BRAIN INJURY SOURCE

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Defense and Veterans Head Injury Program (DVHIP)

Andres M. Salazar, MD

DVHIP Background & Goals

Traumatic brain injury (TBI) is the principal cause of death and disability for young Americans, with an estimated societal cost of over $39 billion per year, including direct care and loss of productivity. The problem of TBI encompasses a legion of issues, including some of the most important challenges in medicine today. These issues include: education and prevention issues; cell biology; neuronal degeneration; neuroprotection; neuroplasticity and recovery of function in the injured brain; acute trauma care and rehabilitation; and psychosocial adaptation of individuals with TBI and their families.

By virtue of the relative uniformity and accessibility of their populations, as well as their existing facilities, the Department of Defense (DoD) and Department of Veterans Affairs (DVA) health care systems offer a unique peacetime setting in which to address many of these issues. There are over 7,000 peacetime TBI admissions to DoD and DVA hospitals each year. In addition to the costs of acute and long-term care, a conservatively estimated $30 million in obligated medical retirement payments is added each year from TBI in the military alone. Yet, until the creation of the Defense and Veterans Head Injury Program (DVHIP), there had been no overall systematic program for providing TBI-specific care and rehabilitation within the DoD or DVA. This article describes DVHIP background, objectives and progress over the last several years.

The DVHIP represents a close collaboration among the DoD, DVA, the Brain Injury Association (BIA) and the International Brain Injury Association (IBIA). One of the principal goals of the program is to ensure that military personnel and veterans with traumatic brain injury receive TBI-specific evaluation, treatment and follow-up, while at the same time help to define optimal care for individuals with TBI nationwide. The DVHIP has evolved into a unique “disease management system” that is guided by the principle that we should “learn as we treat,” and is based on a prudent integration of clinical care and follow-up with clinical and laboratory research, TBI prevention and education.

Another important goal of the DVHIP is to address basic questions relating to military TBI, including acute care and the combat casualty care process as well as the effects of mild TBI on combat performance. The program includes a Head and Spinal Combat Injury registry similar to that used by the Vietnam Head Injury Study (VHIS). Thus, program efforts seek to facilitate the treatment of TBI resulting from battlefield operations. Much of the acute mortality and ultimate damage occurring after TBI results from a chain reaction of biochemical and physiologic events set in motion by the injury, which continue for hours and days. Acute TBI care is directed at preventing this secondary injury and breaking the vicious cycle of tissue damage. Presently, “state-of-the-art” care for TBI, as for many other conditions, is often experimental, and, thus, unavailable outside of experimental protocols for many years after its initial discovery. The DVHIP has developed basic combat casualty care protocols that can ensure treatments for TBI are available in the field. If properly designed, such protocols can be integrated into normal care without additional burden, and have the potential for improving outcomes and significantly relieving the resources needed in combat hospitals.

One of the most rapidly evolving areas in the field of TBI is rehabilitation. Important advances have been made, yet the costs of TBI rehabilitation also have grown rapidly over the past two decades. This increase in cost has occurred in spite of the fact that few TBI rehabilitation modalities have been subjected to the degree of scientific scrutiny for efficacy and cost efficiency that is usually applied to other medical treatments. The escalating economic burden that TBI places on individual families and society is unlikely to be controlled until cost-effective rehabilitation modalities have been established. The military and veterans medical systems are well suited to help address this question through prospective randomized controlled rehabilitation studies.

The basic national infrastructure of the DVHIP is now consolidated and the program is entering a growth phase, as general recognition in the professional and patient com-

munities has led to increased patient referrals. This also will allow the DVHIP to continue improving the pace and scope of its TBI clinical research and treatment programs. Initial specific objectives of the DVHIP were designed to establish a TBI care and research infrastructure in military and DVA medical centers that would provide TBI services to military and DVA beneficiaries and also allow for more targeted TBI projects. Eight general program objective areas have been identified for the DVHIP, each of which is integrated within the disease management system. These are:

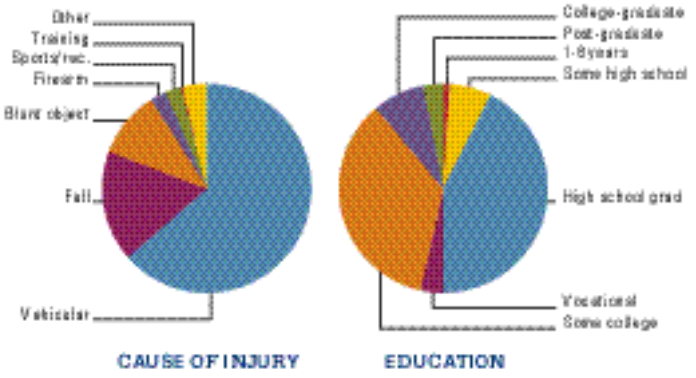
- A military and veterans TBI registry
- A TBI care and follow-up network
- A standardized TBI patient outcome evaluation program
- TBI rehabilitation clinical studies
- TBI pharmacologic trials
- Clinically-linked laboratory studies
- TBI education, prevention and advocacy efforts
- The Violence and Brain Injury Project, which is investigating the brain injury risk factors for violent behavior

DVHIP SPECIFIC OBJECTIVES

Objective I

Establishment and maintenance of DoD/DVA peacetime and combat traumatic brain injury patient registries

The DVHIP registry serves not only to identify patients with TBI requiring treatment and follow-up in the military and DVA systems but also as an epidemiologic and research tool. It is based on simple one- or two-page forms completed by trained nursing personnel at each of the primary and secondary centers, as well as by BIA Family Helpline personnel and state associations. The information includes names, addresses, demographics, injury and early outcome data. While the DVHIP registry presently includes mostly participants from DVHIP centers, one goal of the program is to expand it to the entire military and veterans medical systems. This objective also includes a parallel, combat head and spinal injury registry maintained in a format that will facilitate analysis and research as well as clinical follow-up.



The DVHIP registry now includes over 8,000 individuals covering the spectrum of TBI.

Objective II

Establishment of a regionally distributed national DVHIP TBI referral network

Ideally, most military personnel and veterans with TBI are entered in the DVHIP registry, and those with moderate or severe injury are referred through a DVHIP center for evaluation and treatment. The initial TBI patient referral network is centered around specialized treatment services provided at seven regional lead TBI centers located in three DoD and four DVA medical centers, as well as secondary referral sites at about 20 additional DVA medical centers. The lead centers are listed in Table 1.

Table 1: DVHIP Lead TBI Centers

Medical Center	Location
San Diego Naval Medical Center	San Diego, California
Walter Reed Army Medical Center	Washington, DC
Wilford Hall Air Force Medical Center	San Antonio, Texas
Minneapolis Veterans Medical Center	Minneapolis, Minnesota
Palo Alto Veterans Medical Center	Palo Alto, California
Richmond Veterans Medical Center	Richmond, Virginia
Tampa Veterans Medical Center	Tampa, Florida

The following elements also are integrated in the DVHIP network:

- A DVHIP central referral case manager for health care providers, including a toll-free referral number for caregivers in DoD and DVA facilities
- Regional DVHIP case managers at each of the primary TBI centers
- A regional network of additional secondary veterans hospitals capable of providing TBI rehabilitation, and linked to the primary lead centers for training, referrals and consultation. This is coordinated by a dedicated central DVA TBI coordinator and includes an active TBI case manager training program
- A TBI treatment and referral algorithm designed to assist primary caregivers in the management and referral of their patients with TBI. This now has been implemented at DVHIP sites and is being disseminated throughout the DVA medical system
- Close links to veterans programs such as the Vocational Rehabilitation Service of the DVA. This service includes an “independent living” program which can contract for long-term rehabilitation and transitional services in the veterans’ home or community
- A central toll-free TBI referral hotline for caregivers (1-800-870-9244)

- In collaboration with BIA, a toll-free national “Family Helpline” for individuals with TBI and family members (1-800-444-6443)
- An integrated transitional and long-term community-based TBI
  follow-up program modeled in part on the veterans Spinal Cord Injury program. Close collaboration with BIA TBI education and community
  support services is also an important part of follow-up services
- In close collaboration with CHAMPUS/TRICARE, TRICARE demonstrations project providing specialized treatment reimbursement at the four DVHIP lead veterans sites. This program allows for rehabilitation treatment of military beneficiaries at the four veterans DVHIP TBI centers. It is hoped that this agreement will serve as one model for future interagency collaboration in other medical specialty areas
- A Brain Injury Resource Center™ (BIRC) developed in collaboration with BIA. This is an interactive touchscreen multimedia TBI information resource that was designed for patients, families and caregivers. The BIRC typically is presented in a self-enclosed kiosk and allows patients and families in particular to access specific TBI information at the time that they need it and are most receptive to it. This ranges from medical, treatment and rehabilitation to legal and financial issues. The BIRC is now deployed at all DVHIP sites as well as multiple additional military and civilian centers. Future expansion includes a Spanish language version and abbreviated versions on CD-Rom and the internet.
- A DVHIP web site

Objective III

Establishment of standardized multidisciplinary patient outcome
evaluations as well as development and validation of outcome
measures which define the short- and long-term neurologic, cognitive, behavioral and psychosocial consequences of TBI
The principal purpose of this element of the DVHIP is to provide standardized, sequential outcome testing of military personnel and veterans with TBI for immediate clinical care purposes, while at the same time generating a TBI research database that will allow for outcome prediction, evaluation of treatment efficacy and cost-efficiency. The DVHIP core battery is intended as a flexible instrument, which will be updated and refined as data is collected.

Essential elements include:

1. A standardized core TBI patient evaluation battery in use at all DVHIP primary centers, with supplementary testing as indicated. The current core multidisciplinary battery includes neurological, neuropsychological, language, psychiatric, rehabilitation, MRI, QEEG and psychosocial measures. All individuals with TBI receive the same core battery. The data also is included in the research database when the participant has signed a volunteer informed consent.
2. Central office project management, data management and statistical capability. This includes creation of user-friendly research data files, as well as preparation of data collection and analysis computer programs. There are now over 3,300 multidisciplinary TBI evaluations in the DVHIP research files. Over 870 formal research protocol evaluations were done in 1998. This represents a 65% growth rate in 1997 and 1998 over previous years. The database is now supporting analyses of full, multidisciplinary baseline evaluations for approximately 1030 participants, six-month follow-up on approximately 410, 12-month follow-up on approximately 510 participants and 24-month follow-up on approximately 250. In fiscal year (FY) 1998, DVHIP investigators produced 80 professional publications, 13 manuscripts under review, 10 abstracts and 65 presentations.
3. Quality assurance across all lead sites, including regular monitoring site visits by central office and subspecialty leaders. Communication measures include e-mail, twice monthly conference calls for all principal investigators, subspecialty conference calls and formal DVHIP investigator meetings one or two times per year.
4. Brief data-validated TBI screening instrument that will help local
   facilities make decisions regarding further care and referral of persons with TBI.
5. A combat training and sports TBI program which seeks to identify the impact of mild TBI (MTBI) on military performance and develop treatments to minimize its effect. Active programs are currently ongoing at Fort Bragg, North Carolina; West Point U.S. Military Academy, Pennsylvania; and Camp Pendleton, California. The Fort Bragg program involves pre-injury baseline testing of about 2,500 paratroopers and more extensive post-injury evaluation of about 400 persons; over 800 baseline evaluations have been completed to date.
6. A multidisciplinary evaluation and workplace follow-up study for
   service members with symptomatic MTBI at San Diego Naval
   Medical Center.
7. Studies of prefrontal cortex function and neuroplasticity after TBI, in collaboration with Dr. Grafman of the National Institute of Neurological Disorders and Stroke (NINDS). This has been coupled with an advanced neuroimaging program at the National Institutes of Health

(NIH). This includes a protocol for a Phase III follow-up of Vietnam Head Injury Study (VHIS) participants, who are now some 30 years post-injury. Not only has the VHIS provided systematic, multidisciplinary follow-up evaluations to Vietnam War veterans with head injury, but it also represents a truly unique opportunity to study the patterns of recovery from localized brain wounds and their interaction with the aging process (see Grafman & Salazar article on page 12).

8. Advanced studies of qEEG and qMRI, in collaboration with Dr. Thatcher at Bay Pines Veterans Hospital. Dr. Thatcher has defined a strong biophysical linkage between MRI, qEEG and cognitive function, as well as increased brain homogeneity in persons with TBI. Based on these findings, he has developed a powerful TBI discriminant function that can distinguish individuals with TBI from individuals with Alzheimer's disease and "normal" control subjects. Development of a new qEEG technique, LORETA, has begun which will provide low cost, real-time functional brain imaging. This technique will be comparable in spatial resolution to functional MRI but has the technical advantage of being based on actual brain EEG activity rather than blood flow and has markedly greater temporal resolution and repeatability. When fully validated, these techniques promise to change significantly our approach to the evaluation, follow-up and treatment of individuals with TBI, as well as our understanding of the pathophysiology of TBI. In particular, they may serve as "instantaneous" surrogate measures of brain response to various therapies. This will allow a more scientific approach to interventions such as neurofeedback therapy. (See Dr. Thatcher's article on page 20).

Objective IV

Evaluation of the effectiveness and relative cost efficiency of alternative TBI rehabilitation strategies

Over the past two decades there has been a rapid growth of TBI rehabilitation programs. These have filled a vacuum in TBI care, but the exact form and intensity of TBI rehabilitation required for a given individual remains highly controversial. TBI rehabilitation is often labor-intensive, expensive and emotionally demanding of patient and staff alike. Yet, most rehabilitation strategies have not been subjected to the degree of scientific scrutiny for effectiveness and cost-efficiency that has been expected of other medical therapies in general use. In particular, the remarkable ability of the young adult brain to compensate for injury naturally often has not been considered in the evaluation of outcome from various treatments.

Open design studies have suggested that an interdisciplinary inpatient rehabilitation approach may improve outcome in these persons, and that the ones with severe head injuries benefited more from early versus late inpatient rehabilitation. Few controlled studies of long-term outcome have been reported, however, and none have used a prospective, randomized design. The relative paucity of scientific program evaluation may in turn make it more difficult to focus rehabilitation efforts on those therapeutic elements most likely to return the individual to independent living and/or gainful employment. Some programs even may be counterproductive, particularly if they inadvertently exhaust the person or foster continued dependence. These issues are unlikely to be satisfactorily resolved other than by prospective, randomized and controlled clinical studies. Not only does this study design remain the "gold standard" for determining efficacy of treatments in other medical fields, but the randomization process is especially valuable in helping to correct for the multiple, poorly understood variables impacting on recovery after TBI. The scarcity of such studies in the field of TBI may be due to a number of factors, among them methodological complications and the explosive growth of rehabilitation modalities within a third party payment structure that has failed to stimulate rehabilitation research.

The military and veterans health care systems offer a unique peacetime setting in which to address this national problem. Their populations are relatively large, and their injuries are similar in nature and cause to those occurring in the general civilian population. In addition, the military cohort is relatively uniform, young, healthy and employed pre-injury, thus minimizing the impact of many of the variables that plague TBI studies in civilian, and especially urban settings. Similarly, the military provides a generally supportive environment that is conducive to recovery, including healthcare and standardized disability compensation.

Clinical rehabilitation research treatment trials utilizing a randomized, controlled design are currently being conducted by the DVHIP, and include the following:

1. A prospective randomized controlled study of home treatment versus an intensive, eight-week institutional cognitive rehabilitation program in 120 service members with moderate to severely brain injuries at Walter Reed Army Medical Center. Estimated cost of the in-hospital cognitive rehabilitation program is $51,000 per individual, compared with approximately $500 per individual for the home program. Analysis of results has now been completed and is being reported formally elsewhere.
2. A second multicenter DVHIP study is comparing in-hospital cognitive therapy to in hospital functional rehabilitation for individuals with more severe TBIs at the DVHIP lead veterans' centers. The primary outcome measures are return to work and level of independence at one year post-injury. To date, approximately 170 of 350 projected

participants have been accrued to date. Interim analysis is expected when nearly half of the participants have completed the one-year follow-up.

3. A third randomized trial now starting at Wilford Hall Air Force Medical center will target persons with acute MTBI. It will compare a program of counseling, weeks of rest on convalescent leave and graded return to work, versus counseling and graded return to work alone. Primary outcome measures will be post-concussion symptoms and work supervisor ratings.
4. A separate prospective, randomized controlled trial of neurotherapy (qEEG biofeedback) is based on DVHIP findings reported in the accompanying article by Dr. Thatcher in this issue of Brain Injury Source, as well as elsewhere in the literature. This will evaluate neurotherapy for postconcussion symptoms and cognitive loss after mild to moderate TBI.
5. A collaboration with the clinical program of the Department of Neurosurgery at the University of Virginia and the John Jane Brain Injury Center (JJBIC) at Martha Jefferson Hospital. This includes functional MRI, executive function and other descriptive studies in persons with mild and moderate TBI, as well as controlled randomized therapeutic and rehabilitation studies that complement DVHIP programs. This represents the first major collaboration of DVHIP with a private sector clinical institution.

These studies represent among the first multicenter randomized TBI rehabilitation trials in the nation with long-term follow-up. One secondary goal of the DVHIP is to help refine the methodology of such studies in TBI rehabilitation and help stimulate comparable studies in the private sector.

Objective V

Pharmacologic trials

Another goal of the DVHIP clinical network is to explore the use of both symptomatic and neuroprotectant pharmacologic agents in persons with TBI. Symptomatic drugs to be tested in the initial phases of the program include psychoactive agents such as the selective serotonin enhancers, as well as memory enhancers such as donepezil. Neuroprotectant agents considered for more acute use include free radical scavengers such as SOD and Vitamin E, glutamate antagonists, agents that protect energy metabolism in injured neurons and neurotropic factors. Typically, these studies will be designed as pilot trials and often will focus on agents that are unlikely to attract initial support from the pharmaceutical industry for financial or other reasons. Some DVHIP pharmacologic trials planned or now underway include:

1. A phase I-II trial of pyruvate neuroprotection in individuals with severe acute TBI. This multicenter trial is now in its final stages of development, is designed to easily integrate with standard care and will utilize relatively simple physiologic and functional outcome measures such as intracranial pressure control, complication rate and the extended Glasgow Outcome Scale. It will be conducted by the DVHIP at several, collaborating trauma centers. The trial and its rationale is described in more detail in Dr. Verma's article on page 16.
2. Ongoing randomized trials of donepezil and sertraline in persons with frontal lobe dysfunction, in collaboration with Dr. Litvan at NIH.
3. A randomized trial of sertraline for persons with post-concussion symptoms such as depression, irritability and aggressive behavior, in collaboration with Dr. Warden at Walter Reed Army Medical Center.
4. A randomized trial utilizing antioxidants such as tocopherol or alpha lipoate for prevention of post-traumatic epilepsy is currently in planning phase.

