Forensic Applications of Cerebral Single Photon Emission Computed Tomography in Mild Traumatic Brain Injury

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Traumatic brain injury (TBI) is a substantial source of mortality and morbidity world wide. Although most such injuries are relatively mild, accurate diagnosis and prognostication after mild TBI are challenging. These problems are complicated further when considered in medicolegal contexts, particularly civil litigation. Cerebral single photon emission computed tomography (SPECT) may contribute to the evaluation and treatment of persons with mild TBI. Cerebral SPECT is relatively sensitive to the metabolic changes produced by TBI. However, such changes are not specific to this condition, and their presence on cerebral SPECT imaging does not confirm a diagnosis of mild TBI. Conversely, the absence of abnormalities on cerebral SPECT imaging does not exclude a diagnosis of mild TBI, although such findings may be of prognostic value. The literature does not demonstrate consistent relationships between SPECT images and neuropsychological testing or neuropsychiatric symptoms. Using the rules of evidence shaped by *Daubert v. Merrell Dow Pharmaceuticals, Inc.,* and its progeny to analyze the suitability of SPECT for forensic purposes, we suggest that expert testimony regarding SPECT findings should be admissible only as evidence to support clinical history, neuropsychological test results, and structural brain imaging findings and not as stand-alone diagnostic data.

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Approximately 1.5 million traumatic brain injuries (TBIs) occur each year in the United States and more than 5 million Americans, about 2 percent of the United States population, are living with disabilities related to brain injuries.[1] The majority are mild in both initial severity and outcome. However, the size of that majority varies as a function of the definition of mild TBI used and also with the types and severities of consequences included within the scope of a "good" outcome.[2] The neuroanatomic and neurophysiologic consequences of mild TBI, as well as the clinical significance of such consequences, are also sources of considerable scientific controversy.[3] As a result, many individuals with cognitive, emotional, behavioral, and neurological problems following mild TBI face a difficult challenge when trying to establish—whether at home, work, or in court—that their symptoms are the direct result of brain injury.

A growing body of literature suggests that single photon emission computed tomography (SPECT) may be able to identify abnormalities in cerebral blood flow, metabolism, or function resulting from mild TBI, even in the absence of structural imaging

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abnormalities. The frequency of mild TBI, the increasing clinical availability and application of SPECT, and a litigious environment have united to produce an atmosphere in which the introduction of evidence involving the interpretation of SPECT images is inevitable.

Several legal cases illustrate the trend toward utilizing SPECT as objective evidence of brain injury and the difficulty surrounding admissibility of such evidence. In *Guilbeau v. W. W. Henry Co.*,[4] cerebral SPECT imaging evidence was offered and admitted, to establish a diagnosis of severe chronic toxic encephalopathy. In *Rhilinger v. Jancsics*,[5] SPECT imaging results were allowed as evidence to establish injuries consistent with toxic encephalopathy. The court opined *In re Air Crash at Little Rock Arkansas*[6] that SPECT evidence might have been useful in establishing requisite physical injury from PTSD. A Google search of the terms brain injury/SPECT/lawyer yielded 207,000 hits; these sites suggest that SPECT is now a part of the attorney's evidentiary arsenal in brain injury litigation. The possible use of cerebral SPECT as evidence in medicolegal proceedings tantalizes not only medical and legal professionals but also the public at large. "It's safe to say that once a subject becomes a cover story in the New York Times Magazine, people are paying attention, as is the case with a March 11 feature article[7] on the rapidly emerging field of 'neurolaw' " (Ref. 8, p 1).

The medical literature is devoid of a rigorous review of the rules surrounding admission of evidence and the application of cerebral SPECT for forensic purposes. In the service of providing forensic psychiatrists a review of the points relevant to the forensic application of cerebral SPECT to mild TBI, we first review briefly the definition of mild TBI. The literature describing cerebral SPECT findings in mild TBI is then summarized. Next, findings from that literature are analyzed in terms of the rules of evidence established by *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993), and its progeny. Finally, preliminary recommendations are offered regarding the contexts and manner in which cerebral SPECT might be incorporated appropriately into legal proceedings related to mild TBI.

Mild TBI

The majority of TBIs are of mild severity, with 70 to 80 percent of all such injuries falling into this category.[9] The Glasgow Coma Scale (GCS)[10] is commonly used to gauge injury severity and is a useful clinical tool when applied in the acute injury period. When GCS assessments are not present in the medical record, the American Congress of Rehabilitation Medicine (ACRM) criteria for mild TBI[11] may help identify mild TBI by clinical history. According to these criteria, mild TBI is defined as a mechanically induced physiologic disruption of brain function manifested by any one of the following: a loss of consciousness, a loss of memory for events immediately preceding or following the injury, an alteration in mental status (feeling dazed, confused, or disoriented) at the time of injury, or focal neurological signs that may or may not be transient. To remain within the category of mild TBI, the associated loss of consciousness must be less than 30 minutes in duration, post-traumatic amnesia must not exceed 24 hours, and the GCS score must be 13 or better within 30 minutes after injury. Although not without criticism, this definition remains the most widely accepted among experts in the field.[9]

