Response to Commentary

Neurobiology and neuropathology underlie the neuropsychological deficits associated with traumatic brain injury

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Abstract

The neurobiological and neuropathological bases that underlie the neuropsychological deficits associated with traumatic brain injury (TBI), including mild TBI, are further reviewed. The article provides an update on neuroimaging methods and findings in the study of TBI since the author’s published address of the 1999 Distinguished Neuropsychologist Award of the National Academy of Neuropsychology (see Bigler, 2001a). The review addresses and answers criticisms raised about the interface of neuroimaging abnormalities and neuropsychological deficits, particularly in mild TBI. The article provides further guidelines in making the link between neuroimaging findings and neuropsychological outcome in the clinical practice of neuropsychology. The article also opines on the future role and importance that neuroimaging will play in neuropsychological practice, particularly functional neuroimaging methods. © 2002 National Academy of Neuropsychology. Published by Elsevier Science Ltd. All rights reserved.

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1. Introduction

The critique by Lees–Haley, Green, Rohling, Fox, & Allen (2003) reads like a legal document defending why objective findings of a lesion on neuroimaging or positive findings from
a neuropsychological examination cannot be the basis for concluding presence of a neuropsychological deficit in traumatic brain injury (TBI), particularly mild TBI. The critique is written like a précis given by an attorney defending a mild TBI case offering the premise that: Here is all you need to know to obfuscate the issues that concern mild TBI—since it is “psychological” then it means the patient has either a weakness in character, is over reacting, is using symptom magnification or embellishment, malingering or has some other nonorganic functional disorder that explains the problem(s), but it is definitely not an injury. The concluding statement of Lees-Haley et al. (2003) chastises me for leaving “psychology” out of neuropsychology and that currently psychology alone can offer a better explanation for effects of the mild TBI than can neuroimaging, understanding the pathophysiology of injury, or the relationship of these factors to neuropsychological impairment.

Lees-Haley et al. (2003) critique this lecture on three grounds: (1) “blurring the effects of MTBI with moderate and severe brain injury” (p. 585), (2) “the pervasive tendency to suggest physiological origins” to neuropsychological deficits, where “... Physiological origins are presumed far beyond the explanatory power of the available scientific literature.” (p. 585), and (3) the “broad tendency to ignore and discount psychological explanations for the observed effects...” (p. 585). For simplification in referring to my lecture given as part of the Distinguished Neuropsychologist Award published in Archives of Clinical Neuropsychology (ACN) (see Bigler, 2001a), from this point on I will refer to this as the ‘Lesion(s)...’ paper, since the title is, “The lesion(s) in traumatic brain injury: implications for clinical neuropsychology.” My focus in the ‘Lesion(s)...’ paper was that neurobiology and pathophysiology underlie neuropsychological performance and behavior following TBI. Furthermore, there are also neurobiological explanations that are part of the so-called psychological features that accompany the trauma of being in an accident, development of chronic pain and stress-mediated disorders.

My response will focus on three main issues that demonstrate that Lees-Haley et al. (2003) either: (1) lack understanding the fundamentals of neurobiology, neuropathology, and pathophysiology, (2) lack historical perspectives on how psychological interpretations are supplanted when the underlying neurobiology of the disorder is understood and/or, (3) they are writing from a biased perspective. I will discuss historical perspective first, followed by Section 3, where I will discuss further details of the pathophysiology of brain injury and the concluding sections will focus on biased research and its implications.

2. Historical perspectives in the advances of clinical neuropsychology

Neuropsychology did not come about as a discipline to describe just the psychology of behavior, rather the neurobiology of behavior. This is demonstrated in Figure 1, which shows the multilevels of looking at what underlies behavior. If the focus is on only the psychology, it misses all of underlying neurobiology of brain–behavior relationships. Lees-Haley et al. (2003) espouse putting a greater emphasis on psychology than neuroscience in an era of the most tremendous scientific growth in the understanding of brain–behavior relationships in the history of humankind. For example, understanding the history of schizophrenia and its past archaic “psychological” terminology and conceptualizations offers an excellent analogy of how psychological theories give way to neurobiological theories as we better un-
Fig. 1. This figure depicts different levels of neuropsychological inquiry from the most basic to complex social relationships that form societies. Above the point of asterisks is what traditional psychology has addressed. Traditional neuropsychology has been interested in all levels of inquiry below the asterisk as well as those above. (Acknowledgment: This chart is a modification of a graph from O'Connor & Tasman, 1990).

My undergraduate abnormal psychology textbook from the 1960s (Rosen & Gregory, 1965), taught me that “... the schizophrenic is an individual with an ego that has broken down and retreated from reality” (p. 327). Looking back at these so-called psychological explanations or assumptions (i.e., broken egos, conflicted ids, etc.) for what we now know to be neurobiological disorders (see Andreasen, 2001) merely reflects the limited knowledge of that time period.

Taking the schizophrenia analogy further, neuropsychologists who completed their training by the early 1970s, as I did, all remember the apologetic conclusions of numerous early neuropsychological studies trying to differentiate patients with schizophrenia—those with “broken egos”—from true “organics.” True organics were those patients who had suffered a stroke or brain tumor and were unquestionably known to be “brain damaged,” since their paralysis, sensory deficit, aphasia, and so forth, could be observed. The true organics were the “gold standard” as a comparison group. As clinical neuropsychology emerged from clinical psychology in the 1960s, patients with schizophrenia were a troublesome group because they looked brain damaged (Watson, 1971). Since schizophrenia was nothing more than a psychological aberration—broken egos, bad parenting, unresolved double bind conflicts, and so forth,—it was a “functional” disorder, something psychological. Out of the ranks of neuropsychology, Mirsky (1969) offered his now classic paper in 1969 reviewing literature that “possible” organic factors were the basis for schizophrenia. We now look back on this and realize that the reason patients with schizophrenia looked organic is because schizophrenia is an organic disorder, a disorder of the brain with neuropsychological manifestations, where abnormal neurochemistry, structure and function exist (Thompson et al., 2001). I submit that the same analogy holds true for bona fide cases of mild TBI, especially where contemporary
neuroimaging studies demonstrate abnormalities (i.e., lesions). Mild TBI is a neurobiological
disorder at its base, with neuropsychological manifestations best conceptualized by careful un-
derstanding of underlying functional neuroanatomy and neuropathology. Framing the effects
of mild TBI as purely a psychological disorder is a retrenchment to earlier times in clinical
psychology, not neuropsychology.

