Repeated Mild Brain Injury: Myths and New Direction

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Repeated Mild Brain Injury
Mild traumatic brain injury (MTBI) accounts for the vast majority (i.e., 75-90%) of the estimated two million brain injuries that occur in the United States every year. Of the annual 1.5 million MTBI cases estimated, many individuals with MTBI actually may be receiving their second, third or even greater MTBI. According to statistics listed by the Brain Injury Association of America, an individual who has experienced one brain injury is three times as likely to experience a second brain injury. Additionally, the Brain Injury Association of America reports that the risk for subsequent injury is eight times greater in individuals who have experienced two prior brain injuries. Incurring repeated MTBIs, or what is known as repeated mild injuries (RMI) (>3), may have persistent cumulative effects on cognitive performance and neuropathology.

For decades, questions regarding the recovery process from MTBI have puzzled patients, family members, doctors and scientists. Courtroom battles regarding malingering often have been fought between insurance companies and clients who claim to have post-concussion symptoms (i.e., headache, vertigo, memory deficits). In fact, such cases of possible malingering involving MTBI were a very important contributor to the motivation behind early clinical studies regarding MTBI. Unfortunately, these few initial studies of MTBI were poorly-designed retrospective studies (i.e., excluded proper control groups). Conclusions from these early studies may have contributed to a misunderstanding of behavioral and pathological consequences of MTBI, both single mild injury (SMI) and RMI. Recent studies suggest MTBI recovery has been over-estimated grossly in the past. Current studies indicate approximately one-third of individuals with MTBI do not recover to pre-morbid ability. Additionally, clinical evidence clearly indicates persistent cognitive deficit, particularly following RMI.

MTBI Myths
In previous years, several myths have developed regarding MTBI and RMI. Recent evidence from well-designed studies and utilization of more sophisticated technology clearly indicates that earlier concepts of MTBI and RMI and their subsequent deficits were wrong. Listed below are many of the concepts we now know to be myths regarding MTBI and RMI.

Myth 1: The Head Must Make Contact with an Object to Experience Brain Injury
Several scientific investigations have demonstrated that the head does not need to come in contact with anything to induce brain injury. Neither contact, fracture nor penetration of the skull is required to impose fatal damage to the brain.

As early as 1943, Holbourn et al. explained that sliding of the brain within the skull following impact results in "bending of brain constituents" or "shear-strain." According to Holbourn, this movement is much like the deformation in bending a deck of cards, and is the major cause of brain injury. By 1981, West et al. clarified that compressional or rarefactive (i.e., decrease in density or crowding) strains resulting from linear acceleration forces produce changes in pressure gradients and result in transient perturbations of neuronal membranes. Though acceleration/deceleration and rotational injury seemingly may induce milder forms of brain injury, scientific studies show these types of injury—rather than the head striking an object—play a far more critical role in the ensuing subsequent secondary injury (i.e., swelling, edema, excitotoxicity, diffuse axonal injury). It is the secondary injury rather than the primary injury (i.e., the actual physical injury) that significantly contributes to mortality and morbidity.

Myth 2: If Someone Does Not Lose Consciousness, There is not a Brain Injury
Clinical and experimental studies demonstrate there is very little correlation between how long a person is unconscious and his/her cognitive outcome following MTBI. Loss of consciousness (LOC) does not predict outcome nor does it predict the number of previous injuries in individuals with RMI. For example, if someone has received two prior concus-
sions, the first with 5-10 minutes of LOC and the second with 10-20 minutes of LOC, this does not mean that they will experience 20-30 minutes of LOC with a third concussion. On the same note, we cannot predict for someone who experienced 20-30 minutes of LOC that this is his/her third concussion. Even without LOC, individuals with MTBI often show signs of combativeness, confusion, headache, nausea, sleep disturbances, memory problems and other subtle behavioral changes. Duration of LOC does not predict outcome in SMI or RMI, nor does it predict frequency of injury.