The impairments caused by mild TBI are often subtle but not trivial. Unfortunately, the nature of the neuropsychiatric consequences of mild TBI remains the subject of contentious debate that can prove problematic to individuals seeking treatment and support. Most survivors of mild TBI can expect a full recovery within one year of injury. For an unfortunate 1 to 20 percent of victims, postconcussive disturbances of cognition, emotion, behavior, and physical function may become chronic problems.[9,12–18] Postconcussive cognitive impairments tend to involve attention, memory, and executive function. Common emotional or behavioral disturbances include irritability, anxiety, depression, affective lability, impulsivity, and apathy. Physical symptoms may include headache, dizziness, pain, seizures, fatigue, visual disturbance, hyposmia, and hyperacusis. Despite the frequent use of the term postconcussive syndrome in the literature, which implies a uniform clinical profile, it is important to realize that the symptoms related to mild TBI vary widely between as well as within individuals over the course of recovery after TBI. This variability is consistent with the differences in injury mechanism, preinjury personal factors, and postinjury interventions (or lack thereof) associated with these injuries. Although the characterization of this constellation of symptoms as a postconcussive syndrome is debatable,[9,19] post-traumatic cognitive, emotional, behavioral, and physical

impairments are substantial sources of disability and suffering.[9,20–23]

The language surrounding traumatic brain injury can be confusing, and a brief clarification is warranted to solidify proper understanding. The terms mild TBI and postconcussive syndrome have both been introduced. It is important to realize that these terms are not interchangeable. Rather, they represent two very different diagnostic entities. Mild TBI is essentially a pathophysiologic event manifest by various acute occurrences (such as loss of consciousness or altered mental state) at the time of injury and is not at all dependent on the emergence of postconcussive signs or symptoms. Postconcussive syndrome, on the other hand, is predicated on the emergence of a specified constellation of signs and symptoms, and presumes that the etiology of such sequelae is a traumatic brain injury. Of course, not all cognitive, emotional, behavioral, and physical impairments that occur in the wake of a brain injury are necessarily directly or entirely referable to the traumatic event. Rather, this is a determination that must be made on a case-by-case basis with careful consideration of the entire biopyschosocial context. The language of mild TBI, therefore, represents the preferred approach to brain injury, as this diagnosis ultimately rests on a well-defined event, recognizes that mild brain injuries can occur with and without clinically apparent sequelae, and avoids presumptions of etiology when signs or symptoms do emerge. Finally, these advantages, especially the clarity of definition, help to enable meaningful research on mild TBI, such as investigations determining the rates of abnormalities observed in various neuroimaging or electrophysiologic studies.

Given the often subjective nature of many postconcussive symptoms and the sometimes difficult-to-understand relationship between these symptoms and functional disability, it is not surprising that a means of demonstrating objective, clinically relevant cerebral dysfunction caused by mild TBI is much sought after by patients, clinicians, and attorneys. Conventional electroencephalography (EEG) may demonstrate abnormalities in up to 10 percent of patients who have sustained a mild TBI.[24] Absent overt post-traumatic seizures, the clinical relevance of such EEG abnormalities is unclear. Computed tomography (CT) of the brain demonstrates abnormalities in the acute injury period among 5 to 10 percent of persons with mild TBI.[25–27] However, the vast majority of patients with mild TBI have no demonstrable abnormalities on either conventional diagnostic electrophysiologic or structural neuroimaging studies. Accordingly, the best methods of identifying objective evidence of brain dysfunction among symptomatic brain injury survivors remain uncertain. While many modalities have been considered, the advantages offered by SPECT in cost and availability have led some to suggest that it holds promise as a diagnostic study for this purpose. In addition, SPECT, when compared with positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) enjoys a relative abundance of published research investigating its application to mild TBI.

SPECT Principles and Clinical Applications

SPECT is a functional imaging modality with several technical approaches that utilize the unstable properties of injected radiopharmaceuticals to evaluate regional cerebral blood flow, metabolism, or neurotransmitter-related physiology. Photons emitted by the rapid radioactive decay of injected radiopharmaceuticals are detected by SPECT cameras. The sensitivity of SPECT to functional brain abnormalities and the spatial resolution of this imaging modality are limited by constraints on photon detection during the image acquisition process.[28]

The most commonly used radionuclides are 99m-technetium (^{99m}Tc) and 123-iodine (^{123}I),[28] and the most commonly used radiopharmaceutical for clinical SPECT imaging is technetium-99m-hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO). This molecule accumulates in areas of rich blood flow in detectable concentrations up to 24 hours, a relatively long *in vivo* accumulation that enables delay between injection and scanning, as well as performance of multiple scans after a single injection. Ideally, the radiopharmaceutical should be injected in a calm and quiet setting a few minutes before the study, to minimize any alterations in blood flow secondary to diagnostically confounding patient activity or other undue environmental influences.[29]

