Subconcussive Head Trauma

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Neuropathology

In this Forensic Science Newsletter we will discuss subconcussive head trauma, its definition, general information, clinical presentation, pathophysiology and biomarkers.

Definition

Subconcussive head trauma is head trauma that does not result in recognized concussion symptoms or signs. It is due to blows to the head, which are below the threshold to cause or elicit any symptoms or signs of a concussion.

To refresh, concussion is defined as trauma-induced alteration in mental status, usually characterized by confusion and amnesia that may or may not involve loss of consciousness, link “Mild Traumatic Brain Injury (Concussion) in Infants, Toddlers, Children and Adolescents.”

In 1993 the American Congress of Rehabilitation Medicine defined Mild Traumatic Brain Injury, as head trauma resulting in one of the following: Loss of consciousness for less than 30 min, alteration in mental status for up to 24 hours (being dazed, confused or disorientated), or loss of memory for events immediately before or after the trauma (retrograde or anterograde amnesia).

General Information

Both animal and human research have shown that subconcussive blows can cause damage to the central nervous system and pathophysiological changes in the brain despite not evoking any apparent acute behavioral changes. These studies have shown injury to the brain not only comes from concussive episodes, but also from repetitive subconcussive blows. Like concussions, blows that produce subconcussive head trauma can transfer both linear and rotational acceleration forces to the brain, which can cause pathophysiological changes in the brain. However, the difference between concussion and repetitive subconcussive blows are the latter are not recognized nor are they treated. Thus, unlike the treatment protocols designed to address athletes who have sustained a concussion, no such protocols exists to address repetitive subconcussive blows. This despite recent publications, which clearly point out
the damaging effects of repetitive subconcussive head trauma in male contact sport athletes when compared with aged-matched male non-contact sport athletes.

**Imaging studies** such as Diffusion Tensor Imaging (DTI), Magnetic Resonance Imaging (MRI), Fractional anisotropy (FA) and Mean diffusivity (MD) have shown significant abnormal changes in contact sport athletes. Abnormal changes were primarily seen in the corpus callosum, external capsule, and inferior fronto-occipital fasciculus. These are areas of the brain containing long myelinated axonal fiber tracts. These abnormal findings were not only seen preseason in contact versus non-contact groups, but increased when the groups were compared with preseason and postseason. *This preseason-postseason difference suggest long term effects from repetitive head trauma sustained just by playing one season in a contact sport.*

**Fractional anisotropy** is a scalar value between zero and one that describes the degree of anisotropy (property of being directionally dependent, which implies different properties in different directions when measured along different axes) of a diffusion process. A value of zero means the diffusion is isotropic, i.e., it is unrestricted or equally restricted in all directions. A value of one means that diffusion occurs along one axis and is fully restricted along all other directions. Fractional anisotropy is a measure often used in diffusion imaging where it is thought to reflect fiber density, axonal diameter, and myelination in white matter. Fractional anisotropy measures the overall directionality of water diffusion that is greater in organized white matter tracts and lower in cerebral spinal fluid and disorganized fibers.

**Mean diffusivity** is a measure of the average molecular motion independent of any tissue directionality. It is affected by the cellular size and integrity. When applied to the study of the brain, it describes the rotationally invariant magnitude of water diffusion within the brain. Differences of mean diffusivity reflects variations within the intra- and extracellular space and a reduction in neuropil (parenchyma), and for index global increases in cerebral spinal fluid. Although mean diffusivity is nonspecific, it is very sensitive, measuring the affects of any disease process that affects the barriers that restrict the motion of water, such as cell membranes. For example, both mean diffusivity and fractional anisotropy can serve as indicators of disease and genetic liability to schizophrenia.

Although the majority of these studies have involved football players, some have included soccer and hockey athletes.

**What these studies have shown, all head trauma, including subconcussive brain trauma, can result in brain damage in susceptible individuals.**

**Postmortem studies** have identified that repeated subconcussive impacts have an cumulative effect, and it is thought they accelerate the cognitive aging process, leading to altered neuronal biology later in life, in the form of early-onset Alzheimer’s disease, dementia, depression, and **chronic traumatic encephalopathy (CTE).**
Clinical Presentation

The effects of subconcussive head trauma regarding neurocognitive, behavioral, and underlying neural substrates have not been fully elucidated.

**Neurocognitive functions** are cognitive functions closely linked to the function of particular areas (neural pathways), or cortical networks in the brain substrate layers of neurological matrix at the cellular and molecular level. The understanding of the link of cognitive function with particular areas of the brain is linked to the practice of neuropsychology and cognitive neurosciences, which are two disciplines that try to understand how the structure and function of the brain are related to perception defragmentation of concepts, memory imbeded, association and recall both in thought process and behavior.