Objective VI:

Clinically linked DVHIP laboratory projects

While the DVHIP is primarily a clinical program, it also is conducting certain laboratory and preclinical studies that provide support to its TBI clinical research projects. Some of these studies include:

- With Dr. Verma at the Uniformed Services University of the Health Sciences (USUHS), DVHIP has elucidated the mechanism by which cells adapt to hypoxia, and further characterized certain determinants of failed energy metabolism in injured nerve cells. In collaboration with the University of Pennsylvania, localized PARP activation after TBI in rodents has been demonstrated and its time course has been characterized, confirming our earlier hypotheses. In related work, Dr. Verma also has demonstrated a marked neuroprotective effect of several non-toxic, inexpensive energy-sparing compounds in three standard models of neuronal injury. This work has identified several potential and relatively simple clinical therapeutic neuroprotective approaches to persons with TBI. They are described in more detail in Dr. Verma's article on page 16.
- With Dr. Meyerhoff at Walter Reed Army Institute of Research (WRAIR), DVHIP has developed a rat model of post-traumatic epilepsy (PTE), which will be used to screen promising neuroprotective approaches to PTE, with an initial emphasis on low toxicity antioxidants such as tocopherol and alpha-lipoate. These studies also have demonstrated a strong protective effect of alpha-lipoate in a hemoglobin neurotoxicity model.
- With Dr. Long and colleagues at WRAIR, DVHIP has begun systematic neuroprotectant trials in a rat model of fluid percussion injury with hypoxia. Initial trials of the PARP inhibitor nicotinamide have been completed; behav-

ioral, histological and neurochemical analyses are now underway.

- With Dr. Festoff at the Kansas City VAMC, DVHIP has identified abnormal fibrin monomer activation in 93% and abnormal D-dimer in 47% of individuals with moderately severe brain injury at about one to three months post-injury. Additional assays, as well as clinical correlation analyses are underway. Dr. Festoff's laboratory also has demonstrated the mechanism of induction of neuronal apoptosis by thrombin, suggesting that this process may be activated after TBI and may be amenable to treatment.
- With Drs. Lipsky and Goldman at the Laboratory of Neurogenetics, NIAAA, NIH, DVHIP has begun studies of certain genetic markers that may influence recovery from TBI. These include serotonin receptor, dopamine transporter and other alleles. Initial studies involve patients at Walter Reed, Fort Bragg and the U.S. Disciplinary Barracks, Fort Leavenworth. DVHIP also is working on a broader, collaborative study evaluating the role of APO E alleles in cognitive recovery after TBI.
- With Drs. Dobi and Agoston, DVHIP and USUHS Anatomy & Cell Biology have characterized further the molecular genetics and function of the endogenous opioid, enkephalin, in preparation for development of transgenic mouse models. Enkephalins mediate the immune response and repair after TBI, and also may modulate certain aggressive behaviors. Understanding of their function may thus have implications for various aspects of recovery from TBI. In related work that is the subject of a proposed patent application, Dr. Dobi also has characterized mechanisms that regulate neuronal differentiation. This also may have profound implications for therapies that promote neuronal repair and regeneration.
- In a related collaboration utilizing physiologic and anatomic methods, Dr. Juliano, USUHS, has demonstrated differing patterns of neuronal recovery in juvenile or adult mammalian cortex after injury. These differences appear to be related to the action of various neuro-trophins and neurotransmitters such as acetycholine, and could provide clues to enhancement of recovery.

Objective VII

TBI Prevention and Education

From its inception, DVHIP has had a very close relationship with the Brain Injury Association (BIA), and now has developed one with the International Brain Injury Association (IBIA). As initially envisioned, BIA has taken the lead in the primary prevention, education and community support elements of the program. These efforts have been outlined elsewhere in BIA publications to include:

- Development and expansion of the Brain Injury Association's project HeadSmart® Schools, a primary TBI and violence prevention program now instituted at over 130 schools nationwide, including over 26 military dependent schools. Over the past five years, the program has reached over 100,000 children. HeadSmart® Military Communities programs also have been initiated at 12 military facilities
- BIA's toll-free Family Helpline (800-444-6443), which provides information and support to individuals with brain injury and their families
- Partial support of numerous BIA and IBIA educational conferences and workshops and numerous educational materials
- The Brain Injury Resource Center™ (BIRC™)
- Development and maintenance of BIA state and community service programs
- Development of evidence-based guidelines for the management of mild TBI, penetrating head injury, pediatric head injury and behavioral consequences of TBI in collaboration with IBIA, the University of Virginia, the Aitken Foundation and various professional organizations.

Objective VIII

Violence and Brain Injury Project (VBIP)

Violent criminal behavior has reached crisis proportions in America. The homicide rate in the U.S. is the highest in the world; it is the principal cause of death among young adults in many cities. There are multiple predisposing risk factors for criminal violence, including biological and sociological ones. In particular, a broad range of acquired brain injury syndromes may be related to the dyscontrol of aggressive and impulsive behavior. Thus, the interactions between medical, psychological, neurological and psychosocial factors must be considered fully in the debate over the origins of violent behavior. Past research has yielded important information on social, cultural and psychological factors contributing to violent behavior, yet the multiple predisposing risk factors for criminal violence remain poorly understood. Traumatic brain injury, in particular, may pose a significant risk impacting the control of aggression and impulsive behavior.

The Violence and Brain Injury Project (VBIP) is a collaboration of DVHIP, BIA and the National Institutes of Health (NIH), emphasizing a medical/biological approach to the problem of violent behavior. This rigorous scientific approach does not seek to absolve individuals of responsibility for their behavior, but rather identify promising avenues for prevention and rehabilitation. The project is driven by the following hypotheses:

1. Acquired brain injury/impairment is a significant risk factor for violent, impulsive and/or aggressive behavior
2. This risk for violence is accentuated by excessive exposure to adverse external stimuli, such as physical or substance abuse, or social deprivation

3. Certain types of violent or impulsive behavior can be ameliorated by treatments using medical/psychological as well as educational/social approaches
4. Certain types of acquired brain injury can be prevented or minimized through education and supportive as well as medical interventions

Initial implementation has three principal components.

1. The VBIP Core Diagnostic Protocol currently underway at the U.S. Disciplinary Barracks (USDB), Fort Leavenworth, Kansas: This consists of an extensive evaluation of three randomly selected cohorts of inmate volunteers with different confining offenses: 1) violent, 2) non-violent and 3) sexual offenders, as well as non-inmate military control subjects (prison guards). The evaluation includes a detailed medical and developmental history, as well as neurologic, psychological, neuropsychological, psychiatric and psychosocial assessments. It also involves advanced computerized electroencephalographic evaluation, magnetic resonance imaging (MRI) and laboratory studies including neuroendocrine, neurotransmitter, molecular biology, trace metal and other parameters. USDB offers a number of advantages for such a study since all participants were healthy, educated and employed on active duty at the time of their offense, and induction intelligence testing and personnel records also are available on all of them. This alone helps to control many variables that would confound analysis in other prison populations. A related focus group study in the Maryland Department of Corrections has recently been reported.
2. Further development and integration of HeadSmart® Schools, BIA's primary injury and violence prevention program into the curricula of DoD dependent schools: DVHIP has partnered with Mary-Garrett Bodel, MEd, MSW of the Brain Injury Association to develop the Brain Building Basics program for inmates in local correctional systems, and the adolescent program, Changes, Choices and Challenges (CCC). The latter incorporates a double-mentoring strategy, in which adolescents mentor younger children and are, in turn, themselves mentored by adults.
3. Several family-oriented programs: Principally a controlled, randomized comparison of a "couples" approach versus a "gender-based" approach to management of spousal abuse, in collaboration with the Department of Family Medicine, USUHS and Fort Bragg, NC.

Conclusion

DVHIP has evolved into a disease management system that integrates TBI education, prevention, clinical care and follow-up with a coordinated clinical and laboratory research program. Its success to date has been due largely to a close collaboration between the Departments of Defense and Veterans Affairs, the Brain Injury Association and the International Brain Injury Association. It is hoped that with continued progress, it can not only advance the field of TBI, but also serve as one model for integrated disease management in other medical fields.

During his 28-year career in neurology with the United States Army Medical Corps, Andres M. Salazar, MD, developed and became the founding director of the Defense and Veterans Head Injury Program (DVHIP) in 1991. Under his direction, the program's rigorous agenda of ongoing scientific studies combined with provision of clinical services has achieved significant advances in the prevention and treatment of traumatic brain injury (TBI). Dr. Salazar's work in the field of head injury spans nearly two decades, beginning with leadership of the Vietnam Head Injury Study and directing the Army Head Injury Unit at the Uniformed Services Division of the Health Sciences. His research has been widely published and spans a variety of fields, including head injury, AIDS and treatment of brain tumor and multiple sclerosis. After his neurology residence at Walter Reed Army Medical Center in 1972, Dr. Salazar completed a neurovirology fellowship at the National Institutes of Health in 1981. He has held posts at Army medical centers in Korea and West Germany and his work in neurology has earned him three Meritorious Service Awards and an Army Commendation Medal.

Defense and Veterans Head Injury Program (DVHIP)

The William Fields Caveness Vietnam Head Injury Study—Past and Future

Jordan Grafman, PhD and Andres M. Salazar, MD

Editor's Note: This article uses the term "head injury" rather than "brain injury" because that terminology is still used in DVHIP work.

Introduction

Of the 58,000 U.S. combat fatalities in the Vietnam war, approximately 23,000 or 40%, were due to head and neck wounds. Overall, about 19% of battle casualties and 14% of survivors sustained a head injury during that war. Early field care, helicopter evacuation and the deployment of neurosurgical teams close to the battlefront resulted in survival of much more severely wounded men than in previous wars. Among individuals with penetrating head injuries arriving alive at military field hospitals, about 20% had extremely severe wounds and died without surgery shortly after admission; the remaining 80% were treated surgically, with a mortality rate of about 10%. Nevertheless, long-term follow-up studies suggest that once the acute phase is over, most of these persons can return to meaningful and very often productive lives.

In addition to the Defense and Veterans Head Injury Program's (DVHIP's) continuing obligation to provide medical care to these veterans, this particular cohort presents us with a unique opportunity for study. Unlike most other populations with head injury, military subjects were healthy and employed pre-injury. Pre-injury vocational and intelligence testing is available on most of these individuals for comparison with post-injury function, and the Military and Veterans Affairs Medical Systems have allowed the DVHIP to track these individuals over a long follow-up period. In addition, their low velocity shrapnel wounds are relatively focal, allowing for unique structure-function correlations in humans.

The Vietnam Head Injury Study (VHIS) is a prospective long-term follow-up study of those Vietnam veterans injured during the war. The initial registry was planned and conducted during the Vietnam Conflict by Dr. William F. Caveness, then at the National Institutes of Health. Simple registry forms outlining demographic, injury and initial outcome data were completed by military physicians in Vietnam on their soldiers who had survived the first week after a severe head injury. Almost all had undergone intracranial débridement. About 2000 persons were entered into the registry between 1967-1970 and the registry forms were initially collated and analyzed by Dr. Caveness. Since 1993, the VHIS has been integrated into the Defense & Veterans Head Injury Program.

VHIS Phase I & II

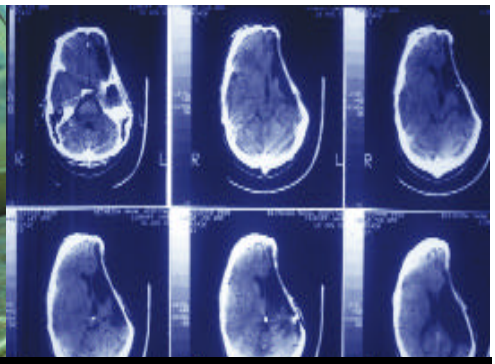
Phase I of the VHIS was a medical records review conducted some five years post-injury in which investigators collected, tabulated and analyzed data contained in the patient's military, VA medical and personnel records. At that time, the official VHIS cohort was decreased to 1,220 men with either penetrating or closed head injury on whom adequate field, acute hospital, rehabilitation and follow-up records were available.

Phase II of the VHIS, a comprehensive, multidisciplinary inpatient evaluation at Walter Reed Army Medical Center, was conducted between 1981 and 1984, some 12-15 years post-injury. Approximately 520 Vietnam War veterans with head injury, all volunteers from the registry, participated with 85 matched "normal" volunteers. The one-week evaluation included neurological, neuropsychological, speech & language, audiological, EEG, CT scan, rehabilitation and psychosocial examinations. Over 20,000 data points were collected on each participant and entered into a computerized database for analysis.

The results of both Phase I and II VHIS studies have been reported extensively in the medical and scientific literatures. These results have changed the way in which the military and VA evaluate and treat soldiers and veterans with head injury and how we approach persons with frontal lobe lesions. Scientific publications resulting from the VHIS Phase I and II have contributed to knowledge of the effects of penetrating head injury on the development of post-traumatic epilepsy, recovery of cognitive function following head injury and the neural representation of specific cognitive processes and mood states.

Perhaps one of the most encouraging overall findings has been the remarkable capacity of the young adult brain to compensate for injury. Although detailed testing generally could identify deficits referable to the particular area of the brain sustaining injury, most individuals were able to function independently in society. Eighty percent had been gain-

Armed Forces Otis Historical Archives, National Museum of Health and Medicine, Armed Forces Institute of Pathology,



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fully employed within the five years prior to Phase II evaluation and 56% were working at the time of that evaluation, many in spite of large anatomic brain lesions. Detailed analyses identified seven relatively equipotent deficit domains which related to unemployment post-injury, but no specific functional domain appeared to be predictive. Rather, it was the total number of distinct domains of affected brain function that best predicted return to work.

Most injuries were caused primarily by low velocity shrapnel, and most persons had only brief or no loss of consciousness at the time of injury, suggesting that their brain injury was relatively focalized and limited to the area of the lesion as seen on CT scan (Salazar et al., 1986b). This contrasts with most other types of head injury and offers a unique opportunity to evaluate the function of specific areas of the brain. Almost half of VHIS participants had lesions involving the frontal and temporal lobes, the functions of which have been the target of many VHIS analyses and will be the focus of future studies as described below.

The long-term goal of the VHIS continues to be the longitudinal neuropsychological and medical study of VHIS participants from injury to old age, which we believe will lead to new insights into functional neuroplasticity, mechanisms of motor and cognitive recovery, post-traumatic epilepsy, and the functions of various regions within the cerebral cortex–particularly the prefrontal cortex.

VHIS Phase III (Planned)

An important feature of the VHIS cohort of participating individuals is that it was prospectively identified at the time of injury and has had systematic record collection and evaluation over time. The VHIS has now collected data on this group of individuals at roughly three time points:

a) At injury

b) Phase I at post-acute follow up in the first five years post-injury

c) Phase II some 15 years post-injury, when the subjects were approximately 35 years old.

Phase III is now planned for the years 2000–2003 at about 30 years post-injury and when the individuals are about age 50. Finally, Phase IV is envisioned some 15 years after that. These evaluations will provide reliable and comparable longitudinal data on:

- The effects of head injury on the development of neurological disorders in old age
- The rate of physical and cognitive decline, including social cognition
- The effects on function of various PHI variables (e.g., presence of epilepsy or hemiparesis, size of lesion)

The bulk of the Phase III and IV evaluations will be devoted to examining targeted, cutting-edge cognitive neuroscience issues and will utilize state-of-the-art technologies to address basic research questions. Re-examination of VHIS participants on a small subset of tasks administered during prior evaluations also will help determine the stability of neuropsychological and neurological functions over long periods of time.

Experimental Studies Planned for Phase III

The evaluations planned in Phase III are based on knowledge acquired in previous research as well as current interests in the functions of the human prefrontal cortex, social cognition, aging of the injured brain, functional neuroplasticity and forms of memory.

Functions of the Human Prefrontal Cortex

1. Studies of social cognition and modulation of mood state– social attribution, attitudes and priming: Evidence has accumulated that the learning of social rules and social inferential skills parallels the pace of development of the human prefrontal cortex in childhood. Following brain lesions to the ventromedial prefrontal cortex or the onset of frontal lobe dementia in adults, an individual's behavior often undergoes a dramatic change leading to a breakdown in social behavior (Dimitrov et al., 1996; Goel et al., 1995; Grafman et al., 1996).

   Despite frequent observations of social abnormality, there has yet to emerge a comprehensive framework for

the representation of social behavioral processes in the human frontal lobes. Previous VHIS Phase II evaluation used scales to obtain individual self-report and observer ratings of behaviors in order to objectify changes in the-social and emotional behavior of VHIS participants (Grafman et al.,1986a). For phase III of the VHIS, we plan to administer a set of experments to obtain information about the following social skills:

a) Whether participants can develop inferential knowledge about the actions of others. These tasks will be based on Theory of Mind models.

b) Whether participants can become socially primed by exposure to previous affectively-laden information. This will allow us to judge whether some aspects of automatic or implicit social behavior can be dissociated from conscious social attitudes.

c) Whether participants can determine the socially appropriate behavior among a set of competing social solutions. This will allow us to judge the degree and type of social knowledge that the individual has. While it is anticipated that persons with ventromedial frontal lobe lesions will be impaired the most on these tasks, we are interested particularly in examining whether we can obtain across-task dissociations in social behavior depending on the exact location of the ventromedial lesion.

2. Studies of planning: Planet H and chores repeated exposures: Ill- versus well-structured plan solution, adaptive versus procedural knowledge:
We have conducted research over the last few years that attempted to determine the involvement of the frontal lobes in planning processes. We were able to show that the prefrontal cortex has an important role in planning but were unable to specify in enough detail the exact computational processes involved in planning (Arnett et al., 1997; Goel & Grafman, 1995; Goel et al., 1995; Grafman et al., 1991; Grafman et al., 1992; Grafman, 1995; Partiot et al., 1995; Partiot et al., 1996; Sirigu et al., 1995a; Sirigu et al., 1995b; Sirigu et al., 1996; Zalla et al., 1998). During phase III of the VHIS, several components of planning are scheduled to be examined. For example, we are interested in:
a) How subjects encode plans through practice and re-exposure
b) The computational differences of ill- versus well-structured plans
c) The computational processes required so that a planner may react to an unforeseen circumstance during the plan in order to adapt the overall plan in the context of the unforeseen circumstance

3. Studies of branching, task switching and control mechanisms during plan execution:
An additional set of studies involve specifying the underlying computational processes subserving plan development and, in particular, execution. Here we would investigate two major computational processes: branching and repetitive task-switching. Branching is defined in relationship to a goal tree and indicates when a subject leaves a main goal path to attend to a sub-goal before returning to the main goal path at the point he/she left it. Task-switching is defined as alternating between two distinct goal paths. Returning to each path occurs at a point beyond where he/she previously left the path.