SPECT scans are available at most major medical centers and are relatively inexpensive (approximately $800 per study).[29] Neurological disorders studied with SPECT imaging include cerebrovascular disease, dementias, epilepsy, TBI, cerebral neoplasms, and movement disorders. Psychiatric disorders stud-

ied include obsessive-compulsive disorder, schizophrenia, depression, panic disorder, and substance abuse and dependence.[29,30] Although patterns of abnormal SPECT imaging are commonly observed in the studies of persons with neurological or psychiatric conditions when compared with normal comparison subjects, these patterns are generally not specific to any individual neurological or psychiatric condition and instead demonstrate considerable overlap with one another. For example, patients with migraine headache have been reported to demonstrate hemispheric asymmetry in the superior frontal and occipital regions.[31] Decreases in thalamic flow have been described in the setting of both chronic pain[32] and fibromyalgia.[33] Abnormalities have been reported in association with primary insomnia,[34] rapid eye movement-sleep behavior disorder,[35] and narcolepsy.[36] Studies investigating SPECT in depression have reported decreased flow in the lateral prefrontal cortex as well as in the temporal cortex, cingulate, and left caudate.[37,38] SPECT studies of obsessive-compulsive disorder have described increased perfusion at the anterior cingulate, orbitofrontal cortex, and basal ganglia.[39,40] In schizophrenia, SPECT studies have described low flow through the frontal cortex, basal ganglia, and temporal lobe.[41] In addition SPECT has been cited as demonstrating diffuse hypoperfusion among abusers of cocaine and alcohol.[37,42]

Despite the frequency of its use in research contexts, both scientific and clinical interpretations of SPECT images are not without problems. Confounding the interpretation of SPECT findings is the problem of neuropsychiatric comorbidity: many persons with mild TBI experience more than one postconcussive neuropsychiatric condition (for example, depression, migraine headaches, and chronic pain) each of which may produce abnormal SPECT imaging findings and each of which may or may not be related to the mild TBI. In addition, some patients may have had neuropsychiatric conditions (e.g., mood disorders, substance use disorders, or migraines) before experiencing mild TBI, and therefore might demonstrate cerebral SPECT abnormalities, not as a result of the injury, but instead as a function of preinjury condition(s). Accordingly, extreme caution is merited before attributing SPECT results to any single etiology such as mild TBI.[29] The interpretation of SPECT findings in this context is complicated further by the dearth of information on how various medications, drugs of abuse, and dissimilarities in testing conditions may influence results.[43]

SPECT in the Mild TBI Literature

Expert Reviews

In 2002, Davalos and Bennett[3] published a review of the literature on the use of SPECT imaging in mild TBI. A MedLine and PsycInfo database search for the years 1967 to 2000 focusing specifically on TBI and SPECT yielded 31 studies. Some of these studies were then excluded based on failure to adhere to standards established by the Society for Nuclear Medicine Brain Imaging Council and the Therapeutics and Technology Assessment subcommittee of the American Academy of Neurology, failure to adhere to clear definitions of mild TBI, or failure to differentiate between mild and moderate injury when reporting SPECT results after brain injury. These exclusions left only 13 studies deemed valid for further analysis. Three of these studies investigated the relationship between neuropsychological testing and SPECT imaging, and they generally failed to establish any consistent relationships between them. In addition, these studies suggested a potential role for depression in impacting SPECT results and therefore the need to assess depression symptomatology at the time of testing. The authors express considerable concern about the significantly different results in the three studies, raising the possibility of subtypes within mild TBI as well as confounding roles for psychological and psychiatric factors.

Davalos and Bennett[3] next evaluated studies in which the relationship between SPECT and other forms of neuroimaging or electrophysiological studies was examined. They concluded that the literature suggests that SPECT may be superior to both CT and magnetic resonance imaging (MRI) in identifying abnormalities after mild TBI. The abnormalities discovered by SPECT most commonly involved frontotemporal areas, suggesting that SPECT may be particularly sensitive to detecting damage in these regions, or that there is a predominance of frontal and temporal lesions after mild TBI. Again, the possibility of mild TBI subtypes is presented as a potential explanation for conflicting study results. While studies frequently described the ability of SPECT to identify lesions missed by CT or MRI, one study described eight contusions identified by CT and missed by SPECT, supporting the existence of two

types of contusions: those causing a change in blood flow, and those with a level of blood flow equal to that in surrounding tissue. A study by Masdeu *et al.*[44] from 1994 is reviewed and is particularly worthy of note. This study not only looked at the ability of SPECT to identify abnormalities after mild TBI, but also its ability to differentiate such lesions from those related to human immunodeficiency virus (HIV) encephalopathy. While results generally supported a strong sensitivity of SPECT to abnormalities among persons with mild TBI, they also indicated problems with specificity: two independent SPECT readers identified 46 percent of mild TBI cases incorrectly as HIV encephalopathy.

Davalos and Bennett[3] next addressed the role of SPECT in the prediction of clinical outcome. The presence of abnormal findings on SPECT was generally regarded to be a less valuable prognostic indicator than the absence of abnormal results, with one study reporting the predictive value of an abnormal scan to be only 59 percent, due to inconsistencies between initial SPECT scans, clinical evaluations, and future SPECT readings. However, the same study reported that 97 percent of patients with normal initial SPECT scans experienced complete recovery by a three-month follow-up. SPECT appears to be most useful, although not infallible, as a means of predicting outcome when no abnormalities are found, but of more questionable utility when defects are discovered.

