THE NEW NEUROSCIENCE FRONTIER: PROMOTING NEUROPLASTICITY AND BRAIN REPAIR IN TRAUMATIC BRAIN INJURY

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Increased awareness of traumatic brain injury (TBI) in the military, a persistent call for evidence-based treatment, and recent government funding have revealed new research opportunities in neuroscience. This paper describes a relatively new frontier for research: that of the facilitation or enhancement of neuroplasticity and brain repair in TBI using novel treatment protocols. Such protocols, algorithmically introduced, may be tailored to the individual through the matching of neuromarkers with specific interventions. Examples of neuromarkers and interventions employed for the purpose of neuromodulation are reported. Problems with lack of controlled studies and inferring causation in correlational research are noted. Healthy skepticism and open-minded creativity are needed so that we can think in unorthodox ways, create partnerships, harness available knowledge and expertise, and ultimately develop effective treatments.

Keywords: Neuroplasticity; Neuromarkers; Neuromodulation.

INTRODUCTION

Frontiers in science and medicine are not uncommon, as they are the introduction and extension of any new, untapped field of learning or thought. The purpose of the present article is to indeed present a new frontier in neuroscience, which invites systematic investigation, empirical research, and standardized methods: the facilitation or optimization of neuroplasticity and brain cell repair in traumatic brain injury (TBI). Urgently spurred on by the needs of wounded military personnel and their families, and by the calls of the “Report of the International Conference on Behavioral Health and Traumatic Brain Injury” (2008) and the Congressional Task Force on Traumatic Brain Injury (see Pascrell, 2009...
this issue) we, as neuroscientists, face an unprecedented opportunity to substantially advance our knowledge and treatment of brain injury.

Frontiers are often precipitated by major cultural or world events. The field of neuropsychology was so unleashed by the serendipitous experience of Alexander Luria’s work with brain-injured soldiers for the Soviet military in World War II. As with all new scientific frontiers, skepticism and resistance may hinder the integration of novel schemata and anecdotal case studies into contemporary theoretical frameworks. Skepticism, applied in science, is a valuable attribute that provides safeguards. Luria and his mentor Lev Vygotsky, although restricted by the political philosophy of their times, inevitably challenged the psychological arenas of their era, moving from an introspective psychology to a new frontier that considered the sociocultural influences on cognition, and brain–behavior relationships (see Cole & Cole, 1979).

Similarly, in the 1940s Jerzy Konorski, a Polish neurophysiologist, forged the concept of brain “plasticity,” suggesting that the brain has the ability to modify, strengthen, and create, as well as eliminate, synaptic connections in response to stimuli and life events (Zielinski, 2006). Hebb (1949) developed this concept further, describing “use-induced plasticity” of the nervous system, thus heralding a new frontier in brain science which resulted in the later discoveries of the importance of enriched environments on the developing brain (Rosenzweig & Bennett, 1996). The property of plasticity results from the broad connectional organization of the cortex and the capacity for activity-driven synaptic strength changes (Sanes & Donoghue, 2000). Plasticity can occur via four processes. First, unmasking can occur whereby neural pathways that had been kept dormant by inhibition are made functional by the removal of the inhibitory signal (Jacobs & Donoghue, 1991). Second, a strengthening or weakening of existing synapses can occur through the process of long-term potentiation (LTP) or long-term depression (LTD) (Hess, Aizenman, & Donoghue, 1996). Third, there can be a change in neuronal membrane excitability (Halter, Carr, & Wolpaw, 1995). Fourth, anatomical changes can occur such as the sprouting of new axon terminals or the formation of new synapses (Toni, Buchs, Nikonenko, Bron, & Muller, 1999). Currently, brain plasticity training and interventions are being developed in an effort to combat the downward spiral of negative plastic changes that occur in age-related functional decline (Mahncke, Bronstone, & Merzenrich, 2006). The idea that one might be similarly able to manipulate the brain’s external and internal environments and affect neuroplasticity in patients with TBI follows logically and thus appears promising.

The current paper presents a glimpse of this concept of neuroplasticity and its role in a new frontier, healing injured brain cells. This new frontier will challenge our thinking and may require us to table some old notions, at least for now, in order to consider the possibility of being able to prevent neuroplasticity degradation that follows TBI and to promote recovery of injured brain cells through novel treatments.