4. Decision-making studies:
A number of studies have attempted to determine the role of emotional markers in decision-making by using a prototype gambling task. These studies revealed that persons with ventromedial lesions perform particularly poorly in making gambling decisions. The inference was that such individuals did not have access to somatic markers that could help them choose the best from among several alternatives. These studies are of great interest but limited in their general application. Instead, we plan to use tasks developed by economists and decision theorists that have sufficient theoretical support. Performance on these tasks should enable us to refine the exact nature of any decision-making deficit observed, and in conjunction with performance on related tasks, will help us identify the specific cognitive processes required for decision-making under varied conditions.

5. Tests of inhibition:
Persons with frontal lobe lesions may have a difficult time inhibiting inappropriate behaviors. This disinhibition has been characterized subjectively many times. We will use recently developed paradigms which can distinguish among automatic versus effortful inhibitory processes as well as processes that obey domain-specific constraints (e.g., inhibitory processes linked to social versus cognitive behavior). We hope then to identify which forms of inhibition are affected in individuals with differing focal frontal lobe lesions.

6. Visuomotor skill learning studies:
Visuomotor sequence learning is a skill mediated by the cerebellum, basal ganglia and the frontal lobes (Pascual-Leone et al., 1993; Pascual-Leone, Grafman & Hallett, 1994; Pascual-Leone, Grafman & Hallett, 1995; Pascual-Leone et al., 1996). We will examine how visuomotor serial reaction time tasks may fractionate the ability of persons with lesions to specific brain regions in transferring sequence knowledge among similar sequences, managing long versus short sequences and/or predicting which member of a sequence will follow the current event. We are interested particularly in

better pinpointing the role of the prefrontal cortex in sequence encoding.

7. Inductive, deductive and analogical reasoning studies:
   Persons with frontal lobe lesions often have reasoning deficits. It is possible that:
   a) Limitations in resources devoted to multiple concurrent events;
   b) Structured event complexes are fragile so that sequence order cannot be maintained in memory;
   c) Associated abstract representations cannot be retrieved; and/or
   d) Goals cannot be abstracted across events.
   We plan to address each of these hypotheses by administering carefully designed pragmatic and analogical reasoning tasks.
8. Violence, aggression and psychotherapy evaluation:
   Violence and aggression is a prominent social problem in western cultures. Understanding the brain basis of aggressive behavior is an important goal of cognitive neuroscience research. Previous research conducted by our group has demonstrated the negative effects of orbitofrontal and ventromedial lesions on impulsivity and the inhibition of aggressive behavior in VHIS participants (Grafman et al., 1996). We propose to expand our studies in this area by using standard scales combined with social cognition tasks that experimentally induce the priming of aggressive thoughts.
9. Anxiety evaluation:
   In a previous study, we determined that focal lesions to the right orbitofrontal cortex resulted in increased anxiety (Grafman et al., 1986a). We propose to further our work in this area by administering measures of self-report and observation of anxiety and determining the relationship between reports of anxiety and planning (perceiving the future) performance.
10. Post-traumatic stress disorder evaluation:
    Given that these veterans were injured in Vietnam and experienced stressful combat and a confused national response on their return to the United States, we will administer scales and an interview designed to specifically and explicitly assess post-traumatic stress disorder (Warden et al., 1996). If detected, subjects will be referred for therapeutic intervention.
11. Rationality and free-will:
    Rationality, reasoning and the ability to see alternatives to performance outside those that “fit” within a context will be examined with two kinds of tasks. One task will require subjects to randomly generate numbers and words under single and dual-task conditions. Statistical determination of the randomness of the generation will be determined. A second set of tasks will examine the subjects’ ability to provide modes of actions to accomplish goals framed by ill- or well-structured problem.

Cognitive Neuroplasticity

1. Functional neuroimaging (PET, fMRI, LORETA) studies of skill learning and visuomotor procedures (selected patients and normal subjects):
   How plastic are brains 30 years post-injury (Grafman et al., 1986c; Grafman et al., 1988)? In this study, we plan to teach a subset of the VHIS population a skill and simultaneously monitor the concurrent plastic changes in their brains using PET. Subjects selected for this study include those with lesions in structures that are required to perform the task (cerebellum, basal ganglia, motor and prefrontal cortex), in structures not viewed as relevant to perform the task (temporal lobes) and injured controls.
2. Divided attention and secondary task management (determine the relationship of volume loss and type of cognitive deficits to reduction in cognitive resources):
   We will administer a simple dual task to persons in order to see if there are any “general” effects of resource allocation in individuals with brain injury compared to normal control subjects. Some investigators have argued that the cerebral cortex has both specific and general functions. One general function can be conceptualized as an intellectual resource factor. If persons have a certain amount of tissue missing, the capacity of this general resource would be proportionally reduced. The usual way to test resource allocation is to ask subjects to perform a dual task since attention has to be divided between the tasks leading to a depletion of the resource. If stimuli and task demands are simple enough that they do not stress a particular cognitive domain, then we may be able to determine if a particular brain region is most responsible for this general intellectual resource.

Memory and Amnesia

1. Distinguishing among strategic processes used to encode and retrieve plans:
   Plan development and execution has been studied, but little is known about the on-line strategies subjects use to encode and retrieve a stored plan. We intend to administer a set of tasks that require subjects to encode various aspects of an event sequence (e.g., landmarks/events or spatial paths) and determine which is most effective in facilitating plan execution and memory. Control conditions include those concerned with simply maintaining surface information (e.g., sounds or the image) in memory.
2. Name retrieval mechanism studies–comparing first trial fluency search versus exhaustive fluency search:
   Word fluency is a common task that is used to assess

subject search strategies for lexical items (Rueckert et al., 1994). In this study, we propose to use several forms of word fluency to examine how quickly subjects exhaust their lexical memory. One task will involve a letter search; another, a category search; and the last will involve a task where subjects have to switch between letters, between categories and between letters and categories. For each task, subjects will receive at least eight consecutive administrations. It has been shown in repeated trials, that almost all normal subjects are able to increase the number of items retrieved and almost exhaust their lexical memory after several trials. The purpose of this study is not simply to note differences in fluency between individuals with lesions in different brain areas but to examine how long such persons take to exhaust (by looking at a flattening of the retrieval curve) their lexical memory. The relationship of the retrieval slope to brain tissue volume loss in cortical regions that critically support lexical memory will be analyzed.

Outcome

Return to Work / Functional Independence

As noted above, the majority of VHIS participants have been able to return to gainful employment, which has been identified as one of the most important self-perceived determinants of a good quality of life. Phase III will continue to evaluate factors impacting the ability to return to work, particularly in relation to the frontal lobe functions outlined above.

Quality of Life

In this study, we are concerned with using modern methods of outcome and quality of life to determine each subject's current status (Schwab et al., 1993). This evaluation will be divided into three different examinations:

1) A family interview conducted in the individual's home, possibly in collaboration with the American Red Cross
2) A subject interview at the National Naval Medical Center (NNMC)/National Institutes of Health (NIH)
3) A limited Focus Group study in which a small number of participants will be interviewed together during their stay at the NNMC

The Focus Group will include open-ended discussions on long-term recovery from penetrating brain injury and what problems and successes participants have had in coping with their injury. The individual interview will include formal scales and open-ended questions examining subject work history, family relationships, infractions of the law (including arrest records and outcomes), alcohol and drug abuse history and social interactions (including those concerned with one-on-one and small and large group gatherings). Other issues to be examined include the participant's self concept and his/her current social roles. During the individual session, the subject (if consent is given) will be audio and videotaped for subsequent verbal protocol analyses (using a digital video camera and software for this purpose).

Genetic Analysis

Many factors contribute to quality of life and outcome after a brain injury. One of the least studied factors is genetic predisposition for recovery of function. In this study, we will utilize state-of-the-art molecular genetics to address genetic and other factors that might contribute to subject recovery of function. Each subject will generate a family pedigree of neurological injury, and additional information such as social status, educational status and learning disability that will be used to predict outcome.

Molecular epidemiologic studies have supported a role for allelic variants in recovery from acute and chronic brain injury. We will attempt to ascertain whether any genetic polymorphisms are associated with physical or psychological changes among persons participating in the Vietnam VHIS-Phase III. Candidate genes for molecular characterization will be selected based upon previous studies suggesting genetic
factors that may contribute to the remodeling and survival of neurons following head trauma as well as behavioral recovery. These include APO-E alleles, as well as serotonin, dopamine and other neurotransmitter receptor and transporter genes which have been associated with
certain behavioral phenotypes. These studies, which also will include gene discovery, will be conducted in collaboration with Drs. Lipky and D. Goldman in the Molecular Genetics Branch of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) of the NIH. The identification of such polymorphisms and their association with post-injury recovery may provide valuable insights for the development of acute and chronic therapies for brain injury.

Psychiatric Interview and Diagnosis

In past VHIS evaluations, the psychiatric status of the subject has been evaluated primarily through scales and abbreviated informal interviewing. For VHIS Phase III, we plan to conduct a formal short psychiatric interview and scale to determine subject current psychiatric diagnosis.

Neurological Studies

Epilepsy Status

Phase II analyses showed that post-traumatic epilepsy (PTE) occurs in over 50% of VHIS subjects, and is associated with a number of injury factors. Present patient status will be studied via a careful history examination and a correlation with injury and other outcome variables, as well as analysis of molecular genetic, computerized EEG and func-

tional neuroimaging data. Specific questions to be addressed include:

- Long-term risk factors for onset of post-traumatic epilepsy (VHIS phase II indicated a relative risk of 25 times higher than the normal population even at 10-15 years post-injury)
- Duration of post-traumatic epilepsy
- The role of long-term anticonvulsants
- The impact of post-traumatic epilepsy on behavioral and cognitive function in the aging brain, as well as on social function and survival.

Motor Control

About 40% of VHIS individuals were reported to have had motor paralysis after injury, but by approximately five years post-injury, over half of them had made a virtually full recovery. A number of injury and anatomic factors were associated with that recovery, but more sophisticated motor studies were not possible in Phase II. Motor control provides a domain of investigation that is precise and important for subject outcome. In collaboration with Dr. Hallett of the Medical Neurology Branch of the National Institute of Neurological Disorders and Stroke (NINDS), we plan to conduct a set of experiments to evaluate motor control ability and other functional correlates in selected individuals.

Formal visual field examination

Each VHIS Phase III subject will get a complete formal visual field examination.

Neuroimaging

All subjects will undergo repeat state-of-the-art CT scans, and newly developed computer imaging software will be used to reclassify each subject's lesion according to Brodmann's areas and Talairach coordinate space. MRI also will be utilized, but its universal application may be limited because of the high incidence of retained ferric metal fragments in this population. Functional neuroimaging may be among the most promising tools, however, to be used during VHIS Phase III. PET scanning will be used maximally to address specific research questions in selected persons. When possible, functional MRI will be used in individuals without retained metal fragments.

Finally, low resolution electroencephalographic tomography (LORETA) is a relatively new functional imaging technique that relies on measurement of electrical activity of the brain and thus can provide a high degree of temporal resolution. It also can be co-registered with anatomic images, to provide spatial location resolution comparable to that of fMRI. Such studies may prove to be a valuable and inexpensive tool to address certain functional questions. These and other qEEG studies will be conducted in collaboration with Dr. Thatcher at the Bay Pines VAMC.

qEEG analysis

Each evaluation will consist of power spectral analyses of electroencephalogram (EEG) recorded from 40+ scalp locations referenced to age-matched norms. In previous closed head injury studies, the best combination of predictor variables for recovery from head injury was EEG and GCS-T, which accounted for 74.6% of the variance in the multivariate regression analysis of intermediate outcome scores and 95.8% discriminant accuracy between good outcome and death. The best single predictors of outcome in both the discriminant and regression analyses were EEG coherence and phase, although their value as predictors of outcome, especially in persons with penetrating head injuries, requires more study. In addition, EEG coherence and phase may be used to estimate the efficiency and effectiveness of short- and long-distance neural synchronization which may be useful in helping determine the effectiveness of frontal lobe control mechanisms over processes located more posteriorly in the brain.

Conclusions

The VHIS constitutes a unique national resource. Not only has it been able to provide important insights into brain function and recovery from head injury, but it also has served to provide continued care to America's veterans who have sustained injury. This could not have been possible without the continued interest and participation of the individuals themselves. Similarly, Phase III of the VHIS, which will take advantage of state-of-the-art technology, promises to break new ground in the understanding of the frontal lobes, long-term recovery from head injury and its interaction with the aging process.

Jordan Grafman, PhD received his BA from Sonoma State University in Rohnert Park, California in 1974. He then worked for a year as a surgical orderly before returning to graduate school. He received his PhD in Human Neuropsychology from the University of Wisconsin-Madison in 1981. After receiving his doctorate, Dr. Grafman joined the Vietnam Head Injury Study being conducted at Walter Reed Army Medical Center in Washington, DC as neuropsychology chief. In 1986, Dr. Grafman moved to the National Institutes of Health as a senior staff fellow in the National Institute of Neurological Disorders and Stroke. In 1991, he was named Chief of the Cognitive Neuroscience Section, a position he currently holds. Dr. Grafman also is on the faculty of the Department of Cognitive Science at Johns Hopkins University, holds a number of other adjunct faculty positions at Washington area universities, and is a co-principal investigator with the Defense and Veterans Head Injury Program.

Dr. Grafman is co-editor of the Handbook of Neuropsychology as well as several other texts on the frontal lobes, head injury and neuroplasticity. He is the author of over 200 publications and is recognized for his work on the functions of the human prefrontal cortex, recovery of function following brain injury, and learning and memory.

During his 28-year career in neurology with the United States Army Medical Corps, Andres M. Salazar, MD, developed and became the founding director of the Defense and Veterans Head Injury Program (DVHIP) in 1991. Under his direction, the program's rigorous agenda of ongoing scientific studies combined with provision of clinical services has achieved significant advances in the prevention and treatment of traumatic brain injury (TBI). Dr. Salazar's work in the field of head injury spans nearly two decades, beginning with leadership of the Vietnam Head Injury Study and directing the Army Head Injury Unit at the Uniformed Services Division of the Health Sciences (USU). His research has been widely published and spans a variety of fields, including head injury, AIDS and treatment of brain tumor and multiple sclerosis. After his neurology residence at Walter Reed Army Medical Center in 1972, Dr. Salazar completed a neurovirology fellowship at the National Institutes of Health in 1981. He has held posts at Army medical centers in Korea and West Germany and his work in neurology has earned him three Meritorious Service Awards and an Army Commendation Medal.

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Neuroprotection Opportunities in Traumatic Brain and Spinal Cord Injury

Ajay Verma, MD, PhD

OVERVIEW

Traumatic injury of the brain and spinal cord involves disruption of axons, cell bodies and blood vessels and is followed normally by little or no axonal regeneration and virtually no recovery of function by the lesioned tissue. The lack of functional regeneration in the traumatized central nervous system (CNS) appears to result largely from severe damage and deterioration at the site of the injury as well as suppression of axonal elongation and neurite outgrowth by astrocytic scar formation and myelin-associated inhibitory factors.

Neuroprotective strategies employed in the acute period after traumatic CNS injury use pharmacological tools to reduce the progressive secondary injury processes that follow after the initial lesion occurs, in order to limit overall tissue damage. Other strategies initiated shortly after the lesion occurs aim at promoting axonal regeneration by acting pharmacologically on inhibitors or barriers of regeneration, or by providing neurotrophic support to enhance the regeneration of lesioned axons.

Although clinically effective neuroprotective therapy for individuals with traumatic brain and spinal cord injury (TBSI) is yet to be realized, advancements in our understanding of trauma-induced cellular injury soon may offer several mechanistically-based therapeutic strategies. Many of the injury mechanisms at work in CNS trauma also are encountered in settings of other CNS injuries, such as stroke. Thus, effective neuroprotective strategies discovered in stroke research often lend themselves for trial in CNS trauma. Results from experimental animal studies using a wide variety of drugs that modulate neurotransmitter function, scavenge free radicals, interfere with cell death cascades or inhibit inflammation point towards many new opportunities for pharmacological intervention in the acute, sub-acute and chronic period following clinical stroke and traumatic injury. This article will review the mechanistic concepts and targets that have guided development of the neuroprotective agents currently being considered for use in TBSI.

SECONDARY INJURY AND RECOVERY FOLLOWING TBSI

Clinical dysfunction following TBSI becomes evident rapidly while the complete response of injured CNS tissue elements actually proceeds from hours to days or longer after the initial insult. CNS tissue elements that are not destroyed immediately following traumatic injury may be sub-acutely injured or killed by secondarily generated auto-destructive factors. This protracted period of secondary injury offers the hope for intervention with agents that can prevent the actions of auto-destructive factors and thus limit the overall injury outcome. Secondary injury in the nervous system is now well appreciated following stroke and trauma and is currently the main target for neuroprotective therapeutic intervention in these settings. Anoxia, cell membrane lipid metabolites, glutamatergic neurotransmission, intracellular calcium overload, free radicals, inflammatory responses and depletion of energy stores are among the major identified auto-destructive factors implicated in this secondary injury cascade (Faden, 1997; McIntosh et al., 1998).

Traumatic injury disrupts brain and spinal cord blood vessels, axons and cell bodies resulting in hemorrhage and loss of cell membrane integrity. This loss of cell compartmentalization results in a rapid disintegration of cellular structure and function and leads to a necrotic form of cell death. Cellular necrosis is characterized by a rapid influx of calcium into the cell via the damaged plasma membrane, acute swelling of endoplasmic reticulum and mitochondria, and immediate activation of calcium-dependent degradative enzymes such as lipases, proteases and nucleases.

Within minutes, several different membrane lipid metabolites are generated at the focus of the injury, including arachidonic acid derivatives (prostaglandins, thromboxanes and leukotrienes), platelet activating factor (PAF) and lipid peroxidation products such as 4-hydroxynonenal (Demediuk & Faden, 1988; Hall & Braughler, 1986; Hsu et al., 1985; Kiwak et al 1985). These lipid metabolites have a wide spectrum of biological actions including blood vessel contraction, capillary permeability, platelet aggregation, activation of inflammatory cascades and direct cytotoxicity. Such actions are believed to play a major role in the initiation of secondary injury. Cells nearby the injury focus can be affected directly by some of these metabolites, or indirectly by the resulting reduction in nervous tissue blood supply. These events can affect all cell types in the CNS including neurons, astrocytes, oligodendrocytes and endothelial cells.