In their conclusion, Davalos and Bennett[3] acknowledged that many studies have reported a promising role for SPECT in mild TBI, but they also noted the questionable quality of many of these investigations when appropriate exclusion criteria are applied. The standards established by the Society for Nuclear Medicine Brain Imaging Council and the Therapeutics and Technology Assessment subcommittee of the American Academy of Neurology were sparsely represented in the literature at the time of their review, and the authors concluded that "until SPECT research is conducted in a systematic manner adhering to the recommendations proposed by these committees, SPECT and the added information SPECT scans provide will continue to be considered investigational" (Ref. 3, p 102). In short, this 2002 review identified no consistent relationship between SPECT results and neuropsychological deficits, and a potentially serious confound of depression on SPECT findings. Although SPECT was identified in some studies as a more sensitive indicator of postconcussive frontotemporal dysfunction than conventional structural neuroimaging, this finding was not without exception. Finally, normal SPECT findings appeared to be useful as a prognostic indicator of good recovery after TBI, but abnormal SPECT findings are not clearly useful in establishing clinically relevant and TBI-related cerebral dysfunction.

A more recent review of the literature is offered by Anderson *et al.*[29] These authors echo the sentiment that there is a paucity of methodologically sound studies in this area and note that there are even fewer that pair SPECT imaging with other methods of clinical assessment, such as neuropsychological testing or standardized ratings of TBI recovery. They draw conclusions similar to those of Davalos and Bennett,[3]—namely, that SPECT may demonstrate abnormalities not apparent on structural neuroimaging studies, but the converse is also sometimes true. In addition, they note that while an initially negative SPECT scan following mild TBI bodes well for postinjury recovery, the prognostic utility of an abnormal SPECT study is unclear. The authors note that SPECT results fail to correlate consistently with neuropsychological performance, and SPECT imaging cannot be employed to forecast neuropsychological impairment. They also note the potentially confounding influences of depression and substance abuse, and the importance of carefully considering psychiatric or neurological comorbidities when interpreting SPECT images.

Most recent is a review by Belanger *et al.*[45] of neuroimaging techniques as applied to mild traumatic brain injury. The authors begin by establishing a set of criteria with which they evaluate findings: (1) the technique should be sensitive to brain injury; (2) the technique provides incremental validity above and beyond conventional structural images; (3) the technique should correlate with clinical examination or symptom presentation or have predictive validity. The authors reviewed multiple imaging modalities and found the most promise in functional imaging, including SPECT, PET, and fMRI. SPECT enjoys a greater volume of published research, with 16 studies included in this review, relative to 4 for PET and 3 for fMRI. Conclusions are in keeping with previously described reviews, noting inconsistent relationships between SPECT findings, symptom complaints, and neuropsychological testing. The authors conclude:

> Particularly in the area of functional neuroimaging, if these neuroimaging techniques are to become clinically useful, it will be necessary to interpret positive findings . . . . There is no unique PET or SPECT profile that has been clinically validated with TBI . . . . It is difficult to have confidence in the specificity of the abnormalities demonstrated in these studies [Ref. 45, p 16].

In short, cerebral SPECT imaging, even with its relative abundance of research in mild TBI relative to PET and fMRI, is of uncertain clinical utility in the context of mild TBI.

Individual Studies of Forensic Relevance to Cerebral SPECT in Mild TBI

In a study published by Audenaert *et al.*[46] in 2003, the utility of radioactive cobalt (^{57}Co) as an alternate radionuclide to ^{99m}Tc-HMPAO for SPECT scanning in mild TBI was investigated. In explaining the reasoning behind this investigation, the authors report an intrinsic problem with ^{99m}Tc-HMPAO as a SPECT tracer due to the requirement for intact neuronal cell metabolism for tracer fixation and the prevention of back diffusion and washout. They postulate that this requirement may often be lost as a consequence of neuronal damage in mild TBI, yielding potential increases or decreases in perfusion and possible sources of artifact. They demonstrated that SPECT imaging with ^{57}Co was less affected by these problems than was cerebral blood flow imaging with ^{99m}Tc-HMPAO, suggesting the possibility that the most commonly used SPECT radionuclide may not be well suited for use among persons with mild TBI.

A clinical case report making a similar point is offered by Barkai *et al.*[47] They describe successful use of acetazolamide-enhanced SPECT imaging in detecting perfusion abnormalities following mild TBI in a patient without other neurological or structural imaging findings. Acetazolamide, a carbonic-anhydrase inhibitor and a vasodilator, has been reported to enhance the contrast between healthy brain regions of normal cerebral blood flow and ischemic regions. The patient underwent SPECT imaging, both with and without acetazolamide, before and after treatment with valproate. While routine SPECT failed to reveal a cerebral blood flow defect, the pretreatment acetazolamide-enhanced scan did. In addition, this prefrontal cerebral blood flow defect resolved following treatment with valproate, coincident with reported neurobehavioral improvement. The failure of ^{99m}Tc-HMPAO to identify a clinically relevant functional neuroanatomical abnormality that was both evident and reversible with an alternate imaging methodology (i.e., acetazolamide with and without valproate) suggests that the most commonly used clinical cerebral SPECT method may not be the most clinically relevant method of SPECT imaging in persons with TBI.