3. Understanding brain injury

As clearly stated in the lesion paper, the first issue concerning brain injury has to do with the
occurrence of an actual injury. This is all about the physics of injury (see Bain, Raghupathi, &
Meaney, 2001), discussed at length in the ‘Lesion(s) . . .’ paper, and the presence of clinical
signs (i.e., LOC, PTA, etc.). Obviously, there are many conditions where minor blows occur to
the head that do not produce any type of injury (Alexander, 1998; McCrory & Berkovic, 2001).
In fact, the brain is well suited for clinically inconsequential impacts due to its compactness
within the calvarium and its buoyancy from ventricular and subarachnoid cerebral spinal fluid
(CSF). One only has to watch a toddler learning to walk to understand that such minor blows are
insignificant. In the ‘Lesion(s) . . .’ paper I am not talking about trivial injuries that do not meet
any standard for head injury (i.e., American Congress of Rehabilitation Medicine, 1993). All
of what I had to say was based on meeting acceptable standards for brain injury. Lees-Haley
et al. (2003) seem particularly troubled by my statement for neuropsychologists to trust in
the presentation of neuropsychological deficits having a neuropathological basis when brain
injury criteria are met and the clinician feels that the test results are a valid representation
of deficits. In the specific example used, I defined mild TBI as “documented LOC with 12 h
PTA” (Bigler, 2001a, p. 123). If Lees-Haley et al. (2003), or those reading this response, cannot
agree that those characteristics meet every standard for TBI, including mild TBI, then there is
little reason to read further. Given that level of injury, I ask the reader to now review Figure 2.
This details the pathological and biochemical changes induced (some potentially transient)
when injury of this magnitude occurs. As shown in this figure, the biochemical environment
for the neuron is complex. In addition the brain, composed of hundreds of billions of cells, is a
very complex, intercalated biological system that is sensitive to mechanical and biochemical
injury at multiple levels and in multiple ways (Faden, 2001). Those who question the validity of
neuropsychological sequelae from brain injury may have little understanding or appreciation
for neither how complex neural structure and function is, nor for the underlying biochemistry of
behavior (Carlsson, 2001; Kandel, 2001). Short of postmortem histological examination, most
pathology cannot be observed in TBI, particularly mild TBI with any type of in vivo imaging
technology. However, what we can visualize clearly demonstrates incredible neural complexity.
This can be appreciated by the intricacy of the vascularization and cellular organization of
the hippocampus as shown in Figure 3. I selected this view of the vascular supply to the
hippocampus because the hippocampus and surrounding white matter of the temporal lobe
is particularly vulnerable to injury and because the hippocampus is a key structure in the
neuropsychology of cognition and emotion (Bigler, Anderson, & Blatter, 2002; Sugawara,
Lewén, Noshita, Gasche, & Chan, 2002; Zec et al., 2001). I will revisit hippocampal and white
matter pathology later in this rebuttal, but now, with the delicate nature of brain vascularization
visualized as depicted in Figure 3, and the complexity of biochemical interaction, as shown in Figure 2, fresh in the reader’s mind I want to introduce a recent clinical case we have seen of mild TBI with postmortem confirmation of injury.

4. The case

Following is an overview of a mild TBI case that we are in the process of publishing elsewhere (see http://psych.byu.edu/bigler_manuscripts.index.htm) but deals specifically with the issues raised by Lees-Haley et al. (2003).

Figure 5 depicts the day of injury CT scan (normal) and gross postmortem brain (also normal) at the time of autopsy in a patient who had sustained a significant, yet mild TBI 7 months earlier when he was involved in a high-speed head-on freeway collision with a tractor-flatbed-trailer, that had lost its load. There was positive LOC independently documented at the scene and he had a larger frontal laceration; the patient had an on-the-scene Glasgow Coma Scale (GCS) score of 14 by emergency personnel who arrived within 15 min of the collision. The patient was life-flighted to our hospital and at the time of lift-off had a GCS of 15, which remained 15 throughout emergency room assessment. CT imaging of the neck demonstrated cervical fracture, which required neurosurgical repair. He spent a total of 4 days in the hospital. I first examined this patient 4 months after injury due to complaints of mild cognitive impairment particularly problems with short-term memory and attention, moodiness, and fatigue. His neuropsychological exam was basically normal, as were his follow-up neuroimaging studies.
However, his subjective complaints were that he could not achieve the same “mental effort” as he had before injury; his memory seemed “off” to him and he no longer had the “drive” he did before the accident. To those front line clinicians who see real mild TBI patients, this probably sounds very familiar. Unfortunately and unbeknownst to him and everyone else, he had a fatal cardiovascular condition and at 47 years of age (7 months postinjury) spontaneously died from a myocardial infarction. As stated above, Figure 5 shows the actual postmortem brain and admission CT scan, both normal. Detailed gross neuropathological examination found no evidence of focal contusion or other abnormality. However, microscopically, hemosiderin deposits were identified in the white matter along with other evidence of inflammatory reaction. Hemosiderin is a marker of blood by-products, indicating that micro-hemorrhaging had likely occurred in the brain. In other words, at the microscopic level, pathological changes were observed in the white matter. Now, using the Lees-Haley et al.’s logic, because this patient had a “normal” neuropsychological exam (i.e., all test scores were within the average range or above) and his symptoms are only subjective, having sustained only a mild head injury with no positive imaging findings, then no conclusion can be made about neuropsychological sequelae actually being related to unseen underlying brain pathology.