**Cognition** is the mental action or process of acquiring knowledge and understanding through thought, experience, and the senses; it encompasses processes such as knowledge, attention, memory and working memory, judgment and evaluation, reasoning and computation, problem solving and decision making, comprehension and production of language.

**Neural pathways** or **neural tracts** connect one part of the nervous system with another through cylindrical like structures called **axons**, which are the long fibers extending outward from neurons (Fig. 1).
Each neuron has one axon. Neural pathways or neural tracts serve to connect distant areas of the brain. Each specific neural pathway runs from one discrete area of the brain to another. The axons from each discrete area of the brain are bundled together, with each specific bundle being referred to as a tract (Fig. 2).

Each axon within a finite tract is covered in a coating called myelin (Fig. 1). Myelin has a light appearance due to its lipid content, Thus, the axons forming each tract have a white color, hence the term **white matter** (Fig. 3). To recapitulated, the white matter is composed of bundles (tracts) of myelinated axons, which are nerve cell (neuron) projections, which connect various gray matter areas (area where the nerve cell bodies, neurons, are located) of the brain to each other, carrying nerve impulses between neurons.

The **gray matter** represents the cerebral cortex, which consist mainly of cell bodies (neurons, horizontal cells of Cajal, cells of Martinotti and astrocytes, the latter of which are the most abundant cell type in the cortex) and capillaries.
Neurocognitive deficit refers to a reduction of function of the brain as it would relate to perception defragmentation of concepts, memory imbed, association and recall both in the thought process and behavior. It is especially concerned with any physical changes that can be seen in the brain, such as after neurological illness, mental illness, drug use or brain injury.

One of the neural pathways (networks) within the brain that has been studied reference to the acute effects of subconcussive head trauma is the default mode network (Figs 4 & 5).
Fig. 4. The above image is a functional MRI scan showing regions of the default mode network. (en.wikipedia.org)

Fig. 5. This image shows the connectivity of the default mode network. This image shows main regions of the default mode network (yellow) and connectivity between the regions color coded by structural traversing direction. (en.wikipedia.org)
Default Mode Network

The default mode network consist of a specific set of brain regions, which are engaged when we are left to think for ourselves undisturbed (Shulman et al. 1997, Mazoyer et al. 2001, Raichle et al. 2001). It is also active when we are thinking about others and remembering the past and planning for the future. The network activates “by default” when a person is not involved in a task. More broadly, the default network is hypothesized to represent a brain system (or closely interacting subsystems) involving anatomically connected and interacting brain areas. It has also been described as a network of interacting brain regions known to have activity highly correlated with each other and distinct from other networks with the brain.

Raichle coined the term “default mode network” in 2001 to describe resting state brain functions; his concept rapidly spread throughout the neuroscience community. A clue that brain activity persists during undirected mentation emerged from early studies of cerebral metabolism. It was already known by the late nineteenth century that mental activity modulated local blood flow (James 1890). Louis Sokoloff and colleagues (1955) used the Kety-Schmidt nitrous oxide technique to determine whether cerebral metabolism changed when going from a resting cerebral state to a focused cognitive effort. What they found was the metabolic rate remained the same.

Early studies, such as those of Andreasen et al. (1995) noted that the resting state is quite vigorous and consists of a mixture of freely wondering past recollections, future plans, and other personal thoughts and experiences. Second, the analysis of brain activity during the resting state revealed involvement of the prefrontal midline regions as well as a distinct posterior pattern that included the posterior cingulate and retrosplenial cortex. Later studies confirmed, these regions are central components of the core brain system that is consistently activated during an undirected mental state. The core regions associated with the brain's default network included along with the ventral medial prefrontal cortex and posterior cingulate and retrosplenial cortex; the inferior parietal lobule; lateral temporal cortex; dorsal medial prefrontal cortex; and the hippocampal formation. The hippocampal formation includes the entorhinal cortex and the parahippocampal cortex.

There is clear evidence these core brain regions within the default network contribute specialized functions which are organized into subsystems that converge on the hubs, such as:

1. **Information regarding self:** posterior cingulate cortex and precuneus; medial prefrontal cortex; and the angular gyrus.