In a 2003 study, Bonne *et al.*[48] used ^{99m}Tc-HMPAO SPECT and neuropsychological testing to assess patients with chronic mild TBI and healthy control subjects. Neuropsychological test results were used to stratify the subjects into subgroups based on the presumed locations of impairment: right posterior, left posterior, frontal, and subcortical. SPECT analysis was then conducted between the patient subgroups and the healthy control group. The authors report a moderate degree of correspondence between SPECT-demonstrated hypoperfusion and neuropsychological test results in all subgroups except for the right posterior subgroup. While the authors conclude that SPECT demonstrates regional hypoperfusion in patients with symptomatic mild TBI, they also acknowledge that their findings derive from between-group comparisons and are not readily applicable to the clinical situation involving an individual patient:

> Although group analysis is appropriate for the generation of statistically significant differences, the clinical application of brain SPECT imaging in [mild] TBI calls for a capacity to associate clinical examination, neuropsychological assessment and cerebral perfusion at the individual subject level. Such competence is still to be attained [Ref. 48, p 1].

Echoing the findings presented in the preceding section of this article, Gowda *et al.*[49] conducted a prospective study on the use of SPECT in mild TBI to investigate the relationship between cerebral SPECT (using technetium Tc99m ethyl cysteinate dimmer, or Tc99m-ECD) and CT imaging. Ninety-two patients with mild brain injury were studied within 12 to 72 hours after injury. SPECT identified abnormalities more frequently than CT (63% vs. 34%), and SPECT abnormalities were more sensitive to the presence of clinical symptoms (i.e., loss of consciousness, post-traumatic amnesia, and ICD-10 postconcussion syndrome) than was CT. In most patients with CT lesions, corresponding SPECT cerebral blood flow defects tended to be more extensive than those on CT. In addition, some patients demonstrated areas of hypoperfusion that appeared normal on CT, and two patients (both with subarachnoid hemorrhages) with negative SPECT imaging demonstrated positive findings on CT. These unusual findings notwithstanding, this study suggests

that SPECT may be a more sensitive method than CT for detecting clinically relevant neuroimaging abnormalities following mild TBI. However, the authors note that the lack of a sufficient gold standard for detecting brain lesions after mild TBI makes calculations of sensitivity and specificity for SPECT impossible at this time. Of interest, they propose that SPECT may be more useful than CT in forensic evaluations related to the assessment of persons with mild TBI. However, the legitimacy of this claim, particularly given their concurrent statement of the impossibility of calculating sensitivity and specificity for SPECT imaging in mild TBI, should prompt a careful consideration of the rules by which evidence is admitted into legal proceedings in such cases.

Rules of Evidence: *Frye*, *Daubert*, and Others

> Just when a scientific principle or discovery crosses the line between the experimental and demonstrable stages is difficult to define. Somewhere in this twilight zone the evidential force of the principle must be recognized . . .[Ref. 50, p 1014].

This statement, taken from the landmark case of *Frye v. United States*,[50] captures a frequently recurring conundrum in a time of rapidly emerging medical technologies. This very question is now at hand with cerebral SPECT imaging, and particularly its courtroom application to the demonstration or exclusion of mild TBI. For 70 years, the rules surrounding the admissibility of scientific evidence were dictated by the *Frye* test, which demands that the science behind the expert's testimony "be sufficiently established to have gained general acceptance in the particular field in which it belongs" (Ref. 50, p 1014).[50–52]

The *Frye* test's supremacy came to an end with the 1993 Supreme Court ruling in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*.[53] The Supreme Court ruled that the *Frye* test had been outmoded by the Federal Rules of Evidence. Most pertinent to the matter at hand was Rule 702:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise [Ref. 54, p 13].

The Court found the old *Frye* standard to be too narrow and not in keeping with the more liberal inclinations of the Federal Rules to favor admitting reasonable expert testimony. However, the Supreme Court did not abolish the trial judge's gatekeeping role for the admission of expert testimony. Such testimony must still be relevant, reliable, and derived by the scientific method. To assist in this consideration, the Court proposed several inquiries (commonly referred to now as the *Daubert* criteria) to be reflected on: (1) Can the theory behind the evidence be tested? (2) Has that theory been subjected to peer review and publication? (3) Is there a known rate of error and established standards surrounding the technique/practice? (4) Has the theory, technique, and/or practice been generally accepted within the pertinent scientific community? No single factor is absolutely essential to pass the test, nor is any single factor necessarily sufficient. Rather, these inquiries are to be flexibly applied on a case-by-case basis to assist in the gatekeeping process and determination of admissibility.[51–53]

The trial judge's role as gatekeeper was next tested in the 1997 case of *General Electric v. Joiner*.[55] This Supreme Court decision supported the trial judge's ability to scrutinize the reasoning process behind an expert's testimony and to exclude that testimony if too great a gap exists between the expert's stated opinion or conclusions and the data on which it is based. The *Joiner* decision allowed that a trial judge's gatekeeping duties occasionally necessitate considering the expert's conclusions, as well as the logic and methods behind them, recognizing that the two are inevitably intertwined.[51,52,55]

Application of *Daubert* Criteria to SPECT in Mild TBI

The criteria established in the *Daubert* and *Joiner* cases are intended to be applied flexibly on a case-by-case basis. Given the potential variability in equipment, technique, experience level, and clinical circumstances surrounding any given single cerebral SPECT scan, case-by-case analysis is essential. However, a useful starting point involves a consideration of the *Daubert* criteria as they apply to the state of cerebral SPECT in general.