Furthermore, if you believe or agree that the Lees-Haley et al. (2003) critique uses appropriate logic, then here is how you must interpret this case: First, ignore all basic neurobiological confirmation in animal and human models of mild TBI (Adams & Duchen, 1992). Second, ignore all of the neuropsychological literature that is positive on this topic (e.g., see Goldstein & Levin, 2001), including neuroimaging (Bigler et al., 2002; Ricker, 2002) but most importantly as the third component, ignore all the individual facts of the injury. Such facts as: A head-on
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Fig. 4. This illustration is from our ongoing traumatic brain injury (TBI) data base and represents 151 subjects with varying levels of severity of injury as defined by Glasgow Coma Scale (GCS). Plotting either brain volume, hippocampal volume, or the ventricle-to-brain ratio (VBR, a measure of global atrophy) results in linear and quadratic relationships that demonstrate brain or hippocampal atrophy is directly related to the severity of injury. Note that the relationship is best fit by a linear rather than quadratic function for whole brain volume (Blue color), the ventricle-to-brain ratio atrophy index (Red color) or hippocampal volume (Yellow color). The hippocampal data is based on a subset comprised of 46 subjects. In each case there is a linear loss of brain parenchymal volume directly related to severity of injury. Accordingly, loss of tissue is a function of severity of injury.

collision without braking (impact speed of 65 mph for the vehicle and lost load), independently documented loss of consciousness, on the scene EMS report of a GCS of 14, a 7-in. frontal laceration to the head where apparently a piece of lumber came through the windshield striking the patient, impact forces sufficient to result in cervical fracture, presence of retrograde and anterograde amnesia, histological proof of hemosiderin, and lymphocytic reaction in the white matter of this patient’s brain. You must also conclude that none of this has any bearing on his neuropsychological status and that his subjective symptoms of mild cognitive deficits, changes in mood and energy are psychological (must be another case of fractured ego!) because as a profession we have not met the “rigorous proof of burden . . . . Of multiple validations across several (large) samples and multiple criterion measures.” (Lees-Haley et al., 2003, p. 591). Nonsense!

5. Three main points of critique

Because of editorial constraints, I can only address the highlights of their critique; an overview of their three main points follow. I will close with some additional clinical caveats, addressing other issues relevant to their critique, and then offer my conclusions.
Fig. 5. (Left) Day of injury CT scan that was interpreted as within normal limits in a patient with mild TBI. (Middle) Postmortem gross brain at the time of autopsy demonstrating, similar to the CT scan, no abnormalities. (Right) Histological findings of hemosiderin (arrow) indicating prior hemorrhagic lesions, most likely trauma induced. Histological findings also demonstrated disseminated leukocytes found in the white matter indicating injury as well.
5.1. Blurring of mild traumatic brain injury (MTBI)

There was no blurring. I believe the human and animal data clearly demonstrate that brain injury is on a continuum from mild to severe. Numerous lines of evidence point to this and were cited in the ‘Lesion(s) . . . ’ paper. Biological markers (i.e., serum 5–100 protein) demonstrate this (Herrmann et al., 2001; Ingebrigtsen et al., 2000; Ingebrigtsen, Waterloo, Jacobsen, Langbakk, & Rommer, 1999; Raabe et al., 1999). For example, in the article I point out the significant linear relationship between severity of injury as measured by the Glasgow Coma Scale (GCS) and structural changes. Let me revisit this point with Figure 4, which demonstrates that as severity of injury increases (i.e., lower GCS), brain or hippocampal volume decreases and cerebral atrophy increases. As discussed by many excellent and detailed neuropathological explications of brain injury, neuropathological studies most frequently demonstrate a continuum, from mild to severe. However, a distinction has to be made in terms of the physical or structural changes versus the biochemical. Referring back to Figure 2, an injury can occur when the tensile effects on axons or parenchymal deformations do not surpass the level where structural damage occurs, but biochemical perturbations are induced. These can be transient and are most commonly seen in falls and sports-related impact injuries, and would typically produce only a grade I concussion. Therefore, at the mildest end of the spectrum, as would be predicted by a linear model, there may indeed be no lasting effect. However, once crossed, the linear model also predicts increasing grades of neuropathological and neurobehavioral sequel. Further evidence for this position comes from the epidemiological literature on head injury. For example, Holsinger et al. (2002) found almost identical odds ratios for depression in mild (LOC or PTA of less than 30 min with no skull fracture) and moderate (defined as LOC or PTA >30 min and/or presence of skull fracture) head injury. The results of Plassman et al.’s (2000) findings, on the risk of dementia associated with head injury, also demonstrated brain injury effects on the risk of dementia were on a continuum (see Fig. 6). Guo et al. (2000) also found that “the magnitude of the risk (for dementia) is proportional to severity of brain injury” (p. 1316), where “head injury with loss of consciousness and, to a lesser extent, head injury without loss of consciousness increased the risk of AD” (p. 1321). Presumably, in both these very large population-based studies of Guo et al. (2000) and Plassman et al. (2000) most of these individuals had fully “recovered” and returned to “normal” lives, but nonetheless injury had occurred and ultimately increased the risk of dementia later in life. If brain or hippocampal volume is linearly related to GCS and even mild injury results in lifetime enhancement for neuropsychiatric disorder, including dementia, I posit, just as I did in the ‘Lesion(s) . . . ’ paper that mild TBI is pathologically similar to more severe injury, just of a lesser degree.