Ischemic tissue elements rapidly become energetically compromised and the failure to maintain energy-dependent trans-membrane ionic gradients results in intracellular edema and calcium overload, again leading to necrosis. Neuronal pre-synaptic endings normally secrete neurotransmitters in response to depolarization and calcium influx; therefore, it is not surprising that prominent neurotransmitter secretion is associated with nervous tissue injury and ischemia. Since many neurotransmitters, in turn, modulate ionic permeabilities of postsynaptic neurons, this action can have a major impact on the further propagation of injury. The availability of drugs capable of regulating neurotransmitter release or receptor function has made this particular aspect of CNS injury an attractive target for neuroprotective intervention. Necrosis of CNS tissue is followed by a recruitment of inflammatory cells to the site of injury and the resulting inflammatory response generally produces further tissue damage.

Cells that are less severely injured can make adaptive responses following the injury. These responses can lead to repair of the injured elements or the active elimination of cells that presumably cannot be repaired. This latter action has been termed programmed cell death or apoptosis, and has several unique features that distinguish it from necrosis. During apoptosis, cells respond to certain extracellular or intracellular cues and proceed to dismantle their nuclear contents and genetic material in an organized, enzyme catalyzed manner to ensure their non-viability. Other cellular compartments do not disintegrate as rapidly as in necrosis. Instead, apoptotic cells become fragmented into a number of small apoptotic bodies which are eliminated via phagocytosis by surrounding cells. Apoptosis is seen in a wide variety of biological settings and is important for several normal physiological processes such as development and homeostasis of organ size and cell number. Although many different cells can undergo apoptosis in response to cell-specific cues, it is becoming apparent that certain key intermediary steps may be common to all forms of apoptosis. This realization has prompted the development of drugs that can prevent the apoptotic cascade and such drugs may offer further neuroprotective therapeutic options in the near future (Faden, 1997; McIntosh et al., 1998).

TARGETING SPECIFIC NEUROTRANSMITTER SYSTEMS

Trauma reduces nervous tissue blood flow either via a direct mechanical action or through the actions of certain injury-induced factors mentioned earlier. Compromised blood flow rapidly impairs ATP synthesis and thus the ability of excitable cells to maintain polarized resting membrane potentials. The resulting membrane depolarization favors an influx of sodium and calcium ions through voltage sensitive channels and promotes the release of neurotransmitters from neuronal pre-synaptic endings. The extracellular buildup of neurotransmitters is exacerbated by the impairment of energy-dependent reuptake mechanisms in neurons and glia that normally remove these substances.

Many different neurotransmitters exist in the brain and spinal cord and these may influence secondary tissue injury in unique ways. Glutamate is the major excitatory transmitter in the CNS and, thus, its elevation in ischemic tissue has the potential to further disrupt the ionic homeostasis and energy status of cells. Indeed, large elevations of glutamate have been documented in the cerebral spinal fluid (CSF) of individuals with brain and spinal cord injury (Brock et al., 1997; Koura et al. 1998; Stover, et al. 1999). Many neuroprotective strategies for limiting CNS injury in recent years have focused therefore on reducing the release of glutamate from presynaptic endings and preventing its actions at postsynaptic receptors.

While excessive extracellular glutamate levels undoubtedly promote secondary brain injury following trauma (Liu et al., 1997), it is important to recognize that several neurotransmitters are likely to accumulate in the extracellular space by a similar sequence of events. Inhibitory transmitters such as GABA and adenosine may in fact counteract the actions of glutamate by reducing overall tissue excitability. Indeed, recent approaches have attempted to augment these inhibitory transmitter actions in brain injury (Lyden, 1997; Winkler et al, 1997). Monoamine neurotransmitters such as serotonin, on the other hand, may contribute to injury progression via further reduction of spinal cord blood flow through actions on blood vessels or platelets. Peptide neurotransmitters that act at opioid and other specific receptors also have been implicated in the secondary injury response (Faden, 1997) and also may represent useful targets for neuroprotection.

Inhibition of Glutamate Release

Following brain injury in stroke or trauma, excess release of glutamate from nerve terminals results from failure of ATP-dependant Na+/ K+ pumps and depolarization of voltage-gated presynaptic sodium and N-type voltage-sensitive calcium channels. This released glutamate acts postsynaptically by activating NMDA and non-NMDA types of glutamate receptors which, in turn, results in a large increase in intracellular calcium (Muir & Lees, 1995) and leads to calcium-mediated cell death. Agents that block presynaptic sodium or calcium channels may potentially prevent the large increase in extracellular glutamate concentrations following brain injury. Several such agents including riluzole, lubelazole, BW619C89, phenytoin and fos-phenytoin are currently under study. Riluzole and lubelazole are benzothiazole compounds, which prevent the increase in extracellular gluta-

mate concentrations, normalize neuronal excitability in ischemic regions and inhibit glutamate-induced neurotoxicity (Scheller et al., 1995).

In the first Phase III trials of such drugs in stroke, lubeluzole did not increase morbidity among individuals sustaining ischemic stroke nor any other safety concerns. In the overall study population, however, treatment with intravenous lubeluzole within six hours of the onset of ischemic stroke did not affect mortality or clinical outcome. Among persons with mild to moderate ischemic stroke, lubeluzole decreased mortality without increasing morbidity (Diener, 1998). These initial studies do show some promise and the use of similar agents in traumatic brain and spinal cord injury may not be far off. The anticonvulsant drugs phenytoin and fos-phenytoin are sodium channel antagonists with cytoprotective properties (Fisher, 1995), which also may reduce the release of glutamate in ischemic brain tissue. Despite early positive findings in an animal model of spinal cord injury (Gerber et al., 1980), however, clinical trials using phenytoin in TBSI have not been pursued.

Inhibition of Glutamate Receptors

Postsynaptic glutamate receptors may be divided into two major groups, metabotropic and ionotropic. Metabotropic receptors are coupled to intracellular second messenger systems, especially the phosphatidylinositol pathways, and have an as yet incompletely understood physiological role. Ionotropic receptors are ligand-gated ion channels that mediate rapid changes in postsynaptic membrane permeability to sodium and calcium. Subtypes of the glutamate ionotropic receptors are defined by the binding affinity of the specific synthetic ligands N-methyl-D-aspartate (NMDA) and ct-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). Both types of ionotropic glutamate receptors have been implicated in secondary injury following TBSI (Faden, 1997; Liu et al, 1997; McIntosh et al., 1998).

NMDA Receptor Antagonists

The NMDA subtype of glutamate receptors is a complex structure with several distinct sites of action for pharmacological modulators. Several compounds that inhibit NMDA receptors non-competitively or competitively with respect to the glutamate binding site have been developed for potential use as neuroprotective agents. Non-competitive NMDA antagonists like ketamine, phencyclidine (PCP), dizolcipine (MK-801), dextrorphan and dextromethorphan bind to the phencyclidine recognition site in the NMDA-gated ion channel (Wong et al., 1986).

Studies with dizolcipine and other NMDA receptor blockers indeed have demonstrated that such agents do improve functional outcome and histological morphology following experimental TBSI (Haghighi et al, 1996; Rienert & Bullock, 1999). The clinical development of dizolcipine has been discontinued, however, as a consequence of safety concerns emerging from its use in stroke trials. These include prominent behavioral side effects such as cataplexy and locomotor disturbance, EEG changes, transient hypotension and dose dependent depression of the level of consciousness (Muir & Lees, 1995). Likewise, the clinical development of dextrorphan also has been terminated due to intolerable clinical side-effects (Albers et al., 1995).

Cerestat, another non-competitive NMDA antagonist, has been shown to significantly reduce infarct volume when given either 15 minutes (Minematsu et al., 1993) or as a delayed treatment (Meadows et al., 1994) after permanent occlusion of the middle cerebral artery in rats. A pivotal safety and efficacy trial of Cerastat on individuals with acute ischemic stroke is in progress. Such studies will have a significant impact on the utility of this and related agents in TBSI. Magnesium causes a voltage-dependant block of the ion channel of the NMDA-receptor and acts as a noncompetitive NMDA antagonist at higher concentrations (Harrison & Simmonds, 1985).

Unlike other noncompetitive NMDA antagonists, magnesium appears to be well tolerated and has been shown to improve neurological outcome in pilot studies of clinical stroke (Strand et al., 1993). Intrathecal magnesium has been shown to prevent spinal cord injury despite markedly negative spinal cord perfusion pressure during thoracic aortic cross-clamping in a canine model of spinal cord ischemia (Simpson et al., 1994). More recent experimental findings in the rat head injury model offer new encouragement for using magnesium in TBSI. Indeed, blood magnesium levels actually drop following head injury and correction of this derangement affords neuroprotection (Bareyre et al., 1999). The mechanism underlying the drop in blood magnesium levels remains unclear but its clinical measurement and correction in individuals with head injury appears to offer a simple and safe neuroprotective option.

Competitive NMDA antagonists, such as APH, CPP, selfotel (CGS-19755) and MDL 100,453 block the NMDA receptor site and also reduce infarct size in animal models when the treatment is started after onset of ischemia (Muir & Lees, 1995). Selfotel, the most extensively studied agent in this group, is thought to act directly on the glutamate-NMDA binding site. Phase III clinical trials of Selfotel in stroke recently were terminated because of a statistically non-significant increased mortality in the active treatment groups. Eliprodil, a polyamine site antagonist of the NMDA receptor, also has been shown to reduce infarct size in stroke models (Poignet et al., 1991). A safety pilot study, however, revealed several side effects (Fisher, 1995) and a large Phase III trial recently was terminated. The use of these agents in TBSI awaits further studies.

AMPA Antagonists

The AMPA subtype of glutamate ionotropic receptors is more widespread in its distribution throughout the CNS than the NMDA subtype and is involved widely in excitatory neurotransmission. Antagonists of AMPA receptors such as NBQX or GYM 52466 are neuroprotective in both focal and global cerebral ischemia animal models. In experimental studies, NBQX produces dose-dependent reduction in tissue loss following CNS injury with significantly increased residual amounts of both gray matter and myelinated white matter at four-weeks post-injury as compared to control (Rosenberg et al, 1999). AMPA antagonists have not been developed fully yet for human studies.

Overall, the inhibition of glutamatergic transmission has shown benefit in animal stroke and TBSI models but (with the exception of magnesium) also has been associated with significant clinical side-effects. These findings may signify the importance of glutamatergic mechanisms to the normal functioning of the brain.

Activation of GABA Receptors

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the brain (Fagg & Foster, 1983). GABA-A receptors seem to be present in all neurons and act by gating a chloride channel. Activation of the receptor/ion channel complex results in hyperpolarization of the cell membrane, thus inhibiting action potentials elicited by depolarization. The GABA-A receptor binds several drugs including barbiturates and benzodiazepines that potentiate the activation of chloride conductances by GABA. The main physiological role for GABA is to balance the action of the major excitatory transmitter, glutamate. Thus, in contrast to glutamatergic transmission, neuroprotective strategies involving GABA seek to enhance its synaptic levels and activate its post-synaptic receptors. Elevation of GABA levels with the GABA transaminase inhibitor y-vinyl-GABA (vigabatrin), which inhibits elimination of GABA, was shown to reduce overall energy utilization in the gerbil bilateral cerebral ischemia model (Abel 7) (McCandless, 1992).

A recent experimental study demonstrated that pretreatment with diazepam (valium) attenuated the early decline of spinal cord evoked potentials (SCEP) induced by the trauma and reduced the later development of edema and cell injury (Winkler et al., 1997). These results suggest that GABA-A receptors are involved in trauma-induced alterations in SCEP changes, edema formation and cell injury and GABA-A receptor stimulation may represent a way to provide as much neuroprotection as glutamate antagonism with much fewer adverse side-effects. The combined use of glutamate antagonists and GABA agonists has not been explored fully.

Activation of Adenosine Receptors

A large body of evidence supports the role of adenosine as an endogenous neuroprotective agent (Schubert et al., 1997). The levels of adenosine are increased in ischemia and this nucleoside stimulates several processes that can decrease secondary brain damage. These include an increase in blood flow, decrease in excitatory amino acid release, hyperpolarization of cell membranes and reduction of free radical formation. Local delivery of adenosine has been shown to reduce CNS damage following ischemia. Adenosine acts through several different types of receptors, and selective drugs which can capitalize on the neuroprotective properties of these receptors without peripheral side effects are awaited.

Targeting Other Receptors

Use of 5-HT antagonists has been shown to improve outcome in experimental spinal cord injury with the best results having been found with combined 5-HT_1/5-HT_2 receptor antagonists, such as (S)-emopamil and mianserine (Puniak et al., 1991; Salzman et al., 1991). These compounds have not been studied clinically. Beneficial effects of opioid receptor antagonists have been shown in a large number of experimental studies (Faden, 1997).

Protective effects have been shown using a variety of structurally different, stereo-specific, opioid receptor antagonists strongly indicating a receptor-mediated mechanism of action. High doses of nonspecific antagonists like naloxone are required for therapeutic action. The protective effects of the highly selective K-Opioid receptor antagonist norbinaltorphimine, however, suggest that K-opioid receptors may be involved. The National Acute Spinal Cord Injury Study 2 (NASCIS 2) compared methylprednisolone, naloxone and placebo. Although preliminary reports of the study indicate that naloxone produced clinical improvement that did not reach statistical significance, subsequent one-year follow-up of patients indicated that naloxone had indeed significantly improved clinical outcome (Bracken & Holford, 1993). Beneficial effects of opioid receptor antagonists may occur through a variety of potential mechanisms, including improvement of SCBF, reduction of calcium influx, enhancement of free magnesium concentration and cellular bioenergetic state and/or modulation of EAA release (Faden, 1993).

Thyrotropin-releasing hormone (TRH) and TRH analogs are able to physiologically antagonize a variety of proposed autodestructive factors, including endogenous opioids, PAF, peptido-leukotrienes and excitatory amino acids. They also appear to improve SCBF, restore ionic homeostasis and cellular bioenergetic state, as well as reduce lipid degradations (Faden, 1997). A recently published experimental and clinical study has suggested that TRH may be effective in

human spinal cord injury (Pitts et al., 1995).

TARGETING CYTOPATHIC EVENTS

Calcium

Intracellular calcium dysregulation has emerged as a common pathogenic factor for the generation of irreversible cellular injury (Kass & Orrenius, 1999). This includes the secondary cellular damage that develops after TBSI. Intracellular calcium may become elevated following trauma through the activation of voltage-gated calcium channels in cells depolarized as a consequence of ischemia or through activation of the ligand-gated calcium channels associated with NMDA receptors. Several energy-requiring mechanisms normally maintain a low cytoplasmic calcium level in all cells. These include plasma membrane and endoplasmic reticulum ATP-dependent calcium pumps and respiring mitochondria.

With ischemia and the ensuing depletion of cellular energy, these mechanisms fail, resulting in intracellular calcium overload. Particular attention has become focused recently on the failure of mitochondria to buffer calcium. Normally a prominent protective feature of cells, the large calcium buffering capability of mitochondria becomes abruptly disabled after mitochondria take up a certain maximal amount of calcium. This mitochondrial event is referred to as the mitochondrial permeability transition (Murphy et al., 1999). The exact molecular events involved in this injury-induced inner mitochondrial membrane derangement remain unclear. This phenomenon, however, can be delayed or prevented using the immunosuppressive agent cyclosporin, thus offering novel pharmacological neuroprotective options for brain injury (Murphy et al., 1999). Once elevated beyond a certain threshold, intracellular calcium can activate several degradative enzymes including proteases, lipases and nucleases which can destroy cellular integrity. With lesser elevation of cytosolic calcium, intracellular signaling mechanisms (such as nitric oxide production) are activated and some of these may themselves lead to cytotoxic outcomes. Neuroprotective strategies which attempt to combat cellular calcium overload have thus focused on inhibiting calcium channels or blocking calcium activated enzymes.

Channel Antagonists

Nimodipine, a dihydropyridine derivative, has been tested for more than 10 years in extensive randomized controlled trials for a cytoprotective effect in acute ischemic stroke. Nimodipine blocks calcium inflow through voltage-sensitive calcium channels of the L-type and has proven benefit in the prevention of vasospasm after subarachnoid hemorrhage. A series of randomized controlled trials between 1984 and 1994 were, however, unable to demonstrate an overall benefit in stroke outcome. The overall conclusion of these studies is that nimodipine treatment in stroke does not improve neurological or functional outcome or mortality compared to placebo treatment (Wahlgren, 1995).

Two major concerns with these studies are worth noting. The first is that few patients were included within a reasonable time interval of 12 hours after onset of the neurological symptoms. The second is that a hypotensive effect of nimodipine may have outweighed any neuroprotective effect. Other voltage sensitive calcium channel blockers such as PY 108-068, isradipine and flunarizine also have not shown significant benefit in small clinical trials for stroke. Initial studies using calcium channel antagonists in experimental trauma, however, did not show protective actions (Ford & Malm, 1985). In part, this may have been related to the hypotensive effects of such treatment, as subsequent studies using combinations of cal-cium channel blockers with agents that sustain blood pressure showed some degree of protec-tion (Ross & Tator, 1991). Clinical studies have not been performed with calcium channel blockers in TBSI.

Mitochondrial Membrane Permeability Transition Inhibitors

As described above, the abrupt inability of mitochondria to buffer excessive cellular calcium loads during cell injury is a crucial event in the demise of a cell. When the mitochondria reach a certain capacity to take up calcium, their inner membrane develops a large non-specific pore (mitochondrial permeability transition or MPT) which not only spills their accumulated calcium back into the cytosol, but also prevents mitochondria from doing their normal business of ATP production. This event has been viewed as a final blow to the cell, making it give up its fight to stay alive and let the calcium-triggered necrotic events proceed uninhibited.

Several other chemical mediators also may be capable of initiating the MPT. A few drugs have been realized that may block this event. The most well studied of these is the immunosuppressive agent, cyclosporin. The actions of this drug in preventing the MPT represent a distinct action apart from its immunosuppressive effect and nonimmunosuppressive analogs that prevent the MPT are now being developed actively. That the MPT represents an attractive target for neuroprotective efforts recently has been demonstrated in rat models of traumatic CNS injury where cyclosporin treatment preserved axonal mitochondrial integrity and limited calcium induced axonal damage (Okonkwo et al., 1999; Okonkwo & Povlishock, 1999).

Calpain Inhibitors

With the advent of specific inhibitors capable of inhibiting calcium-activated proteases (calpains), calcium-activated

proteolysis now represents a therapeutic target in TBSI (Kampfl et al., 1997; McIntosh et al., 1998). Clinical testing of these agents will have to await their further development (Lee et al., 1997).