The first question *Daubert* asks is whether the theory behind and the techniques related to the performance of cerebral SPECT can be, or have been, tested. Cerebral SPECT's ability to identify mild TBIs has been the subject of considerable scientific inquiry at multiple institutions worldwide. On this

point, cerebral SPECT imaging in mild TBI appears to meet the first criterion proposed in *Daubert*.

The second *Daubert* factor asks whether those theories and techniques have been subjected to peer review and publication. As the literature review provided earlier in the article details, SPECT has been subjected to numerous publications, many of which appear in respected peer-reviewed journals. However, and as is made clear by the Society for Nuclear Medicine[56] and by Davalos and Bennett,[3] the publication of a study in a peer-reviewed journal is not necessarily indicative of the clinical usefulness of the findings reported therein. In the Davalos and Bennett analysis of the literature, more than half of the studies published regarding SPECT imaging in mild TBI were considered uninterpretable because of methodological problems. Their report highlights the potential problems of accepting uncritically the fact of publication in a peer-reviewed journal as meeting the second *Daubert* criterion. While it is true that findings testing the theory of cerebral SPECT as a marker of post-traumatic brain dysfunction have been subjected to peer review and publication, expert critique as to the quality of the data reported in most of those publications is needed when considering their evidentiary usefulness in legal proceedings. These reports present problems for cerebral SPECT in mild TBI as regards its ability to meet the requirements of the second *Daubert* criterion.

The third of the *Daubert* criteria asks whether there is a known or potential error rate. As noted by Gowda *et al.*,[49] the lack of a gold standard for the diagnosis of mild TBI makes any definitive determination of error rates (i.e., sensitivity, specificity, positive and negative predictive values of cerebral SPECT as a diagnostic assessment for mild TBI) impossible at present. The literature suggests that cerebral SPECT with ^{99m}Tc-HMPAO may identify regional cerebral blood flow (rCBF) abnormalities among persons with a suspected or known history of mild TBI. However, the direct causal relationship, if any, between such SPECT-identified rCBF abnormalities and mild TBI remains uncertain. Multiple potential confounding factors, including comorbidities, environmental influences, medications and substances of abuse, and patient activity, are usually operative in individual patients and are capable of generating rCBF patterns that are indistinguishable from those produced by mild TBI. In addition, the possibility of mild TBI subtypes producing different patterns of rCBF abnormalities, as well as the problems with ^{99m}Tc-HMPAO cerebral SPECT imaging in mild TBI described by Audenaert *et al.*,[46] suggest that the usefulness, if any, of cerebral SPECT imaging as it is usually performed in clinical practice may be limited, at best, to only a portion of the mild TBI population. Furthermore, Gowda *et al.*[49] and Roper *et al.*[57] have reported cases wherein lesions following mild TBI were detected on CT but not by SPECT, suggesting that "normal" cerebral SPECT imaging does not exclude definitively the presence of injury-related brain abnormalities. Collectively, these concerns suggest that considerable uncertainty remains regarding the sensitivity, specificity, positive and negative predictive values, and other possible sources of error when cerebral SPECT imaging is applied to the evaluation of both groups and individual patients with mild TBI. As a result, cerebral SPECT imaging in mild TBI does not appear to satisfy this aspect of the third *Daubert* criterion.

This *Daubert* criterion also requires consideration of the standards that serve to ensure that quality control exists and is maintained with respect to the technique in question, in this case cerebral SPECT imaging. In 1999, the Society of Nuclear Medicine released version 2.0 of its Procedure Guideline for Brain Perfusion Single Photon Emission Computed Tomography (SPECT) Using Tc-99m Radiopharmaceuticals.[56] The guide provides a comprehensive manual for the conduct of SPECT studies. Proper procedures for performing such studies, whether in clinical or research contexts, are described, as well as the types of collateral information (i.e., clinical history, neuropsychological testing results, structural imaging findings) that should also be obtained. The guide concludes with clear recommendations regarding the interpretation and appropriate reporting of cerebral SPECT imaging findings and offers several cautionary notes as to potential pitfalls in the interpretation and reporting of such findings.

Among these cautionary notes are those that regard the wide range of normal variability in cerebral SPECT imaging, both between and within subjects, which makes definitive identification of "abnormalities" challenging at best. The guide recommends that the laboratory conducting the study use a normal database for comparison of individual imaging findings to improve interpretation of such data. Second, the guide urges caution in selecting contrast levels, background subtraction, and thresholding lev-

els; failure to do so may make artifactual findings appear clinically important. Third, the guide states that cerebral SPECT images are best evaluated in the context of structural imaging findings. Finally, the guide recommends that clinicians attempting to interpret cerebral SPECT imaging data familiarize themselves with the report of the Ethical Subcommittee for Functional Brain Imaging.[56] In the section on ethical reporting, the guide emphasizes that patients will present with nonspecific perfusion patterns and that the implication of direct relationships between a lesion and a particular etiology, behavior, or neuropsychiatric symptom is to be avoided. An adequate report will contain a statement regarding the technical quality of the study and a description of any abnormalities, including the criteria used to define abnormal. A complete differential diagnosis, based on peer-reviewed and generally accepted patterns, should be offered, and the interpretation should be qualified with pertinent information surrounding medical history, other illnesses, current medications, or any other variables that might influence the results. Any limitations surrounding the study and the available clinical data should be stated explicitly, as should any departures from standard techniques, instruments, or methods.