5.2. Psychological explanations are better than physiological explanations of mild TBI

Some of this was introduced above. I want to expand on this by returning to Figure 3 and viewing the hippocampus, because, as previously stated, it is at the temporal lobe-hippocampal-fornix level that I believe much of the ill effects of mild TBI occur (Bigler et al., 2002; Bigler & Tate, 2001). As an introduction, every serious clinical neuropsychologist interested in mild TBI should read Santhakumar, Ratzliff, Jeng, Toth, and Soltesz (2001). They demonstrate that
Fig. 6. This graph is taken from Plassman et al. (2000) and represents the “Hazard Ratio” related to history of head injury and the subsequent development of dementia. A Hazard Ratio of 1.0 is based on the comparison sample, analogous to an odds ratio. Thus a score of 1.0 means no increased risk. As clearly observed in this graph, the increased Hazard Ratio increases linearly and curvilinearly with increasing severity of brain injury. These findings support the notion that severity of injury induces a continuum of pathological effects dependent on severity of injury. (Reproduced by permission of the authors and the American Academy of Neurology.)

in an animal model “after a single episode of concussive head injury” (p. 714), permanent changes in the structural and functional organization of the hippocampus occurs (see also Lowenstein, 2001). Kors et al. (2001) demonstrate a special circumstance where fatal outcome follows mild TBI; Laurer et al. (2001) demonstrate how a single concussion sets the stage for further injury with a second concussion and Nariai, Suzuki, Ohta, Ohno, and Hirakawa (2001) demonstrate focal hyperemia bilaterally in the mesial temporal lobe regions following what they describe as “postconcussive amnesia.” These studies clearly underscore how even concussion can injure the brain. Understanding how limbic circuitry functions in the context
of behavior and its vulnerability in injury, including concussion, is the key to understanding brain–behavior relationships following mild, or any type of TBI. Again, I ask the reader to examine the complexity of the vasculature to the hippocampus, the number of synaptic connections, and visualize impact forces on this delicate region of the brain as an example of how easily this area can be injured.

5.2.1. Limbic circuitry

Hopefully, every neuropsychologist has committed the diagram outlined in Figure 7 to memory (no pun intended!). One glance at this limbic network, that includes the hippocampus, demonstrates its complexity, but the diagram belies what is beneath—billions of cells, pathways, and interconnections, all with delicately balanced electrophysiology (Mellor, Nicoll, & Schimtz, 2002). Returning to Figure 3 demonstrates numerous synapses revealed by immunofluorescence (Cowan, Südhof, Stevens, & Davies, 2001) in a hippocampal neuron. Neurons typically have thousands of synaptic interfaces with other neurons (Williams & Stuart, 2002). We, as well as others, have demonstrated the vulnerability of the hippocampus in TBI (Bigler et al., 2002), and such injury disrupts the limbic loop depicted in Figure 6. Lees-Haley et al. (2003) use the debate method of trivializing an important fact when they state “we can lose a few neurons everyday, and it does not have an effect” (p. 10). First, what is their citation for this statement? Where is the discussion about cognitive or brain reserve (Satz, 1993; Stern, 2002) in the context of neuronal loss? What about synaptic plasticity and collateral sprouting that may counter normal neuronal loss but may not occur in damaged cells as a product of TBI (Condic, 2001; Faden, 2001; Hutchison et al., 2001; Shors et al., 2001)? But more importantly, let us take their very example and explore in the context of Figures 2 and 3 what it means to lose a neuron and these synaptic connections depicted in the figure(s). Suppose a single hippocampal neuron is lost to injury. Obviously, this example is an oversimplification, but nonetheless, assumes a single hippocampal neuron dies. Let us next assume that the now dead hippocampal neuron (remember only one neuron is lost in this example) had a terminus involving 100 synaptic end points that influenced 100 different postsynaptic cells. By the time the circuitry works its way around the Papez circle, depending on what loop is taken and the point of terminus, the effect of one cell loss, in this simplified model, impacts tens of thousands or more cells!

5.3. Claims of ignoring the psychological

This is an almost impossible response to make within the constraints of this paper because it gets at the very nature of biological and psychological inquiry and what is meant by “psychological.” Simply stated, we call behavior “psychological” because we do not have a better term to describe the behavior in question. As we gain biological understanding of the psychological event, we no longer have to view such phenomena within the context of psychological terminology. Have we forgotten what William James wrote in 1890 in the Principles of Psychology where he states, “The causes of our mental structure are doubtless natural, and connected, like all our other peculiarities, with those of our nervous structure.” (James, 1890, p. 688)? The Lees-Haley et al. (2003) arguments are the same old tiresome ones offered when one does not like biological explanations of behavior. Andreasen’s
Fig. 7. Limbic circuitry is depicted in this diagram that reflects what has traditionally been labeled the “Papez Circuit.” The integrity of this circuit is disrupted in TBI (Yount et al., 2002). The black loop designates the classic Papez circuit (hippocampal loop). The mid-gray loop represents the lateral limbic loop connecting the orbitofrontal cortex with the amygdala. The bright gray connection indicates pathways of both loops with the septum verum. Amy, amygdala; aNc, anterior nucleus of the thalamus; bFb, basal forebrain; CG, capsular genu; Fo, fornix; Hipp, hippocampus; HT, hypothalamus; MB, mamillary bodies; MD, dorsomedial nucleus of the thalamus; MTT, mamillo-thalamic tract; OFC, orbitofrontal cortex; pHpc, parahippocampal gyrus; rSplC, retrosplenial cortex; SV, septum verum (medial and lateral parts). (Reprinted from Brain Research Reviews, 36, A. Schnider, Spontaneous confabulation, reality monitoring, and the limbic system—a review, pp. 150–160, Copyright 2001, with permission from Elsevier Science.)
two texts (Andreasen, 1984, 2001) provide ample background to refute such arguments. However, I do have some specific commentary, addressed by each of the headings below.