Free Radical Scavengers

Oxygen free radicals apparently damage cells during reperfusion into the ischemic area following spontaneous or induced recanalization (Chan, 1994). Reactive oxygen metabolites such as superoxide, hydrogen peroxide and hydroxyl radicals can be produced by incomplete reduction of oxygen as a result of enzymatic activity, blood, iron and heme catalyzed reactions, or the re-introduction of oxygen into an environment rich in reducing equivalents (i.e., an ischemic focus). Formation of oxygen free radicals can result in peroxidation injury of lipid membranes, protein oxidation and damage to DNA. Mitochondrial membranes and mitochondrial DNA may represent some of the more sensitive sites of attack for free radicals.

Several potential agents exist for neuroprotective strategies aimed at reducing free radical formation in the acute setting following TBSI. These include superoxide dismutase (SOD), catalase, vitamin E, iron chelators, lazaroids and phenyl-t-butyl-nitrone (PBN). Tirilazad, a lipid peroxidation inhibitor, which had been found to reduce infarct size in several stroke models (Xue et al., 1992), did not show improved functional outcome in patients with acute cerebral ischemia (Peters et al., 1996), although a larger trial using higher doses is in progress. PBN, a spin-trapping agent, has been shown to reduce damage in animal stroke models, supporting the concept that free radicals contribute to brain injury.

Indeed, the rationale for the use of steroids in traumatic spinal cord injury relates to their ability to inhibit free radical-induced lipid peroxidation, which is optimally found for methylprednisolone in the dose range of 30 to 60 mg/kg (Braughler & Hall, 1982). Experimentally, doses in this range reduce trauma-induced perturbations of calcium, increase spinal cord blood flow and enhance behavioral recovery after impact in spinal cord trauma (Braughler & Hall, 1988). Protective effects have not been as consistently demonstrated with other cortico-steroids, such as dexamethasone.

The first major randomized clinical trial of methylprednisolone in humans used doses <30 mg/kg and reported negative findings (Bracken et al., 1984). A large randomized multicenter clinical trial using higher doses of methylprednisolone, however, showed that it significantly enhanced neurologic recovery in humans, if the drug was administered within the first eight hours after trauma (Bracken et al., 1990; Bracken et al., 1993). The 21-amino steroids, or lazaroids, similarly are capable of inhibiting free radical-induced lipid peroxidation, al-though they have no glucocorticoid or miner-alocorticoid action. One of these compounds, tirilizad mesylate, has been found to improve motor recovery after impact injury in cats (Anderson et al., 1988). Clinical studies comparing methyprednisolone and tirilizad are now pending. The dual efficacy of methylprednisolone as an immunosuppressive agent and free radical scavenger is noteworthy in the context of this drug being the only truly effective clinical neuroprotective agent that we have today. It is conceivable that other drugs having specific sites of action also may be designed to have antioxidant properties as in the case of methylprednisolone. Cyclosporin, for example, also has been shown to limit lipid peroxidation in spinal cord injury (Diaz-Ruiz, 1999) and such dualism of action may be a key feature to develop into future neuroprotective agents.

Nitric Oxide

Nitric oxide (NO) is a novel neurotransmitter which is both a free radical and a gas. Formed via the calcium-activated enzyme nitric oxide synthase (NOS), this messenger molecule plays a major role in regulating vascular tone and several other physiological functions. Although the full scope of NO-mediated functions in the brain is yet to be realized, it does appear that when NO is produced in excess, it contributes to neurotoxicity. Indeed, NO has been shown to play a significant role in NMDA receptor- mediated neurotoxicity as this toxicity is blocked by NOS inhibitors and NO scavengers (Strijbos et al., 1996).

The toxic effects of NO actually may be mediated by peroxynitrite, which results from the combination of superoxide and NO. Peroxynitrite can generate hydroxyl radical-like species in addition to potent nitrating species which may attack lipids, proteins and DNA. The oxidative damage to DNA may in fact represent a crucial step in neurotoxicity. Previous inhibitors of NOS suffered from lack of specificity in that several isoforms of NOS, including those in neurons and endothelium, were all blocked by the inhibitors.

The benefit of inhibiting NOS in stroke has been illustrated by the reduction of infarct size in animals treated with NOS inhibitors and in neuronal NOS knockout mice (Hara et al., 1996). The role of NO in traumatic nervous tissue injury appears to be complicated as it has been reported to both enhance the toxicity of motor neurons and protect non-motor neurons (Urushitani, 1998). Recent evidence suggests that the neuroprotective effectiveness of gangliosides may be attributable, in fact, to their ability to block nitric formation (Dawson et al., 1995). The advent of more selective agents such as 7-nitroindazole, which display neuronal

specificity, may open the way for clinical trials of NOS inhibitors in TBSI (O'Neill et al., 1996).

Poly (ADP-Ribose) Polymerase

Poly (ADP-Ribose) Polymerase (PARP) is a nuclear enzyme expressed in most cells which is activated by DNA damage. PARP activation results in the incorporation of multiple ADP ribose groups from NAD onto PARP itself and several other DNA associated proteins. This modification is believed to release DNA associated proteins from DNA resulting in altered chromatin structure. While this action of PARP is believed to assist the work of DNA repair enzymes, overactivation of PARP results in a marked depletion of cellular NAD and ATP supplies, which in fact promotes cytotoxicity. A role for PARP overactivation in NMDA-mediated neurotoxicity and in stroke (Eliasson et al., 1997; Enders et al., 1997) has been demonstrated.

The sequence of events envisioned in this cascade begins with an overactivation of neuronal NMDA receptors due to the elevated glutamate levels found in ischemic cerebral tissue. Excessive calcium influx through NMDA receptors then activates neuronal NOS. Increased production of NO by itself, or through peroxynitrite formation, leads to oxidative DNA damage resulting in DNA strand breaks. This, in turn, activates PARP, which in an attempt to assist DNA repair actually further compromises cellular energy stores and promotes cell death.

Why an enzyme normally involved in DNA repair should contribute to cell death is not clear. What is clear is that PARP may be dispensable for DNA repair as PARP knockout mice show no obvious neurological deficits. In fact, these mutant animals show much reduced infarct volumes following stroke as compared to normal mice (Eliasson et al., 1997; Enders et al. 1997). Recent experiments using a hybrid neuroblastoma-spinal cord cell line also have demonstrated that peroxynitrite and hydrogen peroxide-induced cell death can be ameliorated with PARP inhibitors (Cookson, 1998). The inhibition of nitric oxide-activated poly (ADP-ribose) synthetase via intrathecal administration of NOS or PARP inhibitors attenuates transsynaptic alteration of spinal cord dorsal horn neurons and neuropathic pain development in a rat model of chronic constriction injury of the common sciatic nerve. (Mao et al., 1998).

Furthermore, direct activation of neuronal PARP in experimental head trauma has been demonstrated (LaPlaca et al., 1999). This activation occurs early and appears to be widespread throughout the brain, implying a major derangement of brain NAD and energy metabolism occuring shortly following brain injury. Indeed, transgenic mice made deficient in PARP recently have been found to have reduced cognitive and motor deficits after traumatic brain injury (Whelan et al., 1999). Future studies of PARP inhibitors in TBSI are eagerly awaited.

TARGETING INFLAMMATORY PROCESSES

Inflammation also may contribute to ischemic cell damage after cerebral infarction (Hallenbeck et al., 1986) and trauma (Ghirnikar et al., 1998). The migration of leukocytes into ischemic tissue is a regulated process involving paracrine messengers and specific interactions between molecules on the surfaces of both the leukocytes and the endothelial lining of vessels. The expression of ICAM- 1 (intercellular adhesive molecule), a vascular endothelial cell surface protein, facilitates the adhesion of leukocytes. The adhering neutrophils may promote injury in several ways. These cells may release toxic oxygen radicals and proteases or they may produce mechanical obstruction of the microcirculation, thus futher reducing spinal cord blood flow. Anti-ICAM antibody treatment reduces neurological deficits in animal stroke models (Bowes et al., 1993; Zhang et al., 1994). A clinical trial of anti-ICAM antibody in stroke is in progress. Specific cytokines and chemokines generated in the traumatized CNS also appear to contribute significantly to the intensity of the subsequent inflammatory reaction (Ghirnikar et al., 1998; Ransohoff & Tani, 1998). The receptor-mediated signaling mechanisms used by these messengers soon may be important targets for neuroprotective therapy in TBSI.

TARGETING ADAPTIVE TISSUE RESPONSES

As described earlier, nervous tissue elements which are not lethally injured by the initial trauma can make adaptive responses which range from repair and regeneration to active cell suicide or apoptosis. Repair and regeneration of nervous tissue, long believed to be impossible, recently has become an exciting prospect with the discovery of several neurotrophic factors and regenerative neuronal precursor cells (Kuhn, 1996; McIntosh, 1998; Takagi, 1999). While these topics may be associated more appropriately with neurorehabilitation, the prevention of apoptotic cell death certainly has become an important target for neuroprotection in TBSI. The identification of a key set of enzymes, known as caspases, as important bottlenecks in the apoptotic death cascade soon may allow clinically effective and safe inhibitors to be used in clinical TBSI (McIntosh, 1998). A major issue in saving cells from dying via apoptosis is the functional integrity of such cells. If apoptosis is a normal response to eliminate damaged cells, will saving such cells return normal function to them? Long term survival studies with apoptosis inhibitors in brain injury should clarify this issue.

TARGETING CELLULAR ENERGETICS

Much of the focus for neuroprotective strategies has been placed on specific targets elucidated through basic studies of neurotoxicity. It should be noted that each of the neuroprotective therapeutic targets identified in some way contributes to the sparing of energy in nervous tissue (Obrenovitch & Urenjak, 1997). Thus, agents such as voltage dependent sodium and calcium channel blockers, glutamate receptor agonists, GABA and adenosine agonists all decrease membrane excitability and reduce the utilization of ATP for membrane repolarization and calcium compartmentalization. Reduction of oxygen free radicals and nitric oxide may lower the utilization of ATP for membrane and macromolecular repair and may prevent the futile depletion of NAD and ATP via PARP activation (Azbill et al., 1997).

Other therapeutic strategies such as hypothermia probably also work by reducing demands on cellular ATP levels. Future clinical neuroprotective strategies in TBSI may benefit by focusing on the maintenance of brain spinal cord energy levels through a combination of pharmacological approaches. This focus may reduce the dose requirements of several of the above mentioned neuroprotective agents and thus reduce their toxicity. This approach is currently being pursued aggressively by a series of investigations sponsored by the Defense and Veterans Head Injury Program.

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QEEG and Traumatic Brain Injury: Present and Future

Robert W. Thatcher, PhD

Introduction

The human brain is a highly energetic three-pound mass of soft tissue that sits in a hard bony vault. This small but vital organ is particularly vulnerable to rapid acceleration/deceleration by virtue of its relationship to the skull as well as its geometry and relative density of different brain regions. Although the brain only constitutes approximately 2% of total body weight, it consumes approximately 20% of oxygen intake with each breath, as much as our muscles consume in active contraction. One must ask: how is this disproportionate amount of metabolic energy utilized? The answer is that most of the brain's metabolic energy is transformed into electrical and magnetic energy by which the essential perceptual, cognitive, emotive, regulatory and motoric functions are carried out at each moment of time.

The electroencephalogram (EEG) is typically recorded at the scalp surface with reference to the ear and represents the moment-to-moment electrical activity of the brain. The EEG is produced by the summation of synaptic currents that arise on the dendrites and cell bodies of billions of cortical pyramidal cells that are located primarily a few centimeters below the scalp surface. The quantitative measurement of the electrical activity of the brain through the use of high-speed computers is referred to as quantitative EEG (QEEG) (Niedermeyer & Da Silva, 1995).

Since 1929, when the human EEG was first measured (Berger, 1929), modern science has learned an enormous amount about the current sources of the EEG and the manner in which ensembles of synaptic generators are synchronously organized. It is known that short distance local generators are connected by white matter axons to other local generators that can be many centimeters distant. The interplay and coordination of short distance local generators with the longer distant white matter connections has been mathematically modeled and shown to be essential for our understanding of the genesis of the EEG (Nunez, 1981; Nunez, 1995; Thatcher & John, 1977; Thatcher et al., 1986). The relevance of QEEG to the diagnosis and prognosis of traumatic brain injury (TBI) stems directly from the QEEG's ability to measure the consequences of rapid acceleration/deceleration to both the short and long distance compartments of the brain.

This article will review briefly the present state of knowledge about the diagnostic and prognostic value of QEEG in TBI and then speculate about some of the future roles of QEEG in TBI, with special emphasis on the integration of QEEG with MRI and other imaging technologies. Criticisms of the use of QEEG and TBI have been discussed and rebutted elsewhere (Thatcher et al., 1999).

Test-Retest Reliability of QEEG

The clinical sensitivity and specificity of QEEG is directly related to the stability and reliability of QEEG upon repeat testing. The scientific literature shows that QEEG is highly reliable and reproducible (Aruda et al., 1996; Burgess & Gruzelier, 1993; Corsi-Cabera et al., 1997; Duffy et al., 1994; Gasser et al., 1985; Hamilton-Bruce et al., 1991; Harmony et al., 1993; Hughes & John, 1999; Lund et al., 1995; Pollock et al., 1991; Salinsky et al., 1991). The inherent stability and reliability of QEEG can be demonstrated with quite small sample sizes. For example, Salinsky et al. (1991) reported that repeated 20-second samples of EEG were about 82% reliable, at 40 seconds the samples were about 90% reliable and at 60 seconds they were approximately 92% reliable. Gasser et al. (1985) concluded that 20 seconds of activity are sufficient to reduce adequately the variability inherent in the EEG and Hamilton-Bruce et al. (1991) found statistically high reliability when three different individuals independently analyzed the same EEG. Although the QEEG is highly reliable even with relatively short sample sizes, it is the recommendation of most QEEG experts that larger samples sizes be used, for example, at least 60 seconds of artifact free EEG, and preferably two to five minutes, should be used in a clinical evaluation (Duffy et al., 1994; Hughes and John, 1999).

Present Use of QEEG for Diagnosis of TBI

The scientific literature presents a consistent and common QEEG pattern correlated with TBI. Namely, reduced amplitude of the higher frequencies of EEG (Mas et al., 1993; Ruijs et al., 1994; Tebano et al., 1988; Thatcher et al., 1998a; von Bierbrauer et al., 1993) and changes in EEG coherence (Hoffman et al., 1995; Hoffman et al., 1996a; Thatcher et al., 1989; Thatcher et al., 1991; Thatcher, 1996a; Thatcher, 1998b; Trudeau et al., 1998). The reduced amplitude of EEG is believed to be a result from a reduced number of synaptic generators and/or reduced integrity of the protein/lipid membrane structures of neurons (Thatcher et al., 1997; Thatcher et al., 1998a). EEG coherence is a measure of the amount of shared electrical activity at a par-

ticular frequency and is analogous to a cross-correlation coefficient. EEG coherence is amplitude independent and reflects the amount of functional connectivity between distant EEG generators (Nunez, 1981).

Of the few QEEG studies of the diagnosis of TBI, quite a high level of sensitivity and specificity has been demonstrated. For example, a study of 608 individuals with mild TBI and 103 age-matched control subjects demonstrated discriminant sensitivity=96.59%; Specificity=89.15%; Positive Predictive Value (PPV)=93.6% (Average of tables II, III, V) and Negative Predictive Value (NPV)=97.4% (Average of tables III, IV, V) in four independent cross-validations. Trudeau et al. (1998) and Hoffman et al. (1995) published a similar sensitivity and specificity for QEEG diagnosis of TBI. All of these studies met most of the American Academy of Neurology's criteria for diagnostic medical tests:

1. The criteria for test abnormality was defined explicitly and clearly
2. Control groups were different from those originally used to derive the test's normal limits
3. Test-retest reliability was high
4. The test was more sensitive than "routine EEG" or "neuroimaging tests"
5. The study occurred in an essentially "blinded" design (i.e., objectively and without ability to influence or bias the results).

The QEEG/MRI project of the Defense and Veterans Head Injury Program (DVHIP) has replicated and extended the earlier QEEG studies of TBI, thus adding additional validity and reliability to the use of the QEEG in the diagnosis of TBI (Thatcher et al., 1998a; Thatcher et al., 1998b)

Present Use of QEEG for the Prognosis of TBI

An example of the prognostic value of QEEG in predicting outcome one year following TBI is demonstrated in a study by Thatcher et al. (1991). In this study, a total of 162 individuals were diagnosed as having a closed head injury. Of the 162 individuals, 60% sustained motor vehicle-related injuries, another 10% were pedestrians and the remainder of the injuries were incurred in industrial or home incidents or as a result of violent crime. Glasgow Coma Scores were obtained at the time of admission (GCS-A) and at the time of computerized EEG testing (GCS-T). CT scans were obtained within one to seven days after admission. QEEG and evoked potential testing occurred within 1 to 21 days following injury. Outcome scores were obtained at one year post-injury using the Rappaport Disability Rating Scale (DRS) (Rappaport et al., 1982). Multiple regression analyses were performed in which the DRS was the dependent variable and the CT scan, GCS-A, GCS-T, age and computerized EEG and evoked potentials were the independent variables.

The best individual EEG predictor was EEG phase which had a univariate R^2=44.21%, while the least predictive was absolute power with R^2=19.14%. When the most statistically significant univariate EEG variables were entered in the multiple regression analyses then the multiple R=0.75 and accounted for 52.56% of the variance of the DRS scores. The QEEG was the single best category of variables for predicting outcome at one year post-injury. Figure One shows the comparative strength of the predictability of DRS scores at one year following injury. The best multivariate predictor for each category of variables was the QEEG (R^2=64.91%), the second strongest predictor was GCS –T (R^2=38.71%), the third was the brain stem auditor evoked potential (BSAEP) (R^2=29.76%), the fourth was CT scan (R^2=28.16%) and the weakest was age (R^2=18.55%). The age range of the individuals involved in the study was between 14 and 32.

If these multivariate variable sets then were combined in order to find the best predictor of outcome at one year post-injury using the least number of variables and thus the highest probability of replication, then the combination of QEEG and GCS-T was the best with a R^2=74.65% of the variance. This combination of variables used only 12 variables (i.e., 11 QEEG variables and 1 GCS-T variable) with an N=129.

Future Uses of QEEG in TBI

This section will be restricted to only three future uses of QEEG:

1. Integration of QEEG and MRI
2. EEG current source localization
3. EEG biofeedback.

This limited number of possible future uses of QEEG is due to page limitations and already established uses of the QEEG in TBI.