Myth 3: The Brain Has Infinite Resources
It becomes more and more apparent that the brain has limited resources, even in cases of seemingly very mild injury. Not only does clinical and experimental evidence clearly show cognitive deficit following RMI, numerous studies have demonstrated increased vulnerability of specific brain regions and cell types following various central nervous system (CNS) challenges such as stroke, ischemia, hypoxia, genetic predisposition (i.e., genetic risk factors) and neurodegenerative diseases.

Along similar lines, brain injury increases the risk of neurodegenerative disease (i.e., Alzheimer’s disease) regardless of the severity of injury. Thus, even MTBI serves as a risk factor for Alzheimer’s. In fact, individuals with TBI increase their risk of Alzheimer’s by four-fold. If an individual with TBI also carries a genetic risk factor for Alzheimer’s (apolipoprotein E-4 allele), his/her risk increases by 10-fold.

Also, experimental studies indicate that if rats are trained on a highly skilled paw task, cortical representation for their paws and digits increases. However, cortical representation for their elbows and shoulders decreases.

The brain is plastic and certainly can adapt to new tasks and environments. However, clinical and experimental evidence points to a finite amount of resources with which the brain has to work. If these resources are challenged by any means— including even mild brain injury—the overall total resources declines, there is no “reserve” or reservoir from which the brain can draw.

Myth 4: Functional Recovery is the Same as Pathological Recovery
Experimental studies indicate that even though a rat may regain the ability to use a limb that initially was paralyzed by TBI, the cortical neurons originally associated with that limb do not grow back. In fact, a different cortical area takes over the job of the lost neurons. Though surviving neurons may generate new connections, the original network does not return. Thus, the assumption that someone with functional recovery or a resolve of symptoms is as “good as new,” is not true. Yes, they may function normally. However, their total brain resources have been challenged, which is why individuals with mild brain injury often appear to function quite normally under non-stressful, relaxed testing environments. However, if individuals with MTBI are tested under stressful conditions (i.e., exercise, drug induced, high altitude or mild hypoxia) performance scores significantly decline. Additionally, clinical evidence clearly indicates individuals with RMI perform significantly more impaired than those with SMI.

Myth 5: MTBI Does Not Have Long-Term Effects
Initially, adverse effects of MTBI were believed not to endure beyond observable neurological symptoms such as dizziness, nausea and headache. Subconcussive (i.e., minor) brain injuries with no LOC were thought to produce little, if any, adverse effects, either in the short- or long-term. However, it is estimated that one third of individuals with MTBI experience deficits significantly impairing their ability to return to work. Gronwall and Wrightson (1975) demonstrated that recovery of information processing speed to “normal” standards following an incident of MTBI was prolonged significantly in patients with a history of previous MTBI.

Studies suggest the attention and memory deficits experienced by individuals with MTBI are transient and/or episodic. However, in light of evidence that indicates individuals with MTBI perform poorly under stressful conditions, it may be that these individuals simply have learned to cope with their deficits and it is their ability to cope that is episodic. For instance, symptoms may appear transient as persons acquire new coping skills to deal with attention and memory deficits. Additionally, when individuals experience stress (i.e., exercise, mild hypoxia), their coping mechanisms are less effective.

One of the most pronounced traits distinguishing SMI from RMI is the persistence of symptoms or what is known as Persistent Post-Concussive Syndrome (PPCS). Unlike the episodic nature of SMI and/or an individual’s ability to cope, RMI results in persistent, latent and long-term cognitive deficits.

Myth 6: Subsequent MTBIs Are No Different Than the First MTBI
Severity of symptoms following RMI is greater than SMI. Clinical data show individuals with RMI experience more than the attention and memory deficits that individuals with SMI experience, and which they often learn to cope. In addition to attention and memory deficits, individuals with RMI also experience impaired executive functions including: planning, visual perception, spatial orientation (i.e., navigation) and complex learning. Experimental data support these clinical findings (i.e., rodents subjected to RMI show impairment on complex learning paradigms involving visuo-spatial orientation).