5.3.1. What is “psychological?”

In the ‘Lesion(s) . . . ’ paper I made inferences between posttraumatic stress disorder (PTSD) and issues that surround neuropsychological sequela associated with TBI. We used to invoke numerous ‘psychological’ explanations for what we now term PTSD. Yehuda (2002) provides an excellent description on the pathophysiological explanation of PTSD as have other recent studies (Aardal–Eriksson, Eriksson, & Thorell, 2001; Carrion et al., 2001; Park, Campbell, & Diamond, 2001; Rasmusson et al., 2001; Shin et al., 2001). Stress factors lead to increased morbidity and mortality for a number of diseases, including neurological. Why is it so difficult for Lees-Haley et al. to see a biological relationship between stress factors of being in a motor vehicle accident (MVA), PTSD and TBI? As already pointed out the hippocampus represents one of the target structures for the ill-effects of stress, including PTSD (Bremner, 1999; Rusch, Abercrombie, Oakes, Schafer, & Davidson, 2001; Sapolsky, 1996) as well as TBI. I think it no coincidence that many symptoms of mild TBI, PTSD, generalized anxiety disorder, chronic pain disorder and mood related disorders are comorbid following a significant accident (Fullerton et al., 2000; Mayou, Black, & Bryant, 2000). The vulnerability issues of direct trauma (biomechanical as well as biochemical) to the hippocampus, as discussed above, and the modulation of limbic circuitry in response to trauma, even the emotional aspect and pain of trauma, are likely why these different disorders share so much in common (Bryant, 2001; Davidson et al., 1996; Feinstein, Hershkop, Ouchterlony, Jardine, & McCullagh, 2002), including a pathophysiology. These relationships get even more complicated but explanations still find communality when one considers immune reaction and cytokines in response to injury and illness, including neuropsychiatric effects (see Capuron, Lamarque, Dantzer, & Goodall, 1999; Reichenberg et al., 2001). As already stated in the ‘Lesion(s) . . . ’ paper the other connection between mild TBI and PTSD is that memory function is affected in PTSD (Vasterling et al., 2002). Why is this a leap for Lees-Haley et al. (2003) to see a connection with injury and a stress producing event and that these effects have neurobiological roots not just psychological?

5.3.2. If it is “psychological” it should easily pass the IRB test!

Lees-Haley et al. (2003) appear to make light of being in an accident and having a head injury, even a mild one. When confronted with the question of whether a given accident/injury is severe enough to have an effect, I teach a very basic principle to my graduate students in clinical psychology who want to specialize in neuropsychology. I call it the Institutional Review Board or IRB test—a two part test. If you think the injury a patient has sustained is a trivial one, and that the symptoms are best explained by invoking psychological constructs, can the IRB test be passed? The first question to ask is whether you are willing to subject yourself to the identical impact forces and injury to support the null hypothesis? Next, try writing an IRB, including the consent form, where you explain the impact forces of the “experimental accident” and why you know the brain cannot be injured and that only temporary “psychological” effects (that are in no way negative or harmful) are the only consequences. If the answer is no to either
of the IRB test questions, then serious consideration should be given to what the patient has experienced as an accidental injury.

5.3.3. Neurobiology of pain, stress disorder, brain injury and neuropsychological performance

While certainly not irrefutable, it is generally assumed that children make poor malingerers and are more genuine about symptoms when they occur. Thus, “true” effects of a disorder may be best observed in children. A recent study by Callaghan and Abu–Arafah (2001) examined posttraumatic headache (PTH) in children and concludes, “The etiology of PTH is not known . . . however,” these authors state, “there is good evidence that minor head injuries are associated with pathological changes in the brain that may contribute to the pathogenesis of chronic headache” (p. 821). While their sample size is small, they found a significant number of children have persistent headaches following head injury, even a mild one. What effects does headache or pain have on neuropsychological performance? Studies consistently show diminished cognitive efficiency in the presence of pain and pain-related problems are commonplace in TBI (Anderson, Kaplan, & Felsenthal, 1990; Lahz & Bryant, 1996). Accordingly, if pain is present, it may be assumed that it is more likely that a MVA patient is going to perform more poorly due to pain, but this does not mean that the effects of pain are mediated purely by psychological factors or are not part of the brain injury spectrum? Pain typically disrupts the sleep cycle, and disrupted sleep often exacerbates problems with mood regulation (Nilsson, Nilsson, Hedblad, & Berglund, 2001), all of which adds to the pain (Steriade, 2001). A vicious cycle develops that can coalesce with the effect of postconcussive syndrome (PCS) to render the patient dysfunctional. Functional magnetic resonance imaging (fMRI) studies have clearly shown different activation patterns in response to pain (Petrovic, Kalso, Petersson, & Ingvar, 2002) including activation of the cingulate cortex. Cingulate cortex is affected in stress (Shin et al., 2001) and we have recently shown this region to also be affected by TBI (see Yount et al., 2002). The combination of injury and pain effects may be additive in disrupting important cognitive-emotional regulatory centers of this part of limbic cortex. Pain-mediated disruption of cognition occurs because of neurobiological effects, not just something purely psychological. In fact, chronic peripheral pain may actually result in reorganization at thalamic and cortical areas that process pain pathways (Peyron et al., 1998). As neuropsychologists, why would we just be interested in a psychological and not neurobiological explanation of pain and its effect on performance in patients who have also suffered a TBI?

