"Cognitive effort" is difficult to define, and interacts with both brain status (i.e., injured vs. non-injured) and task difficulty. The suggestion that individuals with TBI must exert

greater effort during cognitive tasks is intuitively appealing, but its implications are far-reaching. Clinically, survivors of TBI often report that they must now "work harder" to perform tasks that they previously found to be simple. The PET and fMRI data that we have reviewed suggests that individuals with TBI may indeed exert more "brain resources" (as inferred from increases in rCBF and greater dispersion of brain activation) even to achieve the same level of overt behavioral performance as healthy controls.[29,37] Such a finding suggests that traditional behavioral tasks (i.e., neuropsychological tests) may have significant limitations in accurately characterizing the nature and extent of cognitive impairment following TBI. This is clearly a prime target for future functional brain imaging research in clinical populations.

IMPLICATIONS FOR FUTURE RESEARCH

The findings from the PET and fMRI literature are clearly in line with other research indicating a major role for the frontal lobes in learning and memory functions.[30,48] Although many learning and memory components are often thought of as primarily temporal lobe or hippocampal function, current research and the present findings support the concept of distributed neural networks for memory-related functions, with greater emphasis on the role of the prefrontal cortex on memory tasks requiring increased cognitive demand.[49] In addition, investigating the substrates of learning and memory impairment in TBI may assist in determining patterns of cerebral reorganization.[44] If patterns are found, they may be of use in making inferences regarding the effects of spontaneous recovery versus rehabilitative intervention.

Although functional activation studies of working and episodic memory after TBI are still quite investigational in nature, such studies may eventually be of clinical relevance and applicability. In addition, increased Tesla power is providing refinement of spatial resolution and issues of temporal resolution are beginning to be addressed with methods such as event related fMRI.[50] Continuing advancements improve research paradigms and allow for researchers to address more specific questions regarding cognitive functioning. Greater specificity when defining a TBI patient's acquired learning and memory disorder may assist in predicting potential or level of benefit from rehabilitation or pharmacologic intervention. In view of the small sample sizes, it cannot be ruled out that certain true group differences remained undetected. Finally, expanded information regarding the cerebral substrates of learning and memory impairment and other cognitive deficits following TBI may eventually assist in differential diagnosis, as various premorbid psychiatric conditions or other states of emotional disruption are associated with alterations in functional neuroimaging findings.

Functional brain imaging studies have important implications for TBI rehabilitation. One of the major goals of cognitive remediation is to help TBI patients learn new information more accurately and efficiently, and to improve their performance in activities of everyday life.[51] Because working memory impairments are so prevalent in TBI, the present study can help to shed light on the cerebral underpinnings of cognitive impairment. In spite of the prevalence and popularity of cognitive remediation strategies and procedures, little empirical support remains for their efficacy, and virtually no understanding is found for the underlying neurocognitive processes that facilitate intervention.[52] If the previously demonstrated finding of increased "cognitive effort" at the cerebral substrate is needed by TBI subjects—even to attain the same net behavioral effect, such findings would suggest that the goal of rehabilitation/intervention should not simply be one of behavioral

increase (i.e., training someone to take tests so that they can overtly perform within normal limits on superficial cognitive tests). Instead, it should be an attempt to elicit change at the level of the cerebral substrates of working memory. As discussed previously, the components of working memory are dissociable, and case studies exist that demonstrate specific impairment in one type of working memory but not another.

An increased understanding of working memory impairment may lead to improved interventions. For example, if it is determined that a deficit in rehearsal exists, strategies can be developed to teach patients to spend more time engaging in rehearsal as a compensatory strategy. Alternatively, the findings may indicate a disproportionate impairment in phonological processing as compared to visual processing, which would lend itself to another direction in cognitive intervention.

As stated previously, very few studies are available that directly address the neurofunctional substrates of cognitive impairment after TBI. Until much research is conducted and reliable results are obtained, it will be quite difficult to make claims for an empirically based science of cognitive rehabilitation. Although the need for rehabilitation of cognitive processes following brain damage is beyond doubt, the vast majority of the principles underlying clinical approaches to cognitive rehabilitation have not been scientifically verified.

A recent consensus conference sponsored by the National Institutes of Health on the need for cognitive rehabilitation research following traumatic brain injury (TBI) echoes these points.[52] Specifically, this conference stated that: "Studies are needed to evaluate the relationship between specific cognitive deficits and global outcomes." In their review of the cognitive rehabilitation literature with TBI, Carney and colleagues[53] outlined the significant need for cognitive rehabilitation, and called for methodologically sound scientific research to study cognitive impairments and its rehabilitation. Achieving this level of understanding will be a major goal of research. Functional neuroimaging is a novel and innovative way to examine the precise mechanisms compromised in the efficiency of processing information within working memory and thus may be potentially useful in the process of measuring effectiveness of cognitive rehabilitation.

Although fMRI is still a relatively new procedure, it nonetheless has several potential future applications in medical rehabilitation that can only be realized if the enormous amounts of benchmarking research are conducted. FMRI has been used in the study of treatment outcome in stroke rehabilitation.[47] To date, however, there have been no investigations that have used fMRI in the context of TBI rehabilitation, particularly in the realm of cognitive functioning. Potential applications of fMRI in TBI rehabilitation include the following:

1. fMRI could be used to evaluate the efficacy of interventions by providing objective demonstration of long-term or permanent changes at the cerebral level.
2. fMRI could be used as an assessment tool in and of itself. For example, once neurofunctional "markers" or correlates of particular cognitive disturbances have been established, it will be possible to compare an individual's performance to that of populations who are known to be impaired (similar to the manner in which psychometric test results are compared to normative databases or standardization samples.)[54]
3. fMRI may eventually be used as a prognostic tool. For example, if following an intervention that has a known efficacy duration (i.e., therapeutic efficacy onset window), patients do not show improvement at the neural level, future strategies

and planning can be focussed at the level of compensating for permanent deficits. For instance, we have data from our research from very severe learning and memory impaired subjects who, despite a generally effective cognitive rehabilitation intervention, are unable to effectively learn new information.[13] If it is determined through neuroimaging that particular brain regions are associated and perhaps predictive of this level of behavioral debilitation, then such information could potentially be used as a marker for targeted and tailored cognitive rehabilitation approaches. It holds the promise of improving our ability to evaluate and compare different approaches to cognitive remediation, predict functional outcomes, and judge the effectiveness of new medications.

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