A CALL FOR RESEARCH AND TREATMENT

The wars in Iraq and Afghanistan are major world events that currently provide an increased awareness of the enduring and devastating effects of TBI. Medical and health care advances have decreased the rate of mortality in
trauma cases. Whereas it was an average of 45 days before a soldier wounded in the Vietnam conflict returned to the continental United States for medical treatment, a soldier wounded in Iraq may arrive at the Landstuhl trauma center in Germany in as little as 12 hours and then be transported home to the United States within a period of 3 days (Hyer, 2006). Survival rate for the Vietnam conflict is documented at 76% compared to the rate for the current wars in Iraq and Afghanistan, which is at 90.5% (Hyer, 2006).

With improved trauma care, those individuals who survive the most serious injuries are left to manage neurological disorders and impairment. For cases of mild TBI that do not resolve, the effects may not seem readily visible but are nonetheless far-reaching, affecting loved ones, family, friends, and community, and often resulting in chronic unemployment, increased hospitalizations, homelessness, substance abuse, and suicide (Kube & Johnson, 2009). Similarly, the opposite end of the severity spectrum of TBI, comprised of severe disorders of consciousness (SDOC), traumatizes family members, drains the hospital care system, and tears at the fabric of our greater society.

Injuries sustained by military service members in Operation Enduring Freedom and Operation Iraqi Freedom have prompted the United States Congress and the Department of Defense to take swift action, searching for effective evidence based treatments for traumatic brain injury (see Department of Defense, 2009). With millions of dollars allocated toward the assessment and treatment of wounded warriors and their families, frustration has been mounting as to whether scientists, clinicians, technologists, and others are truly able to provide answers, "cures," and deliverables. The pressure is on the scientific community, whether the military, private, or non-profit sectors, to generate innovative, novel approaches that are scientifically validated and maximally effective. Recently, scientists have the prospect of unprecedented access to government funding sources to facilitate breakthroughs and conduct research that will lead us down new treatment pathways and render benefits for all those who suffer from TBI.

The International Conference on Behavioral Health and Traumatic Brain Injury provided a think-tank platform for the presentation of state-of-the-art, forward thinking about ways to address the problems of TBI, not only in the military, but also in the large civilian community. The creation of this venue was in part fueled by families and loved ones of wounded warriors who are desperate to access the products of translational research in their search for hope, and who are often willing to try any reasonable treatment possibility.

There are many experimental treatments being employed to address the entire spectrum of brain injury, from severe disorders of consciousness and acute injury to mild TBI/concussion. What is currently needed is to validate the clinical and translational work on neuroplasticity that is being conducted globally, so that we can expedite treatment in an evidence-based manner. We are called to build this bridge, starting with anecdotal, variably controlled, small research or case studies and treatments (see Whyte et al., 2005). The goal is to create a menu of operationalized and standardized treatment algorithms. This bridge, however, requires a theoretical framework from which to draw hypotheses. One such framework is that of the identification of a spectrum of neuromarkers to guide treatment, and the utilization of a complex menu of neuromodulation and
other interventions, to normalize brain functions and promote neuroplasticity and brain cell repair: the new neuroscience frontier.

A NOVEL TREATMENT FRAMEWORK

How can we facilitate recovery of neuroplasticity in TBI? We assume that we cannot bring back the function of dead brain cells. However, is it possible to normalize the brain environment, electrochemically and metabolically? Perhaps by establishing a more normalized environment, the brain may be better able to reorganize itself, resulting in quicker recovery, decreased cell death, and the re-emergence of lost functions. The idea is to (1) identify neuromarkers, such as specific neurotransmitters or hormones, for example, that are directly related to the biochemical cascade of TBI, (2) validate specific interventions, such as neuromodulation (e.g., use of electromagnetic stimulation), cognitive rehabilitation, off-label pharmaceuticals (that target neurotransmitters), nutraceuticals (such as vitamins, minerals, proteins, amino acids), median nerve stimulation, and neurofeedback, which might be effective in normalizing those neuromarkers within the brain environment, and (3) determine the safety, efficacy and affordability of these new treatment protocols through controlled, blinded studies. Thus, treatment would consist of identifying/quantifying neuromarkers in the injured brain, and then individualizing multimodal interventions that would normalize the brain environment so that it would maximize natural healing, in turn facilitating rehabilitation and neuromodulation.

The concept of tailoring treatments to patient characteristics is gaining great attention internationally (Gordon, 2007; The Royal Society, 2005) especially in the arena of pharmacogenomics, in which pharmaceutical treatments are matched to the patient’s genetic traits via identification and use of biomarkers. However, it has been difficult to conduct well-controlled studies on individualized treatments, as each patient may possess a different set of traits and thus receive a unique set of applied interventions.