5.3.4. Hypochondriasis, somatization disorder, or ‘real’ functional disorders

Do these disorders exist? Certainly they do (see Barsky, Sainfort, Rogers, Borus, 2002). Can they occur in the MVA patient and can PCS be misdiagnosed, because really the symptoms are “functional?” Certainly this occurs. The points I made in the ‘Lesion(s) . . .’ paper specify, before one concludes that PCS or mild TBI is the proper diagnosis, that brain injury has in fact occurred and that it is based on the history and the physics of injury. Putting this together requires clinical acumen but after careful consideration, testing and assessment, if clinical correlation cannot be used in our profession, then the discipline ceases to exist. It may be that these disorders have their own neurobiological roots as well (Barsky et al., 2002; Holden, 2002; Petrovic, Kalso, Petersson, & Ingvar, 2002).
5.3.5. Take a lesson from dementia research

Truly important research about subjective complaints, predicting who actually becomes demented, have come from several studies (Chen et al., 2001; de Groot et al., 2001; Gron, Bittner, Schmitz, Wunderlich, & Riepe, 2002; Mitchell et al., 2002; Tabert et al., 2002). Retrospective examinations of who develops Alzheimer’s disease or some other type dementia show that the earliest clinical signs are subjective, often vague symptoms, not necessarily obvious or detected by any neuropsychometric technique. These symptoms start out as subjective and develop into mild cognitive impairment (MCI); MCI may progress to dementia (Petersen et al., 2001a, 2001b). van Zandvoort et al. (in press) have shown that small strokes thought to be inconsequential do disrupt cognitive function. The key here is that these subjective or inconsequential symptoms are probably based on disrupted frontotemporal and limbic functions that typically disturb episodic memory as their earliest sign. Such symptoms are commonplace in mild TBI. By the tone of their critique, and other published work (i.e., Lees-Haley et al., 2001), subjective symptoms represent a very unsettling proposition for Lees-Haley et al. (2003). They state we cannot make brain–behavior statements at this time because our understanding of these relationships requires “rigorous psychometric analyses if we are to make probabilistic statements as to the cause of any particular behavior.” (Lees-Haley et al., 2003, p. 591). With this they want to rule out all subjective symptoms or subtle findings on neuropsychological testing because it cannot be ‘statistically’ proven. To use their logic following a legitimate mild TBI, as in the case presented above, no neuropsychological explanation is appropriate. So, when it comes to DSM-IV classification, give the head injury patient an axis III diagnosis of “history of mild TBI or concussion,” insert a hyphen and say resolved and then give an axis I diagnosis of depression, anxiety, or whatever. That way, the rigors of neuropsychological practice have been met because we do not have the data to “make probabilistic statements as to the cause of any particular behavior.” (Lees-Haley et al., 2003, p. 591).

5.3.6. Healthy debate versus hidden assumptions in forensic neuropsychology: tactics to be used in the courtroom

In academe, healthy, vigorous debate is essential to the progress of a field. Recently, on February 28, 2002, Charles Brewer, the famous contemporary teacher of psychology (Davis & Buskist, 2002), in an address to our faculty and students said, “If your critics agree with everything you have said, then you better change your opinions.” I welcome criticism of my work and others who examine neuropsychological findings in the context of neuroimaging; there is no shortage of genuine criticism (Brett, Johnsrude, & Owen, 2002). However, deciding what is good criticism that helps move a field forward versus criticism that comes from special interests and is tethered to holding a field back, is often difficult to discern. Typically, the accuracy of critiques comes only through the perspective of time. However, some guidelines can be offered and as an informed reader, you can make the decision. First, the contestants in an academic point/counter-point should state their bias, their underlying assumptions and what has guided their research. No research can be free from bias, and researchers are mostly unaware of how bias influences their thinking, decision making and the conducting of their research (Slife & Williams, 1995). Second, deeply connected to the first, biased debate often uses sophistry and arguments of pseudosophistication which appear to have considerable external validity,
but really are arguments best described as ‘straw man’ in nature. Third, in science, including behavioral science, proper debate and interchange uses a common language, and refutation of the findings of one proponent requires an experiment, example or critical thinking of similar rigor and caliber. For example, how much neurobiological explanation does Lees-Haley et al. (2003) offer in their response or in any other of their published work or do they just say that it is unexplainable, unresolved paradoxes, and best seen as psychological? I ask the reader to review the Lees-Haley et al. (2003) reference list and determine how much contemporary neurobiological and clinical neuroscience exposition and sophistication can come from the literature they cite in support of their arguments? Lastly, the fourth principle involves the principle of Occam’s razor—the most parsimonious explanation that truly captures the data to be explained, is usually the correct explanation. How parsimonious is it to just say it is psychological?

6. Bias in research and writing

6.1. What are the assumptions underlying this critique? or Why has this critique been written in such a legalistic manner?

What is the commonality and aim of research from this group of authors? What if their focus is on methods to refute neuropsychological testimony in plaintiff litigation or toxic tort cases and publish articles to support their position in the courtroom? In the world of litigation, adversarial positions are taken and “truth or justice prevails” on the “weight of evidence;” but as depicted in most courtrooms, including the Supreme Court, the figurine that typically exemplifies justice holds a balanced scale. In legal parlance, the term “more probable than not” is what tilts the scale (i.e., 50.1%), not the statistical rigor of $P \leq 0.05$ (or higher) found in scientific endeavors. Therefore, a major tactic in the legal defense of one’s position, be it defense or plaintiff, is to raise doubt, particularly scientific doubt, about conclusions adversarial to defending a particular position. How best to do this? Publishing articles that raise the specter of doubt for a scientific method or conclusion is a perfect way to address this in the courtroom. Having something published that has gone through peer review is one of the standards for admissibility of testimony. There are other methods as well, but from my perspective of 27 years of offering forensic testimony, it comes down to several basic tactics that I will euphemistically identify as: (a) a good defense starts with a full offensive frontal assault, (b) attack the logic and scientific merit of any conclusion typically by trivializing the importance of any finding, (c) pseudosophistication or it is all “junk science” and lastly, (d) make light or poke fun at an opponent’s conclusions. All of these methods were used by Lees-Haley et al. (2003) in their critique.