In a related report, the Ethical Subcommittee for Functional Brain Imaging[58] guidelines for the use of SPECT imaging note that even when previously published recommendations for SPECT studies are strictly followed, the quality of the study will vary between institutions. This variance arises as a result of differences in instrumentation, subjects' behavioral states, the timing between scan and injection, the duration of the scan, patient movement, attenuation, reconstruction, analytic methods, and quality control. To the extent that these sources of variance can be controlled, interpretation of cerebral SPECT imaging findings is best guided by comparison to published data, and the instruments used must perform at a level generally consistent with those used to establish the relied-upon published data. As in the Society of Nuclear Medicine's Procedure Guideline for Brain Perfusion Single Photon Emission Computed Tomography (SPECT) Using Tc-99m Radiopharmaceuticals, the Committee comments on the uncertain relationship between SPECT imaging patterns and any given etiology or symptom and specifically notes the insufficient state of evidence surrounding cause-and-effect relationships between SPECT images and mild TBI, substance abuse, infectious or toxic exposures, environmental illness, and foreign body reactions. The requirement for a direct statement of limitations in technical quality or available clinical information, a full differential diagnosis supported by the literature, and all potentially confounding factors is emphasized.[58]

In principle, it is possible for cerebral SPECT imaging to satisfy the third *Daubert* criterion—namely, that standards exist that serve to ensure quality and that those standards are maintained when performing this technique and interpreting its data. However, the extent to which these standards are adhered to varies considerably in both clinical and research settings. As discussed earlier in the article, in the report of Davalos and Bennett,[3] more than half of the published reports describing cerebral SPECT imaging findings among persons with mild TBI were excluded from analysis on the basis of such technical failings. It is therefore likely that clinical providers in the community will have similar difficulty in routinely meeting the numerous requirements that enable the production of cerebral SPECT data of acceptable scientific and ethical reporting quality.

These observations suggest, at a minimum, the need for careful review of the technical quality and ethical reporting of cerebral SPECT imaging findings in individual cases of mild TBI. The possible, perhaps even commonplace, disconnection between the existence of and adherence to the standards for the performance, interpretation, and ethical reporting of cerebral SPECT imaging findings in persons with suspected mild TBI is of concern in regard to the suitability of this technique for forensic purposes in such cases. Although *Daubert* and its progeny call for consideration of evidence on a case-by-case basis, the need for careful review of individual case data under the third *Daubert* consideration is of paramount importance before admitting cerebral SPECT data into legal proceedings related to mild TBI.

The remaining *Daubert* inquiry asks if general acceptance of the theory and technique has been achieved in the relevant scientific community. In the case of SPECT imaging and mild TBI, the most accurate answer, based on the literature, appears to be no. By and large, it seems that most authors recognize that SPECT, if performed under technically sound protocols, may be a useful source of adjunctive data in some clinical circumstances, provided that

the data are in fact considered only as adjunctive to clinical data, neuropsychological tests, and structural imaging studies and are presented in reports that abide by published technical standards and ethical reporting guidelines. In this context, cerebral SPECT imaging may corroborate a diagnosis of mild TBI but is not itself diagnostic of this condition. Moreover, there is at present no credible evidence for nor general acceptance of the use of cerebral SPECT as a stand-alone technique for the identification of mild TBI and prediction of clinical outcome. Similarly, it is neither scientifically established nor generally accepted that cerebral SPECT can link patterns of abnormal rCBF to any specific etiology (i.e., mild TBI) or clinical neuropsychiatric condition.

Related Opinions Relevant to the Forensic Use of Functional Cerebral Imaging

Although few authors have directly addressed the use of SPECT imaging for forensic applications, a strong theme of caution is nearly ubiquitous in publications on this subject. In their ethics treatise on SPECT imaging, the Society of Nuclear Medicine Brain Imaging Council[58] confronts this "especially controversial" issue. The Council reports that "the forensic application of nonreplicated, unpublished or anecdotal SPECT or positron emission tomography (PET) observations is inappropriate and has ominous implications. This can lead to unsupportable conclusions if introduced as 'objective evidence' " (Ref. 58, p 1257). Given the lack of evidence supporting this technology and the expert's duty to testify with "reasonable medical certainty," the Council concludes that there are very few clinical situations in which expert evidence based on SPECT images can be provided appropriately. At the same time, the council acknowledges that nearly every clinical diagnostic procedure in medicine will sooner or later make a court appearance, and this eventuality highlights the legal and ethical necessity for careful application of evidentiary rules.