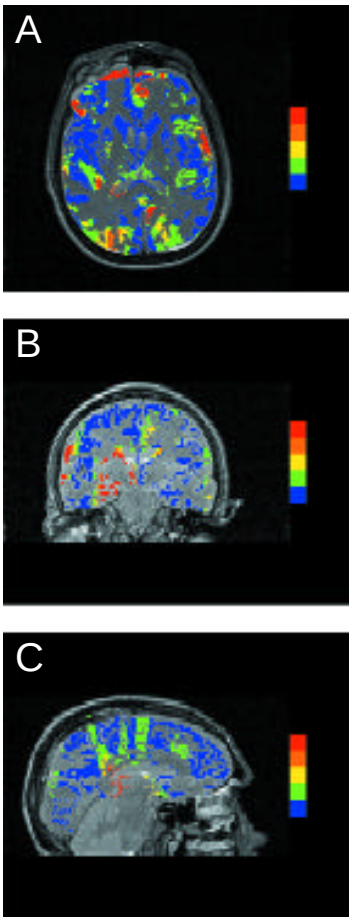
QEEG and MRI Integration and TBI

Magnetic resonance imaging (MRI) provides much more than just a structural picture by which the spatial location of EEG generators can be identified (Thatcher et al., 1994). For example, the spectroscopic dimensions of the MRI can provide information about the biophysics of protein/lipid water exchanges, water diffusion, blood perfusion, cellular density and mitochrondrial energetics (Gilles, 1994). The marriage of QEEG with the biophysical and structural aspects of MRI offers the possibility of much more sensitive and specific diagnostic and prognostic evaluations, not to mention the development and evaluation of treatment regimens in TBI. A recent series of DVHIP studies have helped pioneer the integration of QEEG with the biophysical aspects of MRI for the evaluation of TBI (Thatcher et al., 1997; Thatcher et al., 1998a; Thatcher et al., 1998b). These

studies have provided MRI quantitative methods to evaluate the consequences of rapid acceleration/deceleration (Thatcher et al., 1997) and to integrate the MRI measures with the electrical and magnetic properties of the QEEG as they are affected by TBI (Thatcher et al., 1998a; Thatcher et al, 1998b). Future studies are expected to further extend our understanding of the molecular consequences of TBI as measured by the QEEG and, hopefully, lead to inexpensive but highly sensitive and specific QEEG measures of TBI.

QEEG Current Source Localization and TBI

FIGURE 2: 3-D EEG Current Source Localization



An example of the current source density that gives rise to the scalp EEG co-registered with the 3-dimensional MRI in a DVHIP TBI patient. The color scale to the right of each view is the EEG current source density in nano-amps/cm^2. Top (A) is an axial view, middle (B) is a coro nal view and bottom (C) is a sagittal view. The current sources of the scalp EEG are derived using this method (LORETA) and then correlated with the MRI derived T2 relaxation times within the interior of the brain.

Figure Two shows the axial, coronal and sagittal views of the current sources of the QEEG in an individual with TBI. The DVHIP is using current source localization procedures, such as those shown in Figure Two, to identify the current density of MRI registered voxels within the interior of the brain. This approach, referred to as Low Resolution Electrotomography (LORETA) (Pascual-Marqui et al., 1994), is being used to further our understanding of the consequences of TBI on the biophysical integrity of the electrical and magnetic generators of the brain. The future applications of EEG current source localization and MRI biophysical measures is expected to eventually improve the sensitivity and specificity of the QEEG in the evaluation of TBI.

One of the ways that the integration of current source density and MRI will advance the diagnostic accuracy of QEEG is by extending our understanding of the genesis of the EEG itself. For example, all inverse solutions of scalp recorded EEG assume a linear dependence based solely on the conductance of the four shells of brain, CSF, skull and scalp (Malmivuo & Plonsey, 1995). These inverse solutions of the sources of the EEG treat each moment of time as a discrete and instantaneous event in which the attenuation of the scalp distribution of electrical potential is determined solely by the distance and resistivity between the generator sources and the QEEG scalp electrodes and assumes that the capacitive effects inside the interior of the brain are negligible (Malmivuo & Plonsey, 1995).

The integration of QEEG with the MRI biophysical measures of the brain, however, indicate that in the future the capacitive and inductive properties of the brain also will be taken into consideration in the evaluation of TBI. For example, it is expected that future QEEG studies, when integrated with the biophysical measures of the MRI, will provide estimates of the dielectric constants of the electrical generators and the medium in which they are embedded, thus providing for more accurate source localization and a deeper understanding of the consequences of TBI.

EEG Biofeedback

Electroencephalograhic (EEG) biofeedback, often referred to as neurofeedback, is an operant conditioning procedure whereby an individual modifies the amplitude, frequency or coherency of the neurophysiological dynamics of his/her own brain (Fox & Rudell, 1968; Rosenfeld et al., 1969; Rosenfeld & Fox, 1971; Rosenfeld, 1990). The exact physiological foundations of this process are not well understood; however, the practical ability of humans and animals to directly modify their scalp recorded EEG through feedback is well established (Fox & Rudell, 1968; Hetzler et al., 1977; Rosenfeld et al., 1969; Sterman, 1996).

An emerging and promising treatment approach is the use of quantitative EEG technology and EEG biofeedback training for the treatment of mild to moderate TBI. One of the earliest EEG biofeedback studies was by Ayers (1987), who used alpha QEEG training in 250 cases of individuals with brain injury and demonstrated a return to pre-morbid functioning in a significant number of cases. Peniston et al. (1993) reported improved symptomology using EEG biofeedback in Vietnam veterans with combat related post-traumatic disorders. Trudeau et al. (1998) reported high discriminant accuracy of QEEG for the evaluation of combat veterans with a history of blast injury.

More recently Hoffman et al. (1995), in a biofeedback study of 14 individuals with TBI, reported that approximately 60% of individuals with mild TBI showed improvement in self-reported symptoms and/or cognitive performance as measured by the MicroCog assessment test after 40 sessions of QEEG biofeedback. Hoffman et al. (1995) also found statistically significant normalization of the QEEG in those individuals that showed clinical improvement. Subsequent studies by Hoffman et al. (1996a; 1996b) confirmed and extended these findings by showing significant improvement within 5–10 sessions.

A similar finding of QEEG normalization following EEG biofeedback was reported by Tinius and Tinius (1996). Ham and Packard (1996) evaluated EEG biofeedback in 40 indi-

viduals with posttraumatic head ache and reported that 53% showed at least moderate improvement in headaches; 80% reported moderate improvement in ability to relax and cope with pain and 93% found biofeedback helpful to some degree.

In summary, EEG biofeedback is a possible future treatment regimen that may help marry the basic science of QEEG and TBI with a cost-effective method of symptom amelioration. Future controlled studies will help determine the clinical efficacy of this methodology.

Dr. Robert W. Thatcher received his bachelor degree in chemistry and his PhD in biopsychology at the University of Oregon. He joined the faculty of New York Medical College as an assistant professor and New York University Medical School as an associate professor and a full professor at the University of Maryland School of Medicine, where he was the director of the Applied Neurosciences Research Institute and the Neurometrics Clinical Service in Shock Trauma. In 1991, he joined the staff at the National Institutes of Health and the National Institutes of Neurological Diseases and Stroke as the project manager for the 128-channel EEG system and the program on functional neuroimaging. Currently, he is a full professor in the Department of Neurology and Radiology at the University of South Florida School of Medicine and Program Manager for EEG and MRI analyses of head injury and quantitative MMRI analyses of aging and dementia at the VA Medical Center in Bay Pines, Florida. Dr. Thatcher has published six books and more than 150 journal articles, book chapters and abstracts. These publications cover the fields of basic neuroscience, neurobiology, developmental psychology, neurometrics, environmental toxicology, clinical medicine and multimodal integration of MRI, EEG and PET scans. He has extensive clinical experience, having performed more than 2,000 clinical evaluations for individuals with a wide variety of clinical disorders (e.g., head trauma, strokes, tumors, epilepsy, attention deficit disorders, Alzheimer's Disease and organic dementias).

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Sleep Disturbances Following Traumatic Brain Injury

Angela Drake, PhD and David Bradshaw, MD

Sleep is a complex phenomenon, controlled by multiple neuronal systems within the brainstem, hypothalamus, thalamus and basal forebrain. In fact, it is likely that two systems exist: one promoting wakefulness, the other sleep. For sleep to occur, the system maintaining wakefulness must subside.

Current recording technologies have allowed researchers to document the architecture of the nocturnal sleep cycle, which is both regular and predictable. Nocturnal sleep is characterized by a cascade of neuroanatomical and neurochemical changes in the brain. As sleep approaches, the sleep promoting neurons in the brainstem, thalamus, hypothalamus and basal forebrain become more active and initiate the cycle of sleep. Deactivation of the reticular activating system, which maintains wakefulness, results in a release of synchronous spindle oscillations of the thalamus. Serotonin is released, dampening the sensory input from the environment and inhibiting motor activity, resulting in the initiation of slow wave activity in the cerebral cortex. Rapid eye movement sleep (REM) begins in the brainstem and is characterized by neuronal involvement of multiple areas of the brain, including the forebrain, cerebellum and lateral portions of the nucleus reticularis pontis oralis (RPO). Although researchers have suggested that the various stages of REM sleep are modulated by specific areas in the brain, these areas have yet to be identified (Culebras, 1992). It appears that acetylcholine may be involved in initiating and maintaining REM sleep.

Yet as predictable as the stages of sleep are, the interactions between the neuroanatomic, neurophysiological and neurochemical systems responsible for maintaining the delicate cycle of sleep and wakefulness are vulnerable to disruption due to any condition which affects the brain. It is not surprising, then, that alterations in the sleep/wake cycle have been well documented following traumatic brain injury (TBI). These difficulties with sleep have been reported across all levels of severity of TBI.

A myriad of difficulties with sleep have been associated with TBI, including difficulties initiating and maintaining sleep, a lack of restorative sleep and excessive daytime sleepiness (Beetar et al., 1996; Cohen et al., 1992). Disruptions in the sleep-wake cycle following TBI appear to be greatest immediately following the injury and decrease over time (Ron et al., 1980). Persistent difficulties with sleep have been reported following TBI, particularly in those individuals with a history of extended coma or a significant degree of diffuse injury (Askenasy et al., 1989).

One study of the sleep patterns of individuals with TBI revealed impaired rapid eye movement (REM) recovery and multiple nocturnal awakenings (Prigatano et al., 1982). Multiple awakenings during nocturnal sleep can result in an absence of restful sleep and excessive daytime sleepiness. Disturbances of REM sleep have been observed to lessen in some individuals with TBI and these changes parallel improvements in cognitive functioning observed during the natural course of recovery (Harada et al., 1976).

Individuals with a mild traumatic brain injury (MTBI) who are subsequently diagnosed with post-concussive syndrome report a great number of sleep-related difficulties. Perlis (1997) found that individuals with MTBI and post-concussive syndrome reported significantly more difficulties with sleep compared to orthopedic controls, particularly with regard to initiating and maintaining sleep. The individuals with post-concussive syndrome also reported significantly more daytime sleepiness than did controls. One polysomnogram (PSG) study completed on individuals with MTBI revealed a possible cause of the sleep-related complaints observed following MTBI. This study showed increased fragmentation in the architecture of nocturnal sleep (Prigatano et al., 1982). This pattern of disturbed sleep also has been associated with other neurological conditions and results in lighter, less restful sleep, which is more vulnerable to nocturnal arousal and awakenings. It is likely that the fragmentation of nocturnal sleep observed in these individuals is related to their problems with excessive fatigability, daytime sleepiness, nonrestorative sleep and possibly even depression.

Several case studies of narcolepsy have been reported following TBI (Good et al., 1989; Maccario et al., 1987). Lankford et al. (1994) completed a PSG study in a small group of individuals with documented mild to moderate TBI and persistent sleep complaints. Although the individuals included in the study did not have any history of sleep disturbances prior to their TBI, the results from the PSG studies were diagnostic of post-traumatic narcolepsy. The individuals also underwent a standardized Multiple Sleep Latency Test (MSLT) following the PSG. The results of this testing revealed significant daytime sleepiness and two or more sleep onset REM periods. Although post-traumatic narcolepsy is controversial, some of the difficulties with sleep reported following TBI are similar to those associated with narcolepsy, including excessive daytime sleepiness, fatigability and fragmented nocturnal sleep, with frequent arousals and awakenings.

Although a few studies of sleep in individuals following TBI have documented alterations in nocturnal sleep, to date no large-scale studies of sleep disturbances and their impact on various aspects of everyday functioning following TBI have been published. It is certainly possible that disturbances of sleep and wakefulness have the potential to contribute to poor quality of life (Culebras, 1992) and may exacerbate the psychosocial difficulties and cognitive impairments occurring post-TBI.

Currently, the gold standard for assessing sleep is the polysomnogram with continuous EEG monitoring. This type of evaluation requires an overnight stay in the sleep lab, where the individual is monitored using multiple EEG sensors. The advantage of PSG is that it records the entire sleep process, including the distinct stages of sleep (spindle, slow wave and paradoxical or REM sleep), and can document any disturbances in the progression of the stages of sleep. The disadvantages include the high cost of PSG and the need to monitor individuals in an unfamiliar environment with multiple EEG monitors in place. As a result, the monitoring itself can directly affect both sleep quality and quantity.

An alternative method of assessing the sleep/wake cycle is through the use of actigraphy. Actigraphy measures an individual's movements on a 24-hour basis. Although actigraphy represents an indirect measurement of sleep, it has been found to accurately reflect sleep/wake cycles in several previous studies (Ancoli-Israel et al., 1997; Sadeh et al., 1989). The actigraphy monitor resembles a standard wristwatch and can be worn over the course of several days to enable recording of the sleep/wake cycles over time.

A sleep study using this technology is currently underway at Naval Medical Center San Diego. The study is a subproject of a larger study of MTBI and everyday functioning which was funded by the Defense and Veterans Head Injury Program beginning in 1996. These two studies will gather useful information on the potential causes of sleep disruptions following MTBI. In addition to three days of actigraphy monitoring, each individual will complete a comprehensive sleep questionnaire, a measure of sleepiness, and sleep diaries for the recording interval. In combination, these measures will allow assessment of sleep hygiene and subjective experience of sleepiness, sleep patterns, sleep quantity and circadian rhythms. These results then will be examined with regard to the multiple measures of cognitive, psychosocial and vocational functioning gathered as part of the standard protocol of the larger MTBI study. The initial goal of the sleep study is to more precisely identify sleep disturbances following MTBI and document their impact on daily functioning. Once we have established the etiology of the sleep disturbances associated with MTBI, we hope to develop and evaluate potential treatments to assist in the regulation of sleep post-TBI.

Dr. Drake is a clinical neuropsychologist and the San Diego site Principal Investigator for the Defense and Veterans Head Injury Program at the Naval Medical Center San Diego. She completed graduate training in clinical psychology at Auburn University, receiving a masters degree in 1988 and a PhD in 1991. Both her thesis and dissertation focused on issues relevant to neuropsychology. She completed a pre-doctoral internship in clinical psychology at the Department of Veterans Affairs Medical Center in La Jolla, CA and the University of California, San Diego. She also completed a two-year post-doctoral fellowship in clinical neuropsychology at the VA, working with Dr. Nelson Butters. During her fellowship, she received funding for a post-doctoral research project from the National Institute of Drug Abuse to study the cognitive effects of polysubstance abuse in women. She has published a number of articles and presentations on various topics relevant to neuropsychology. She is especially interested in the neuropsychological implications of drug and alcohol abuse following TBI, issues related to everyday functioning, especially return to work after a traumatic brain injury, functional neuroimaging and gender differences in cognition.

David A. Bradshaw, MD, CDR, MC, USN, is the Pulmonary Division Head and the Director of the Sleep Laboratory at Naval Medical Center San Diego. He completed a sleep disorders fellowship at the Standford Sleep Disorders Clinic. He is board certified in sleep, pulmonary medicine, critical care and internal medicine.

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FINDING AND EVALUATING TRAUMATIC BRAIN INJURY RESEARCH ON THE INTERNET

Karen Schwab, PhD and Mary Rosner

The easy availability of vast stores of articles, bulletins, abstracts and thought pieces on the internet makes current and past research on new treatments and rehabilitation strategies for traumatic brain injury (TBI) accessible in a way never before envisioned. This article discusses how to access information on the internet and evaluate the information obtained. This discussion will be helpful to professionals beginning to access the TBI research literature on the internet, as well as family members and individuals with brain injury learning how to access and evaluate relevant information.

Accessing Information on the Internet

About 25% of American households now have immediate access to the internet (Schultz, 1999). That percentage does not include those who access the Web at their public libraries, through their computer labs at school or in households of friends and relatives. A recent study reported that 42% of Americans could access the internet, and 27% actually had access (Schultz, 1999).

Internet searches can save money and time. Rather than scouring libraries for relevant material, requesting searches from librarians and/or ordering articles that may or may not prove to be relevant through inter-library loan, the internet provides immediate access to thousands of article summaries and hundreds of organizations' web pages. More family members and individuals with brain injury are frequently turning to the internet for information about TBI and rehabilitation alternatives. Clinicians also use the internet for their own research needs on TBI, and to answer continuing questions from individuals with brain injury and family members.

The internet also can be used to research appropriate clinical services. For example, the brother of an individual with brain injury recently contacted the Defense and Veterans Head Injury Program (DVHIP). After sustaining a traumatic brain injury in the late 1970s, the individual spent several years in his parents' home. The parents' age and declining health, however, prohibited their continuing care for the individual who also was exhibiting continuing behavioral problems. This 100% service-connected veteran had spent 14 years in a locked psychiatric facility when his brother searched the internet and found information about a DVHIP lead site. The DVHIP center subsequently evaluated the individual with brain injury and arranged placement in a non-psychiatric residential facility that could provide appropriate care for him. Had it not been for the brother's internet search, the individual might have remained in a locked unit.

Search Engines

Searches conducted on the internet with a good engine strategy (i.e., AOL, Google, Lycos, Infoseek, Yahoo, AltaVista) give access to thousands of articles and other types of information about traumatic brain injury. These search engines operate on a system of "key terms." When an internet user specifies a key term, the search engine will list articles and web pages using the key term or combination of key terms. Some search engines organize articles by the number of times the article or web page has been accessed by users (e.g., the number of "hits") or referenced by others. In a recent attempt to find information about brain injury, the author entered the terms "Brain Injury Association" into a Google search and received back 335 matches, including the Brain Injury Association's (BIA's) homepage at http://www.biausa.org, as well as numerous state association web sites. Meta search engines explore the search engines, taking advantage of the multiple search strategies utilized by various services. Entering "traumatic brain injury" into one such meta search engine resulted in over 200,000 references, arranged within each of 9 search engines. Another search engine, http://www.askjeeves.com, is based on the user entering a question, rather than key terms.