6.1.1. A good offense starts with a good defense

Because of the posture one must take to defend a position, extreme statements may be made because hypotheses can never be proven true, only disproved. Extreme positions are taken because anything less is tantamount to some endorsement of the other sides’ position. For example, because of the defensive posture they had to take, each President of each major
Tobacco company when facing a Senate hearing (Glantz et al., 1996) took their arm to the square and said, “I believe tobacco is not addicting.” (p. 100)—all seven of them! Essentially, Lees-Haley et al. (2003) are doing exactly the same thing—paraphrasing their position, they are saying lesions on neuroimaging do not matter nor does the history of injury, because the best we will ever be able to do is call it psychological. Presence of an objective finding of a lesion influencing behavior represents a major obstacle if you are on the defense side, so how to attack this position? Take the offense: We have no proof that lesions relate to behavior and in scans where lesions cannot be identified there is no way to prove injury. If you lose a few neurons, no problem. Smoking is not addicting.

6.1.2. Attack the logic: reductio ad absurdum or exemplum absurdum

A good example may be all that is needed to disprove a theory. However, good examples require good logic and facts based on accurate assumptions. The example offered by Lees-Haley et al. (2003) breaking down a fall from a three story building (360 in.), which they agree could cause brain injury, to single, separate falls of only one-inch-at-a-time is ludicrous and further bolsters my assertion of their trivializing the real issue of mild TBI. Physical forces cause brain injury and if, as stated clearly in the ‘Lesion(s) . . . ’ paper (Bigler, 2001a, p. 23) they are present it is likely that the injury alters brain structure/function which in turn alters behavior. Competent clinical neuropsychologists do not diagnose mild TBI in individuals who fall “one inch.” They do see real patients who have been in high-speed accidents, have been assaulted, experienced significant falls, sports related accidents, etc.

6.1.3. Pseudo sophistication or it is all “junk science”

If Lees-Haley et al. (2003) were truly interested in a genuine debate, why raise the legal standard of the Daubert issue (Daubert v. Merrell Dow Pharmaceuticals, 1993), in an academic discussion on the neurobehavioral sequela of injury? Why bring up toxic tort issues, when my ‘Lesion(s) . . . ’ paper is on TBI? These authors know that this is how the court reviews new methods of proof: Skillfully raise the question of “junk science,” use the language of a scientist and, voilà, you cannot bring neuroimaging or neuropsychological testimony into the courtroom. What are they really trying to argue? I suggest the intent of their argument is to say that lesions do not relate to behavior, minor injury is trivial (no effect), ergo, neuroimaging findings have no place in the discussion of behavioral change following trauma. Furthermore, their position asserts it is even more important when we cannot see a lesion that we do not conclude that there is a relationship between behavioral change and brain injury, even if the history supports such conclusions. Why else would they make the statement “it is statistically and empirically unsound for us to presume MTBI patients to be suffering chronic effects of brain injury until proven otherwise.” (Lees-Haley et al., 2003, p. 591)? That reads purely as a position statement for defending mild TBI cases. If any reader has doubts about biased assumptions from this group, they should carefully read what has been published elsewhere by Lees-Haley et al. in nonacademic outlets (see Kizorek & Lees-Haley, 2002; Lees-Haley, 1985, 1986, 1990, 1994a, 1994b, 1994c, 1994d, 1996, 1997a, 1997b, 1999a, 1999b; McDonald & Lees-Haley, 1995, 1996; Price & Lees-Haley, 1995). In review of these works by this group, which represent only a partial sample, pay particular attention to the title of the articles, where they are published, and the targeted readers.
6.1.4. Make light or poke fun: what quacks just may be a duck with a brain injury or, zebras can have brain injuries too

In legal strategy, a coup de grace in debate may be strategically placed by expertly poking fun at the opponent all the while sensing the seriousness and gravity of the situation. An example of such tactics is Johnny Cochran’s famous words in defense of O.J. Simpson as he tried on the gloves—“If it doesn’t fit, you must acquit” (Schmalleger, 1996, p. 313). The “zebra” analogy that Lees-Haley et al. (2003) offer only works if, in fact, the conclusion is wrong, that is, if a zebra is mistaken for what is actually a horse. I return to the schizophrenia analogy. A little more than 30 years ago, clinicians and researchers who were linking the emerging ideas of neurobiology to mental illness thought that schizophrenia looked like a zebra, but often had to concede that it was a horse because of the strength of the psychodynamic position of the day (circa 1940–1970). Over time, neuropsychology and other disciplines have shown that schizophrenia was not a horse it was a zebra and I put forward that mild TBI is a zebra as well.

7. Clinical practice issues and caveats redux

In the ‘Lesion(s) . . . paper I closed with a number of clinical caveats. As part of this rebuttal, I would like to again close with clinical caveats that address issues raised by Lees-Haley et al. (2003).

7.1. Base rate research

I completely agree with Lees-Haley et al. (2003) that proper baseline research needs to be done and that clinical neuropsychology is hampered by not having proper baseline data. I will let the reader pass judgment on the quality of base rate research cited by these authors in their commentary, including their own base rate research. Proper base rate research should be unbiased, should be based on large sample sizes from multiple sources, and should have agreed upon methods for registering whatever the base rate question may be. Are these articles cited by these authors strictly written for an academic and clinical audience, where the focus is on patient evaluation and care, or are they written to be used in the court room? If the latter, what better information to refute statements by clinicians about a patient’s subjective complaints after an injury, no matter how legitimate the symptoms and neuropsychological deficits are. Improperly done base rate research hurts our profession because the data have both acquisition and data interpretation bias. Base rate data that finds its way into neuropsychological practice has to be done impartially and as rigorously as can possibly be achieved, and it must be independent of bias.

7.2. Disclosure

Science has been confronted with the issues of disclosure (ICMJE, 2001; Marshall, 2002). Conflicts of interest need to be disclosed when publishing. There is nothing wrong with having a neuropsychological practice that is focused on defending TBI cases. Our legal system is based on such an adversarial approach. Likewise, there is nothing wrong with publishing from a
single perspective, defending a single position. However, there should be disclosure if there is financial gain to be made by such approaches. The National Academy of Neuropsychology (NAN) is a society where we are supposed to “foster the development of neuropsychology as a discipline, science and profession” (p. 318, National Academy of Neuropsychology, 2000–2001), this was the intent of my Distinguished Neuropsychologist address. I believe those objectives were achieved in the address that night and as published in the ‘Lesion(s) . . . ’ paper. My disclosure statement is at the end of this article. Disclosure should become a requirement for anything published in Archives of Clinical Neuropsychology or any other official outlet of NAN.