The use of markers to identify and guide treatment is a relatively new approach in the history of medicine, beginning with the focus on single biomarkers and specifically applied pharmacotherapy intervention, such as in the case of the antibody drug breast-cancer treatment for women who exhibit the overly expressed human epidermal growth factor receptor 2 (HER2) (Gordon, 2007). What is novel about the treatment approach presented here is that it builds on our more recent knowledge of the brain chemical cascade, focuses on TBI, and proposes to integrate numerous diagnostic, cutting edge tools to guide new innovative, advanced diagnostic and treatment protocols that are currently being developed (Dingfelder, 2009).

Identifying neuromarkers

The seminal work regarding the relationship between the apolipoprotein E (APOE) allele and the risk of developing Alzheimer’s disease helped to usher in the concept that we can identify genetic brain markers that may predict cognitive disorders (Saunders et al., 1993). Building on that discovery, there is evidence that
the use of functional magnetic resonance imaging (fMRI) technology and the identification of APOE (3 and 4 alleles) may predict memory decline in individuals (Bookheimer et al., 2000). The latter authors reported that “Patterns of brain activation during tasks requiring memory differ depending on the genetic risk of Alzheimer’s disease and may predict a subsequent decline in memory” (p. 450). The identification of neuromarkers has also been demonstrated by single photon emission computed tomography (SPECT) and positron emission tomography (PET) measurements of neurotransmitters for the differential diagnosis of Parkinson’s disease (Ilgin, 1998). Similarly, the attention deficit hyperactivity disorder (ADHD) research abounds with searches for brain patterns that may serve as diagnostic markers. Hermens and his coauthors (2005) documented correlations between specific electroencephalographic indices (resting EEG theta activity) and accuracy/reaction time on cognitive tasks that differentiated children with and without ADHD. The more recent discovery that (cerebrospinal fluid) CSF tau may predict the post-1 year outcome of those patients with severe TBI is groundbreaking (Ost et al., 2006). Not surprisingly, it has been posited that it could lead to a “routine clinical test” as a biochemical predictor of brain trauma severity, noted by James Kelly, MD (Goodman, 2008).

We have come to understand the chemical cascade of TBI (Giza & Hovda, 2001) that reveals a disturbance of the potassium, sodium, and calcium ion balance, as well as the occurrence of hyperglycolosis, glutamate alterations, decreased oxygen, and apoptosis. This astute, methodical research imposed a paradigmatic shift in our thinking about TBI. It now provides the foundation for identifying relevant neuromarkers and discovering treatments to prevent and repair traumatically induced damage. Once theoretical questions are now yielding to action-oriented translational research aimed at improving CNS bloodflow, oxygenation, and nutritional blood supply. Current and future studies will focus on this metabolic cascade, whether trying to prevent it, halt it, or reverse it by targeting neuromarkers with novel interventions to facilitate neurorecovery.

Nevertheless, accurately identifying neuromarkers and determining their sensitivity and specificity is a formidable challenge. For example, the problem of identifying neurofibrillary tangles and senile plaques in Alzheimer’s disease is well known. Imaging techniques are hampered by the lack of suitable agents that can cross the blood brain barrier (Backsai & Klunk, 2002). Identifying brain activation patterns is replete with methodological issues when using MRI measures: scanner sensitivity, accuracy of signal measure, movement of the individual (Bookheimer et al., 2000).

Despite these difficulties, in the last couple of decades we have become better at identifying and measuring biomarkers. We can measure O2, glucose consumption, neurotransmitters, and electro-chemical and spectral brain activity. We also have advanced technologies that provide us with extensive data that still may not be well understood or explained by standard theoretical frameworks. The brain can be assessed in a multitude of ways that go beyond the scope of the present article: PET, SPECT, magnetic resonance spectroscopy (MRS), quantitative magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), functional MRI, magnetoencephalography (MEG), evoked and event-related potentials, near infra-red spectroscopy, autonomic nervous system (ANS) mapping, and bispectral index (BIS).
monitoring, as well as by cognitive rating scales and neuropsychological testing. Importantly, neuromarkers identify preserved functions, and if accurately defined, may be able to guide us to develop prescriptive interventions.