Searches now can be conducted with Medline, the National Library of Medicine's computerized bibliography. Medline permits access to thousands of medical journals, article citations and abstracts published since 1966, making Medline an invaluable resource for anyone researching medical reports and findings. Entering the term "traumatic brain injury" captured 3023 matches. Focusing the search by adding one- by-one extra terms, such as behavioral, memory loss, speech and caregiver, captured shorter lists–217 matches, 128 matches, 80 matches and 26 matches, respectively.

As with any good library search, narrowing a search by interactively adding relevant terms and then reviewing the articles and abstracts produced will garner more focused lists of potentially useful sources of information.

Evaluating Information Gathered on the Internet

Unfortunately, misinformation and poor research exist alongside expert interpretation and excellent research reports on the internet. Good research establishes the probability that a therapy works better than an alternate therapy, and the likelihood that the therapy will or will not cause harm to the individual, thus presenting evidence for or against a particular therapy/treatment. Poor research can lead clinicians and families to make inappropriate treatment decisions. Understanding the principles of good research methods permits the internet researcher to distinguish more helpful from less helpful research.

A clinician's success with a new procedure or drug on one individual or even several individuals may suggest new directions for research, but it is rarely enough to justify a change in medical practice. A practitioner trying a new treatment may inadvertently misread measurements, remember successes and overlook failures or unconsciously influence the individuals they are treating into feeling better. Some individuals will get well on their own, no matter what the treatment given. Research studies are intended to minimize potential biases of investigators, calculate the likelihood that chance has produced a particular finding and measure the difference in outcome between carefully selected groups of individuals receiving different treatments. Ideally, these individuals are randomly assigned into treatment groups. Good research studies produce reliable, valid and relevant evidence. Research can and should be judged by:

1. Whether or not the same results could be replicated by anyone conducting the study, assuming everything was completed equally and carefully
2. Whether the study measured what the researchers intended to measure
3. Whether the study addressed a clinically relevant question

Reliability of Information

The reliability of research results is the likelihood that another similar study would produce the same results. The most reliable studies are those which:

1. Have larger rather than smaller sample sizes
2. Use standardized instruments
3. Are conducted at more than one center

A larger sample size is generally necessary to ensure that the study has sufficient power to test its hypotheses/objectives. When evaluating the number of individuals in a study, it is important to look at the number of them completing a study (that is, reaching the study's endpoints and receiving the outcome measurements). Researchers sometimes report the total number of individuals receiving some part of a study, or the number that is available for study. The telling number, however, is the number of individuals who completed the study's treatment and follow-up assessments. Sample sizes of less than 30 may provide intriguing ideas or the basis for larger studies, but rarely provide reliable conclusions about the efficacy of a treatment. Sample sizes of several hundred individuals or more often are necessary to provide sufficient power to test research hypotheses.

Carefully designed research also includes standardized instruments. It is one thing for a clinician to state an opinion that individuals given a particular treatment have recovered from the effects of brain injury. It is quite another for a researcher to report that certain individuals with brain injury score well on the Glascow Outcome Scale or on a series of neuropsychological performance tests.

Finally, although excellent studies are often done at a single center, multi-center studies further ensure that the results are reliable, since a finding replicated at several centers is more likely to be replicated in future studies as well. A multi-center study also is less likely to find significant results because of an unusual set of circumstances unique to one site and time period (i.e., a highly motivated set of individuals with very supportive families).

Valid Information

A valid research study measures what it intends to. A study is more likely to produce valid results if it:

1. Carefully controls the quality of data collection and treatment
2. Uses appropriate instruments and measurement techniques for the study questions
3. Uses control groups
4. Randomizes individuals into treatment groups
5. Follows individuals to determine whether or not treatment effects are maintained over time

Quality control is critical to the research endeavor. Carefully designed studies include site visits, reliability studies of critical instruments, chart audits, regular training of staff and ongoing review of procedures. Failure to implement careful quality control procedures may result in study inconsistencies and errors over time.

Control groups are most commonly used in drug studies, but without control groups (i.e., individuals receiving a different treatment or no treatment) it is difficult to accurately determine whether or not a particular treatment has affected patient care. The preferred method of allocating individuals

into different treatment groups is random assignment. Any other method of assignment is likely to be biased.

For instance, assigning every other individual into Treatment A and Treatment B would seem unbiased, but in fact, clinicians may delay entry of certain successive individuals into the study in order to maximize their chances of receiving Treatment A.

Relevant Information

The relevance of a study is enhanced when 1) the researchers test effect sizes that are meaningful in clinical practice; 2) the range of individuals studied is similar to the number treated in clinical practice; 3) the hypothesis is relevant and 4) the topic is important to clinical care. The effect of a treatment generally is measured in terms of the number of individuals benefited (often expressed as the percentage of persons with favorable outcome compared to persons receiving a different treatment or no treatment). Many studies are designed with a sufficient number of cases to detect treatment effects of the magnitude of 15% or more – for instance, if 50% of untreated individuals return to work, a study might hypothesize that a new treatment will result in 65% of individuals with TBI returning to work. A treatment effect of that magnitude generally is considered clinically significant.

Overall Evaluation

Studies rarely rank high on all these criteria. Well-designed, randomized controlled trials present the highest level of evidence in research. Randomized controlled trials with flaws, well-done longitudinal studies and quasi-experimental studies rank next. The weakest evidence is gathered in case reports, uncontrolled case series and expert opinion studies. (Chesnut, et al., 1999).

Findings in the research literature are works in progress. Although research findings often are written carefully by authors and reviewed by experts before publication, research varies in quality. Much of the appraisal of a study's findings occurs after publication. Researchers and clinicians, as a collective body, constantly appraise and re-evaluate the meaning and interpretation of findings as they are integrated into the existing store of knowledge. Even remarkable findings may be reinterpreted as researchers develop new instruments and treatments. Readers of the current research literature need to form their own independent assessments of the reliability, validity and relevance of studies.

Some researchers are concerned about the heightened publicity given certain research findings before they are reviewed for publication. Sometimes newsworthy studies are reported pre-publication or even pre-submission to refereed journals. Again, the above criteria can be used to independently assess the helpfulness of the study.

The judgement of a finding's reliability, validity and relevance also depends upon who reports it and where. Research conducted by appropriately trained researchers at a university or respected research institute is likely to be more helpful than research reported by a nonaffiliated, untrained researcher. An article published in a medical journal is likely to be more helpful than an opinion piece on an individual web site that does not cite experts or data. Information synthesis such as provided in the Brain Injury Resource Center™ (BIRC), literature reviews published by BIA (i.e., Brain Injury Source) or medical journals help sort out stronger from weaker findings. Web sites of organizations with excellent reputations in providing service and conducting research on traumatic brain injury are good starting places for periodic reviews of relevant, helpful findings.

If an individual or family member has found research reports on a promising new method, they should be encouraged to discuss the finding along with its likely usefulness with a clinician.

How to Access Research Information without Direct Internet Access

What about clinicians, family members and individuals who wish to conduct a search but do not have access to the internet? Many public libraries will be glad to conduct a search on key terms and then print out a list of relevant articles. BIA maintains a toll-free number answered by knowledgeable professionals who can assist individuals and family- members in their searches for information. BIA also has developed the Brain Injury Resource Center™ (BIRC) that extracts and summarizes important, helpful research and reviews the latest information on treatments for different problems resulting after brain injury.

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Defense and Veterans Head Injury Program (DVHIP). Program developed for individuals eligible for care at military and veterans hospitals described and instructions for contact of centers provided. See DVHIP button on Brain Injury Association web site, menu one. http://www.biausa.org.

National Library of Medicine's Medline. Abstracts and citations from thousands of medical and other clinical journals organized by key terms. http://www.nlm.nih.gov.

Medical College of Virginia National Resource Center for Traumatic Brain Injury. Articles and video tapes on a wide variety of TBI topics, plus a list of TBI experts with addresses and e-mail information. http://www.neuro.pmr.vcu.edu.

Traumatic Brain Injury Model Systems. Seventeen Traumatic Brain Injury Centers funded by the National Institute on Disability and Rehabilitation Research (NIDRR), a branch of the Department of Education. http://www.tbims.org.

Family Caregiver Alliance. Factsheets and reading lists for caregivers of individuals with various chronic conditions, including traumatic brain injury. http://www.caregiver.org.

Open Forum

A Comprehensive Functional Approach to Brain Injury Rehabilitation

Michael J. Raymond, PhD, ABPN, Kristin C. Bewick, MS, CPCRT, Thomas L. Bennett, PhD, ABPP and Kit B. Malia, BED, MPhil, CPCRT

Introduction

Brainwave-R: Cognitive Strategies and Techniques for Brain Injury Rehabilitation (1997) has been designed to assist in the cognitive rehabilitation of individuals with brain injuries. It consists of a large array of exercises (mainly pen and paper based), which are organized into five modules, addressing those areas of cognitive deficit that are most commonly demonstrated following brain injury:

1. Attention
2. Visual Processing
3. Information Processing
4. Memory
5. Executive Functions

The five Brainwave-R modules are hierarchically presented according to Luria's (1963) theory of brain function, which suggested that complex behavioral processes are distributed throughout the brain in functional systems. The three basic functional systems have been described by Golden (1981):

1. Attention - Level of arousal and maintenance of alertness (mainly involving the brain stem and reticular activating system)
2. Information Processing - Reception, integration and analysis of sensory information external and internal to oneself (mainly involving the parietal, temporal and occipital lobes)
3. Executive Functions - Planning, executing and verifying of behavior (mainly involving the frontal lobes)

Each of these functional systems is used in most everyday activities, and the three are hierarchically organized. If attention is poor, therefore, information processing and executive functions will consequently be impaired. Also, if problems exist within formation processing functions, then it is likely that executive functions will be impaired (Ben-Yishay & Diller, 1983).

Program Description

The Brainwave-R program contains the principles upon which the program is based, a general introduction to brain injury and a review of information on each of the cognitive areas addressed in the program. The general introduction to brain injury and the review of information is intended for use by the therapist in educating the client and family. Initial and Final Client Questionnaires are included at the end of the book to help the therapist interview the client. These are described in more detail later.

This introductory book is accompanied by the five modules, each containing a Therapist Workbook and a Client Workbook. The Therapist Workbook includes a list of materials needed for each module, guidelines for the therapist, record sheets for client performance, instructions for how to describe each exercise to the client and answer sheets. The Client Workbook includes exercises to help the client improve performance in the module areas and charts for performance predictions and self-ratings. These exercises aim to educate the client about the problem areas and provide practice opportunities to develop deficit skills and implement strategies to improve functional performance. The purpose of each module can be summarized as follows:

1. Attention–This module aims to develop focused, sustained, selective and alternating attention skills in order to optimize arousal and
   alertness levels
2. Visual Processing–This module aims to develop more accurate saccadic eye movements, visual scanning skills, visual attention, figure-ground discrimination, pattern recognition, visual memory and the ability to mentally manipulate visual information. It also reinforces the exercises on attention completed in the previous module.
3. Information Processing–This module is divided into two sections. Part 1 aims to develop ordered, sequenced thinking skills. Part 2 aims to develop the ability to work more quickly, under time constraints and with more complex information.
4. Memory–This module has been designed to teach the client about memory processes and emphasizes the use of strategies to compensate for memory problems.
5. Executive Functions–This module also has been divided into two
   sections. Part 1 teaches the client about executive functions and strategies that can be used to compensate for deficits in this area.

Part 2 provides a choice of projects for the client to organize, plan and execute using the strategies taught in Part 1.

How to Use the Questionnaires

The questionnaires, which appear at the end of the book, have been included to help the therapist structure the initial and final interviews with the client. These measures focus on functional abilities across a wide range of skills. The initial questionnaire can be used to help determine which of the program modules are appropriate for the client. The final questionnaire can be used to help measure the real-life effects of cognitive rehabilitation efforts. These questionnaires should be used in conjunction with more formalized neuropsychological measures in order to describe patterns of strengths and weaknesses. At present no formalized scoring system has been developed for these questionnaires. The questionnaires may be copied for use with clients.

How to Use the Modules

After the appropriate modules have been selected for the client, the following sequence of events is suggested:

1. The therapist should become familiar with the tasks and should organize any materials that are needed (a list of these for each module are found at the beginning of the Therapist Workbook).
2. The Client Workbook should be opened to the appropriate task and given to the client.
3. The therapist should read the instructions for the task to the client. These spoken instructions appear in boxes in the Therapist Workbooks. Some clients may be able to read and apply the instructions independently, which should be encouraged whenever possible.
4. The client should predict his/her performance using the rating charts in the Client Workbook. Appropriate rating charts are provided with each exercise.
5. The client should complete (or attempt to complete) the task.
6. The client should rate his/her actual performance using the rating charts in the Client Workbook. Appropriate rating charts are provided with each exercise.
7. The therapist should rate the client's performance using the rating charts in the Therapist Workbook.
8. The therapist should discuss performance with the client, encouraging the client to determine the relevance of the task to his/her everyday life, and to suggest strategies that could be implemented to improve performance.

Repetition of Tasks

Most of the tasks are repeated up to five times, using similar exercises. The purpose of this repetition is to enable the client to monitor improvement following practice and strategy implementation.

Time Involved

The program has been designed to include many opportunities to practice cognitive skill areas. Most of the modules are divided into four weeks, and suggestions are made for which exercises to complete on which days (the exception to this is the Memory module, described below). Suggestions also are made for time duration of each task. There are between 60 and 90 minutes of tasks provided each day, if the suggested time frames are followed. These time frames are merely suggestions, and time will vary depending on the severity of the client's problems and the length of the therapy session.

Therapists are often not able to treat clients for these time frames every day of the week. Clinical experience with this program, however, has shown that clients with mild or moderate injuries can be given up to 60 minutes of tasks to complete outside of therapy sessions without direct therapist supervision, once they understand the task requirements. This "homework" has proven to be a very effective method of working through many of the tasks, and clients report a greater sense of control and involvement in their rehabilitation.

If all the modules are completed within the suggested time frames, the whole program will take approximately seven months to complete.

The Memory Module

The Memory module varies in format from the other four modules. This module is divided into four sections. Sections 1 and 2 consist of learning materials to teach the client about memory and how it works, and inform the client of the range of strategies that are available. Given the different rates at which clients can absorb this information, the sections have not been given time frames. This allows the therapist to control the amount of information given to the client during any one session. Sections 3 and 4 consist of practice exercises and tasks to encourage functional implementation of strategies. These have been divided into weeks with suggestions for timings, as in the other modules.

Metacognition

The processes of knowing which factors influence learning skills and the ability to monitor one's own performance is known as metacognition (Bewick et al., 1995). Metacognitive skills include the processes of awareness, evaluation, prediction, anticipation and self-control (Brown et al., 1983; Flavell, 1985). The inclusion of metacognitive processes in cognitive rehabilitation is considered to be an

essential feature of a successful program (Ben-Yishay & Diller, 1993; Bewick et al., 1995). The aim is for the client to be an active participant in the cognitive rehabilitation program. The Brainwave-R program has been designed to incorporate a strong metacognitive component, including the following:

- An educational emphasis, to teach the client about cognitive skill areas and how to use strategies to improve functioning
- Study questions to test acquisition of knowledge
- Rating charts on which the client predicts performance and rates actual performance
- A performance summary sheet that allows therapist and client to compare ratings in order to improve accuracy of prediction and self-evaluation
- Ideas to stimulate the client to determine the relevance and purpose of each task

Who is the Program For?

The tasks and strategies contained in the Brainwave-R program are ideally suited to adult clients of varied ages who have mild to moderate cognitive deficits following brain injury. Many of the tasks, however, also can be used with clients who have more severe problems. The therapist may use the modules as resource books in order to customize appropriate activities for certain clients, and may decide to select only specific tasks with children who have brain injuries. The Brainwave-R program can be used in various settings:

- Inpatient rehabilitation programs
- Outpatient rehabilitation programs
- Community-based or outreach programs
- Family/client support groups (e.g., Brain Injury Association [United States], Headway [United Kingdom])

Ways to Use the Program

The Brainwave-R program has been designed to be flexible so that the therapist can use it in various ways according to the individual needs of the client. The following are some suggested methods:

1. As a whole cognitive rehabilitation program, beginning with the Attention module, progressing through Visual Processing, Information Processing and Memory modules, and ending with the Executive Functions module
2. Use of selected modules to meet the individualized needs of the client
3. As a cognitive activities resource bank from which the therapist can select appropriate tasks from a number of different modules to suit the needs of the client

Principles of Brainwave-R

The following principles of brain injury rehabilitation form the basis of Brainwave-R:

Principle 1–It is possible to overcome or optimize the effects of cognitive deficits to enable the individual to become a better problem solver in real-life situations (Ben-Yishay, 1981; Ben-Yishay et al., 1982; Ben-Yishay & Diller, 1983). Although compensation may be viewed as occurring spontaneously, it can be carried further by direct treatment and education (Prigatano, 1986; Zangwill, 1947). Functional improvements may occur up to 10 to 15 years or more post-injury (Sbordone, 1990).

Principle 2–Rehabilitation combines treatment and educational processes. In the treatment process, specialists work on a client; in the educational process, specialists work with the client and his/her family (Romano, 1984). The former is a passive model, whereas the latter is an active participating model. A client's active participation in a program is a necessary condition for successful rehabilitation (Askensay & Rahmani, 1987). The former model makes it more difficult for the person with a brain injury to develop appropriate executive and psychosocial skills because it does not focus on self-initiation and decision making.

Principle 3–Structured activities can ameliorate some of the emotional and adjustment difficulties that occur following brain injury. Clients frequently become inactive, particularly if left to themselves, because their inability to organize themselves is often dysfunctional (Ruff & Niemann, 1990). They also may develop social and familial problems due to the increased behavioral disturbances, such as social isolation, loneliness and frustration, that their condition imposes on them (Cole, Cope & Cervelli, 1985). These problems occur as the result of organic (brain-related) and/or functional (psychological) consequences post-injury.

Structure imposed from outside will help the person with a brain injury deal more effectively with life's demands. Over time this structure may be internalized and used spontaneously, thus obviating the need for further intensive intervention. Consistency is the key to therapy for people with brain injuries. The client's day must be structured in a predictable, logical and consistent manner (Slade, 1985).