While studying RMI-related pathology in humans is difficult—particularly since there is little medical treatment protocol for MTBI and because individuals with MTBI most often do not demonstrate life-threatening medical problems—the few experimental models of RMI in existence demonstrate RMI-related pathology. This evidence indicates that the cognitive deficits individuals with RMI experience very well may have an organic basis. Advances in magnetic resonance imaging (MRI) technology are providing a venue in which individuals with MTBI can be studied better. Both clinical and experimental studies are in progress to develop improved diagnostic and follow-up tools for assessing SMI and RMI. In fact, MRI technology also may provide a means to evaluate when it is safe for individuals with SMI/RMI to return to their normal daily routine. For example, when is it safe for athletes with concussion to return to active play?

In addition to RMI-related cognitive deficits, second impact syndrome (SIS) also provides clear evidence that outcome from subsequent MTBIs certainly is affected by previous MTBIs. When SIS occurs, an individual sustains an additional concussion that results in death or a non-responsive state (i.e., coma). Clinicians have hypothesized that this catastrophic result occurs due to an inability to modulate cerebral blood flow following the initial concussion that does not resolve prior to incurring the second concussion. This further would increase intracranial pressure (ICP) following the second concussion in a system unable to accommodate the increase. Unresolved ICP is a significant contributor to mortality following TBI.
Whether referring to the cerebrovascular system or the brain, subsequent injury involves injuring an already compromised CNS. Much as we would not be surprised by the repeated injury to a muscle, tendon or ligament resulting in further damage, nor should we be surprised of the cumulative damage to the CNS resulting from RMI.

Repeated Mild Injury In Humans
Increasing awareness of the consequences associated with MTBI—particularly RMI—has been developed from the high frequency of concussive injury in the athletic population. While the possibility of RMI-related moderate to severe cognitive deficits recently has been given more attention, most return-to-play guidelines historically have focused on preventing SIS. Early return-to-play guidelines lacked recognition of potential RMI-related cognitive impairment. Though SIS is a main concern, it is essential return-to-play guidelines also address the much more prevalent adverse effects associated with RMI (i.e., increased vulnerability to damage from subsequent MTBI, cognitive decline, altered quality of life).

Collision sport organizations (i.e., National Football League, National Hockey League) have shown increased interest in MTBI and RMI. Repeated concussion is a significant concern in collision sports at all levels, particularly football, ice hockey, soccer and boxing. Significant media attention has focused on several athletes confronted with career-terminating decisions due to RMI in football, ice hockey, soccer and downhill skiing, just to name a few. Frequency of concussive injury in collision sports ranges from an estimated 10% risk of TBI within a single football season to as frequent as that incurred by boxers, one TBI per 12 rounds. Wilberger and Maroon (1989) estimated a 6.3% knockout rate in professional boxers and a 5% knockout rate in amateurs each season. Because of the frequent occurrence of MTBI in sports-related activities, clinical studies have focused on specific athletic populations in an attempt to study the effects of RMI.

Each year, concussive injuries incurred by high school varsity football players range from 60,000 reported to 100,000-250,000 estimated TBIs. Powell et al. (1999) investigated 10 high school sports, identifying incidence of concussive injury as defined by injured players removed from participation and evaluated for brain injury prior to returning to participation. The highest percentage of brain injuries occurred in football (63.4%). Although quarterbacks currently receive the most media attention regarding incidence of concussive injury, it has been documented that running backs and linebackers are most at risk for incurring concussive injuries in football.

Many researchers argue that the risk of concussive injury in soccer nearly is equal to that in football. Although the clinical literature indicates a great deal of controversy regarding the etiology (i.e., heading, collision with other players or goal posts) of concussive injury in soccer players, data clearly show not only a high rate of MTBI in soccer, but also cumulative effects of RMI. Barnes et al. (1998) estimated male and female elite college soccer players are 50% and 22%, respectively, likely to receive a brain injury during a 10-year period. The average career for a professional soccer player was estimated between 12-16 years.