2. **Dorsal medial subsystems:** Thinking about others: posterior cingulate cortex and precuneus; medial prefrontal cortex; angular gyrus; dorsal medial prefrontal cortex; temporal-parietal junction; lateral temporal cortex; and the anterior temporal pole.
3. **Medial temporal subsystems: Autobiographical memory and future simulations:** posterior cingulate cortex and precuneus; medial prefrontal cortex; angular gyrus; hippocampus; parahippocampus, retrosplenial cortex; and posterior inferior parietal lobule.

**Function of the Default Mode Network**

On the surface the actual function of the brain’s default network appears difficult to approach for it is more active in a passive setting and during tasks that direct attention away from external stimuli. What does give you some insight is the default mode network does not include **primary sensory or motor areas**, but does include areas associated with the **medial temporal lobe memory system**.

There are two possible functions of the network. **One is the default network supports internal mentation that is largely detached from the external world.** Within this concept, the default network plays a role in constructing dynamic mental stimulations based on personal past experiences, such as used during remembering, thinking about the future, and generally when imagining alternative perspectives and scenarios to the present.

The possibility the default network contributes to internal channels of thought is consistent with the subsystems that comprise its anatomy. The medial temporal lobe subsystem is associated with mnemonic processes (a memory device that aids information retention in human memory) and is activated during successful retrieval of old information from memory. In addition, activity within the medial temporal lobe subsystem increases during retrieval of strong memory traces that include remembered associations and content details. When looking at both of these functions, they suggests this subsystem contributes associations and relational information from memory perhaps to provide the critical building blocks of mental exploration.

**The other possible default network function is to support exploratory monitoring of the external environment when focused attention is relaxed.**

All of the task forms noted above that activate the default network have one thing in common, **the imagined perspectives are self-referenced. Also, reference to the self causes selective and preferential activity within the medial prefrontal cortex subsystem.**

With the above in mind, **the default mode network comprises at least two distinct interacting subsystems: one subsystem functions to provide information from memory; the second participates to derive self relevant mental simulations.** Thus, the default network participates in constructing self-relevant mental simulations that are exploited by a wide range of functions including remembering, thinking about the future, and inferring the perspectives and thoughts of other people. **When left undisturbed, this is the network people engage by default.**
You may ask, why is an understanding of the default mode network’s closely interacting subsystems important? It is important because an understanding of the default mode network’s functions and dysfunction gives us insight into mental disorders such as schizophrenia, Alzheimer’s disease, autism, depression, long term trauma such as in child abuse and chronic traumatic encephalopathy, post-traumatic stress disorder, obsessional disorders, and attention-deficit/hyperactivity disorder. What is of interest, recent research has demonstrated a clear association between subconcussive head trauma and dysfunction within the default mode network of the brain.

Recent research has also shown in those athletes who have had previous concussions, they have the potential of long-term consequences manifested by significantly decreased functional connectivity within the default mode network. However, additional studies have shown both hypo and hyperconnectivity within the default mode network. Analysis by Mayer and colleagues of those who have sustained a concussion have shown decrease in functional connectivity within the default mode network in the subacute phase of the injury that were still present during the chronic phase. Other studies, such as those by Zhou and colleagues, have found reduced connectivity in the posterior hubs of the default mode network, such as the posterior cingulate cortex and retrosplenial cortex, as well as increased activity within the ventromedial prefrontal cortex.

More recent studies, such as those by Johnson and colleagues, have found a reduced connectivity and strength of connections in the posterior cingulate cortex and the parietal cortices, along with an increased number of connections and strength of connections in the medial prefrontal cortex. What was also shown in Johnson and colleagues study, was as the number of concussive episodes increased so there was further decrease in functional connectivity within the default mode network.

Johnson and colleagues study also noted significant decreases in the default mode network in those athletes who had a history of previous concussions, in both pre and post-game evaluations, compared to those who had no previous history of concussions, but did have exposure to repetitive subconcussive head trauma. This is consistent with studies that have shown, short-term exposure to subconcussive head trauma, in of itself, can alter functional connectivity within the default mode network. Johnson and colleagues specifically observed reduced functional connectivity in the left supramarginal gyrus in both pre and post-game evaluations, with greater decreases in the post-game evaluations. The left supramarginal gyrus is an area that has been implicated in visuokinestics (the left parietal lobe contains movement representations that are memories of the spatial and temporal components of learned skilled purposeful movements), motor attention along with verbal mediation (language perception and processing), and memory retrieval. What is of interest, the left supramarginal gyrus has been shown to show cortical thinning in Alzheimer’s disease. Those with a history of mild traumatic brain injury also showed a decreased pre-game functional connectivity in the left prefrontal cortex, which
is an area critical in decision making and emotion, and strongly associated with changes in behavior.