Principle 4–Continued appropriate programs of cognitive stimulation will lead to better recovery. Environmental stimulation will lead to greater brain weight, increased neuronal size, prolific dendritic growth and more glial cells (Powell, 1981). Despite skepticism about the "practice makes perfect" principle among neuropsychologists, there is no evidence that this model does not have some effect on improvements (Gianutsos, 1991). Until

evidence indicates to the contrary, it is wise to include mental stimulation in a cognitive rehabilitation program, particularly because traditional learning models support such activity.

The value of training and exercise has long been recognized in the rehabilitation and education of mental functions. In fact, as a process in itself, doing exercises can be a powerful antidote to depression (Gianutsos, 1991).

Principle 5–The first goal is to reduce the client's generalized cognitive confusion. This means optimizing the individual's attention and information processing skills to make him/her more efficient. Therapy should focus on capacity and flexibility of information processing (Hart & Hayden, 1986).

Principle 6–Developing awareness and acceptance of strengths and deficits is an important part of the process (Askensay & Rahmani, 1987; Prigatano, 1986). There is a constant need to deal with the client's poor awareness and appraisal of problems (Prigatano, 1986). Minimally, therapists should be able to help people identify their cognitive losses. Additionally, therapists can help clients to come to terms with these losses and develop coping methods. Finally, therapists can attempt to help clients regain lost function (Gianutsos, 1980).

Principle 7–Therapy should aim to restore real-life abilities rather than abstract skills. Thus, cognitive rehabilitation is important primarily for its effects on interpersonal, leisure and work and/or productive skills (adaptations). Tasks are not chosen for content but to serve primarily as vehicles for the transmission of strategies (Scherzer, 1986). Neuropsychological testing should be supplemented by neurobehavioral assessment, including detailed medical and background histories, family and social relationship information, and behavioral observations (Sbordone, 1990).This constitutes a neuropsychological evaluation. Following this evaluation, cognitive rehabilitation should be geared toward:

- Daily life functions and self-care
- Skill complexes that have a direct bearing on work abilities
- Interpersonal skills and social readaptability (Ben-Yishay & Diller, 1983).

Principle 8–Active participation by family members in the rehabilitation process should be encouraged. Family members should be taught rehabilitation management strategies (Sbordone, 1990). The family needs systematic aid from trained professionals in helping the client achieve his/her highest level. Complair (1989) reported that 50% of caregivers experience significant levels of general psychological distress and impairment in family functioning after a family member sustains a brain injury. These levels of distress are strongly associated with behavioral, cognitive, somatic, communicative and social problems. Emotional distress can be reduced by having problem-focused coping methods, perception of a greater cohesion and emotional expressiveness in the family, and a more positive attitude (Bryan, 1990). The family's adaptation to the injury and its sequelae has a significant impact on the rehabilitation of the person with a brain injury (Bond & Brooks, 1976).

Despite this distress, families usually wish to continue supporting and caring for a person who is injured (Oddy et al., 1985). Thus, it is appropriate that the client is treated as part of the family unit (Sbordone, 1990) and, consequently, that he/she be treated as close to home as possible (Eames et al, 1989). Often family members also require counseling to help them adjust to the individual's stages of recovery.

Principle 9–Clients should be encouraged to maintain appropriate eating and sleeping habits. These patterns often are disturbed after brain injury. Good sleep is essential to avoid catastrophic reaction due to fatigue and metabolic changes (Sbordone, 1990). If needed, a daily calorie and sleep log can be kept.

Principle 10–Long-term rehabilitation is necessary after brain injury. Long-term follow-up studies of individuals with untreated brain injury have shown that without therapy many individuals do not continue to progress (Brooks et al., 1986; Lezak, 1979; McKinlay et al., 1981; Oddy, Humphrey & Uttley, 1978). In fact, Brooks and colleagues (1986) estimated that as many as 50% get worse, developing psychiatric, behavioral and social complications, and becoming an increasing burden on their caregivers.

Principle 11–Generalization of skills occurs over an extended period of time along with specific attempts to help the process (Cicerone, 1987). Generalizations of learning to real-life functions have been programmed into the Brainwave-R study pack. Generalizations to more general cognitive functioning do not seem to occur unless specifically built into a program. Treatments aimed solely at primary cognitive deficits do little other than change functioning specifically on the treated measures (Brooks, 1991).

Principle 12–Executive functions need to be incorporated into a brain injury rehabilitation program. Disturbances of higher executive functions (initiation, planning and self-regulation) may be especially prominent after brain injury and frequently determine the extent of social and vocational recovery (Oddy et al.,1985).

Principle 13–This program is based on Luria's (1963) theory of plasticity (the "reorganization of functional systems")

and is structured in accordance with his elucidated principles. Following a brain injury, specific functions (i.e., language, memory, sensorimotor abilities) may be altered. A reorganization of brain functions may occur through "uninjured" brain areas, allowing then-altered functions to be performed differently.

Principle 14–Tasks are presented in modular form, building from each other over the course of the program. Barth and Boll (1981) stated that tasks should:

- Be structured from simple to complex
- Be objectively quantified
- Lend themselves to immediate client feedback

Principle 15–Instructions within the program are presented clearly and concisely. The format is highly organized and user friendly.

Principle 16–The program may lead to greater readiness for productive activities (educational/vocational), enhanced personal satisfaction, more constructive use of leisure time and improved social relationships. Some programs and therapists focus solely on vocational abilities as an outcome goal. This focus is important but not sufficient and does not address all of the problems. The balance should include work, activities of daily living (ADLs) and leisure skills. If clients are to function at their maximum, their feelings about leisure and its use cannot be left to chance or accident. Rather, it must be part of the rehabilitation process (Hein-Farley, 1983).

Principle 17–An educational component has been incorporated into the program so that the client can learn about the effects of brain injury on different aspects of adaptive functioning. This information is written in a clear and concise manner, and is comprehensive and can be maintained as a reference.

Principle 18–Considering that the field of brain injury rehabilitation has not been fully researched, this program may be viewed as current and flexible in its approach, so that new research findings easily can be incorporated into the overall design as well as the techniques used.

Conclusion

The rehabilitation of individuals who have sustained any form of brain injury continues to be an arduous task. It is time consuming, expensive and frequently physically and emotionally draining for the individual as well as to significant others. Cognitive strategies and techniques, as provided in the Brainwave-R program, can offer a practical contribution to enhancing functional adaptive skills in daily living. Successful implementation of such strategies should minimize the amount of time, money and frustration often reported during brain injury rehabilitation. According to Hartlage (1998), this comprehensive approach to brain injury rehabilitation "can certainly enhance the repertoire, scope and comprehensiveness of facility-based neurological rehabilitation programs, by providing therapists with a wide and useful array of well conceived and carefully designed procedures."

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Kit Malia, BED, MPhil, CPCRT. With the Society for Cognitive Rehabilitation (SCR) in the United States, Malia is the only certified cognitive therapist in the United Kingdom (UK) with a research degree in neuropsychology. He initially trained as a teacher for people with learning disabilities and, following a period of teaching, has spent over a decade working as a cognitive rehabilitation therapist with adults who have acquired neurological injuries at one of the largest brain injury rehabilitation units in the United Kingdom. He has published scientific papers on cognitive and psychosocial rehabilitation and is the primary author of Brainwave-R, an extensive collection of cognitive strategies and techniques for brain injury rehabilitation. Malia has lectured at various conferences in North America, Sweden, Norway and the United Kingdom. He is also on the Board of Directors for the Society for Cognitive Rehabilitation in the United States and the chairperson of the European committee for the SCR.

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Ask the Doctor

Nathan D. Zasler, MD, FAAPM&R, FAADEP, DAAPM, CIME

WHAT CAN YOU TELL ME ABOUT THE RISKS, IF ANY, OF CHILDBIRTH AFTER TRAUMATIC BRAIN INJURY? IN PARTICULAR, I WAS WONDERING WHETHER THE RISK OF STROKE AS A RESULT OF WEAKENED BLOOD VESSELS IS HIGHER IN WOMEN WHO HAVE HAD A TRAUMATIC BRAIN INJURY (TBI).

Thanks for your challenging question. Unfortunately, there is very little literature in the area of obstetrical issues in persons with TBI. In fact, I was unfamiliar with any studies when I received your question, nor could I find any literature on this issue when I conducted a search. I would note several things, however, regarding the issue of childbearing after brain injury.

As a rule, childbearing capacity is not adversely affected by TBI, whether mild or severe. There certainly are individuals who have endocrine (hormonal) problems following TBI that may cause difficulties in becoming pregnant; in particular, amenorrhea, or lack of a period. Generally, however, amenorrhea is transient, with menses normally returning within the first six to twelve months post-injury. If menses does not return on its own, the treating obstetrician and gynecologist, or TBI specialist, could consider administering oral estrogen/progesterone preparations which will not only restore the menstrual cycle but maintain secondary sexual characteristics and reduce the risk of osteoporosis.

It is also important to note that in women who have more significant physical disabilities (e.g., gait disturbances secondary to hemiparesis or ataxia) pregnancy can cause further difficulty in general mobility status. One phenomena that I have also seen frequently over the years in pregnant women who had a history of severe TBI is that their baseline ataxia worsens. This may be related to effects of systemic hormonal changes. Even persons who regularly use wheelchairs need to be aware that pregnancy may compromise their seating and wheelchair mobility and they may need to look at wheelchair modifications or temporary alternative seating.

In persons with significant physical impairments after TBI, pregnancy can also exacerbate post-injury musculoskeletal problems, including arthritis and low back pain due to the alteration in normal body biomechanics associated with pregnancy.

Generally, fertility is unaffected by TBI, whether mild, moderate or severe. What individuals with brain injury and their families need to be aware of is the fact that many of the medications prescribed to persons with TBI have the potential to cause birth defects (also known as teratogenic drugs). These issues are particularly problematic in individuals who have established post-traumatic epilepsy and require long-term maintenance on anti-convulsant drugs. In a situation such as this, it is recommended to continue on the drugs and have close prenatal screening to determine if the fetus has any birth defects, such as neural tube defects. If such defects are found, the individual has the option of continuing the pregnancy or having an abortion. Many commonly used drugs, including anti-depressants such as SSRIs, may be associated with teratogenic effects. There are some drugs for which there is little to no literature on their use during pregnancy. It has been my experience that it is best to avoid such medications during pregnancy, if at all possible.

It must be mentioned that there is no data to suggest, with regard to your specific questions, that women with TBI are at increased risk of stroke during the birthing process due to weakened blood vessels from the brain injury. As a rule TBI does not “weaken” blood vessels. It certainly is possible but rare to have post-traumatic aneurysms which may put a woman at increased risk for aneurysmal rupture if there is significant hypertension during the pregnancy and/or birthing process. This vascular complication of neck and traumatic brain injury is extremely rare, so this should not be a concern for the typical individual. As noted in the beginning of my answer, I would emphasize that there is no literature that I am aware of that actually looks at this question. As concerns exist about risks, they should be discussed on an individual basis with the treating physician and/or a referral should be made to a specialist in TBI and/or obstetrics.

I would note that in more general terms, not specific to TBI, there has been an ongoing controversy regarding the use of low dose oral contraceptives and stroke in young women. Recent studies seem to suggest that the overall risk for stroke was not increased among current users of low dose oral contraceptives. There is controversy, however, regarding this issue. There are also studies that have shown that, although the rate of stroke is falling in young women over the last few years, the rate of relative risk

associated with oral contraceptive use is greater for occlusive stroke and increases with age in hemorrhagic stroke. A recent publication concluded that risk of occlusive stroke increases with increased dosages of estrogen, although the risk related to type or dose of progesterone is less consistent.

Lastly, there is also recent literature to suggest that women in general are at higher postpartum risk (e.g. after childbirth) for stroke. These researchers found that the risk of cerebral infarction (stroke) and intracerebral hemorrhage (bleeding in the brain tissue) are increased in the six weeks after delivery but not during pregnancy itself. This risk is about 8.7 times higher for women in the postpartum period than non-pregnant women.

Overall, there is much that we have to learn regarding pregnancy and its potential risk to women who have sustained traumatic brain injury, particularly those which are more severe. I hope that my answer sheds at least some light on this topic.

Thank you for your questions.

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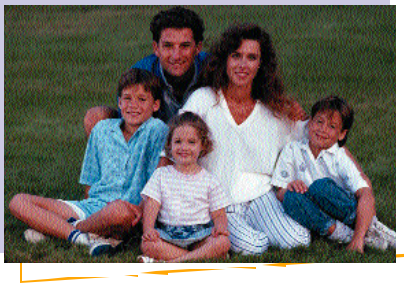
Relatively Speaking

Whose Responsibility Is It Anyway?

by Carolyn Rocchio



The most prevalent impairments subsequent to brain injury are severe cognitive deficits (Sundance & Cope, 1998) and the resulting neurobehavioral sequelae often are poorly understood by those outside the rehabilitation community. For the individual and family, the impact of brain injury is lifelong. Even when families are willing to be the primary support system for the individual with brain injury, they are, in most cases, inadequately prepared for the role.

Brain injury services have taken a step backwards during the reconfiguration of health care delivery brought about by managed care. The media is replete with examples of a scrooge-like system that turns out individuals "quicker and sicker." The proliferation of brain injury services during the 1980s created a booming industry that generated millions of dollars. Along with this rush to provide more and better services, there was unquestionable abuse. For the most part, the appropriate regulatory bodies dealt with these abuses. The 1990s were called The Decade of the Brain, promising great strides in research and treatment. Instead, they became a decade in which managed care labeled physicians as "gatekeepers," whose primary function was to orchestrate care their patients are able to access.

Rehabilitation benefits, once virtually unlimited except by policy caps, are so severely limited now that there is little time to accomplish more than some basic Activities of Daily Living (ADL) training (i.e, personal care, feeding, dressing, toileting) and motor restoration. Gone are the days of extended cognitive and behavioral rehabilitation with family services generously incorporated into the care plan. Neurobehavioral services, costly and labor intensive, were among the first to be denied as too expensive with little supportive data concerning its efficacy. All the more reason that families must now play a larger role because they have no options but to manage the best way they can.

The problems are there. Everyone is aware of them. But are there solutions? The answer is yes, but it takes more than a few family conferences and some literature. Brain injury does not respect age, ethnic origin, socioeconomic status or any other selective segment of the population. It is society's problem and it takes everyone delivering the same message to ensure that the life saved is a life worth living.

Providers, support group leaders, social services agencies and others serving individuals after brain injury ask, "where is the family when support is needed?" Simply stated, the family is one of the casualties of managed care, as reimbursement for family services is no longer a billable item. Once family members were acknowledged and encouraged in meaningful and productive ways by being included as members of the rehabilitation team. How can a family be expected to understand the many ways brain injury can impair an individual without witnessing it first hand in a setting with trained personnel demonstrating strategies for reducing the impairment? Hands-on experience is one of the few methods for families to acquire the skills they will need in the months or years to follow. Managing the cognitive and behavioral sequelae of brain injury is not just a matter of good parenting skills. It is an exhausting, often thankless job of understanding the family member's strengths and weaknesses and how to provide the cueing, monitoring, structuring and other strategies necessary to maintain harmony and safety. Intensive interactive communication is required to accomplish that goal.

New technology that decreases secondary brain damage and allows for improved medical outcomes increases family optimism about recovery. At the same time, families are experiencing less awareness of and preparation for changes affecting cognition and behavior that may not surface until months after discharge. Decreased reimbursement for extended rehabilitation coupled with the busy lifestyle of families whose presence in the rehabilitation setting is not always welcomed or even looked on as a priority increases the possibility for greater dysfunction at a later date.

Good communication is as germane as the treatment one receives. It is particularly important that communication be established from the onset. When establishing this, it is important to keep in mind that immediately after the brain injury, people are usually the most upset and their ability to

listen to and understand often complex medical information is usually very poor (Blume, Carberry & Marion, 1993). Repeating information and requesting that the family keep a list of questions handy when meeting with clinicians enhances communication. Being more introspective, clinicians should remain sensitive to their own value system and philosophies regarding care, thereby improving their ability to communicate with families. In turn, this will maximize adjustment, understanding and involvement, and consequently facilitate the ongoing recovery process of the individual (Zasler, 1993). Balancing honesty while keeping hope alive is difficult but necessary.

No family readily understands how brain injury affects cognition, creating changes in functional capabilities. The neuropsychological assessment is key to the family's knowledge about 1) behavioral expectations following brain injury and 2) the degree of supervision and monitoring of the individual with brain injury (Rocchio, 1998), but often serves little purpose if the family and individual are not privy to the interpretation and recommendations. Every clinician has a role in emphasizing and reinforcing information using a multi-modality method. Information discussed in family conferences should be reinforced using audio or videotaping and supplemented with hard copies that can be reviewed by absent family members at a later time. The family's day-to-day presence on the rehabilitation unit helps them see the problems and learn how trained staff manages them. When the occupational therapist, in the course of evaluating perceptual skills finds significant problems, the individual and family should be shown how that deficit affects the ability to resume activities such as driving.

Families have a better understanding of cognitive deficits when they witness the struggle their family member may have trying to organize a task, perform simple math calculations or find the cafeteria. Successful generalization of skills acquired in rehabilitation is dependent upon the family's acquired knowledge of the problem, a realistic discharge plan, resources to call in crisis and their willingness to stick with it consistently.

During the rehabilitation process, issues almost never discussed with families include:

- Inappropriate behavior
- Sexuality
- Use of alcohol and other substances
- Importance of structured environments
- Consistency of family members in reinforcing strategies
- Planning for a stimulating and productive lifestyle after leaving the shelter of facility based care

All too often, families are blamed for not providing the necessary supports, but the reality is that they are often willing but inadequately prepared to take on the responsibility. Every step of the way, clinicians must be informing and preparing families to become the support network. Discharge planning should specifically outline team recommendations to ensure successful community reentry. Additionally, the plan should include referral to the Brain Injury Association, support groups, Centers for Independent Living, Family Network on Disabilities, Vocational Rehabilitation and other agencies that provide recreation, socialization, legal and mental health services.

Along the recovery process, clinicians and, particularly, discharge planners plant the seeds for future growth and harmony by informing families of the need to sustain the supports beyond the initial stages of rehabilitation and community reentry. Withdrawing supports, once the individual no longer requires the assistance, should be a gradual process. Models for long-term support systems that have been proven successful are Mentoring (Blosser & DePompei, 1995), Circle of Friends and the "Whatever It Takes Model" (Willer, 1993).

Brain injury is a lifetime event and family caregivers must have many tools at their disposal to ensure that the life spared is a life of quality and not an additional burden to be borne and passed from one generation to the next. Effective communication at all levels of recovery and community living can reduce the incidence of re-injury, substance abuse, criminal activity, depression and disharmony.

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