**Identifying interventions**

Many of the myriad interventions mentioned above have been used to facilitate neuroplasticity and remediate CNS dysfunction both in published studies (Boggio et al., 2007; Liepert, 2005; Reis et al., 2008), as well as in studies that have been underway over the past few years (P. DeFina & J. Fellus, personal communication, April 20, 2009). Understandably, those interventions that are non-invasive tend to exhibit many advantages over those that are invasive. Non-invasive techniques tend to be easier to implement, with less physical risk and fewer liability concerns, less arduous IRB clearance, and lower cost than, for example, deep brain stimulation. Such techniques have already demonstrated value in the recovery of motor functions related to stroke. There is promising evidence that non-invasive transcranial magnetic stimulation (TMS) improves motor recovery (Liepert, 2003), and may have other applications (Silvanto & Pascual-Leone, 2008). Transcranial direct current stimulation (tDCS) has shown promise in motor improvement in post stroke cases (Boggio et al., 2007). This approach to motor recovery may guide the development of an application for cognitive recovery.

Non-invasive techniques such as quantitative EEG (QEEG) and MEG, which provide indices of amplitude, phase lag (speed of signal), frequency, and coherence, can be employed not only in the identification of neuromarkers but also to help guide non-invasive interventions. Yet the lack of rigorous controls in this area of electrical research is problematic. For example, in a study of participants with mild TBI or ADHD who received 20 sessions of cognitive retraining and EEG biofeedback, positive results were reported on measures of attention and response accuracy employing the Intermediate Visual and Auditory Continuous Response Test (Tinius & Tinius, 2000). Yet this study’s serious limitations include lack of a placebo condition, and the inability to differentiate the individual efficacy of each intervention. However, recent work using randomized controlled research is promising in the validation of the effectiveness of EEG biofeedback, and overcoming the shortfalls of previous, mainly clinical, findings (Gevensleben et al., 2009).

In their review of the literature on transcranial magnetic stimulation and cortical mechanisms of motor control, Reis and her co-authors (2008, p. 354) elucidate some of the common pitfalls in the published research:

…the specific relationship between physiological changes and motor behavior remains elusive…more work is needed to prove that the associations between specific functional interactions and behavior represent more than mere epiphenomena of the specific behavior. The design of these types of experiments represents one of the crucial challenges ahead of us.

Indeed, McCallister (2009 this issue) has posed the dilemma of using correlational indicators or markers for the psychopharmacotherapy of TBI and post traumatic stress disorder (PTSD). We may choose medications in an effort to
alter the indicators or markers of a disorder, but that does not necessarily mean that we are altering the patient’s outcome or functions. Simply put, causality is difficult to determine.

**Facing the frontier**

Partnerships and consortia around the world, from Charlottesville to Tokyo, are addressing the most severe disorders of consciousness with advanced treatment protocols (Cooper & Cooper, 2008). Such creative, scientific partnerships are also needed to address the entire spectrum of TBI, from mild to most severe. There are TBI treatment protocols and advanced algorithms currently being implemented based on the framework of neuromodulation of neuromarkers (P. DeFina & J. Fellus, personal communication, April 20, 2009). These protocols and algorithms remain in their infancy. Since these novel algorithms are in their early stages of development, clinicians may disregard them as scientifically unvalidated. But what is needed is to harness the relevant global knowledge and expertise to rigorously test such protocols. The Department of Defense and Congress are ready to support such scientific, collaborative ventures (Department of Defense, 2009; Report of the International Conference on Traumatic Brain Injury and Behavioral Health, 2008). Importantly, no one discipline or technology can do this. With sophisticated modes of communication, scientists and laboratories do not need to be isolated in their clinical trials. We can bring together multidisciplinary teams of scientists: neuropsychologists, neurologists, neurosurgeons, physiatrists, physicists, mathematicians, chemists, engineers, and others to develop an interdisciplinary approach to the treatment of TBI and to the facilitation of neuroplasticity. In working with international partners we will need to be culturally sensitive to, and respectful of, different ways of conducting research, and different ways of thinking and taking risks.

We are at a neuroscience crossroad. Do we continue to be bound to a routine, linear paradigm or do we consider novel, experimental, and simultaneous, multimodal ideas? Can we balance our skepticism with open-mindedness to an algorithm buttressed by creativity and solution generation? We bear a serious responsibility to our wounded military service members and their families who search for hope, but who should not be led on by interventions that have no evidence base. We need to better understand the mechanisms and parameters of brain function, derive specific data to guide evidence-based treatment, and more accurately predict outcomes. The current opportunities for research and development of new treatments, within this burgeoning frontier, will serve to improve the lives of all those who suffer from brain injury.

**REFERENCES**


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