Too often, athletes return to the playing field following a minor concussive brain injury unaware of possible long-term neuropathological and cognitive consequences. Return-to-play guidelines must continue to be modified in light of new clinical and experimental evidence, reflecting risk of ensuing cognitive deficits.

RMI-Related Cognitive Deficits
Enduring cognitive deficits, as well as emotional and personality changes, profoundly influence patients’ relationships, families and jobs. Long-term cognitive and psychosocial consequences of TBI are greater contributors to life-long disabilities and poor quality of life than short-term sequelae (i.e., loss of consciousness, motor/sensory impairments) (Bach-y-Rita, 1990; Bruce, 1984).

Tysvaer and Lochen (1991) studied a sample of 37 retired Norwegian national soccer players. Eighty-one percent showed cognitive deficits. Forty-nine percent of those with deficits displayed moderate to severe levels of impaired cognitive ability. Evidence in this area shows that players directing the ball with their head (i.e., heading) more often than other players (i.e., high headers versus moderate or low headers) score significantly lower on IQ assessment. While this study only investigated between group differences and did not account for premorbidity, other studies also indicate that the number of concussive injuries in soccer players correlates to performance on neuropsychological tests of memory, planning and visuospatial processing.

Researchers in RMI have been interested in boxers for nearly the last hundred years. This population provides, perhaps, the most extreme cases of RMI in regards to MTBI frequency, altered neuropathology and the ensuing behavioral/cognitive deficits. Eighty-seven percent of retired boxers display cavum septi pellucidi (CSP)—separation of the two leaves of the septum pellucidum—which has been correlated with cognitive deficits in mental retardation. Comparison of professional boxers early and late in their careers suggests cognitive deficits observed in boxers are acquired rather than characteristic of those who become professional boxers. Experiencing an average of one brain injury per 12 rounds of boxing and a 6.3% knockout rate per season, boxers particularly are prone to chronic traumatic encephalopathy (CTE) and exhibit a gambit of symptomology from motor deficits (i.e., tremor, dystarhria, parkinsonism) to severe cognitive impairment (i.e., memory, mental slowing, dementia pugilistica).

Diagnosis
In past years, diagnosis of MTBI most often relied on an ensuing LOC. However, recent research brings into question the occurrence of LOC in MTBI. Clinical data indicate MTBI may not always induce LOC, particularly in the pediatric population. Clinical studies indicate both short- and long-term deficits may result from MTBI in which LOC is not experienced. In light of these and similar reports, the definition and diagnosis of MTBI is ambiguous and difficult to apply.

The frequent performance of individuals with MTBI within population norms has contributed to the controversy surrounding both the existence of symptoms (i.e., malingering), as well as the confusion in defining MTBI. However, when the performance of individuals with MTBI is compared to their own baseline, impairment is observed more readily. In sports, investigators have reported that symptoms of MTBI are extremely difficult to diagnose, particularly if the trainer or physician is not familiar with premorbid personality and/or performance. In light of the ever-changing definition of MTBI and the controversy ensuing LOC, most likely the number of reported MTBIs is underestimated drastically. Though many teams have implemented guidelines for return-to-play following concussive injury, the definition of MTBI remains controversial. Thus, guidelines are difficult to delineate.
Not only is information of premorbid performance essential in diagnosing and studying MTBI, but the conditions under which individuals are tested must be considered. As mentioned earlier, although the performance of individuals with MTBI can be impaired when they are tested under stressful conditions (i.e., during exercise, mild hypoxia), their performance under non-stressful testing conditions may fall within population norms.