Another study has shown, those athletes who have sustained diffuse axonal injury due to a concussion may have changes in structural connectivity, which in turn leads to decreases in functional connectivity.

Another study by Talavage and colleagues involving 11 high school football players showed significant alterations in the default mode network due to multiple subconcussive impacts sustained during a single season, although clinically, these players showed no evidence of impairment. What was noted in these players was a decreased activation of the default mode network in the dorsal-lateral prefrontal cortex, middle and superior frontal gyri, and the cerebellum that correlated to the number of subconcussive impacts. What is of interest, when you compare the effects of repetitive subconcussive impacts over a single season on the default mode network (increased connectivity in the posterior aspect of the default mode network) they are consistent with the effects of a single concussion on the default mode network.

It has also been reported subconcussive injuries cause changes in the brain's neurophysiology, even though there was no evidence of neurpathological evidence of cognitive, emotional, or sensoriomotor alterations. There was evidence of a short-term increase in microglia, macrophages, and reactive astroglia, which returned to normal at four weeks.

Shultz and colleagues have suggested repetitive subconcussive head trauma in-of-itself, may have cumulative effects leading to neurodegenerations, which are analogous to the behavioral impairment after concussion.

In summary, although much of the focus in traumatic brain injury of athletes has been on concussions, subconcussive impacts occur much more frequently. It is becoming apparent through such studies as the effect of subconcussive impacts on the default mode network, the repetitive nature of subconcussive impacts has a cumulative effect (Broglio and colleagues), which can lead to deterioration of cerebral structures and function later in life. In his book, “Concussions and Our Kids,” Robert Cantu states, “kids playing collision sports can register more than a thousand subconcussive blows in a season. Over many years, they can accumulate tens of thousands.”

Pathophysiology

As previously discussed in the Forensic Science Newsletters on concussion, typically, mild traumatic brain injury causes no gross pathology, such as intracranial hemorrhage or abnormalities that can be seen on conventional CT scans of the brain (Postconcussive Syndrome-Adults, pages 3-11). However, more technically advanced imaging studies such as diffusion tensor imaging (DTI) have clearly shown evidence of
diffuse axonal injury (DAI). The usual picture clinically is one of rapid-onset of neurophysiological and neurological dysfunction that, in most patients resolves in a short period of time. However, approximately 15% of individuals with mild traumatic brain injury develop persistent cognitive dysfunction. The neurophysiological changes induced by the initial impact to the head are due to linear acceleration of the brain, which is usually associated with a rotational component. At the neurophysiological level these mechanical forces lead to stretching and tearing of white matter axons (page 4), which leads to diffuse axonal injury. Although, the focus tends to be on the tearing of axons, stretching of white matter axons is far from being inconsequential.

Stretching of axons results in an unregulated flux in ion concentrations, which includes an efflux of K\(^+\) and an influx of Na\(^+\) from and into the axon respectively, which in turn, causes an increase in intra-axonal Ca\(^{2+}\) concentrations. As the concentration of Ca\(^{2+}\) increases, the protease calpain becomes activated, triggering calpain-mediated proteolysis of cytoskeletal proteins, which can cause irreversible axonal pathology. An increase in intra-axonal Ca\(^{2+}\) concentration also stimulates glutamate release and glutamate-mediated activation of N-methyl-D-aspartate receptors, resulting in further depolarization of neurons. Depolarization of a neuron refers to an opening of the sodium channels in the cytoplasmic membrane of the neuron by a stimulus. Due to the fact there are normally more sodium ions on the outside of the neuron, then on the inside, and the neuron is thus negatively charged as compared to the outside, when sodium ions rush into the neuron, the neuron loses its negative charge, becoming more positive, thus it is considered depolarized. Increased activity of various membrane pumps to restore the ionic balance leads to increased glucose consumption, depletion of energy stores, Ca\(^{2+}\) influx into mitochondria, impaired oxidative metabolism, and glycolysis with lactate production, which causes acidosis and edema.

When these stretched or torn axons are examined under the electron microscope, they show breakage and buckling of microtubles, which in turn leads to progressive microtuble disassembly. These mechanical alterations of the microstructure of the axons leads to interruption of axonal transport and accumulation of protein products. The accumulation of these protein products cause two types of axonal swellings: axonal bulbs (retraction balls) and axonal varicosities, which occur as a series of protrusions along individual axons. The axonal swellings represent a tear in the axon, which leads to axonal disconnection. Neuronal damage represented by axonal balls and swellings are more commonly found deep in the gyri at the interface between the gray and white matter. Studies using advanced imaging techniques, such as diffusion tensor imaging, show the extent of white matter abnormalities after mild traumatic brain injuries correlates with the severity of postconcussive cognitive problems.