These sentiments are echoed by Mayberg[59] in an article exploring the medicolegal inferences that can be derived from SPECT and PET images. Like many authors, Mayberg points out the inability to establish consistent relationships between functional imaging patterns and specific illnesses, and even greater difficulty in establishing convincing relationships between functional imaging abnormalities and specific neuropsychiatric symptoms or signs. She argues that until causative relationships between functional imaging findings and neuropsychiatric conditions are established, the forensic application of SPECT is neither scientifically justified nor legally permissible.

This cautionary, or even prohibitionist, theme surrounding the use of functional imaging in the courtroom is echoed by Reeves *et al.*[43] The technological aspects of modern imaging, inaccessible to many experts and lay persons alike, is a serious source of potential misguidance. While forensic psychiatrists need not possess a physicist's comprehension of the technology, they cannot ignore it. Threshold, color choices, contrast levels, type of imaging device, and testing conditions vary among imaging facilities, and all of these factors influence not only the data produced but also the manner in which those data are interpreted and presented. These technical aspects of functional brain imaging are often confusing to both the general population and professionals. This confusion may serve as a foundation on which to manipulate data and its presentation by parties whose agenda is not purely scientific. Reeves and colleagues offer the example of the seemingly simple matter of color-coding, and point out that color choice can create illusions of huge contrasts in apparent functional activity (or its absence) between brain areas despite the lack of clinically important functional activity differences. Variability within and between individuals, at a single point in time and longitudinally, intrinsically, and also due to confounding factors, further confuses the interpretation and presentation of cerebral SPECT findings in the courtroom. The crucial caveats that guide cerebral SPECT imaging interpretation in clinical practice are easily obscured, clouded, or ignored by an attorney's or expert witness' selective collection and presentation of data. Reeves *et al.* conclude that the use of cerebral SPECT imaging in the courts may offer more in the way of jury seduction than clinical science, and that the responsible expert will make modest claims despite the expectations and desires of lawyers soliciting their testimony.

Conclusions

This analysis of the suitability of cerebral SPECT imaging in mild TBI casts serious doubt on the evidentiary usefulness and appropriateness of this technology in this context at this time. Nonetheless, the relatively liberal admission policies encouraged by

the Federal Rules of Evidence and *Daubert* mean that emerging medical technologies such as cerebral SPECT imaging findings are likely to work their way into the courtroom. The responsibility to ensure that these data are utilized and presented in a reasonable, scientific, and responsible fashion must fall to the expert witnesses offering opinions on the use of this technology in the setting of mild TBI and the judges overseeing the process by which evidence is admitted into those proceedings.

Ideally, experts themselves will step forward as the first line of defense against the misuse or inappropriate interpretation of cerebral SPECT in medicolegal settings. The medical expert providing an opinion on cerebral SPECT imaging results is regarded as more knowledgeable and familiar (relative to court members) with the technology, its limitations, and the relevant literature and is in the best position to ensure that opinions are offered in an ethical manner.

Ethical testimony on cerebral SPECT imaging in mild TBI requires open acknowledgment of limitations surrounding technical quality, clinical data, evidentiary support in the literature, and the unclear relationships between rCBF patterns and their etiologies or clinical correlates. While clinicians and scientists are gaining experience with SPECT in mild TBI, the level of understanding surrounding the injured brain and this relatively new technology have not united to a degree sufficient to establish causal relationships between cerebral SPECT imaging findings and mild TBI or its neurobehavioral sequelae. Expert witnesses therefore should acknowledge this fact; when they fail to do so, officers of the court should require from them such an acknowledgment.

Accordingly, offering an exhaustive differential diagnosis for any "abnormal" cerebral SPECT finding is an ethically mandated element of expert testimony when, if ever, such findings are introduced as evidence in any legal proceeding. When used in conjunction with clinical history, neuropsychological test results, and structural imaging findings, cerebral SPECT may offer findings that complement and support diagnostic impressions derived from these other data sources. In light of the need to regard cerebral SPECT as a secondary line of evidence, however, it appears at best to be a superfluous evidentiary device whose purpose is to augment the communication of diagnostic impressions derived from other sources of clinical evidence through the presentation of colorful and easily understood "brain images" to participants in legal proceedings.

Both experts and officers of the court dealing with this kind of evidence must familiarize themselves with the ethics-related and technical regulations that help ensure scientifically sound and principled use of cerebral SPECT imaging in mild TBI. Officers of the court should be wary of any expert offering testimony involving definitive relationships between a SPECT image and an illness or symptom, or refusing to identify limitations or confounding factors surrounding the study. Experts should be discouraged from claiming too much for this technology, using it to form opinions in isolation of or in conflict with other diagnostic data, or making bold cause-and-effect claims between mild TBI and cerebral SPECT imaging findings. Based on the review of the literature presented in this article, testimony suggesting such relationships is neither justifiable nor appropriate. When misused and left unchallenged, cerebral SPECT imaging findings in mild TBI can be powerfully seductive and misleading. The ethical expert witness will acknowledge as much, and the court should be prepared to exercise its gatekeeping powers when the expert witness fails to offer ethical and scientifically justifiable opinions regarding cerebral SPECT imaging findings in mild TBI.

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