The most sensitive measure of MTBI is neuropsychological examination. Recent investigations suggest that even abbreviated neuropsychological assessments detect MTBI-related deficits in the absence of abnormal MRI. It is essential that cognitive performance—in both non-stressful and stressful testing conditions—be examined concurrently with the assessment of medical signs and symptoms in cases of MTBI, particularly following RMI.

Future Directions
Currently, there is limited pathological definition of MTBI. Larger sample sizes, more detailed analysis and use of additional techniques are required to begin to elucidate possible mechanisms contributing to pathological alterations associated with RMI. Experimental studies indicate RMI induces changes in neuronal cytoskeletal proteins, which correlate with impaired cognitive function. Further investigations are required to better understand the biological mechanism(s) by which repeated injury induces this pathology. It is important to note that injury severity, injury frequency and inter-injury interval must be examined in order to understand the complex dynamics of RMI. Future experimental investigations of RMI dynamics must parallel those of human RMI.

Additionally, several professional sport organizations have developed brain injury databases and continue to examine concussive injury in their respective sport activity. Though frequency of injury is beginning to be addressed, force of impact and inter-injury intervals nearly are undefined clinically. In order to continue developing appropriate experimental models in parallel with the human condition, these details must be examined clinically and the results published. Currently, extensive effort is being made to build collaborative networks between the basic science community, clinicians and sport organizations to ensure scientific research is relevant to minimizing life/career altering cognitive decline following sports-related repeated concussive injury and, ultimately, define an effective treatment protocol, particularly for RMI. Further clinical and experimental investigation of RMI will provide necessary insight into behavioral, pathological and physiological sequelae of RMI with the goal of reducing vulnerability to subsequent injury, as well as returning individuals with MTBI and RMI to normal daily activity faster and healthier.

In Summary
Typically, RMI pathological and behavioral sequelae have been viewed on a continuum of brain injury severity somewhere between single mild and single severe brain injury. (See Figure 1A.) However, repeated brain injury (RBI) involves injuring an already compromised CNS. Initial experimental studies of RMI indicate traditional measures of TBI damage and recovery (i.e., apoptosis/necrosis, diffuse axonal injury, cytoskeletal protein degradation) may not necessarily be effective measures for evaluating RMI. Re-injury processes may mask the previous injury and recovery processes occurring in the RMI brain. Thus, many RMI studies currently are investigating a wide range of markers to identify and evaluate RMI. In light of the initial experimental data, a new template for comparing RMI to single mild–severe TBI is developing. It is becoming apparent that RBI, regardless of severity, may elicit very different sequelae than typically observed in single mild–severe TBI. In fact, rather than attempting to fit RBI sequelae on the continuum of single mild–severe TBI, RBI may fall onto an entirely different continuum. (See Figures 1A, 1B.) Additionally, effective therapeutic interventions for RMI may differ significantly from those currently being developed for single moderate-severe brain injury.

Conclusions
Clinical and experimental studies clearly indicate cognitive deficits may result from MTBI. In fact, RMI often results in persistent cognitive impairment influencing subsequent quality of life. The investigation of repeated brain injury is in its infancy. Initial studies indicate clinical and experimental studies of MTBI and RMI require critical attention to both appropriate control groups, as well as consideration of pathological differences from single TBI. Thus far, experimental data suggest an organic basis for the cognitive symptoms following RMI. However, the biological

Figure 1: Historically, repeated brain injury (RBI) sequelae has been viewed as a variation of pathology and behavioral/physiological symptoms observed following single mild–severe TBI (A). However, initial experimental studies suggest that the behavioral and pathological sequelae of RBI may be very different from the single TBI, such that is does not fall on the same continuum. Rather, RBI sequelae must be viewed from a clinical and experimental perspective on an entirely different continuum than single TBI (B).
Repeated Mild Brain Injury... continued from page 35 mechanisms of observed pathology must be worked out in future studies. Ultimately, this field of research looks to return individuals with MTBI and RMI to active daily routines faster and healthier through the development of effective medical, behavioral and pharmacological treatment protocols.

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