These findings are supported by the elevation of two Biomarkers of traumatic brain injury, neurofilament high polypeptide (NFL) and total tau. High levels of neurofilament high polypeptide have been demonstrated in ventricular cerebrospinal fluid of patients with severe traumatic brain injury. Likewise, high levels of neurofilament high polypeptide have been shown in lumbar puncture derived cerebrospinal fluid in
mild traumatic brain injury, immediately after the injury. Neurofilament high polypeptide is a biomarker of injury to large-caliber myelinated axons, whereas total tau is a biomarker of injury to thin nonmyelinated axons located in the cortex. What is of interest is the magnitude of the rise of neurofilament high polypeptide is larger than that for total tau protein, which suggest mild traumatic brain injury affects the long myelinated axons in the white matter to a greater extent than it affects the short nonmyelinated axons in the cortex. As of this point neurofilament high polypeptide is the most sensitive biomarker of axonal injury.

Many clinicians believe the injuries suffered by the axons and the metabolic changes seen in mild traumatic brain injury are reversed within 1-2 weeks, since this is when most clinical symptoms disappear. However, magnetic resonance spectroscopy findings, electrophysiological data and neuropsychological assessments suggest patients’ physiological parameters do not return to pre-traumatic baseline levels until 30 to 45 days after the mild traumatic brain injury.

Another very important point to remember, once an axon has been completely torn or severely damaged through stretching, it becomes a permanent injury. Axonal regeneration in the adult central nervous system is extremely limited after injury. As a consequence, there is typically little functional recovery for the axons so injured after spinal cord injury, traumatic brain injury, or strokes and related conditions that involve axonal damage and disconnection. Axonal regeneration in the central nervous system fails for two reasons. First, the environment surrounding the damaged axons is hostile, in that it contains growth inhibitors that suppress axonal growth, and second, the damaged axons themselves have a limited intrinsic ability to regenerate. **This is one of the reasons why both concussive and subconcussive mild traumatic brain injuries become cumulative and ultimately, if the injuries are repetitive, lead to altered neuronal biology later in life, in the form of cognitive impairment, early onset Alzheimer’s disease, dementia, depression, and chronic traumatic encephalopathy (CTE).**

Another important consideration affecting a patients’ recovery after mild traumatic brain injury is their age. The developing brains in the child and adolescents seems to be more vulnerable to repeated concussions and subconcussive head trauma than the adult brain, due to the differences in the degree of myelination, volume ratio of brain to water, elastic properties, the dendritic arborizations and cortical interneuronal connections are not fully developed, and blood-brain barrier integrity. The brain does not reach the adult weight until between 12 and 15 years. This information in-of-itself should discourage the participation of children and young adolescents in contact sports in which the head becomes a target, such as in football, ice hockey and soccer.

**Summary**

**Subconcussive head trauma** is head trauma that does not result in recognized concussion symptoms or signs. It is due to blows to the head, which are below the threshold to cause or elicit any symptoms or signs of a concussion. Both animal and
human research have shown that subconcussive blows can cause damage to the central nervous system and pathophysiological changes in the brain despite not evoking any apparent acute behavioral changes. One of the neural pathways (networks) within the brain that is damaged through repetitive subconcussive head trauma is the default mode network (Figs 4 & 5). This is consistent with studies that have shown, short-term exposure to subconcussive head trauma, in of itself, can alter functional connectivity within the default mode network. **It has also been shown exposure to repetitive subconcussive head trauma, as well as concussions, are cumulative due to the failure of axonal regeneration, which in turn can lead to cognitive impairment, early onset Alzheimer’s disease, dementia, depression, and chronic traumatic encephalopathy (CTE).**

There are now several books available for your review on the website, [http://www.forensicjournals.com/books/](http://www.forensicjournals.com/books/). These books are entitled, “Traumatic Injuries to the Head, Vertebrae, Spinal Cord and Peripheral Nerves of the Newborn During Birth,” which is under the heading of Neuropathology. Under the heading of Forensic Pathology are three books entitled, “Nonsexual and Sexual Traumatic Injuries of the Perineum, External Genital Organs and the Breasts: Adult, Elderly and Pediatric,” “Traumatic Injuries of the Organs of the Pelvis: Adult and Pediatric,” and “Traumatic Injuries of the Organs of the Retroperitoneal Space.” A fifth book, “Traumatic Injuries of the Organs of the Abdominal Cavity: Adult and Pediatric,” will be available shortly.