7.3. Why neuropsychologists see forensic cases

In their response Lees-Haley et al. (2003) make disparaging comments about legal cases being the most reported reimbursable case seen by clinical neuropsychologists. The Center for Disease Control and Prevention (CDC, 2000) indicates that the base rate of head injury (all types and all levels of severity) to be \( \sim 95 \) cases per 100,000 population. If our current population is \( \sim 286 \) million (U.S. Census Bureau, 2002) that means about 2.5 million new head injury cases occur per year. The current membership of NAN is about 3,500 members, probably three-quarters have clinical practices or about 2,600. Tripling that number or around 10,000 clinicians probably represents neuropsychologists and psychologists who do neuropsychological testing and consultation of some form in their clinical practice. Using the CDC head injury statistics means that potentially 250 new cases per neuropsychologist per year become available for clinical consultation, testing and treatment. Since these are incident numbers they would build on prevalence rates and over a lifetime of clinical practice; that works out to thousands of potential TBI patients for each clinical neuropsychologist. This is a major factor that explains why neuropsychologists see so many head injury cases. Since many of these individuals are in accidents where there is a question of legal responsibility that is why there is so much litigation. Why is none of this mentioned in the critique by Lees-Haley et al. (2003) or the changes in insurance reimbursement for neuropsychological testing and consultation? They also fail to point out that all aspects of forensic psychology have increased, not just in neuropsychology (Otto & Heilbrun, 2002).

7.4. Neuroimaging and neuropsychology: the future

Clinical neuroimaging is making incredible advances at lightening speed (Linden, 2002). Likewise, there are many neuropsychologists who have been at the forefront of this movement. As clearly stated in my lecture, as well as in the ‘Lesion(s) . . . ’ paper, rather than sit on the sidelines and be excluded, why not embrace this technology and bring aspects of it within our profession? The concluding statements made by Lees-Haley et al. (2003) are absurd, suggesting that neuropsychology should not embrace neuroimaging because it diminishes our uniqueness as a profession because of “the danger of leaving the psychology out of neuropsychology . . . after all we are not neurologists” (p. 591). Their position is actually the one perilous to our profession. Structural and functional imaging will continue to improve our ability to empirically investigate and clinically assess the brain as it processes stimuli and information and
all imaging is becoming more automated (Fischl et al., 2002; Gehring & Willoughby, 2002; Nakahara, Hayashi, Konishi, & Miyashita, 2002; Rutten, Ramsey, van Rijen, Noordmans, & van Veelen, 2002). If we as a profession do not lead the way in integrating neuroimaging with neuropsychological assessment, our profession, as now constituted, will cease to exist.

7.5. Errata

The reader must recall that this article is based on the talk I gave at the 1999 annual NAN meeting when I received the award. The tradition is for NAN to reproduce the talk, with author modifications, as a paper in ACN. This publication was not intended to be an exhaustive treatise on this topic, which would require an entire text to appropriately cover. I found it very curious that Lees-Haley et al. (2003) focused on several figures presenting summary data and criticized them as if I had not presented all the data. This paper was based on a talk and how could all the data be presented in a review paper anyway? The full text for the adverse effects of alcohol on TBI can be found in a forthcoming publication of the Journal of Neurotrauma (Wilde et al., submitted). Likewise, additional research on magnetocephalography can be found in a forthcoming publication by Lewine et al., (submitted-a, submitted-b). The data suggesting greater psychological response in mild than severe TBI patients is based on the dissertation of one of my graduate students, Antonietta Russo, and can be found in the University of Michigan Dissertation microfilm (Russo, 1997). We continue to publish new studies on innovative ways to relate neuroimaging findings to clinical outcome in TBI (Lewine et al., submitted–a, submitted–b) and other disorders (Bigler, 2001b; Bigler, Kerr, Victoroff, Tate, & Breitner, in press; Parkinson et al., 2002; Yount et al., 2002). My university web site lists ongoing publications at http://www.byu.edu/~psychweb of work on this topic.

8. Conclusion

As a scientific or academic review, the Lees-Haley et al. (2003) critique is a nonsequitur. These authors are discounting one of the major revolutions in science, medicine and psychology. Part of the lecture I gave that night was a warning to neuropsychologists to pay attention to the clinical neurosciences, and particularly, neuroimaging. If we as a profession, do not keep up with these advances, and incorporate them into our practice, we will have many good ‘psychological’ explanations but no one to test because clinical neuroscience will pass us by. I believe the ‘Lesion(s) . . .’ paper was a balanced review demonstrating the relationship between neuroimaging and neuropsychology, how the two can interface and be used in clinical practice.

The neuropsychological world that I practice in looks to understand the biology of behavior. As shown in Figure 1 the neurobiology of behavior can be interfaced at multiple levels. Basic neural systems and structure, their integrity and ability to function, is the center point of this figure (see bracket). Above this point is what traditional psychology has studied. It is at this level that Lees-Haley et al. (2003) want psychology, not neuropsychology, to remain. Neuropsychology is the field that connects neural function to behavior.
9. Financial disclosure

Erin Bigler maintains a private practice of Clinical Neuropsychology where he sees patients on a fee-for-service basis. As part of this practice he consults with both plaintiff and defense counsel and performs forensic neuropsychological evaluations.

10. Author contributions

Study concept and design: Bigler
Acquisition of Data: Bigler
Analysis and interpretation of data: Bigler
Drafting of the manuscript: Bigler
Critical revision of the manuscript for important intellectual content: Bigler
Statistical expertise: Bigler
Obtained Funding: Bigler
Administrative, technical, or material support: Bigler
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